Exploring the Reactivity of Hydroxylamine-Containing Species: *O*-Isocyanates and Cope-Type Hydroamination

By

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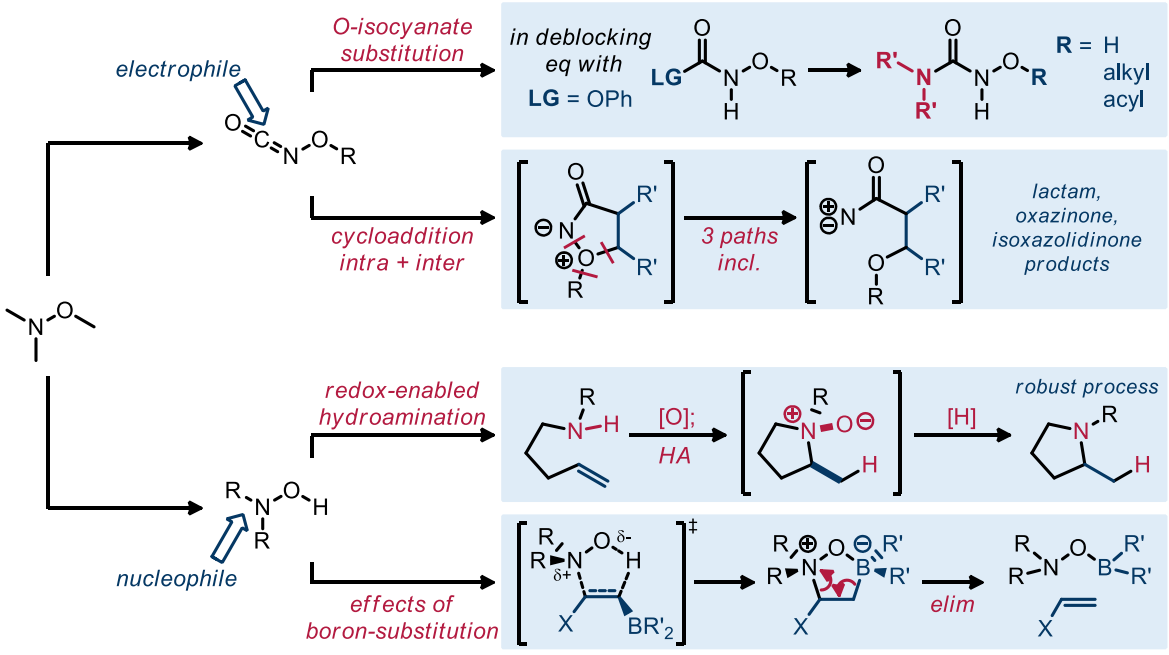
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Abstract

While the chemistry of hydroxylamines has been well investigated since the 19th century, new methodologies and uses of this distinctive functional group continue to be reported, largely for amination. The work reported within this thesis centers around two general uses of hydroxylamines: (1) as an electrophile within highly reactive *O*-isocyanates, and (2) as a nucleophile in Cope-type hydroamination reactions. *O*-Isocyanates are not stable species, homocoupling or degrading readily at ambient conditions, so various blocked carbamate precursors were assessed and developed to form *O*-isocyanates in equilibrium. This maintains a low concentration of free *O*-isocyanate, allowing for efficient substitution reactivity with amines. This blocking group strategy has also been applied to new [3+2] cycloaddition chemistry. Upon deblocking, free *O*-isocyanates can act as uncharged 1,3-dipole equivalents, forming highly reactive aza-oxonium ylide cycloadducts from intra- or intermolecular cycloaddition in stark contrast to conventional dipolar cycloaddition. The divergent reactivity of the novel charged species, aza-oxonium ylides, has been explored for the formation of bicyclic lactams, β-lactams, oxazinones, and isoxazolidinones depending on the reaction conditions and substrates chosen. Computational results support a concerted asynchronous [3+2] cycloaddition, though provided no potential means to broaden the intermolecular dipolarophile substrate scope.



Conversely to the electrophilic reactivity of *O*-isocyanates, acyl and alkyl substituted hydroxylamines have been used to develop new Cope-type hydroamination reactivity, where the hydroxylamine nitrogen acts

as a nucleophile. The cascade substitution and Cope-type hydroamination of *N*-oxyureas is reported, combining *O*-isocyanate and hydroamination reactivity in one sequence. A redox-enabled strategy for intramolecular Cope-type hydroamination was developed to bypass the synthetic difficulties associated with hydroxylamines and *N*-oxides. Using simple secondary amines as reagents, a robust process was developed that did not require the use of chromatography for purification. The successful overall reaction supports the further development of an oxygen-borrowing approach to hydroamination. These studies demonstrated significant solvent effects using trifluoroethanol, which in part, leads to more stable *N*-oxide products. Lewis interactions involving boron-substituted alkenes were also explored as a strategy to increase *N*-oxide stability. Significantly faster reactivity is observed with boron-substitution and the products are stable when X = H. Otherwise, bora-Cope elimination occurs readily, leading to observable alkene products as well as the assumed formation of *O*-borylhydroxylamines. While efforts to exploit *O*-borylhydroxylamines for bora-amination reactivity have not proven fruitful, this reactivity has been exploited for the selective semi-hydrogenation of alkynes via sequential hydroboration then hydroamination and bora-Cope elimination. A computational collaboration allowed for the elucidation of the effects boron substitution, including the lowering the HOMO-LUMO gap and stabilizing the increased electron density at carbon with the B-O π^* orbital.

This work overall demonstrates the breadth and efficiency of metal-free hydroxylamine reactivity. Further studies stemming from the discovery and initial work related to borrowing oxygen approach to hydroamination and the increased Cope-type hydroamination reactivity of vinylboronates are already proving productive.

Acknowledgements

Thank you, André, for your guidance and for the freedom to explore, both well-timed for my development as a scientist. Academic research has been immensely enjoyable and working in your lab has made it all the better. Your enthusiasm for chemistry research is contagious and is always appreciated. NSERC funding for the group and myself is also much appreciated. Thanks as well to Prof. Adrian Schwan and Eric Nicol for the immensely positive experience of scientific collaboration, and to Prof. Tom Woo for the initial help to learn computational chemistry. Thank you to Dr. Glenn Facey and Dr. Peter Pallister of the NMR facility for sharing their expertise and helping me solve a few tricky, though mostly uninteresting, unknowns and to all the guys at the science store for the constant help to maintain a functioning lab.

Thanks to all the lab mates I've had the pleasure to work with in the Beauchemin lab from 2016-2022. To my labmates who I've worked with on projects; Ryan, Dilan, Myra, Huy, Kamel, Rand, Janick, Geneviève, and Daniel, thank you for your endless efforts to make interesting chemistry work. In particular, Ryan and Dilan, as senior PhD students you sparked and helped to grow my curiosity for scientific literature and developing interesting and sometimes useful reactions. Ryan, I thoroughly enjoyed working hard on reactivity that never wanted to cooperate - it was certainly character building. Dilan, you have been an incredibly supportive friend and colleague, so I can't thank you enough for making my first few years in the Beauchemin lab fantastic. Myra, you are an absolute delight to work with and I'm grateful that I had the opportunity.

I would like to thank nitrogen for always keeping things interesting. Special shoutout to boron for coming in as a close second.

My friends in other labs have been incredibly supportive. I'd like to specifically thank Myriam, Leah, Julia, Mel M, Mel C, Elly, and Matt and their respective pets. Having a great support system is sometimes as easy as people to grab a beer with, though you all have helped me much more than that. Thanks in particular to Myriam who makes sure we never have just one beer. On that note, thanks to FnS also.

Thank you to my family for their support and for humouring me with their pet photos. Lastly, thank you to my non-chemist partner, Dag, who makes sure I don't take myself too seriously.

Statement of Contributions

In Beauchemin group I have collaborated with several graduate and undergraduate students for various research projects. I have also collaborated with a group from the University of Guelph on the computational studies for one project. By chapter, I outline my contribution to each project along with the contributions of my peers.

Chapter 2: This work was highly collaborative largely with Ryan Ivanovich and also with Dilan Polat, both senior PhD candidates. Working with both Ryan and Dilan in 2016-2017, we studied the substitution of amines onto *O*-isocyanates, benefiting from related optimized conditions developed by Ryan and Dilan for hydantoin synthesis. Leaving group optimization was performed by myself and Dilan, amine scope was performed by Dilan, oxy-carbamate scope was largely completed by Ryan with some additional help form me, and I completed the cascade Cope-type hydroamination scope for the 2017 Organic Letters publication. This manuscript was written by me with editing help from all authors. Ryan and I are co-first authors for this publication. In winter 2017, I also joined Ryan to explore his preliminary intermolecular *O*-isocyanate cycloaddition finding. Together, we worked to optimize and explore intermolecular reactivity with vinyl ethers and strained alkenes. The isolated substrate scope was divided evenly. I led the exploration of oxy-carbamate substitution effects for alternative reaction pathways or improved stabilization. Together, we also worked to optimize and explore intramolecular reactivity along with alternative reaction pathways, such as nitrene trapping. Ryan began computational work, then helped to teach me how to complete additional computational work. The scope of intra- and intermolecular *O*-isocyanate cycloaddition was published in a 2020 Angewandte Chemie article. This intramolecular portion of this manuscript was written by me, the intermolecular portion was written by Ryan, and editing was done by all authors. Ryan and I are co-first authors for this publication.

Chapter 3: Beginning in September 2016, I continued the optimization of *N*-hydroxyurea Cope-type hydroamination started by Ryan earlier in 2016. Ryan provided key initial data and advice. In December of 2019, I began exploring dialkylhydroxylamine Cope-type hydroamination. I was joined by Genevieve O'Keefe, an honour's student, in June 2020-August 2021. Under my close supervision, she continued the optimization of the intramolecular redox-enabled Cope-type hydroamination using tertiary amine reagents until May 2021. In the summer term, she then helped me for the related isolation procedure development with secondary amine reagents that I had optimized earlier. In August 2021, I was joined by Huy Minh Ly, a junior PhD candidate. Huy helped to isolate products, make some reagents, and obtain

robustness screening data for the 2022 Chemical Science publication under my supervision. I wrote the manuscript and both Huy and I contributed to the supporting information for this publication. I am the first author for this publication. Working from the optimized oxidation conditions, I developed the oxidative synthesis of secondary hydroxylamines and began the optimization of their isolation procedure in February 2021. I was joined by Myroslava Volosheniuk, a Master's candidate, in April 2021, then Daniel Barriault, and honour's student, in May 2021. Daniel took over the optimization of the isolation procedure and initial scope studies for his honour's project under my supervision. Solvent effects and silicon substitution effects were studied my me along with some help from undergraduate volunteer, Mei Xi Chen.

Chapter 4: In November of 2020, I isolated the product of the reaction of *N*,*N*-diethylhydroxylamine with pinacol vinylboronate and determined the structure of the novel cyclic zwitterionic heterocycle. I was joined by Myroslava Volosheniuk, a Master's candidate, in January 2021. Working together, we explored the hydroxylamine, alkene, and boron substitution effects. Under my supervision, we attempted to optimize isolation, various derivatization reactions, and bora-amination reaction cascades. I began computational studies related to this work in 2021, then stopped in favour of a collaboration with the Schwan lab (with PhD candidate, Eric Nicol) at the University of Guelph beginning in July 2021. Specific contributions for computational analysis are outlined within chapter 4. I wrote the manuscript draft and both Myroslava and I contributed to the experimental supporting information for this work yet to be submitted for publication. I conceived and optimized the alkene synthesis within section 4.4 in February 2022 based on data collected by myself and Myroslava.

All text, tables, figures, and schemes are original content.

One needs a reason for doing something – it doesn't matter what the reason is…
A clever person with a will to experiment and the proper tools at his or her command, the most important tool being an open and inquisitive mind, can find interesting science in a study undertaken, in retrospect, for the weirdest reason.

- Roald Hoffmann
from Nearly Circular Reasoning

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Abbreviations

°C	degree Celsius
δ	chemical shift in parts per million
^{1}H	Proton
^{11}B	Boron-11
^{13}C	Carbon-13
^{19}F	Fluorine-19
[H]	general reductant
[O]	general oxidant
Å	angstrom (10^{-10} metres)
Ac	acetyl
anti	opposite side
aq	aqueous
Ar	aryl
B3LYP	Becke-3-Lee-Yang-Parr
BDE	Bond dissociation energy
Bn	benzyl
Boc	*tert*-butoxycarbonyl
bp	boiling point
Bu	butyl
Bz	benzoyl
cat.	catalytic
Cbz	benzyloxycarbonyl
CDI	carbonyldiimidazole
cis	same side
conc.	concentrated
Cy	cyclohexyl
d	deuterium (in NMR solvents)
dan	1,8-diaminonapthalene
DFT	Density functional theory
DMAP	*N*,*N*-4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
E	General electrophile
ee	enantiomeric excess
EI	electron impact
equiv	equivalent
ESI	electrospray ionization
Et	ethyl
FTIR	Fourier transform infrared
g	gram
G	Gibbs free energy
h	hour
*h*ν	light; electromagnetic radiation
HRMS	high-resolution mass spectrometry
Hz	Hertz

i	iso
IR	infrared
J	coupling constant
kcal	kilocalorie
L	Litre or ligand
LG	generic leaving group
µL	microlitre
m	meta
M	Molar or metal
Me	methyl
mg	milligram(s)
MIDA	*N*-methylimidodiacetic
min	minute(s)
mL	millilitre(s)
mmol	millimole(s)
neop	neopentyl glycol
NMR	nuclear magnetic resonance
Nu	General nucleophile
o	ortho
p	para
Ph	phenyl
pin	pinacol
Pr	propyl
py	pyridine
R	carbon-based substituent
Rf	retention factor
rt	room temperature
s	second
sat.	saturated
SI	Supporting information
syn	together, same side
t	tertiary
TBS	*tert*-butyldimethylsilyl
temp	temperature
Tf	trifluoromethanesulfonyl
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	*para*-toluenesulfonyl
X	generic halide
µW	microwave

Chapter 1 Introduction

The following chapter discusses the importance of various nitrogen-containing compounds, the effects and application of blocked (masked) isocyanates, and the synthesis, properties, and reactivity of various hydroxylamine derivatives. These topics serve as a crucial background and context to the research discussed in chapters 2-4.

1.1 Importance of Nitrogen-Containing Compounds

While inorganic and inert nitrogen gas forms the majority of the Earth's atmosphere, nitrogen is also one of the most common elements in organic material. The reactivity and applications of nitrogen-containing species are rich, and certainly extend well beyond the scope of organic chemistry. The following discussion is a brief introduction to the applications of relevant nitrogen-containing organic compounds.

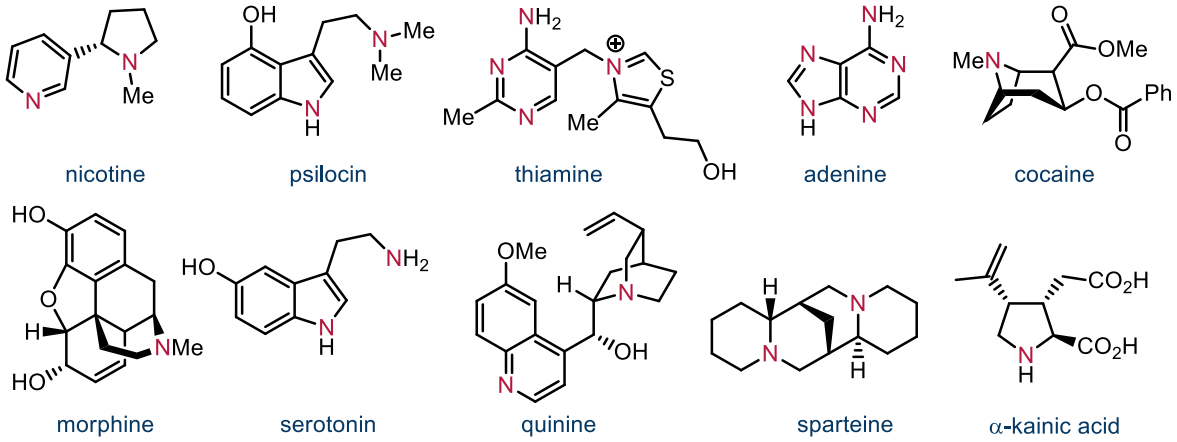
1.1.1 Nitrogen in Bioactive Small Molecules

Amines, amides, and nitrogen-containing heterocycles are ubiquitous in bioactive small molecules from natural sources and from unnatural synthesis. Nitrogen species serve as hydrogen bond donors or acceptors, nucleophiles, or bases in biological systems, and can contain various structural features depending on covalent bonding and intermolecular interactions. While the nitrogen atom is rarely chiral, nitrogen-containing species interact with chiral species regularly, leading to a broad range of bioactivities.

1.1.1.1 Biosynthesis of Nitrogen-Containing Natural Products

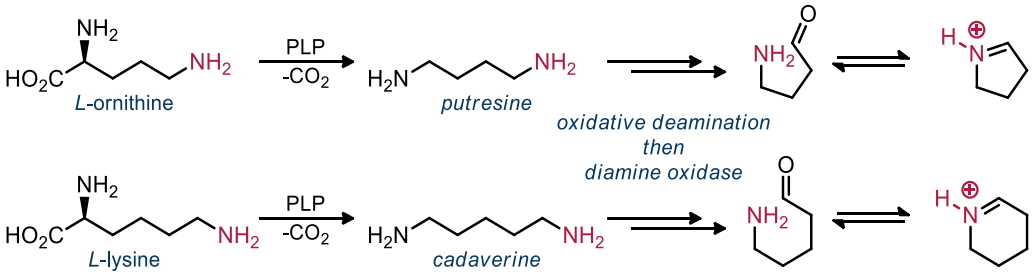
Bioactive amines from nature can be as simple as amino acids or nucleobases or complex like large alkaloids (Figure 1. 1). Plants, animals, bacteria, and fungi all make various nitrogen-containing natural products generally as secondary metabolites to mediate interactions not directly related to growth or reproduction.

Figure 1. 1 Bioactive amines from nature

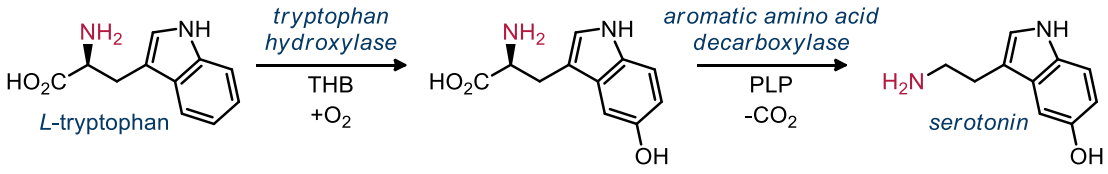


The biosynthesis of nitrogen-containing species often begins from amino acids.[1] *L*-Ornithine, made from glutamic acid, and *L*-lysine serve as NC_4 and NC_5 building blocks respectively using pyridoxal phosphate (PLP)-dependent enzymes for decarboxylation (Scheme 1. 1). α-Alkylation using malonyl-CoA is then a common step for the synthesis of more complicated alkaloid structures. *L*-Tryptophan and *L*-tyrosine are other biosynthetically relevant alkaloid precursors. For example, hydroxylation followed by decarboxylation produces serotonin from *L*-tryptophan (Scheme 1. 2).

Scheme 1. 1 Biosynthesis of pyrrolidines and piperidines



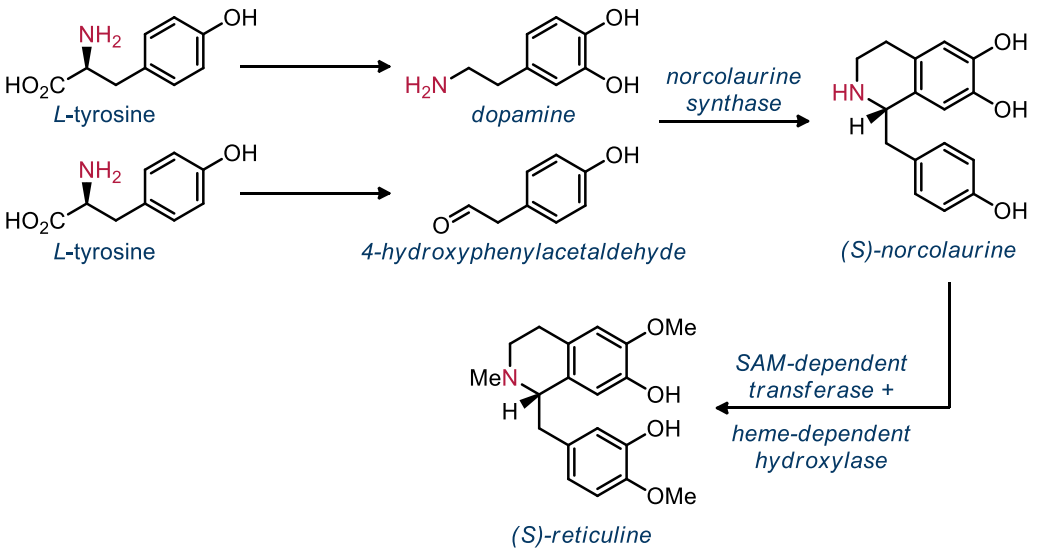
Scheme 1. 2 Biosynthesis of serotonin from *L*-tryptophan



[1] Dewick, P. M. *Medicinal natural products: A biosynthetic approach*, 3rd ed.; John Wiley & Sons, 2009.

The morphine precursor, (*S*)-reticuline, is made from two molecules of *L*-tyrosine (Scheme 1. 3). Decarboxylation and hydroxylation of *L*-tyrosine forms dopamine and oxidative deamination and decarboxylation of *L*-tyrosine forms 4-hydroxyphenylacetaldehyde. Norcolaurine synthase then catalyses the condensation and cyclization to form norcolaurine. A series of SAM-dependent methylations and one hydroxylation then produces reticuline. These examples serve to demonstrate the broad range of nitrogen-containing natural products that can be synthesized from similar amino acid precursors. The evolution of many specialized enzymes helps to diversify these precursors into complex alkaloid species with distinct bioactivities.

Scheme 1. 3 Biosynthesis of reticuline from *L*-tyrosine



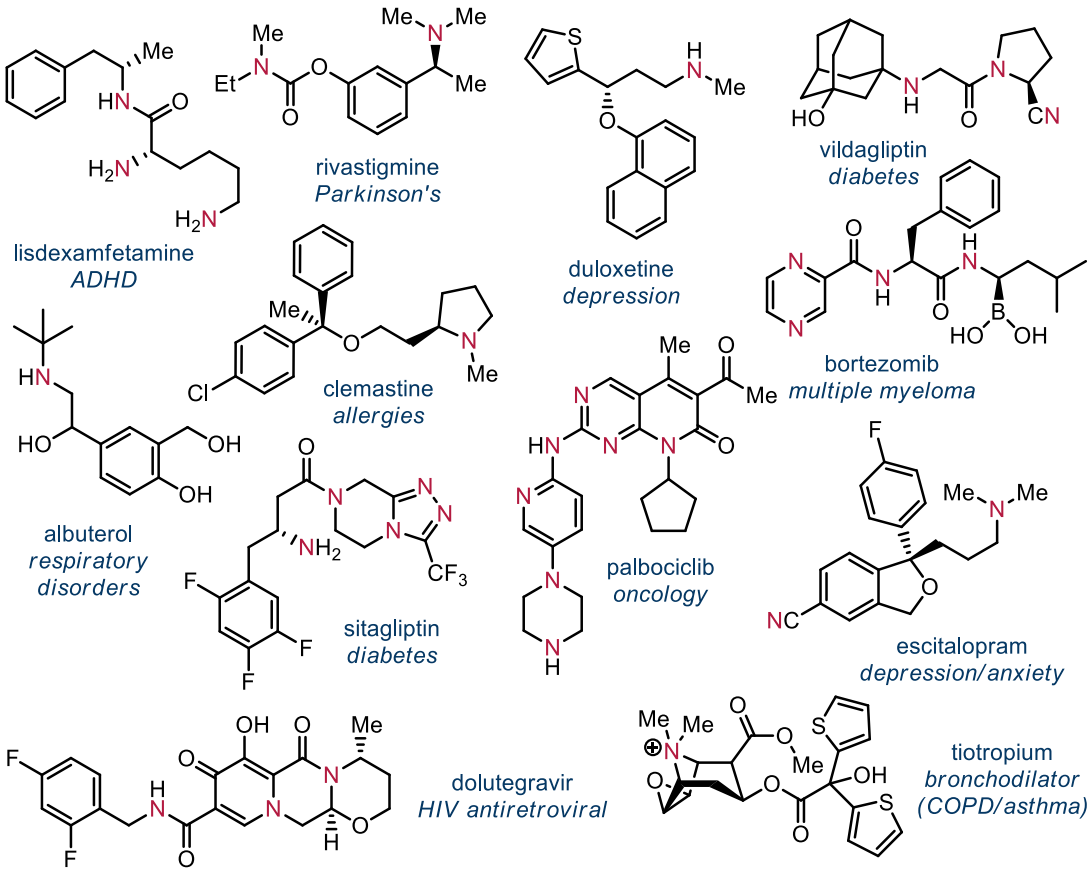
1.1.1.2 Prevalence of Nitrogen in Pharmaceuticals

Due to the prevalence of bioactive nitrogen-containing compounds made by nature, it can be expected that nitrogen's presence would also be highly prevalent in pharmaceuticals.[2] Structural mimics of amine-containing natural products can function as active pharmacophores. Nitrogen heterocycles are particularly common in approved pharmaceuticals (Figure 1. 2).[3] The bioactivity of nitrogen-containing

[2] (a) Rodrigues, T.; Reker, D.; Schneider, P.; Schneider, G. *Nat. Chem.* **2016**, *8*, 531-541. (b) Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2020**, *83*, 770–803.
[3] Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 10257–10274.

small molecules also allows for applications in the agrochemical industry, such as pesticides and fungicides.[4]

Figure 1. 2 Examples of nitrogen-containing pharmaceuticals

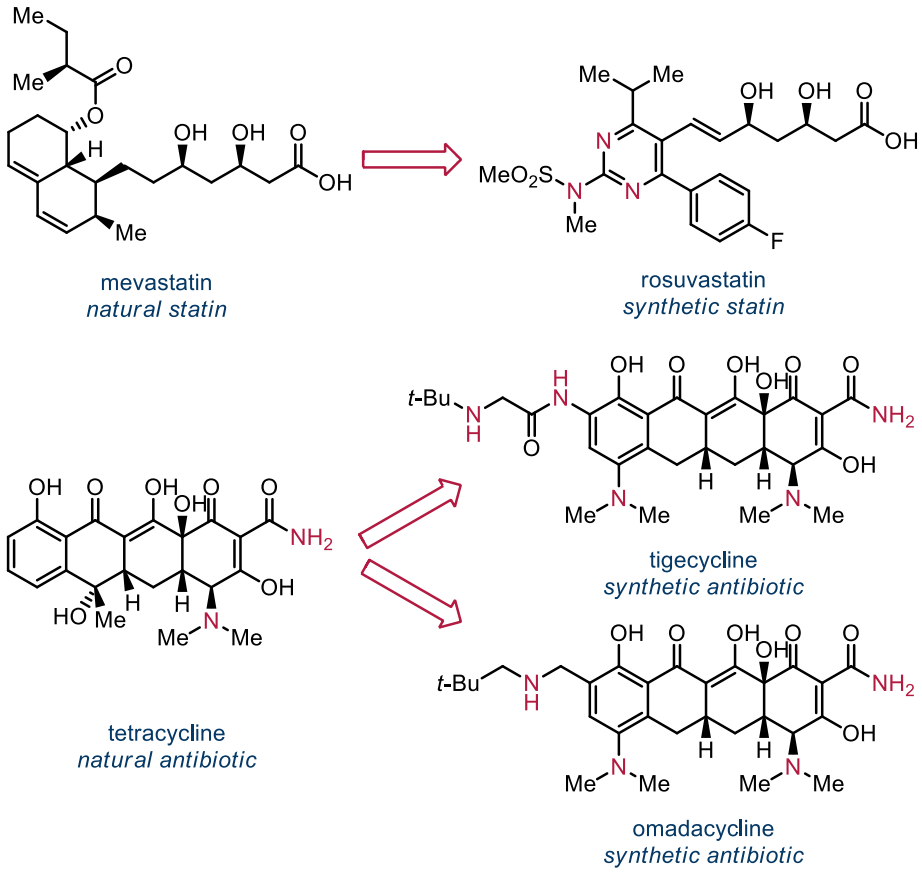


Synthetic pharmaceuticals have a higher nitrogen content than natural products on average.[2a] This is exemplified by the comparison of the natural product, mevastatin, to its synthetic counterpart, rosuvastatin (Figure 1. 3). While both molecules bind to the same target enzyme, 3-hydroxy-3-methylglutaryl-coenzyme A reductase, rosuvastatin has three additional nitrogen atoms. Another example of a nitrogen atom increase for derivatives of natural products is the antibiotic tetracycline and its semisynthetic counterparts, such as tigecycline and omadacycline.[5] Testing and producing synthetic

[4] Clemens, L.; Stephane, J.; Torsten, L.; Andrew, P. *Science* **2013**, *341*, 742–746.
[5] Fuoco, D. *Antibiotics* **2012**, *1*, 1-13.

and semi-synthetic pharmaceuticals therefore requires a broad array of efficient amination reactions, beyond those evolved by nature.

Figure 1. 3 Structures of bioactive natural products vs. synthetic counterparts



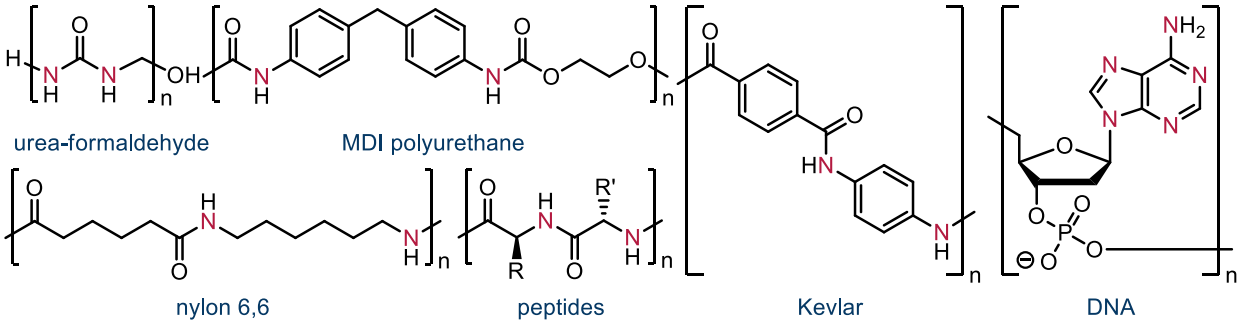
1.1.2 Nitrogen in Other Materials

1.1.2.1 Nitrogen-Containing Polymers and Biopolymers

Nitrogen is extremely common in biopolymers, such as proteins and DNA or RNA. Amide bonds are also found in industrially produced synthetic polymers, such as polyamides or polyurethanes (Figure 1. 4). Amides impart structural rigidity to polymers via their hindered rotation and hydrogen bonding capabilities. For example, strong interchain hydrogen bonding allows, in part, for Kevlar's application in

bullet-proof vests. Polyamides are resistant to organic solvents and alkaline conditions but degrade readily under strongly acidic conditions.[6]

Figure 1. 4 Examples of nitrogen-containing polymers



1.1.2.2 Ligands, Photoactive, and Electrochemical Mediator Species

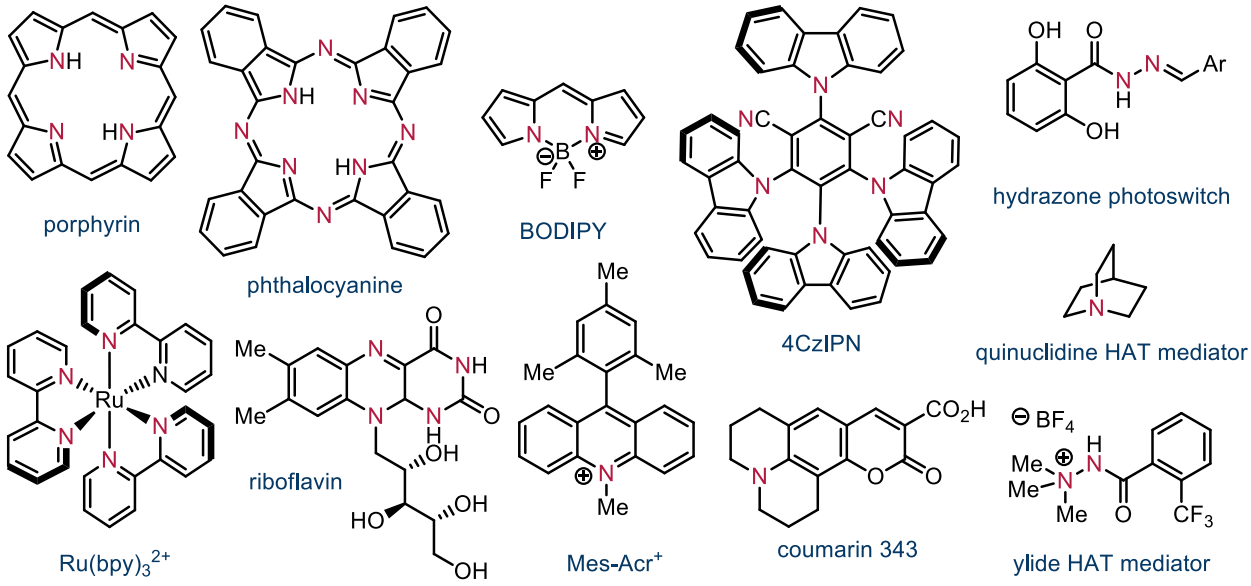
Nitrogen also plays an important role in ligands and photoactive materials (Figure 1. 5). Organometallic ($Ru(bpy)_3^{2+}$) and organic photocatalysts (4-CzIPN, $Mes\text{-}Acr^+$) are common in the recent organic chemistry literature.[7] Several small molecules, such as quinuclidine, have become popular HAT mediators in photochemical and electrochemical systems due to the stability of nitrogen-centered radicals and their conjugate acids.

Unsaturated nitrogen-containing ligands, such as porphyrin in heme, are important ligands in biological systems. Related organic methodology using porphyrin-like ligands has also been developed.[8] Phthalocyanines, BODIPYs, coumarin, and related structures are used as dyes, and more recently, metal phthalocyanines have been used in organic solar cells.[9] While riboflavin is a vitamin used for the formation of coenzymes, flavins have also been used in photocatalysis.[10]

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[6] Palmer, R. J. Polyamides, Plastics. In *Encyclopedia Of Polymer Science and Technology*, 4th ed.; John Wiley & Sons, 2001.
[7] Shaw, M. H.; Twilton, J.; MacMillan, D. W. C. *J. Org. Chem.* **2016**, *81*, 6898–6926.
[8] (a) Baglia, R. A.; Zaragoza, J. P. T.; Goldberg, D. P. *Chem. Rev.* **2017**, *117*, 13320–13352. (b) Huang, X.; Groves, J. T. *Chem. Rev.* **2018**, *118*, 2491–2553.
[9] Kumar, C. V.; Sfyri, G.; Raptis, D.; Stathatos, E.; Lianos, P. *RSC Advances* **2014** *5*, 3786–3791.
[10] Srivastava, V.; Singh, P. K.; Srivastava, A.; Singh. P. P. *RSC Advances* **2021**, *11*, 14251-14259.

Figure 1. 5 Examples of nitrogen-containing photoactive materials or mediators in photoredox or electrochemical reactions

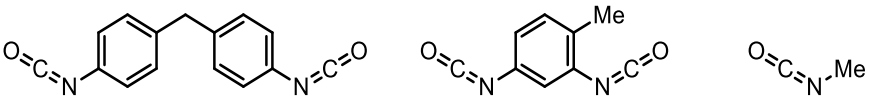


Nitrogen is an immensely common element in organic chemistry and nitrogen-containing compounds show great versatility. The vast reactivity of nitrogen-containing species is crucial to many aspects of daily life. The structure, properties, and reactivity of only isocyanate and hydroxylamine derivatives will be discussed in further detail within the introduction.

1.2 Blocked Isocyanates

Isocyanates are important building blocks for amide, carbamate, and urea bond formation. They are highly reactive electrophiles that are flammable, notably harmful when inhaled, and potentially toxic. Diisocyanates, such as methylene diphenyl diisocyanate (MDI) and toluene diisocyanate (TDI) are used in the polyurethane industry for the industrial production of foams (Figure 1. 6). Aliphatic diisocyanates, such as hexamethylene diisocyanate, are generally used for polymer coatings. Methyl isocyanate (MIC) is commonly used in the synthesis of pesticides and polymers.[11] All isocyanates are sensitive to moisture, decomposing to amines and ureas when exposed to water. Toxicity and moisture sensitivity have made the direct use of isocyanates less desirable.

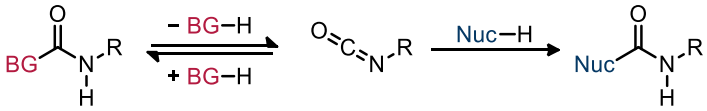
Figure 1. 6 Structures of common isocyanates



1.2.1 Blocking Group Strategy

The polyurethane industry has developed a variety of blocked (masked) isocyanates in attempts to mitigate issues with isocyanate toxicity and moisture sensitivity.[12] Even storage of isocyanates becomes more problematic at large industrial scales. Deblocking of isocyanates occurs as a chemical equilibrium in which the release of the blocking group (BG) forms the free isocyanate, which can then react with a nucleophile (Scheme 1. 4).

Scheme 1. 4 General reaction of a blocked isocyanate with a nucleophile



A blocking group allows an isocyanate precursor to be stable to moisture at room temperature and these precursors are generally much less toxic than the corresponding unblocked isocyanate.[12a] In the polyurethane industry, deblocking is optimized to occur at high temperatures often without any catalyst.

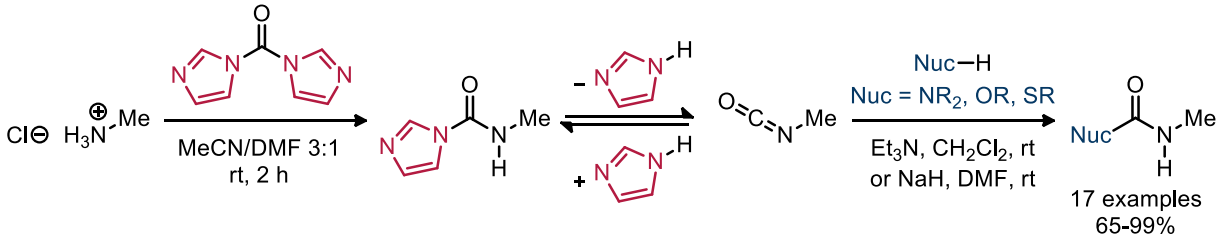
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[11] Six, C.; Richter, F. Isocyanates, Organic. Ullmann's Encyclopedia of Industrial Chemistry. Wiley-VCH, Weinheim, 2005. DOI: 10.1002/14356007.a14_611.

[12] (a) Rolph, M. S.; Markowska, A. L. J.; Warriner, C. N.; O'Reilly, R. K. *Polym. Chem.* **2016**, *7*, 7351-7364. (b) Delebecq, E.; Pascault, J. -P.; Boutevin, B.; Ganachaud, F. *Chem. Rev.* **2013**, *113*, 80-118. (c) Wicks, D. A.; Wicks, Z. W. *Prog. Org. Coat.* **2001**, *41*, 1–83. (d) Wicks, D. A.; Wicks, Z. W. *Prog. Org. Coat.* **1999**, *36*, 148–172.

The deblocking equilibrium also allows for a slower release of isocyanate, which controls the concentration and leads to cleaner polymerization reactions. Common blocking groups include alcohols and phenols, anilines and amines, oximes, amides, and heterocycles (e.g., imidazole or pyrazole). Fine chemical synthesis has also benefitted from the blocking group strategy. For example, a blocked methyl isocyanate can be formed quantitatively using carbonyldiimidazole (CDI), then used with a variety of nucleophiles under mild conditions, avoiding the direct use of toxic methyl isocyanate (Scheme 1. 5).[13]

Scheme 1. 5 Blocked methyl isocyanate synthesis and substitution



1.2.1.1 Effects of Blocking Groups

The identity of a blocking group affects the deblocking equilibrium and therefore the optimal conditions for reactions with the blocked isocyanate. While "deblocking temperatures" may be quoted in various reports on blocked isocyanate use, these values have been found to be rather specific to the method of measurement and not representative of the equilibrium deblocking process, and are therefore not universally useful.[12b] When directly compared in systems like that of the desired reactivity, some trends can be found.[14] For example, a correlation of phenol pK_a values with the deblocking temperature of phenol-blocked TDI monomers was reported by Kothandaraman as measured using IR spectroscopy (Table 1. 1).[15] Notably, these phenols likely have similar mechanisms of deblocking and similar levels of steric hindrance affecting the deblocking equilibrium. The mechanism of deblocking using intramolecular proton transfer (Figure 1. 7) can help inform general predictions on relative reactivity, however, no accurate predictive models have been reported to date.

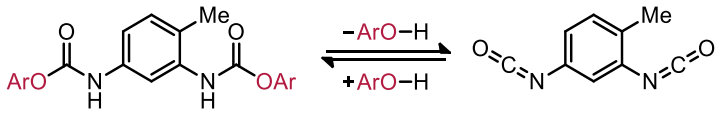
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[13] (a) Duspara, P. A.; Islam, M. S.; Lough, A. J.; Batey, R. A. *J. Org. Chem.* **2012**, *77*, 10362-10368. For a review of the 1984 methyl isocyanate disaster in Bhopal, see: (b) Mishra, P.; Samarth, R.; Pathak, N.; Jain, S.; Banerjee, S.; Maudar, K. *Int. J. Occup. Med. Environ. Health* **2009**, *22*, 193−202; (c) Varma, D. R.; Guest, I. *J. Toxicol. Environ. Health* **1993**, *40*, 513-529.

[14] Nasar, A. S.; Kalaimani, S. *RSC Adv.* **2016**, *6*, 76802-76812.

[15] Kothandaraman, H.; Nasar, A. S. *Polymer* **1993**, *34*, 610-615.

Table 1. 1 Dissociation temperatures of phenol-blocked TDI and graph of relationship of pK_a vs. 50% dissociation temperature



Phenol blocking group (ArOH)	pK_a of ArOH[16]	Minimum dissociation temperature (°C)	50% dissociation temperature (°C)
phenol	9.98	110	130
o-cresol	10.29	120	150
m-cresol	10.08	120	140
p-cresol	10.14	165	>180
guaiacol	9.98[17]	70	130
2,6-dimethylphenol	10.6[17]	125	155
o-chlorophenol	8.56	75	95

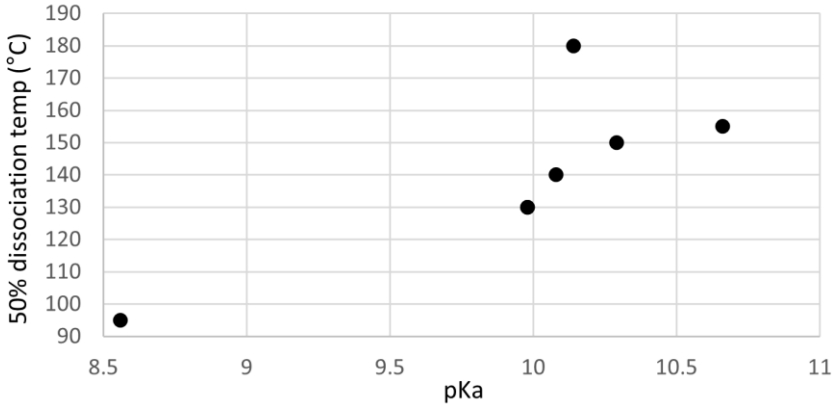
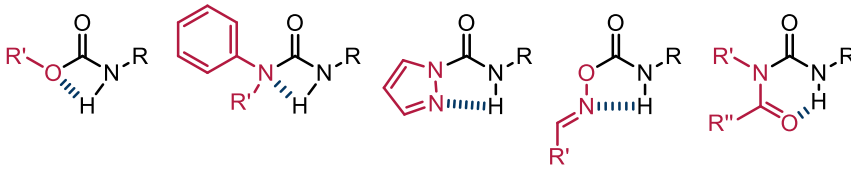


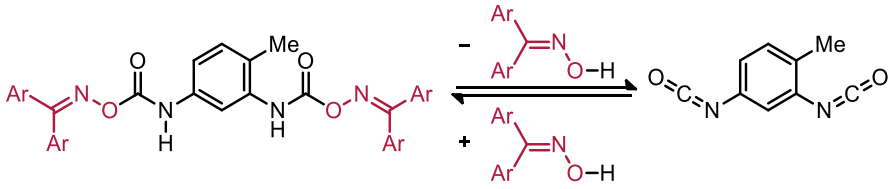
Figure 1. 7 Proposed intramolecular interactions important for deblocking for several blocked carbon-substituted isocyanates



Electronic deblocking trends can also change depending on the blocking group. For example, Kothandaraman demonstrated with thermogravimetric analysis that electron-donating groups on the benzophenone oxime blocking group lower the decomposition temperature while electron-withdrawing

groups increase the decomposition temperature (Table 1. 2).[18] The decomposition can be attributed to deblocking or degradation into CO_2 and the corresponding amine, however, the authors propose that deblocking was the major pathway of decomposition from gas chromatography results. This trend aligns well with the proposed 5-membered mechanism of deblocking in which the oxime N lone pair aids in deprotonating the carbamate N-H (Figure 1. 7). This is opposite to the trend observed for phenol (Table 1. 1). The electronic trend for phenol deblocking appears to be more related to the stability of the resulting phenolate rather than the oxygen basicity. Overall, the effects of blocking groups can be difficult to predict for specific reactions and conditions.

Table 1. 2 Decomposition temperatures of oxime-blocked TDI as determined by thermogravimetric analysis



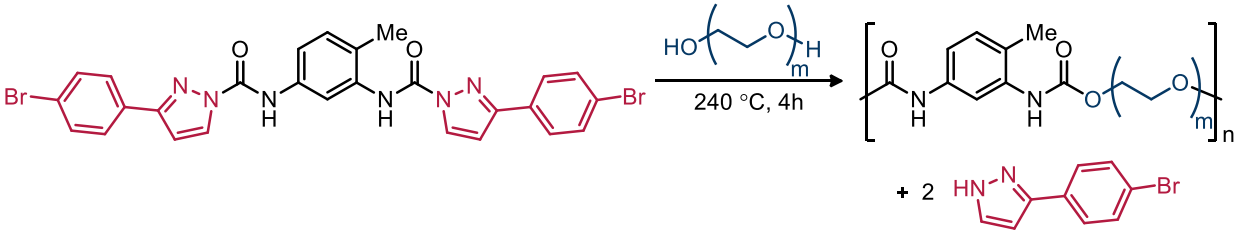
Oxime blocking group Ar (Ar_2CNOH)	Change in weight (%)	Decomposition temperature (°C)
Ph/Ph	90.5	256
4-$OMeC_4H_6$/4-$OMeC_4H_6$	85.7	198
3-MeC_4H_6/4-MeC_4H_6	94.3	251
2-MeC_4H_6/4-MeC_4H_6	89.9	274
2-MeC_4H_6/5-MeC_4H_6	90.5	267
4-ClC_4H_6/4-ClC_4H_6	86.4	290

1.2.1.2 Uses of Blocked Isocyanates

Blocked isocyanates are used in a variety of polyurethane syntheses. In a recent report, Jaisankar and Kim demonstrate that 3-(4-bromophenyl)-1H-pyrazole is an effective blocking group for the common toluene diisocyanate (TDI) monomer to form glycol-derived polyurethanes (Scheme 1. 6).[19]

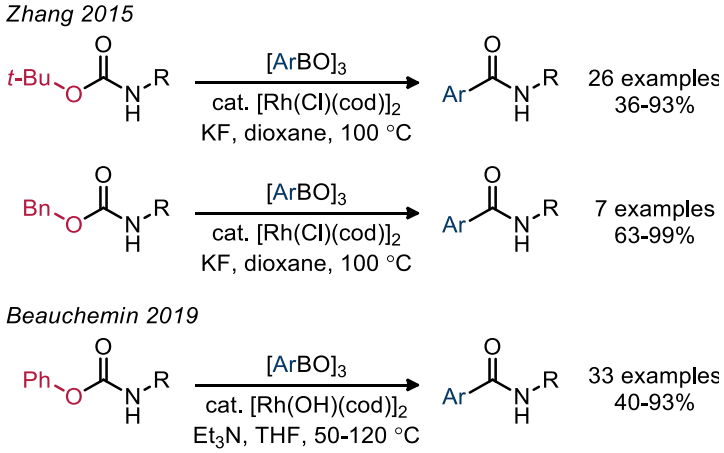
[18] Kothandaraman, H.; Thangavel, R. *J. Polym. Sci., Part A: Polym. Chem.* **1993**, *31*, 2653–2657.
[19] Jana, S.; Samanta, D.; Fahad, M. M.; Jaisankar, S. N.; Kim, H. *Polymers* **2021**, *13*, 2875-2889.

Scheme 1. 6 Example of a blocked TDI polymerization using a pyrazole-based blocking group



Blocked isocyanates have also been used in the transition metal catalyzed synthesis of amides (Scheme 1. 7).[20] The benefit of using blocked isocyanates in this application includes reduced toxicity and a controlled release of free isocyanate. Isocyanates with pendant nucleophiles can also be tolerated when blocked precursors are used and a low concentration of isocyanate is maintained. Blocked isocyanates have notably not been applied to the known [2+2] cycloaddition reactivity of isocyanates.[21]

Scheme 1. 7 Use of blocked isocyanates for transition metal-catalyzed amide synthesis



The blocking group strategy is critical for the research of amphoteric heteroatom-substituted isocyanates, which are known to be extremely unstable, homocoupling at temperatures as low as -40 °C.[22] While the toxicity of nitrogen- and oxygen-substituted isocyanates (*N*-isocyanates and *O*-isocyanates) is a lesser

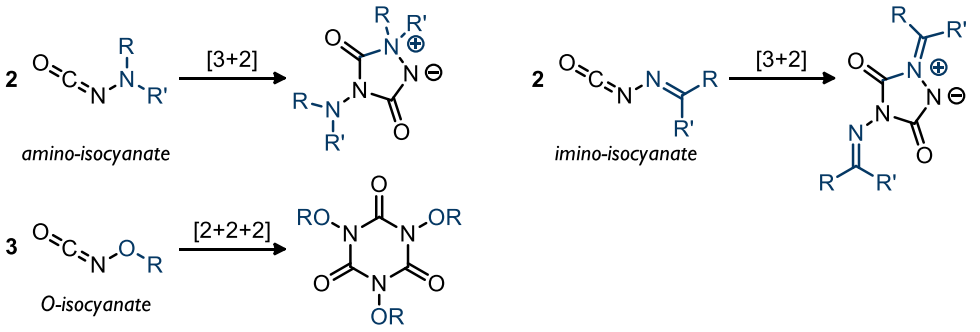
[20] (a) Lim, D. S. W.; Lew, T. T. S.; Zhang, Y. *Org. Lett.* **2015**, *17*, 6054−6057. (b) Derasp, J. S.; Beauchemin, A. M. *ACS Catal.* **2019**, *9*, 8104-8109.

[21] For a report on the substituent and solvent effects of isocyanate [2+2] cycloadditions, see: Cossio, F. P.; Roa, G.; Lecea, B.; Ugalde, J. M. *J. Am. Chem. Soc.* **1995**, *117*, 12306-12313.

[22] (a) Reichen, W. *Chem. Rev.* **1978**, *78*, 569-588. (b) Wentrup, C.; Finnerty, J. J.; Koch, R. *Curr. Org. Chem.* **2011**, *15*, 1745-1759.

concern due to their fleeting existence, a deblocking equilibrium greatly aids in controlling their concentration to reduce unwanted hydrolysis and homocoupling reactions (Scheme 1. 8).[23]

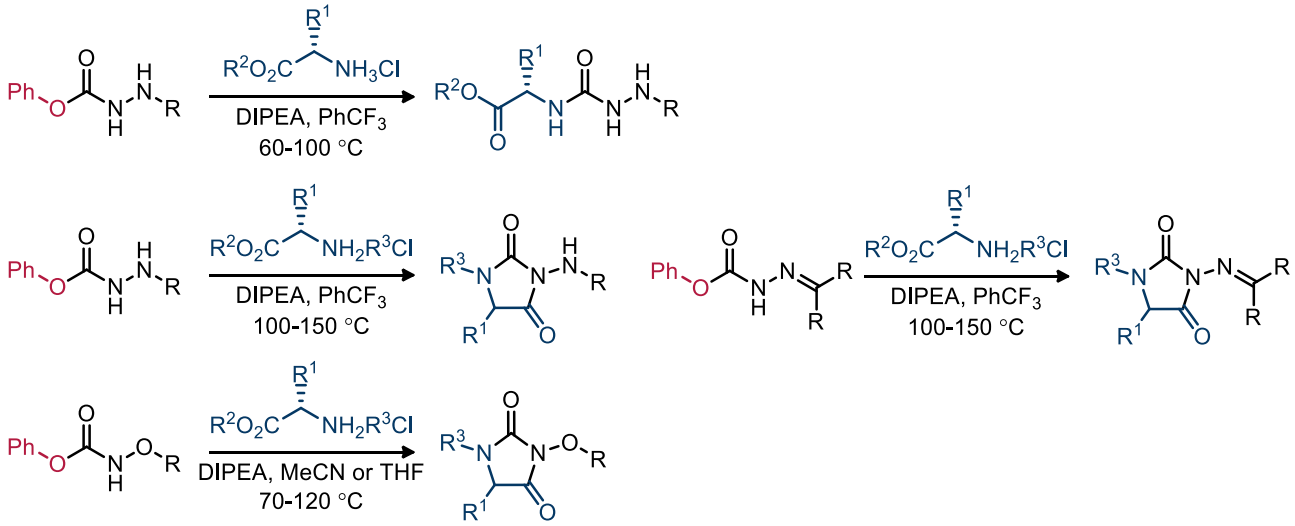
Scheme 1. 8 Homocoupling reactions of *N*-isocyanates and *O*-isocyanates



The success of this strategy is well-illustrated by the various reactions of *N*- and *O*-isocyanates with amino esters (Scheme 1. 9). Firstly, substitution using phenol-blocked amino-isocyanates was used for the synthesis of azadipeptide analogues.[24] Modifying the reaction conditions then allowed for the synthesis of *N*-aminohydantoins via substitution followed by cyclization from both blocked amino- and imino-isocyanates.[25] Similar conditions were then reported for the synthesis of *N*-oxyhydantoins from blocked *O*-isocyanates and amino esters.[23b] Phenol proved to be an effective blocking group for this amine substitution reactivity in all cases. Both heat and base catalysis (catalytic DIPEA or stoichiometric DIPEA when amine hydrochloride salts were used) aided in deblocking, however, small differences in temperature requirements were observed when *N*-isocyanates or *O*-isocyanates were used for hydantoin synthesis, which highlights the reactivity differences among similar heteroatom-substituted isocyanates.

[23] (a) Vincent-Rocan, J. -F.; Beauchemin, A. M. *Synthesis* **2016**, *48*, 3625-3645. (b) Ivanovich, R. I.; Polat, D. E.; Beauchemin, A. M. *Adv. Synth. Catal.* **2017**, *359*, 4289-4293.
[24] Clavette, C.; Vincent-Rocan, J. -F.; Beauchemin, A. M. *Angew. Chem. Int. Ed.* **2013**, *52*, 12705-12708.
[25] Vincent-Rocan, J. -F.; Clavetter, C.; Leckett, K.; Beauchemin, A. M. *Chem. Eur. J.* **2015**, *21*, 3886-3890.

Scheme 1. 9 Reactions of blocked *N*- and *O*-isocyanates with amino esters

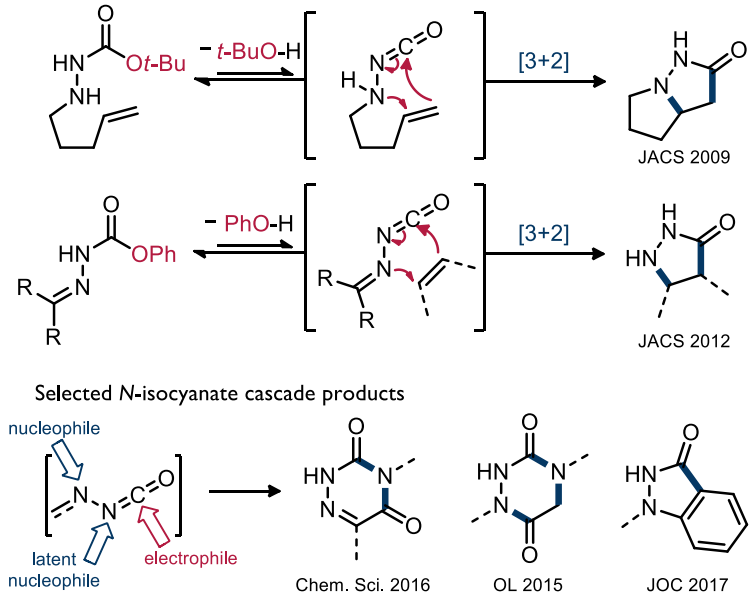


N-Isocyanate reactivity in substitutions and [3+2] cycloadditions has been thoroughly studied in the Beauchemin lab, forming a variety of semi-carbazides and heterocyclic products in cascade reactions (Scheme 1. 10).[26] In particular, the amphoteric nature of *N*-isocyanates has been exploited productively for a variety of cyclization reactions. *t*-Butanol and phenol blocking groups have been used to aid in controlled deblocking for each study depending on the mode of reactivity. In comparison, *O*-isocyanates are even more rare than *N*-isocyanates, with only a few reports in the literature prior to 2017.[27]

[26] (a) Vincent-Rocan, J.-F.; Ivanovich, R. A.; Clavette, C.; Leckett, K.; Bejjiani, J.; Beauchemin, A. M. *Chem. Sci.* **2016**, *7*, 315-328 and references therein. (b) Elkaeed, E. B.; An, J.; Beauchemin, A. M. *J. Org. Chem.* **2017**, *82*, 9890-9897.

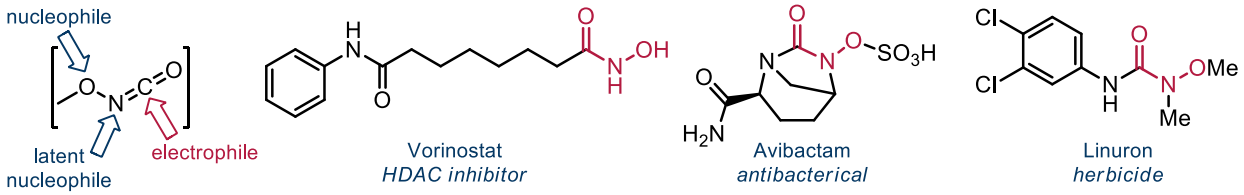
[27] For a single example of *O*-isocyanates in effective synthesis, see: (a) Romine, J. L.; Martin, S. W.; Meanwell, N. A.; Epperson, J. R. *Synthesis* **1994**, 846-850. For an example that likely go through an *O*-isocyanate intermediate, see: (b) Berry, J. F.; Ferraris, D. V.; Duvall, B.; Hin, N.; Rais, R.; Alt, J.; Thomas, A. G.; Rojas, C.; Hashimoto, K.; Slusher, B. S.; Tsukamoto, T. *ACS Med. Chem. Lett.* **2012**, *3*, 839-843. For examples of unexpected Lossen rearrangements forming *O*-isocyanates, see: (c) Hanessian, S.; Johnstone, S. *J. Org. Chem.* **1999**, *64*, 5896-5903. (d) Fioravanti, S.; Marchetti, F.; Morreale, A.; Pellacani, L.; Tardella, P. A. *Org. Lett.* **2003**, *5*, 1019-1021. (e) Krause, J. G.; Leskiw, B. D.; Emery, M. L.; McGahan, M. E.; McCourt, M. P.; Priefer, R. *Tetrahedron Lett.* **2010**, *51*, 3568-3570. (f) Baburaj, T.; Thambidurai, S. *Tetrahedron Lett.* **2012**, *53*, 2292-2294; *Tetrahedron Lett.* **2014**, *55*, 561-563. (g) Baburaj, T.; Thambidurai, S. *Synlett* **2011**, 1993-1996; *Synlett* **2015**, 1137.

Scheme 1. 10 *N*-Isocyanate reactivity developed in the Beauchemin group



O-Isocyanates have been minimally reported in the literature despite the prevalence of the ONCO motif in common chelating pharmaceuticals, such as hydroxamic acid HDAC inhibitors, and agrochemicals (Figure 1. 8).[28] *O*-Isocyanates are amphoteric and unstable like *N*-isocyanates, however, their precursors and reaction products are additionally prone to rearrangement reactions due to the weak N-O bond, further complicating their synthetic use. In fact, unexpected rearrangements account for much of the early studies involving *O*-isocyanates.

Figure 1. 8 *O*-Isocyanate amphoteric reactivity and the ONCO motif in biologically active molecules



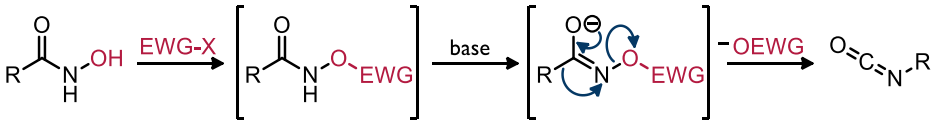
[28] (a) Muri, E. M.; Nieto, M. J.; Sindelar, R. D.; Williamson, J. S. *Curr. Med. Chem.* **2002**, *9*, 1631−1653. (b) Keth, J.; Johann, T.; Frey, H. *Biomacromolecules* **2020**, *21*, 2546−2556. (c) Citarella, A.; Moi, Pinzi, L.; D.; Bonanni, D.; Rastelli, G. *ACS Omega* **2021**, *6*, 21843−21849.

1.2.2 *O*-Isocyanate Synthesis and Reactivity

1.2.2.1 *O*-Isocyanates Synthesized from Rearrangement

The Lossen rearrangement occurs when a hydroxamic acid oxygen becomes activated to act as a leaving group causing a carbon group (R) migration, forming an isocyanate product (Scheme 1. 11).[29] This reaction was discovered in the late 1800s and has been used along with the Curtius and Hofmann rearrangements to synthesize isocyanates and their derivatives for decades.

Scheme 1. 11 General reaction mechanism for the Lossen rearrangement



Heteroatom migrating groups are much less common in the Lossen literature. Only recently has the Beauchemin group reported a thorough study of the aza-Lossen rearrangement using *N*-hydroxyurea precursors.[30] The observation of oxa-Lossen rearrangement products (oxygen-based migrating groups) has generally come unexpectedly during attempted electrophilic amination using bis-protected hydroxylamines.[31]

Hanessian was originally using sulfonyl hydroxylamine derivatives ($PyrSO_2ONHBoc$) with dicarbonyl nucleophiles in an attempt to form NH-Boc α-amino acids.[27c] Instead, *O*-*t*-butoxycarbonylamino derivatives were observed from the addition of enolates onto *t*-butoxy-isocyanate as elucidated via X-ray spectroscopy (Scheme 1. 12). The authors also found similar reactivity using TsONHBoc. Pellacani also reported unexpected Lossen reactivity to form imidazolidin-2-ones, in which an *O*-isocyanate was the proposed intermediate as well.[27d]

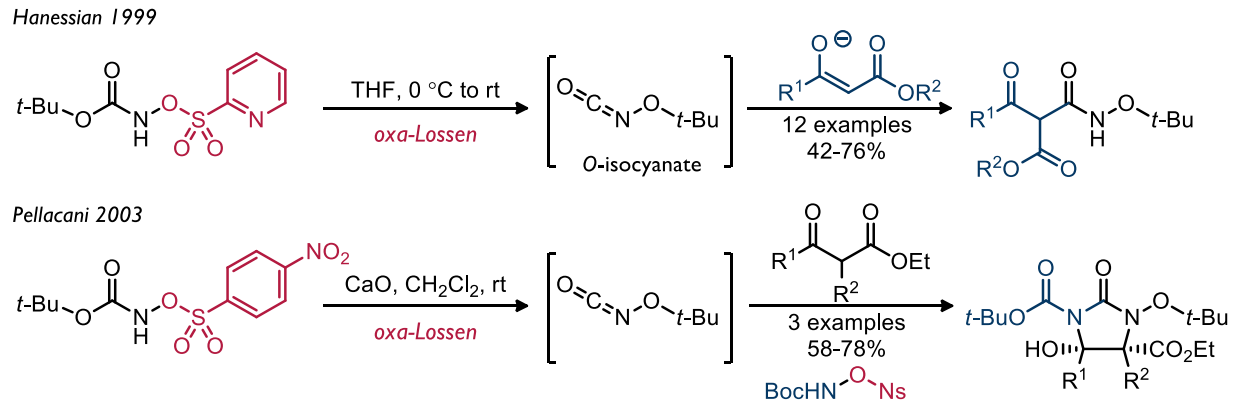
Priefer was originally aiming to form protected hydrazines via the electrophilic amination of amines, though *N*-*t*-butoxyurea products were observed instead (Scheme 1. 13).[27e] The authors proposed an oxa-Lossen mechanism to account for this product, citing Hanessian and Pellacani as precedent for the intermediacy of the *O*-isocyanate. Thambidurai was also originally attempting to aminate amines using

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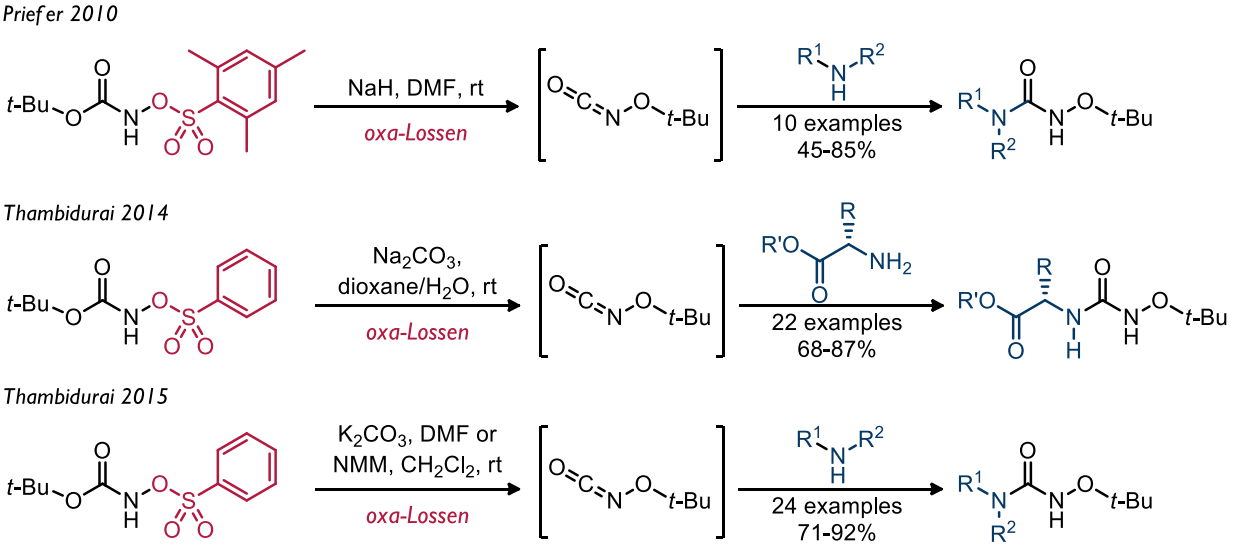
[29] (a) Lossen, W. *Liebigs Ann. Chem.* **1875**, *175*, 271-304. (b) Lossen, W. *Liebigs Ann. Chem.* **1877**, *186*, 1-74. (c) Lossen, W. *Liebigs Ann. Chem*. **1889**, *252*, 170-224. (d) Lossen, W. *Liebigs Ann. Chem.* **1894**, *281*, 169-305.
[30] Polat, D. E.; Brzezinski, D. D; Beauchemin, A. M. *Org. Lett.* **2019**, *21*, 4849-4852.
[31] Romine, J. *Org. Prep. Proc. Int.* **1996**, 251-288.

TsONHBoc, and indeed published in 2011 and 2012 proposing that the reaction conditions led to hydrazine derivatives. However, in 2014 and 2015, they published corrections to both communications, revising the structure of the products to *N*-oxyureas.[27f,g] In the corrections, the authors proposed an *O*-isocyanate intermediate formed via oxa-Lossen rearrangement and subsequent trapping with an amine nucleophile as in Priefer's work. The discussed works all demonstrate the unpredictable reactivity of hydroxylamine containing species. Additionally, they show that *O*-isocyanate substitution reactions can proceed effectively, however, the scope of *O*-isocyanate oxygen substitution studied is minimal (*t*-Bu only).

Scheme 1. 12 Synthesis and use of *O*-isocyanates formed via oxa-Lossen rearrangement with carbon nucleophiles



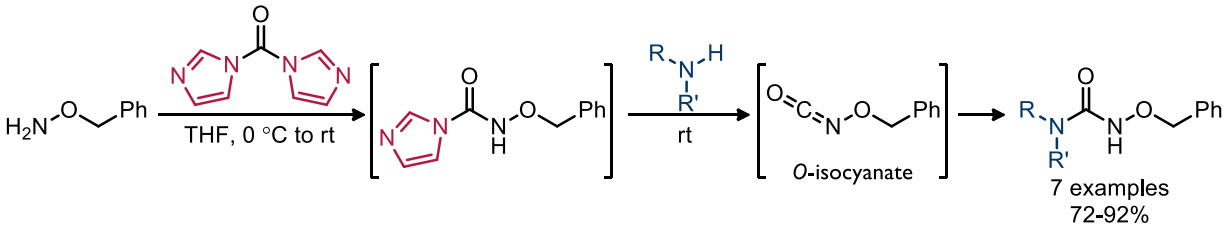
Scheme 1. 13 Synthesis and use of *O*-isocyanates formed via oxa-Lossen rearrangement with nitrogen nucleophiles



1.2.2.2 O-Isocyanates Synthesized using Blocked Precursors

In a communication from the BMS pharmaceutical research institute in 1994, Romine reported the first synthesis and use of a blocked *O*-isocyanate (Scheme 1. 14).[27a] First, the imidazole-blocked *O*-isocyanate is formed using equimolar CDI and *O*-benzylhydroxylamine. Then, an unreported amount of amine or aniline nucleophile is subsequently added to yield the *N*-oxyurea products. While no reactions are reported to directly support or reject the intermediacy of an *O*-isocyanate, an elimination/addition mechanism is likely due to the efficient reactivity demonstrated for modestly nucleophilic anilines.

Scheme 1. 14 First report of blocked *O*-isocyanate reactivity using in-situ formation of an imidazole-blocked precursor

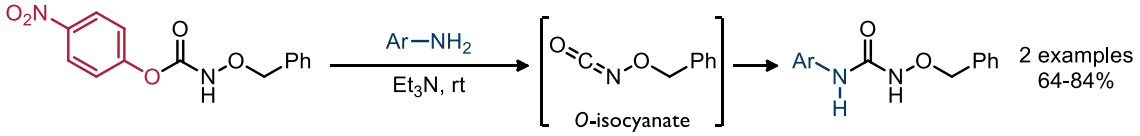


While this process highlights the efficient reactivity of blocked *O*-isocyanates, the conditions are not synthetically ideal. Hydroxylamines are prone to degradation when stored as the free base, so storage as the blocked precursor would be more appropriate.[32] A systematic study of the effects of *O*-substitution is also warranted since only *O*-benzyl substitution was included.

Notably, several medicinal chemistry routes to *N*-hydroxyureas involve an amine substitution using 4-nitrophenyl benzyloxycarbamate (Scheme 1. 15).[27b] *O*-Benzyloxy-isocyanates are possible intermediates in these reactions, though they are uncommonly proposed. Authors generally propose an addition/elimination mechanism when a mechanistic discussion is included, however, no reactions are reported to directly support or reject the intermediacy of an *O*-isocyanate. 4-Nitrophenol is therefore possibly an *O*-isocyanate blocking group but had not been studied with this function in mind.

[32] Wang, Q.; Wei, C.; Pérez, L. M.; Rogers, W. J.; Hall, M. B.; Mannan, M. S. *J. Phys. Chem. A* **2010**, *114*, 9262–9269.

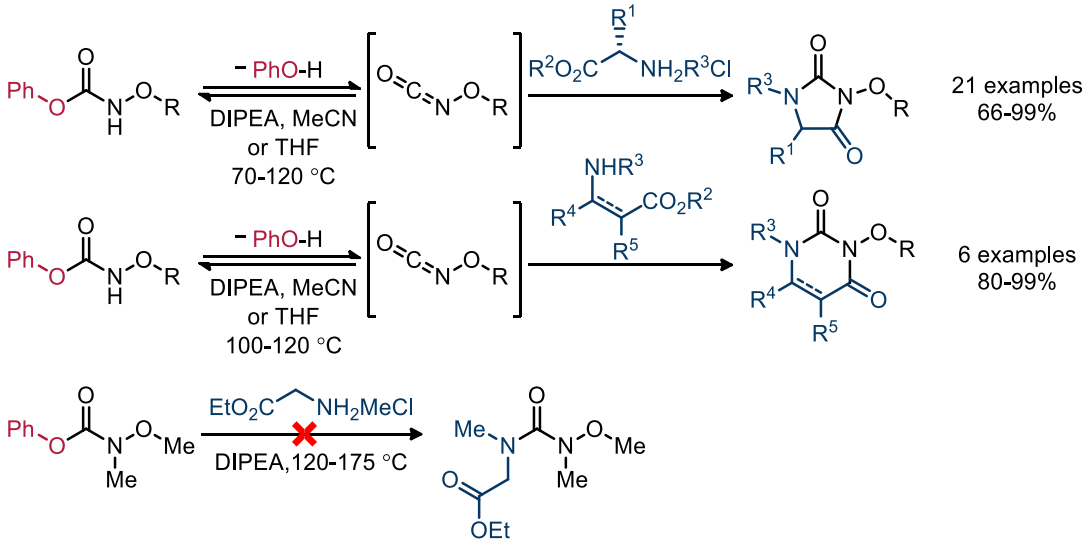
Scheme 1. 15 Example of potential blocked *O*-isocyanate use in medicinal chemistry



1.2.2.3 Cascade Reactions using Blocked *O*-Isocyanates

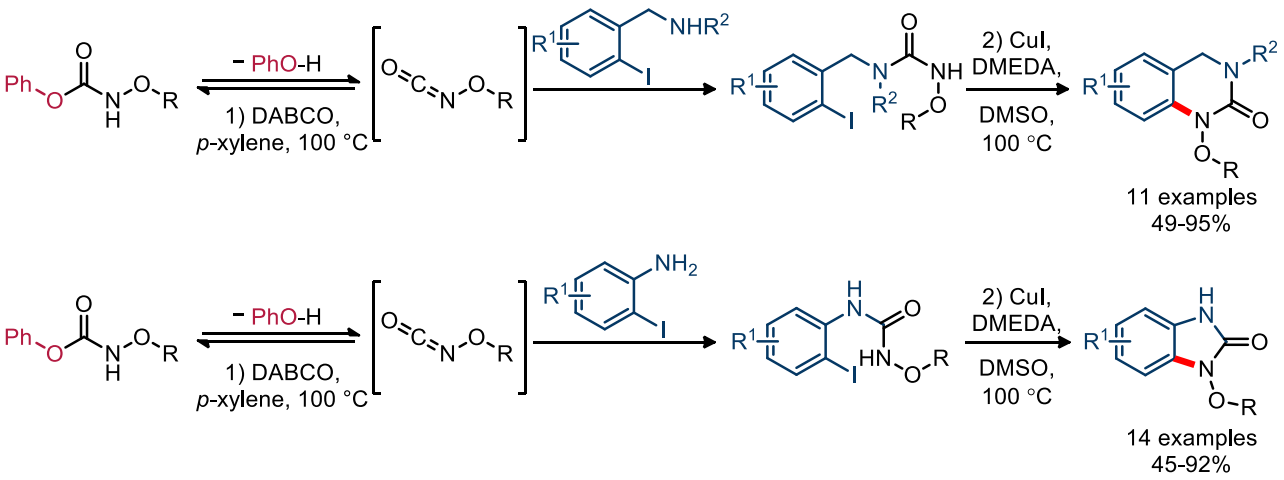
The Beauchemin group began studies of *O*-isocyanates with two reports on their cascade reactivity. First, a substitution and amidation cascade formed oxy-hydantoins from α-amino esters and oxy-dihydrouracils from β-amino esters (Scheme 1. 16).[23b] Phenol was used as a blocking group and was deblocked using heat and base catalysis. Importantly, an *N*-methyl substituted-carbamate was used as a reagent under the optimized reaction conditions and at higher temperatures to probe if an *O*-isocyanate intermediate was likely. The substitution reaction with sarcosine ethyl ester was unsuccessful in all experiments, suggesting that an addition/elimination mechanism is not occurring. The full recovery of both starting materials instead supports an elimination/addition mechanism involving an *O*-isocyanate intermediate. This was an important finding during the development of *O*-isocyanate reactivity in the Beauchemin group and this mechanistic test has since been repeated for a variety of new methodologies with a putative *O*-isocyanate intermediate.

Scheme 1. 16 *O*-Isocyanate cascade reaction for the synthesis of oxy-hydantoins



Secondly, a substitution and copper-catalyzed amination cascade formed oxy-benzimidazolones and oxy-dihydroquinazolinones (Scheme 1. 17).[33] Again, phenol was used as a blocking group and high temperature and base catalysis were used for a suitable deblocking equilibrium. This process was notably completed in a one-pot manner with sequential addition of the reagents rather than adding in all reagents at once. Neither of these reports required or explored the use of other blocking groups and neither studied the optimization of the substitution reaction alone. A more thorough study of the substitution of blocked *O*-isocyanates was therefore warranted.

Scheme 1. 17 Catalytic substitution/cyclization sequence of *O*-isocyanates



The reactivity of the hydroxylamine moiety of *O*-isocyanate reaction products had yet to be developed as well. Within the following chapters, applications of *O*-isocyanates in stepwise or cascade reactions involving the hydroxylamine moiety will be discussed.

[33] Wang, Q.; An, J.; Alper, H.; Xiao, W. -J.; Beauchemin, A. M. *Chem. Commun.* **2017**, *53*, 13055-13058.

1.3 Hydroxylamines

There is a broad range of hydroxylamine chemistry beyond that of *O*-isocyanates. Hydroxylamine derivatives are important for many applications including pharmaceuticals, ligands, antioxidants/radical trapping, bioconjugation, and various amination reactions. The synthesis, structural variation, and applications of hydroxylamine derivatives are discussed herein.

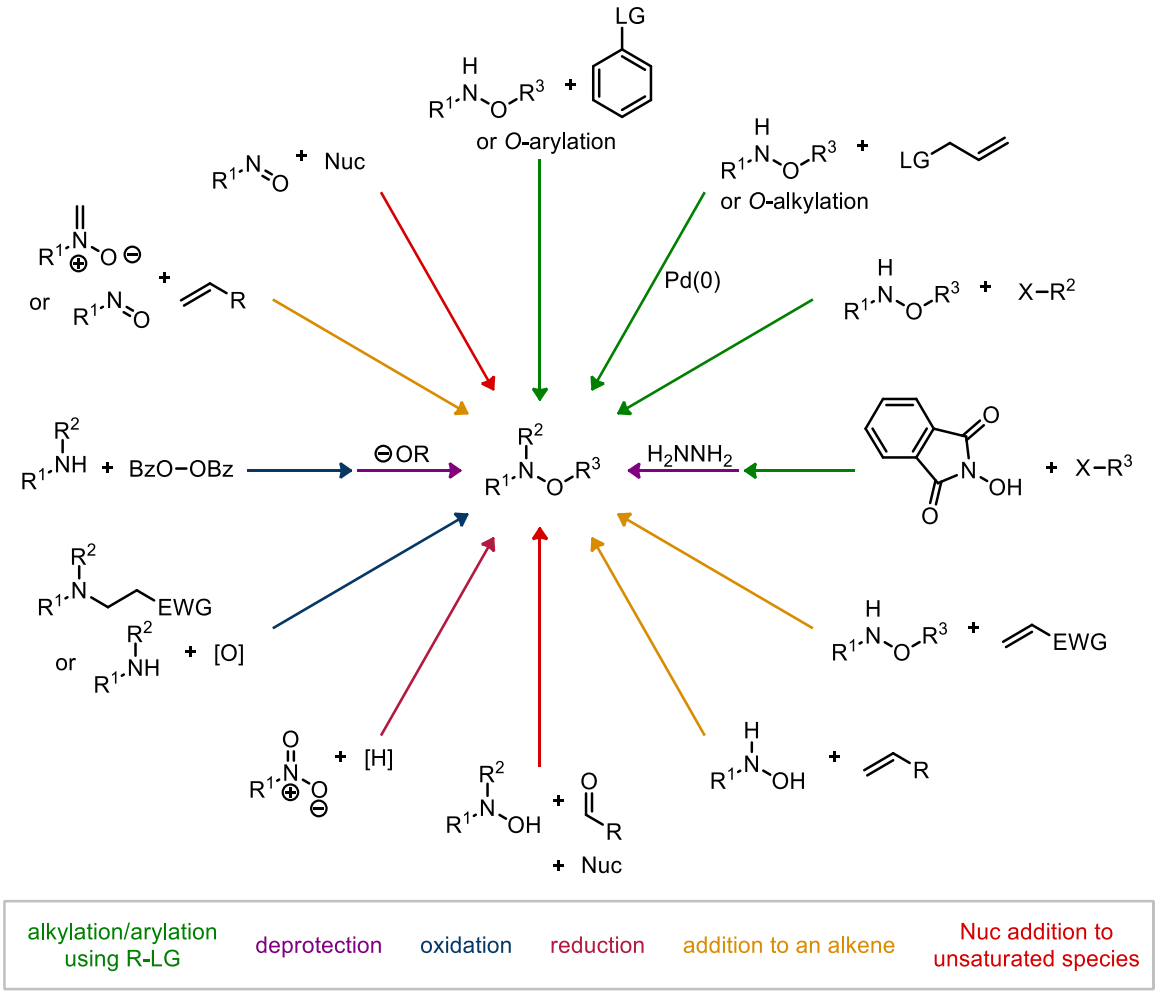
1.3.1 Synthesis and Structure

1.3.1.1 Synthesis of Hydroxylamines

Hydroxylamines can be synthesized using a variety of strategies including alkylation/arylation, deprotection, oxidation, reduction, addition to an alkene, or nucleophilic addition to a nitrone, oxime or nitroso species (Figure 1. 9).[34] Only oxidative and nitro-reductive approaches avoid using a hydroxylamine derivative as a reagent as well. Similar to the synthesis of aldehydes from alcohols or carboxylic acids, over-oxidation and over-reduction are commonly encountered challenges in these approaches.

[34] Melman, A. *The Chemistry of Hydroxylamines, Oximes and Hydroxamic Acids*; John Wiley & Sons, Ltd.: Southern Gate, **2008**, 118-161 and references therein.

Figure 1. 9 General synthetic methods towards alkylhydroxylamines



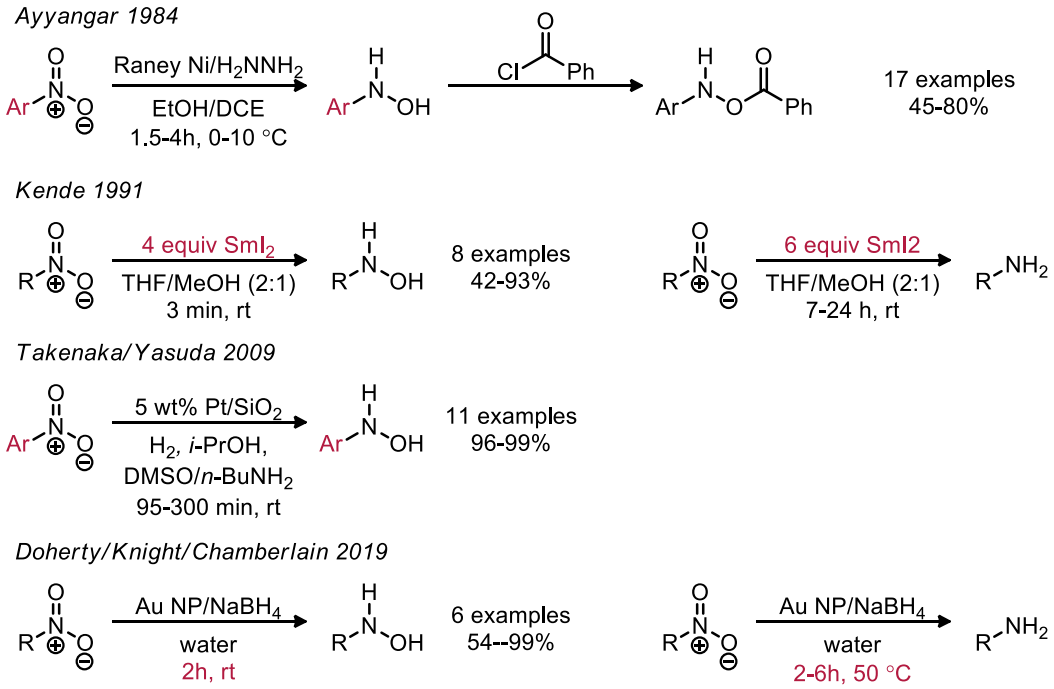
One oxidative method that prevents over-oxidation is the oxidation of tertiary amines which can then undergo Cope elimination to form hydroxylamine products, however, this means low atom economy is achieved and only secondary hydroxylamine can be synthesized.[35] Reductions of nitro groups to hydroxylamines can employ one or two electron reductants (Scheme 1. 18).[34,36] Limitations generally include *N*-aryl substitution or restricting conditions to avoid over-reduction (e.g., low temperature).

[35] (a) O'Neil, I. A; Cleator, E.; Tapolczay, D. J. *Tetrahedron Lett.* **2001**, *42*, 8247-8249. (b) Sammelson, R. E.; Kurth, M. J. *Tetrahedron Letters* **2001**, *42*, 3419-3422.

[36] (a) Ayyangar, N. R.; Brahme, K. C.; Kalkote, U. R.; Srinivasan, K. V. *Synth. Commun.* **1984**, *11*, 938-941. (b) Kende, A. S.; Mendoza, J. S. *Tetrahedron Lett.* **1991**, *32*, 1699-1702. (c) Takenaka, Y.; Kiyosu, T.; Choi, J. -C.; Sakakura, T.; Yasuda, H. Green Chem. **2009**, *11*, 1385–1390. (d) Doherty, S.; Knight, J. G.; Chamberlain, T. W. et al. *ACS Catal.* **2019**, *9*, 4777−4791.

Goldschmidt reported that the relative rates of reduction for relevant species are nitrosobenzene > *N*-phenylhydroxylamine > nitrobenzene, which can explain the difficulty in selectively forming hydroxylamines from reduction.[37] In addition, the hydroxylamine products are generally difficult to store safely without decomposition, so may be protected or used in further reactions in-situ.

Scheme 1. 18 Selected examples of reductive syntheses of hydroxylamines from nitro reagents



1.3.1.2 Hydroxylamine Structure and Properties

Hydroxylamine was first synthesized by Lossen in 1865 as the hydrochloride salt, then by de Bruyn in 1891 as the free base.[38] Hydroxylamines are known to be explosive in the free base form, likely why decades passed before the first free base synthesis. Free hydroxylamines also decompose readily in the presence of iron.[39] Both acidic and basic conditions can also accelerate hydroxylamine decomposition into

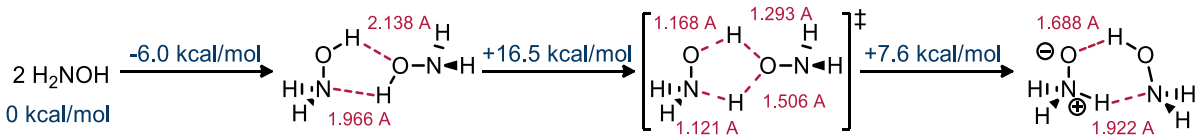
[37] (a) Goldschmidt, H.; Ingebrechsten, K. *Z. Physik. Chem.* **1904**, *48*, 435. (b) Goldschmidt, H.; Sunde, E. *Z. Physik. Chem.* **1906**, *56*, 1. (c) Goldschmidt, H.; Eckhardt, M. *Z. Physik. Chem.* **1906**, *56*, 385. (d) Goldschmidt, H.; Larsen, H. *Z. Physik. Chem.* **1910**, *71*, 437.

[38] (a) Lossen, W. C. *Zeitschrift für Chemie* **1865**, *8*, 551-553. (b) De Bruyn, L. M. C. A. *Recl. Trav. Chim. Pays-Bas* **1891**, *10*, 100-112.

[39] (a) Long, L. A. *Process Safety Progress* **2004**, *23*, 114-120. (b) Cisneros, L. O.; Rogers, W. J.; Mannan, M. S.; Li, X.; Koseki, H. *J. Chem. Eng. Data* **2003**, *48*, 1164–1169.

ammonia, HNO, and water.[40] Two fatal incidents involving the production of hydroxylamine have occurred in the USA and in Japan. Hydroxylamines likely degrade via a bimolecular pathway involving dimerization followed by isomerization to ammonium oxide (Scheme 1. 19).[41,42] Aqueous solutions of hydroxylamine and hydroxylamine salts are therefore significantly safer to use and more stable than the corresponding free bases. In fact, each bond is calculated to be significantly stronger for hydroxylamine salts (BDE_{N-O} = 66.3 kcal/mol; BDE_{O-H} = 112.0 kcal/mol; BDE_{N-H} = 89.3 kcal/mol) than for free hydroxylamine (BDE_{N-O} = 59.0 kcal/mol; BDE_{O-H} = 71.7 kcal/mol; BDE_{N-H} = 81.5 kcal/mol).[42]

Scheme 1. 19 Bimolecular degradation of hydroxylamine into ammonia oxide *(Zhang 2017) (kcal/mol vs. hydroxylamine reagent)*

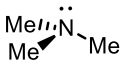
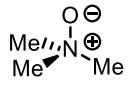


1.3.1.3 Amine *N*-Oxides

N-Oxides are a distinct zwitterionic form of hydroxylamines where the nitrogen has four bonds. Amine *N*-oxides are generally synthesized by the oxidation of a tertiary amine. Hydrogen peroxide, peracids, oxiranes, and oxaziridines are all known amine oxidants.[43] The notable differences between amines and their analogous *N*-oxides are (1) the oxidation state of nitrogen, (2) the geometry of the nitrogen atom, (3) the increased polarity and changes to solubility of *N*-oxides due to the charges, (4) the increased hygroscopicity of *N*-oxides, (5) the changes to hydrogen bonding, and (6) the differences in Lewis and Brønsted acidity (Figure 1. 10).[43]

[40] Izato, Y.; Koshi, M.; Miyake, A. *J. Phys. Chem. B* **2017**, *121*, 4502–4511.
[41] Wang, Q.; Wei, C.; Perez, L.; Rogers, W.; Hall M.; Mannan, M. *J. Phys. Chem. A* **2010**, *114*, 9262–9269.
[42] Ma, Y.; He, X.; Meng, L.; Xue, X.; Zhang, C. *Phys. Chem. Chem. Phys.* **2017**, *19*, 30933-30944.
[43] Bernier, D.; Wefelscheid, U. K.; Woodward, S. *Org. Prep. Proced. Int.* **2009**, *41*, 173–210.

Figure 1. 10 Properties of amines vs. amine *N*-oxides

trigonal pyrimidal, N inversion		tetrahedral, no N inversion
low water-solubility		water-soluble, more polar
minimally hygroscopic		highly hygroscopic
H-bond acceptor at N		H-bond acceptor at O
Brønsted basic (pKa = 10-13)		less Brønsted basic (pKa = 4-5)

Amine *N*-oxides, such as trimethylamine *N*-oxide (TMAO) and *N*-methylmorpholine *N*-oxide (NMO), can be used as stoichiometric oxidants. NMO is commonly used in the Upjohn dihydroxylation of alkenes with catalytic OsO_4 and in the Ley oxidation of alcohols to ketones/aldehydes with catalytic TPAP.[44] Chiral *N*-oxides are used in a variety of asymmetric catalysis reactions as ligands.[45] Amine *N*-oxides are also used industrially as surfactants, stabilizers, emulsifiers, and conditioners when the nitrogen has a long hydrocarbon substituent.

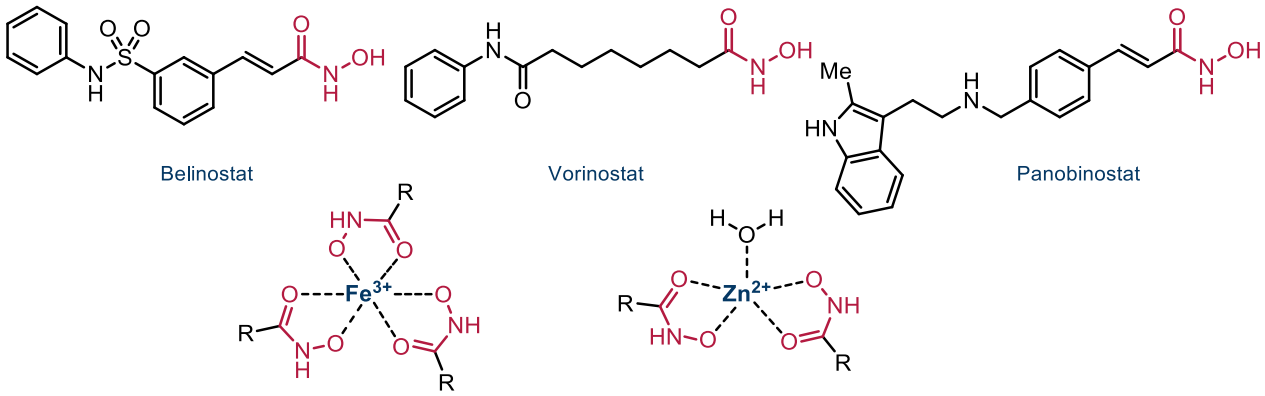
1.3.2 Hydroxylamine in Fine Chemicals

1.3.2.1 Pharmaceuticals and Agrochemicals

The most common hydroxylamine-containing functional group found in pharmaceuticals is hydroxamic acid. Hydroxamic acids chelate well to Fe(III) and Zn(II) and have therefore been studied as metalloprotease inhibitors.[28c] Hydroxamic acids have been most thoroughly studied as histone deacetylase inhibitors, such as Belinostat, Vorinostat, and Panobinostat, which are approved treatments for cancer (Figure 1. 11).[46]

[44] S. B. Ley, J. Norman, W. P. Griffith, S. P. Marsden, *Synthesis*, **1994**, 639-666.
[45] (a) Malkov, A. V.; Kočovský, P. *Eur. J. Org. Chem.* **2007**, 29-36. (b) Liu, X.; Lin, L.; Feng, X. *Org. Chem. Front.* **2014**, *1*, 298-302.
[46] (a) Zhao, C.; Dong, H.; Xu, Q.; Zhang, Y. *Expert Opin. Ther. Pat.* **2020**, *30*, 263–274. (b) Ho, T. C. S.; Chan, A. H. Y.; Ganesan, A. *J. Med. Chem.* **2020**, 63, 12460–12484.

Figure 1. 11 Pharmaceuticals containing hydroxamic acid and the mode of metal ion chelation



N-Alkoxyureas have been reported in rare examples as HDAC inhibitors as well.[47] Only a few natural products contain an alkyl-substituted hydroxylamine within their structures.[48] In contrast, hydroxylamines within 5-membered cycles, isoxazolidines, are considered as a privileged scaffold within medicinal chemistry because they mimic the carbohydrate portion of nucleosides.[49] Additionally, simple hydroxylamines have been demonstrated to be active antibiotics, inhibiting the bacterial ribonucleotide reductase enzyme.[50] The hydroxylamine agents can act as radical scavengers, slowing bacterial proliferation during infection.

1.3.2.2 Antioxidants and Radical-Trapping Agents

A variety of hindered hydroxylamines also act as antioxidants and radical trapping agents. Sterically hindered *N*-oxyl radicals, such as TEMPO, are persistent, while some *N*-oxyl radicals are more reactive. This can be rationalized using the $BDE_{O\text{-}H}$ of hydroxylamine derivatives. For example, the $BDE_{O\text{-}H}$ of TEMPO is 69.6 kcal/mol whereas the $BDE_{O\text{-}H}$ of *N*-hydroxyphthalimide (NHPI) is 88.1 kcal/mol, meaning the NHPI

[47] (a) Pflieger, M.; Hamacher, A.; Öz, T.; Horstick-Muche, N.; Boesen, B.; Schrenk, C.; Kassack, M. U.; Kurz, T. *Bioorg. Med. Chem.* **2019**, *27*, 115036-115042. (b) Pflieger, M.; Sönnichsen, M.; Horstick-Muche, N.; Yang, J.; Schliehe-Diecks, J.; Schöler, A.; Borkhardt, A.; Hamacher, A.; Kassack, M. U.; Hansen, F. K.; Bhatia, S.; Kurz, T.; ChemMedChem **2021**, *16*, 1799–1804.

[48] Lambert, K. M.; Cox, J. B.; Liu, L.; Jackson, A. C.; Yruegas, S.; Wiberg, K. B.; Wood, J. L. *Angew. Chem. Int. Ed.* **2020**, *59*, 9757-9766.

[49] Berthet, M. Cheviet, T.; Dujardin, G.; Parrot, I.; Martinez, J. *Chem. Rev.* **2016**, *116*, 15235–15283.

[50] (a) Torrents, E.; Sahlin, M.; Biglino, D.; Gräslund, A.; Sjöberg, B. -M. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 17946-17951. (b) Julián, E.; Baelo, A.; Gavaldà, J.; Torrents, E. *PLoS One* **2015**, *10*, e0122049. (c) Miret-Casals, L.; Baelo, A.; Julián, E.; Astola, J.; Lobo-Ruiz, A.; Albericio, F.; Torrents, E. *ACS Omega* **2018**, *3*, 17057–17069.

radical is significantly more reactive.[51] The reactivity of *N*-oxyl radicals is important for several fields of research, and as such, has been reviewed in detail many times.[52]

1.3.3 Reactivity of Hydroxylamines

Hydroxylamine reactivity generally relies on one of two distinct features of these species: (1) the strong coordination of hydroxylamine derivatives to metals/metalloids or (2) cleavage of the weak N-O bond. In a recent computational study by Bach, the BDE of several hydroxylamine derivatives was calculated using four methods (CBSQB3, CBS-APNO, G4, and M06-2X).[53] The bond strengths of alkyl- or acyl-substituted hydroxylamines was calculated to be 53-64 kcal/mol (Table 1. 3). This work is an important addition to the hydroxylamine literature because minimal experimental BDE_{N-O} values are available.

Table 1. 3 Calculated N−O Bond Dissociation Enthalpy (BDE at 298 K, kcal/mol) *(Bach 2021)*

	CBS-QB3	**CBS-APNO**	**G4**	**M06-2X**
H_2N-OH	60.72	59.79	58.82	61.35
H_2N-OMe	56.34	56.11	54.88	55.71
Me_2N-OH	63.89	62.81	61.64	63.07
Me_2N-OMe	55.71	55.47	53.97	54.22
Me_2N-OAc	55.62	55.24	53.79	58.53
AcNH-OMe	61.39	62.26	59.72	62.34
Me_3N-O	57.85	56.40	57.06	55.70

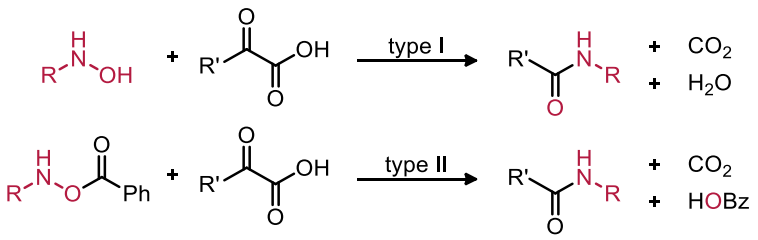
1.3.3.1 Bioorthogonal reactions

Chemical biology, the study of the chemistry in biological processes, relies on various types of bioorthogonal reactions, chemical reactions which proceed selectively under biological conditions without harm to the system.[54] This often requires high reaction rates at low concentrations. Several reactions using hydroxylamines fulfill these requirements using either N-O bond cleavage or strong coordination to boron. α-Ketoacid and hydroxylamine (KAHA) ligation is a protecting group free bioorthogonal method for amide or ester bond formation developed by the Bode group, used as a complementary method to native chemical ligation for protein synthesis.[55] KAHA ligation uses either *N*-

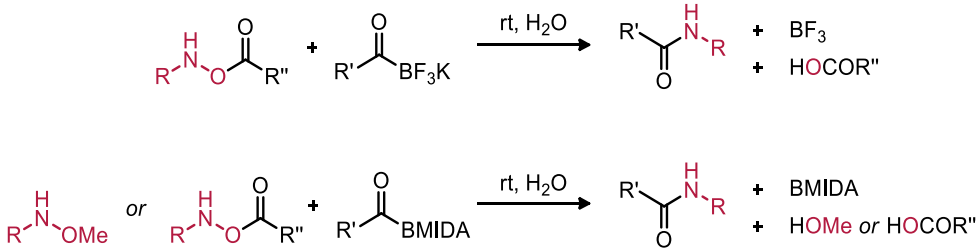
[51] Mahoney, L. R.; Mendenha G. D.; Ingold, K. U. *J. Am. Chem. Soc.*, **1973**, *95*, 8610–8614.
[52] For examples, see: (a) Recupero, F.; Punta, C. *Chem. Rev.* **2007**, *107*, 3800-3842. (b) Galli, C.; Gentili, P.; Lanzalunga, O. *Angew. Chem. Int. Ed.* **2008**, *47*, 4790-4796. (c) Melone, L.; Punta, C. *Beilstein J. Org. Chem.* **2013,** *9,* 1296–1310. (d) Nutting, J. E.; Rafiee, M.; Stahl. S. S. *Chem. Rev.* **2018**, *118*, 4834-4885.
[53] Bach, R. D.; Schlegel, H. B. *J. Phys. Chem. A* **2021**, *125*, 5014−5021.
[54] (a) Bertozzi, C. R. *Acc. Chem. Res.* **2011**, *44*, 651–653. (b) Sletten, E. M.; Bertozzi, C. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 6974–6998. (c) Devaraj, N. K. *ACS Cent. Sci.* **2018**, *4*, 952–959.
[55] Bode, J. W. *Acc. Chem. Res.* **2017**, *50*, 2104–2115.

alkylhydroxylamines (type I) or *N*-alkyl-*O*-acylhydroxylamines (type II) (Scheme 1. 20). Acylboronates also serve as reagents for amide bond synthesis using hydroxylamines (Scheme 1. 21).[56] This method is termed KAT ligation when potassium acyltrifluoroborates are used.

Scheme 1. 20 Type I and type II KAHA ligation

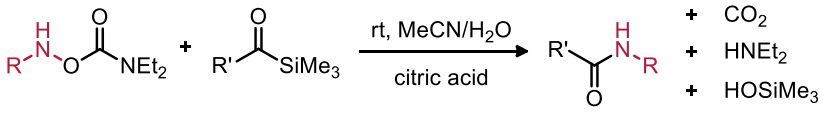


Scheme 1. 21 Acylboronate/hydroxylamine ligation



Recently, Srinivasan has demonstrated that acylsilanes undergo similar ligation chemistry, termed acylsilane and hydroxylamine (ASHA) ligation (Scheme 1. 22).[57] This method relies on a Brook rearrangement concomitant with loss of diethylamine and CO_2 to form amides.

Scheme 1. 22 ASHA ligation



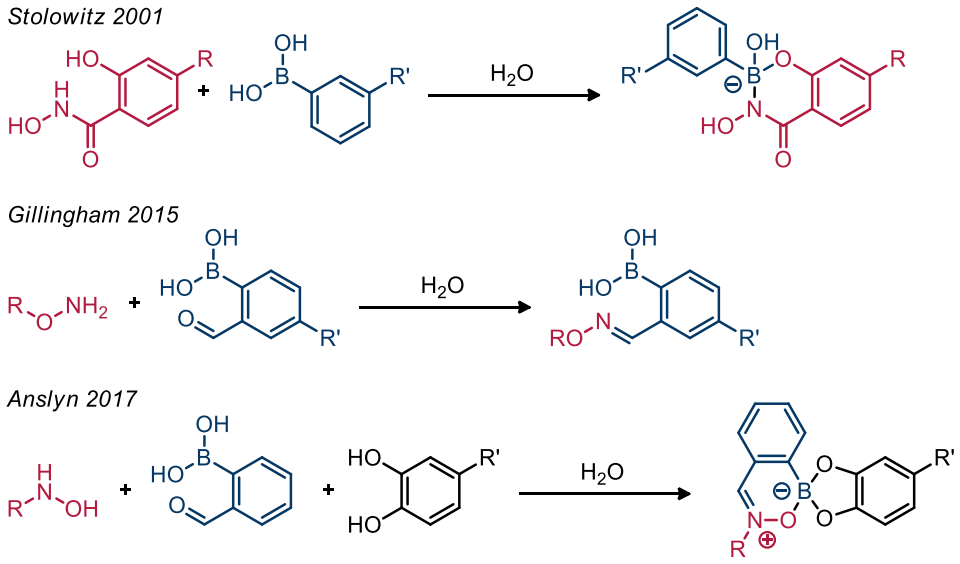
Bioconjugation can also be accomplished using hydroxylamine derivatives. Irreversible or dynamic boronic acid coupling with hydroxamic acids or alkylhydroxylamines acts as a bioorthogonal probe for site-

[56] (a) Dumas, A. M.; Molander, G. A.; Bode, J. W. *Angew. Chem. Int. Ed.* **2012**, *51*, 5683-5686. (b) Noda, H.; Eros, G.; Bode, J. W. *J. Am. Chem. Soc.* **2014**, *136*, 5611-5614. (c) Noda, H.; Bode, J. W. *Chem. Sci.* **2014**, *5*, 4328–4332. (d) Galvez, A. O.; Bode, J. W. *J. Am. Chem. Soc.* **2019**, *141*, 8721–8726. (e) Tanriver, M.; Dzeng, Y. -C.; Da Ros, S.; Lam, E.; Bode, J. W. *J. Am. Chem. Soc.* **2021**, *143*, 17557–17565.

[57] Deng, X.; Zhou, G.; Tian, J.; Srinivasan, R. *Angew. Chem. Int. Ed.* **2021**, *60*, 7024-7029.

selective labelling of proteins (Scheme 1. 23).[58] Oxygen coordination to boron is important for the stability of these complexes.

Scheme 1. 23 Bioconjugation using hydroxylamine derivatives



1.3.3.2 Weinreb amides

Similarly, oxygen coordination using *N*,*O*-dimethylhydroxylamine derivatives serves an important role in carbonyl reactivity. When substituted on an acid chloride to form a hydroxamate ester (Weinreb amide), selective mono-addition of organometallic nucleophiles to carbonyls can occur (Scheme 1. 24).[59] The mode of selectivity is related to the use of hydroxamic acids as metal-chelating drugs. The tetrahedral intermediate after nucleophilic addition has strong metal chelation involving both oxygens of the hydroxamic ester, allowing it to be stable at low temperatures. This strategy for ketone synthesis has since been applied widely.[60]

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[58] (a) Stolowitz, M. L.; Ahlem, C.; Hughes, K. A.; Kaiser, R. J.; Kesicki, E. A.; Li, G.; Lund, K. P.; Torkelson, S. M.; Wiley, J. P. *Bioconjugate Chem.* **2001**, *12*, 229–239. (b) Schimdt, P.; Stress, C.; Gillingham, D. *Chem. Sci.* **2015**, *6*, 3329-3333. (c) Meadows, M. K.; Roesner, E. K.; Lynch, V. M.; James, T. D.; Anslyn, E. V. *Org. Lett.* **2017**, *19*, 3179-3182. For an example of live-cell acylation using hydroxamic acids, see: (d) Adamson, C.; Kajino, H.; Kawashima, S. A.; Yamatsugu, K.; Kanai, M. *J. Am. Chem. Soc.* **2021**, *143*, 14976–14980.

[59] Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815-3818.

[60] Singh, J.; Satyamurthi, N.; Aidhen, I. S. *J. Prakt. Chem.* **2000**, *342*, 340-347.

Scheme 1. 24 General reactivity of Weinreb amides



Related reactivity can also be accomplished using other nucleophiles, such as Wittig salts.[61] Hydroxylamine-derived chiral auxiliaries have also been reported, allowing enantioselective α-substitution of carbonyls.[62]

1.3.3.3 Aminating Agents using an Oxygen-Based Leaving Group

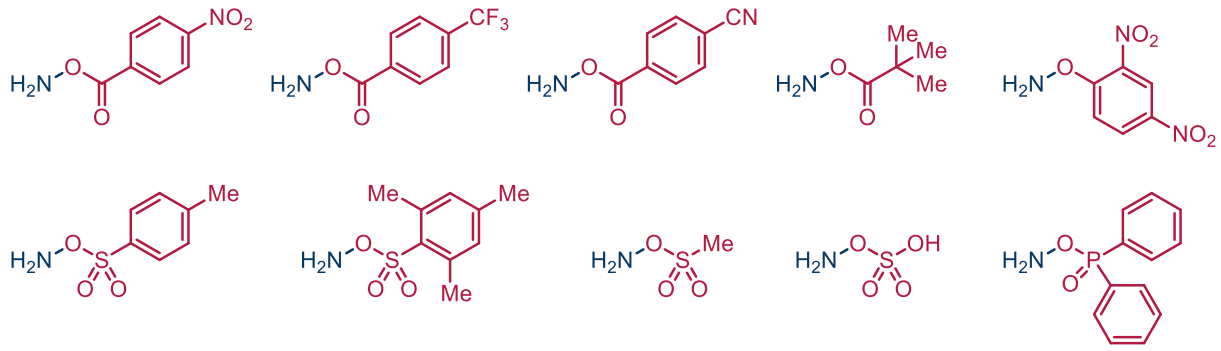
Arguably the most common use of hydroxylamines is as a nitrogen source for electrophilic amination.[63] The hydroxylamine reagents employed have an electron-withdrawing group on the oxygen or an activating group (AG) that adds in-situ (Figure 1. 12). Hydroxylamines can replace less stable N-X species for this reactivity, and the approximately 50-65 kcal/mol N-O BDE ensures mild reaction conditions nonetheless.[64] Metal-catalyzed approaches generally use a preactivated *O*-acyl hydroxylamine, as highlighted by selected recent examples (Scheme 1. 25).[65] Hirano and Miura reported a copper-catalyzed amination of using arylboronic esters and *O*-benzoyl hydroxylamines.[66] This work is a variant of the Chan-Lam coupling, but uses hydroxylamines to allow coupling with alkylamine derivatives.[67] Kürti and Falck formed primary and secondary anilines via protonated rhodium nitrene intermediates using *O*-sulfonyl hydroxylamines and rhodium catalysis.[68] This work was an important example of direct amination, however, this led to regioselectivity issues and some substrate limitations (electron-poor arenes).

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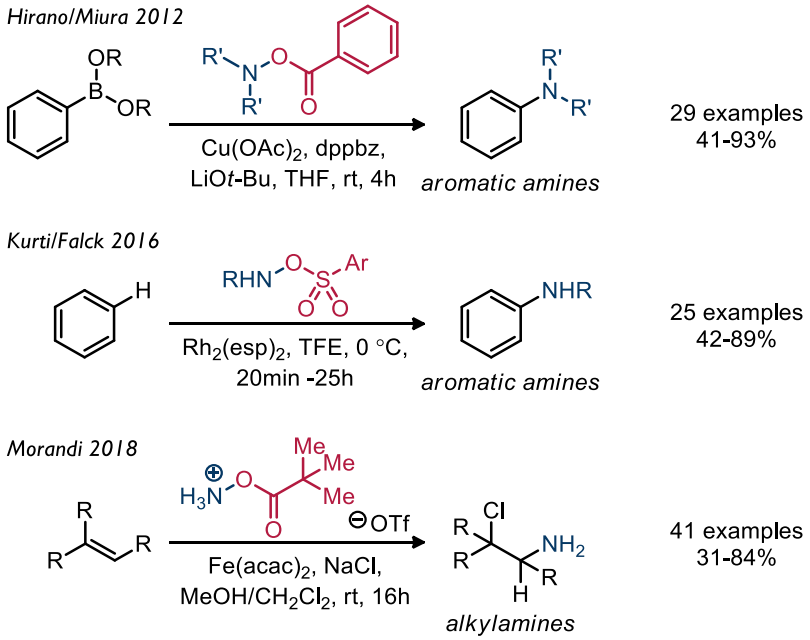
[61] Hisler, K.; Tripoli, R.; Murphy, J. A. *Tetrahedron Lett.* **2006**, *47*, 6293–6295.
[62] Chernega, A. N.; Davies, S. G.; Goodwin, C. J.; Hepworth, D.; Kurosawa, W.; Roberts, P. M.; Thomson, J. E. *Org. Lett.* **2009**, *11*, 3254–3257.
[63] (a) Sabir, S.; Kumar, G.; Jat, J. L. *Org. Biomol. Chem.* **2018** ,*16*, 3314-3327. Jinan, D.; Mondal, P. P.; Nair, A. V.; Sahoo, B. *Chem. Commun.* **2021**, *57*, 13495-13505. (b) O'Neil, L. G.; Bower, J. F. *Angew. Chem. Int. Ed.* **2021**, *60*, 25640-25666.
[64] Y. -R. Luo. *Handbook of Bond Dissociation Energies in Organic Compounds* **2003**, CRC Press. (b) Bach, R. D.; Schlegel, H. B. *J. Phys. Chem. A* **2021**, *125*, 5014–5021.
[65] Dong, X.; Liu, Q.; Dong, Y.; Liu, H. *Chem Commun.* **2017**, *23*, 2481-2511.
[66] Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem. Int. Ed.* **2012**, *51*, 3642-3645.
[67] (a) Chan, D. M. T.; Monaco, K. L.; Wang, R. -P.; Winters, M. P. *Tetrahedron Lett.* **1998**, *39*, 2933-2936. (b) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. *Tetrahedron Lett.* **1998**, *39*, 2941-2944.
[68] Paudyal, M. H.; Adebesin, A. M.; Burt, S. R.; Ess, D. H.; Ma, Z.; Kürti, L.; Falck, J. R. *Science* **2016**, *353*, 1144-1147.

Morandi demonstrated that a simple iron catalyst can catalyze the amino-chlorination of alkenes via a radical pathway.[69] This this mode of reactivity has also been expanded to azido-amination.[70]

Figure 1. 12 Common *O*-substituted hydroxylamine aminating reagents



Scheme 1. 25 Selected examples of metal-catalyzed amination using hydroxylamine derivatives

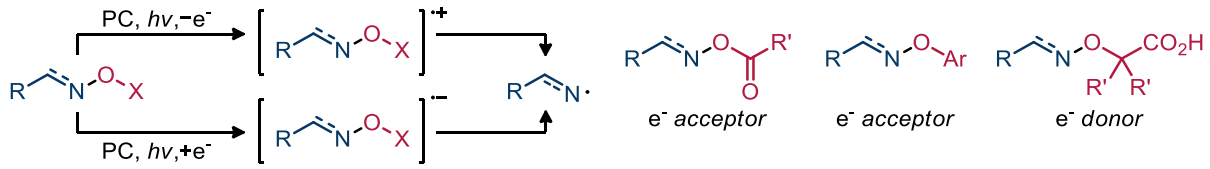


[69] Legnani, L.; Prina-Cerai, G.; Delcaillau, T.; Willems, S.; Morandi, B. *Science* **2018**, *362*, 434-439.

[70] (a) Makai, S.; Falk, E.; Morandi, B. *J. Am. Chem. Soc.* **2020**, *142*, 21548-21555. For previous work using an iron phthalocyanine catalyst, see: (b) Legnani, L.; Morandi, B. *Angew. Chem. Int. Ed.* **2016**, *55*, 2248-2251. (c) For a mechanistic study of iron-catalyzed amino-functionalization, see: (b) Chatterjee, S.; Harden, I.; Bistoni, G.; Castillo, R. G.; Chabbra, S.; van Gastel, M.; Schnegg, A.; Bill, E.; Birrell, J. A.; Morandi, B.; Neese, F.; DeBeer, S. *J. Am. Chem. Soc.* **2022**, *144*, 2637-2656.

Hydroxylamine derivatives have also been popular in recent publications as nitrogen-centered radical precursors using photocatalysis (Scheme 1. 26).[71] A photoredox catalyst can undergo single electron transfer to either an electron-accepting or electron-donating hydroxylamine. Subsequent fragmentation leads to N-O bond cleavage and a nitrogen-centered radical, such as iminyl or amidyl radicals, which can then undergo a variety of reactions.

Scheme 1. 26 General mode of nitrogen-centered radical formation from hydroxylamine precursors



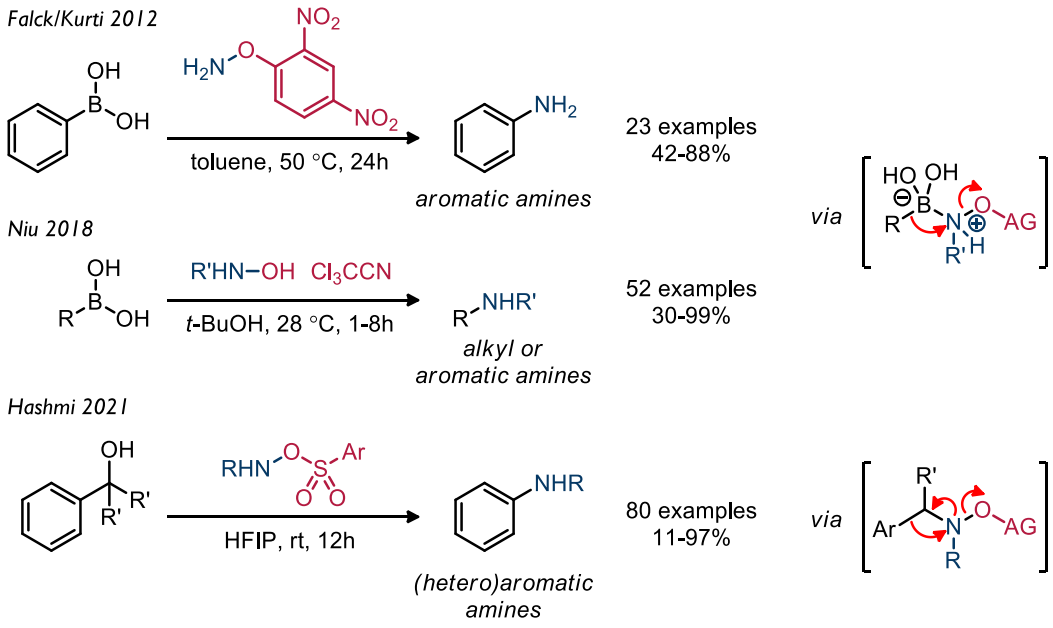
The Beckmann rearrangement is an important example of metal-free hydroxylamine reactivity, converting an oxime into an amide via 1,2-migration, notably used in the industrial synthesis of caprolactam. Several other metal-free approaches have been reported recently using boronic acids where a 1,2-migration and N-O bond cleavage occur simultaneously to form the amine product (Scheme 1. 27).[72] The aza-Hock rearrangement recently reported by Hashmi is mechanistically similar, relying on an HFIP-promoted hydroxyl substitution, then a 1,2-migration and N-O bond cleavage to form an iminium ion intermediate.[73] Once hydrolyzed, aniline and heteroaromatic amine products can be obtained.

[71] (a) Davies, J.; Morcillo, S. P.; Douglas, J. J.; Leonori, D. *Chem. Eur. J.* **2018**, *24*, 12154-12163. (b) Rykaczewski, K.A., Wearing, E.R., Blackmun, D.E. Schindler, C. S. *Nat. Synth.* **2022**, *1*, 24–36. For an early review of oximes as aminating agents, see: (c) Narasaka, K.; Kitamura, M. *Eur. J. Org. Chem.* **2005**, *2005*, 4505-4519.

[72] (a) Zhu, C.; Li, G.; Ess, D. H.; Falck, J.; Kürti, L. *J. Am. Chem. Soc.* **2012**, *134*, 18253−18256. (b) Sun, H. -B.; Gong, L.; Tian, Y. -B.; Wu, J. -G.; Zhang, X.; Liu, J.; Fu, Z.; Niu, D. *Angew. Chem. Int. Ed.* **2018**, *57*, 9456-9460.

[73] Wang, T.; Stein, P. M.; Shi, H.; Hu, C.; Rudolph, M.; Hashmi, S. K. *Nat. Commun.* **2021**, *12*, 7029-7040.

Scheme 1. 27 Selected examples of metal-free amination using hydroxylamine derivatives



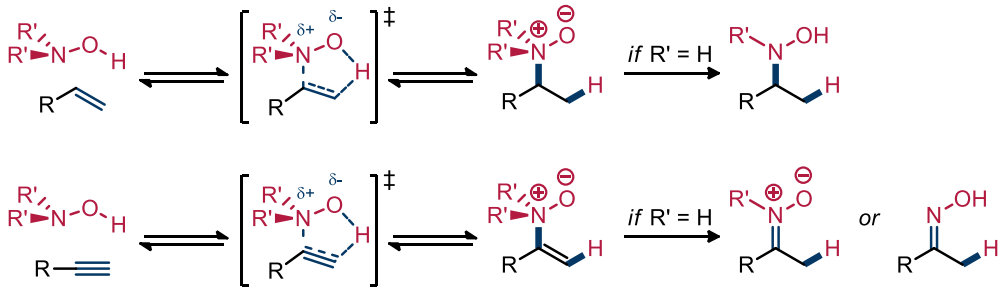
These examples highlight the diverse reactivity of *O*-acyl/sulfonyl hydroxylamines as electrophilic nitrogen sources. Unfortunately, the atom economy of these reactions is inherently poor. The other reagents must always act as a nucleophile for these examples as well (e.g., R migration from boron for Niu amine synthesis). These limitations are not present when using alkylhydroxylamines as a nitrogen source, such as with Cope-type hydroamination.

1.3.3.3 Cope-Type Hydroamination

Cope-type hydroamination is another metal-free amination variant, however, it doesn't involve N-O bond cleavage. Hydroxylamines can undergo a concerted ene-type reaction with alkenes or alkynes in which N-C and C-H bond formation occur at once forming an *N*-oxide product via a 5-membered transition state (Scheme 1. 28). While some *N*-oxide ylides are stable, more commonly, an irreversible proton transfer leads to the final hydroxylamine product or tautomerization forms the more stable nitrone/oxime.[74]

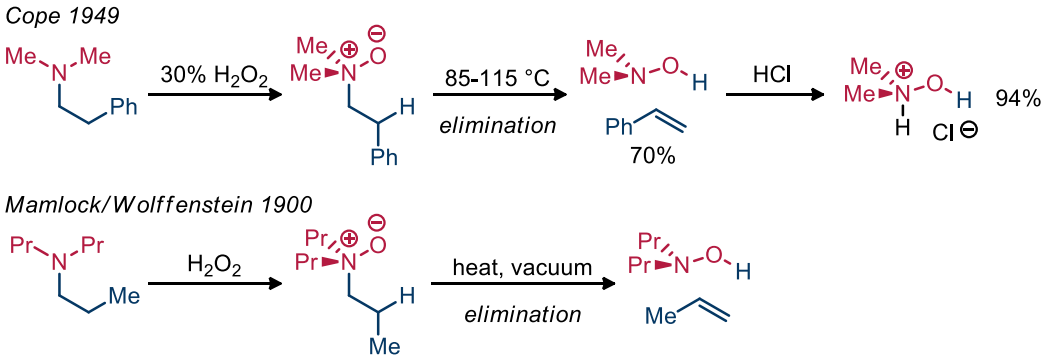
[74] (a) Cooper, N. J.; Knight, D. W. *Tetrahedron* **2004**, *60*, 243–269. (b) Beauchemin, A. M. *Org. Biomol. Chem.* **2013**, *11*, 7039–7050.

Scheme 1. 28 General reaction for Cope-type hydroamination of alkenes and alkynes



The reverse reaction, Cope elimination, was first reported by Arthur Cope in the 1940s, and although previous related work by Mamlock and Wolffenstein was cited within the publication, it lacked many experimental details (Scheme 1. 29).[75] Cope proposes reactivity similar to that of the Hofmann thermal elimination and includes several experiments to support the proposed intramolecular β-H elimination mechanism.

Scheme 1. 29 First reports of Cope elimination

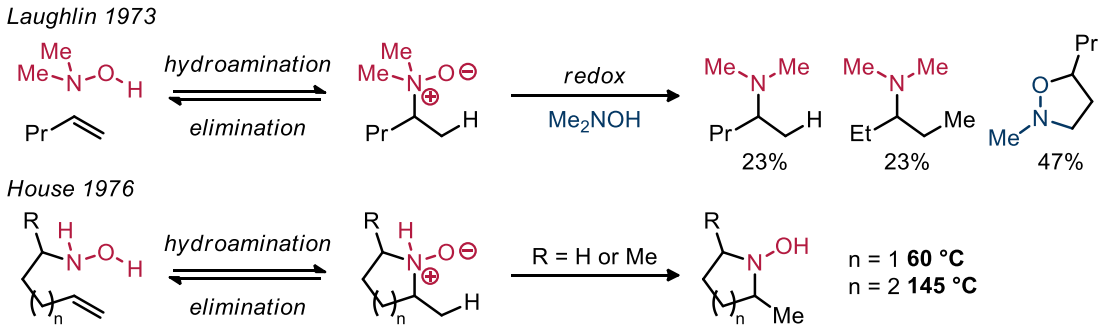


The reverse Cope elimination, or "Cope-type hydroamination, was first reported by Laughlin in 1973 (Scheme 1. 30).[76] Laughlin describes the series of products observed when *N*,*N*-dimethylhydroxylamine is heated with various pentenes. The authors propose a hydroamination, followed by an irreversible reduction of the *N*-oxide using hydroxylamine, forming the observed amines and the nitrone necessary for the isoxazolidine cycloadduct product. The *N*-oxide was not directly observed, the authors report crossover experiments supporting the intermediacy of *N*-oxide in the formation of the isoxazolidines. The

[75] (a) Cope, A. C.; Foster T. T.; Towle, P. H. *J. Am. Chem. Soc.* **1949**, *71*, 3929-3934. (b) Mamlock, L.; Wolffenstein, R. *Chem. Ber.* **1900**, *33*, 159-161.
[76] Laughlin, R. G. *J. Am. Chem. Soc.* **1973**, *95*, 3295-3299.

redox-based degradation products of *N*-oxides reveal the instability of intermolecular Cope-type hydroamination products when proton transfer cannot occur. House later reported the intramolecular variant using mono-substituted hydroxylamines in 1976.[77] The pyrrolidine *N*-oxide product of intramolecular hydroamination can undergo proton transfer to form stable *N*-hydroxypyrrolidines, however, House noted significant differences in the heat required for 5- and 6-membered cyclization reactions (Scheme 1. 30).

Scheme 1. 30 First reports of the Cope-type hydroamination of alkenes

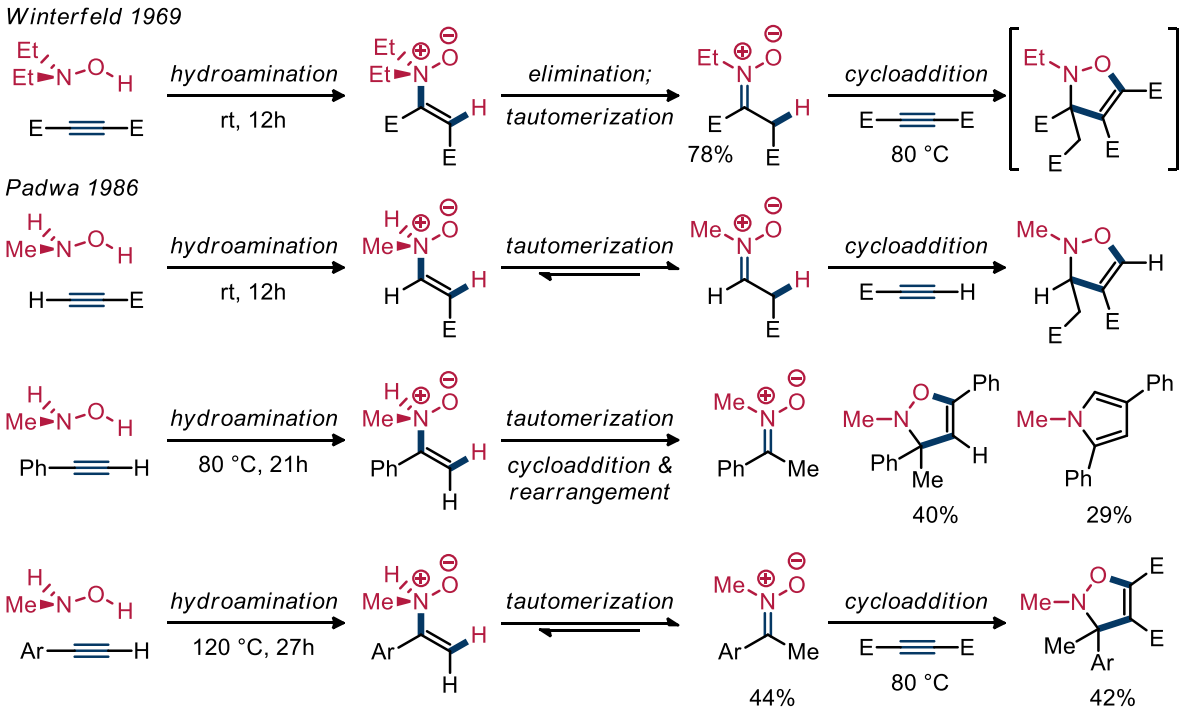


Winterfeld reported the first possible Cope-type hydroamination of alkynes (Scheme 1. 31).[78] Padwa reported another possible example of Cope-type hydroamination of alkynes in 1986 using *N*-methylhydroxylamine.[79] The authors reported several examples of cascade reactivity in which initial hydroamination affords a nitrone, which can then undergo dipolar cycloaddition with a second equivalent of methyl propiolate to form isoxazolidines. It is possible that a Cope-type mechanism is not occurring since the room temperature reactivity of methyl propiolate as a Michael acceptor is known.[80] Additionally, the tautomerization leads to the loss of otherwise informative alkene geometry. The more telling reactions are those Padwa reported with aryl acetylenes. The nitrone still forms for these less electronically activated alkynes. Hydration of the alkyne could still lead to the observed nitrones, however,

[77] (a) House, H. O.; Manning, D. T.; Melillo, D. G.; Lee, L. F.;7 Haynes, O. R.; Wilkes, B. E. *J. Org. Chem.* **1976**, *41*, 855-863. (b) House, H. O.; Lee, L. F. *J. Org. Chem.* **1976**, *41*, 863-869.
[78] Winterfeldt, E.; Krohn, W.; Stracke, H. *Chem. Ber.* **1969**, *102*, 2346-2361.
[79] Padwa, A.; Wong, G. S. K. *J. Org. Chem.* **1986**, *51*, 3125-3133.
[80] Chen, X. Y.; Yuan, S.; Chen, Y.; Sun, C.; Tang, Y.; Chen, G.; Zhu, B.; Chen, K.; Zhenga, S.; Cheng, X. Org. Biomol. Chem. **2021**, *19*, 7914-7919.

the reported hydroamination conditions are significantly milder than reported hydration conditions without additional catalysis.[81]

Scheme 1. 31 Early examples of the Cope-type hydroamination of alkynes

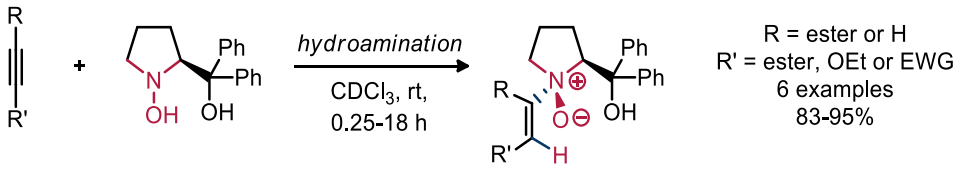


Additionally, O'Neil has reported the hydroamination of several alkynes using proline-derived hydroxylamines (Scheme 1. 32).[82] This reactivity is limited to alkynes with an activating group (e.g., no product observed for alkyl or aryl-substituted alkynes). An X-ray structure obtained by the authors shows the *N*-oxide oxygen hydrogen bonded to the pendant hydroxyl group. This additional stabilizing effect supports the milder conditions used for this reaction.

[81] (a) Kremsner, J. M.; Kappe, C. O. *Eur. J. Org. Chem.* **2005**, 2005, 3672-3679. For a review on catalytic alkyne hydration, see: (b) Hintermann, L.; Labonne, A. *Synthesis* **2007**, *8*, 1221-1150. For a recent example of catalyzed hydration of alkynes, see: (c) Liu, W.; Wang, H.; Li, C. -J. *Org. Lett.* **2016**, *18*, 2184–2187.

[82] O'Neil, I. A.; McConville, M.; Zhou, K.; Brooke, C.; Robertson, C. M.; Berry, N. G. *Chem. Commun.* **2014**, *50*, 7336-7339.

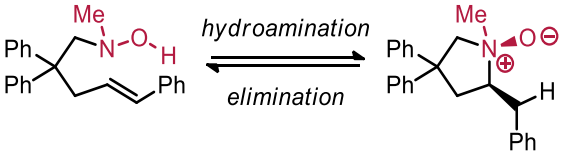
Scheme 1. 32 Hydrogen-bonding stabilized hydroamination products from alkynes



Several distinctive features of Cope-type hydroamination are clear from early work. (1) Due the to polarity of the charged *N*-oxide product, this reaction is highly solvent dependent (Table 1. 4).[83] Polar solvents favour the product side of the equilibrium, while non-polar solvents often favour the reactants. These trends align well with the reverse of those found for the microscopic reverse reaction, the Cope elimination.[84] Protic solvents can also aid in the irreversible proton transfer step when relevant. (2) The concerted nature of this reaction allows diastereoselective hydroamination to occur when applicable. (3) Substituents play a large role in the ease of reaction. Alkyl substituents on nitrogen typically increase reactivity since nitrogen is more nucleophilic. Each alkene substitution on the distal carbon slows the reaction, whereas substitution on the proximal carbon increases reaction rate.[85] The gem-dimethyl effect or Thorpe-Ingold bias also increases the rate of cyclization via Cope-type hydroamination. (4) The ring size for intramolecular reactions greatly affects the ease of reaction. Five-membered rings can form at room temperature, whereas six- and seven-membered rings are progressively more difficult to form (Scheme 1. 33).

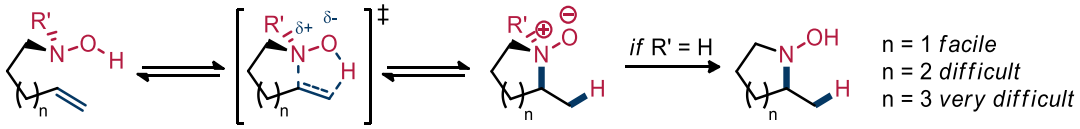
[83] Ciganek, E. *J. Org. Chem.* **1990**, *55*, 3009-3011.
[84] (a) Cram, D. J.; Sahyun, M. R. V.; Knox, G. R. *J. Am. Chem. Soc.* **1962**, *84*, 1734-1735. (b) Sahyun, M. R. V.; Cram, D. J. *J. Am. Chem. Soc.* **1963**, *85*, 1263-1268.
[85] (a) Black, D. St. C.; Doyle, J. E. *Aust. J. Chem.* **1978**, *31*, 2317-2322. (b) Knight, D. W.; Salter, R. *Tetrahedron Lett.* **1999**, *40*, 5915-5918.

Table 1. 4 Solvent dependence for the Cope-type hydroamination equilibrium at 25 °C *(Ciganek 1990)*



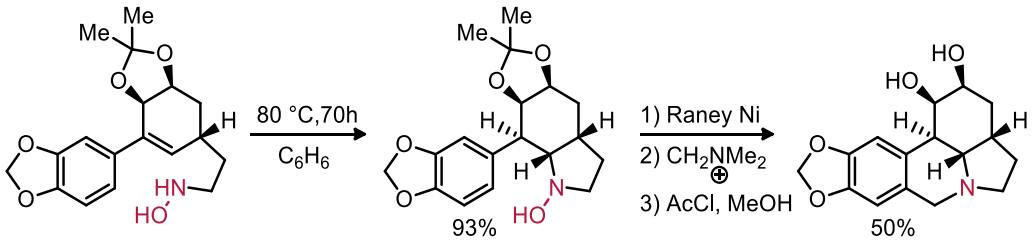
Solvent	% Hydroxylamine	% Pyrrolidine *N*-oxide
$CDCl_3$	0	100
CD_3OD	0	100
$(CD_3)_2CO$	trace	>95
CD_3CN	15	85
C_6D_6	44	56
$(CD_3)_2SO$	55	45
$(CD_3)_2SO$ + CF_3CO_2H	0	100
THF-d_8	60	40
DMF-d_7	67	33
Pyridine-d_6	74	26

Scheme 1. 33 Ring size effects for intramolecular Cope-type hydroamination



The synthetic utility of Cope-type hydroamination was well highlighted by Oppolzer's synthesis of (+)-trianthine (Scheme 1. 34).[86] Intramolecular Cope-type hydroamination proceeds in excellent yield and diastereoselectivity, forming the final alkaloid natural product after N-O reduction, Pictet-Spengler cyclization, then acetal deprotection.

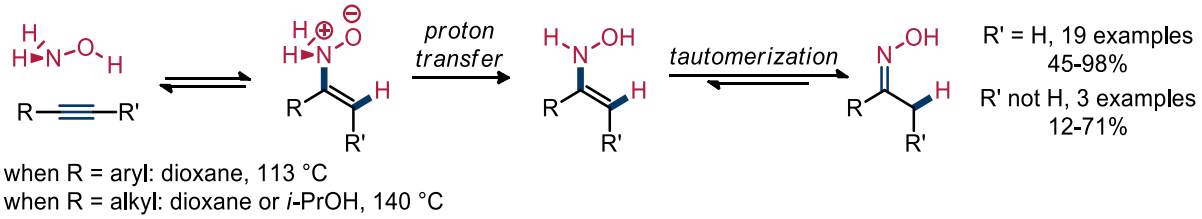
Scheme 1. 34 Synthesis of (+)-trianthine using intramolecular Cope-type hydroamination as a key step



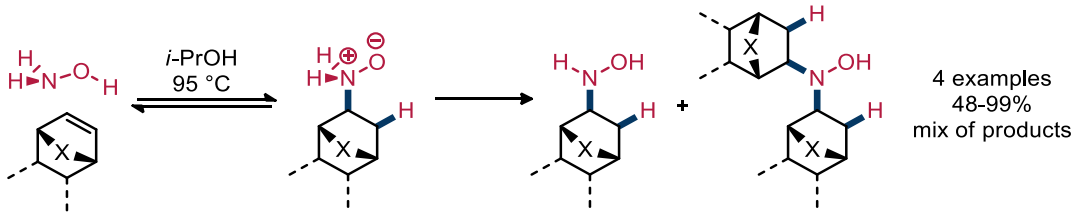
[86] Oppolzer, W.; Spivey, A. C.; Bocher, C. G. *J. Am. Chem. Soc.* **1994**, *116*, 3139-3140.

The Beauchemin group began studies of Cope-type hydroamination of alkynes and alkenes using aqueous NH_2OH and mono-substituted hydroxylamines (RNHOH).[87] Alkynes react well with aqueous hydroxylamine at high temperatures in dioxane or isopropanol to yield oximes after hydroamination, proton transfer, and tautomerization (Scheme 1. 35). Terminal alkynes undergo hydroamination with higher yields than internal alkynes, and all entries proceeded with high regioselectivity. The stability of the oxime products proved greatly beneficial when compared to results using norbornene with aqueous NH_2OH. Both mono- and di-hydroamination products were observed upon heating hydroxylamine with norbornene derivatives, even when using only two equivalents of the alkene (Scheme 1. 36). Low yields were obtained using any non-strained alkene (e.g., 39% for styrene). Both hydroxylamine stability under the reaction conditions and alkene reactivity are problematic in this system. Reactions using alkyl-substituted hydroxylamines were therefore attempted.

Scheme 1. 35 Cope-type hydroamination of alkynes using NH_2OH (aq)



Scheme 1. 36 Cope-type hydroamination of alkenes using NH_2OH (aq)

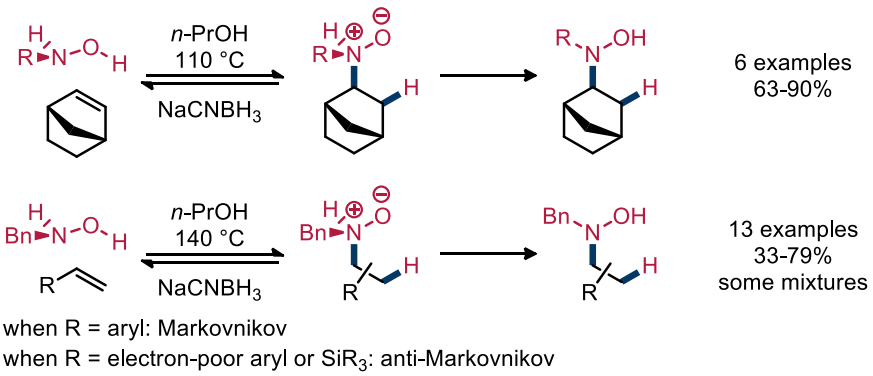


Using *N*-alkylhydroxylamines under related conditions led to the corresponding oximes via an oxidative pathway. Sodium cyanoborohydride ($NaCNBH_3$) was successfully used as an additive to minimize this unwanted product. The additive appears to inhibit the decomposition of both the hydroxylamine starting materials and the products rather than reduce oxidative by-products. Norbornene could undergo

[87] (a) Beauchemin, A. M.; Moran, J.; Lebrun, M.-E.; Séguin, C.; Dimitrijevic, E.; Zhang, L.; Gorelsky, S. I. *Angew. Chem., Int. Ed.* **2008**, *47*, 1410-1413. (b) Moran, J.; Gorelsky, S. I.; Dimitrijevic, E.; Lebrun, M.-E.; Bédard, A.-C.; Séguin, C.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2008**, *130*, 17893-17906.

hydroamination with several *N*-alkylhydroxylamines in *n*-propanol in good yields (63-90%) using $NaCNBH_3$ as an additive (Scheme 1. 37). Using unstrained alkenes required a higher temperature (140 °C), likely because the hydroamination equilibrium is close to thermoneutral.[88] Regioselectivity appears to be dependent on the electronics of the alkene. Electron-rich and neutral styrenes form mostly the Markovnikov products, whereas electron-poor styrenes and vinylsilanes form the anti-Markovnikov products preferentially, though several entries have only modest regioselectivity.

Scheme 1. 37 Cope-type hydroamination of alkenes using RNHOH



The harsh reaction conditions, oxidative degradation issues, and scope limitations for Cope-type hydroamination discussed have stymied the more widespread use of this reactivity without catalysis.[89]

Overall, hydroxylamines currently serve largely as reagents for various amination reactions. Less commonly, examples of their use directly in fine chemicals demonstrate the unique properties of hydroxylamine-based structures. The following chapter will discuss the novel research on the incorporation of hydroxylamines and isocyanates into one reactive species, oxygen-substituted isocyanates (*O*-isocyanates). These unstable intermediates, formed in equilibrium with their blocked precursors, possess properties of both isocyanates and hydroxylamines. The products of *O*-isocyanate reactions also often contain hydroxylamines, leading to further uses.

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[88] A. M. Johns, N. Sakai, A. Ridder, J. F. Hartwig, *J. Am. Chem. Soc.* **2006**, *128*, 9306-9307.

[89] For the Beauchemin lab work on aldehyde-catalyzed Cope-type hydroamination of allylamines, see: (a) MacDonald, M. J.; Schipper, D. J.; Ng, P. J.; Moran, J.; Beauchemin, A.M. *J. Am. Chem. Soc.* **2011**, *133*, 20100-20103; (b) Guimond, N.; MacDonald, M. J.; Lemieux, V.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2012**, *134*, 16571-16577; (c) MacDonald, M. J.; Hesp, C. R.; Schipper, D. J.; Pesant, M.; Beauchemin, A. M. *Chem. Eur. J.* **2013**, *19*, 2597-2601; (d) Hesp, C. R.; MacDonald, M.; Zahedi, M.; Bilodeau, D. A.; Zhao, S.-B.; Pesant, M.; Beauchemin, A. M. *Org. Lett.* **2015**, *17*, 5136-5139.

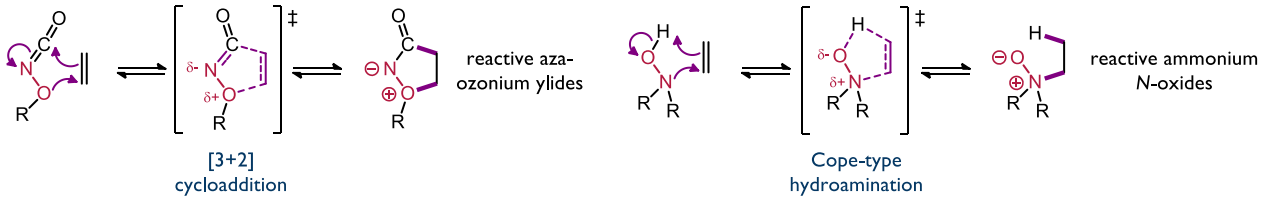
1.4 Goals of Proposed Research using Hydroxylamines-Containing Reagents

The importance of nitrogen-containing compounds, the blocking group strategy for (heteroatom-substituted) isocyanates, and the synthesis and use of hydroxylamines serve to provide context for the novel research included within this thesis. There are many important previous reports in these fields that have provided relevant contributions and serve as the basis for ongoing studies. The hypothesis behind most of the work included within chapters 2-4 is that concerted reactions of hydroxylamine-containing reagents can lead to more diverse reactivity to form nitrogen-containing products than other related reagents. Concerted reactivity of hydroxylamines that retains the N-O bond is still rare in the literature, so many opportunities for research into novel reactivity can be pursued.

Hydroxylamines are a suitable choice for this research goal due to the dual electronegative and nucleophilic character of the N-O subunit, which can lead to increased amphoteric character and improved ylide stability. Amphoteric reagents are used in many highly efficient reactions when their reactivity can be controlled adequately.[90] The weak N-O bond can then also be exploited after the initial concerted step among other reaction pathways.

When included in isocyanate precursors (blocked *O*-isocyanates), hydroxylamines can be nucleophilic at both and the N and O atoms, and additionally, *O*-substitution can further activate the electrophilic isocyanate moiety by lowering the LUMO. *O*-Isocyanates would also then be unstable due to their amphoteric character, leading to the need for a robust blocking group strategy to allow for their reliable synthesis and storage. Divergent reactivity of the aza-oxonium ylide must be explored to drive the likely thermoneutral cycloaddition process forward and to develop new synthetic routes to heterocyclic products (Scheme 1. 38).

Scheme 1. 38 General proposed reactivity of hydroxylamine-containing reagents



[90] He, Z.; Zajdlik, A.; Yudin, A. K. *Acc. Chem. Res.* **2014**, *47*, 1029-1040.

When used for Cope-type hydroamination, hydroxylamines significantly lower the barrier to alkene/alkyne hydroamination compared to analogous amines by modification of the reaction to a more kinetically favourable concerted 5-atom, 6-electron process. The *N*-oxide ylide product is relatively stable and means that a low thermodynamic disadvantage is added. Previous work with this transformation relies on proton transfer or N-C bond cleavage-based degradation of the *N*-oxide to drive the often near-thermoneutral hydroamination equilibrium process forward. General reduction and stabilization-based strategies have not been reported and could lead to more practical examples of this powerful metal-free hydroamination method. Reducing the problems associated with the thermoneutrality of this transformation, as well as the still often prohibitive kinetic barrier to intermolecular reactivity, could expand the substrate scope and increase the frequency of application of Cope-type hydroamination.

Overall, the proposed research involving hydroxylamines aimed to synthesize a diverse series of amines and heterocycles stemming from common zwitterionic intermediaries, aza-oxonium ylides (chapter 2) and ammonium *N*-oxides (chapters 3 and 4). Key opportunities lie in the divergent reactivity of the respective ylides from cycloaddition and hydroamination.

Chapter 2 Reactions of *O*-Isocyanates

Within this chapter, work exploring the substitution and [3+2] cycloaddition of blocked O-isocyanates is disclosed. This chemistry is relevant to the synthesis of biologically relevant N-oxyureas and for development of the field of dipolar cycloaddition, specifically as an uncommon example of uncharged 1,3-dipole equivalents. Literature background, key synthetic findings, computational details, and future directions are included. The research within this chapter was completed in a collaborative manner with Ryan Ivanovich and Dilan Polat. Refer to Statement of Contributions *for more details.*

2.1 Substitution Reactions with Amine Nucleophiles

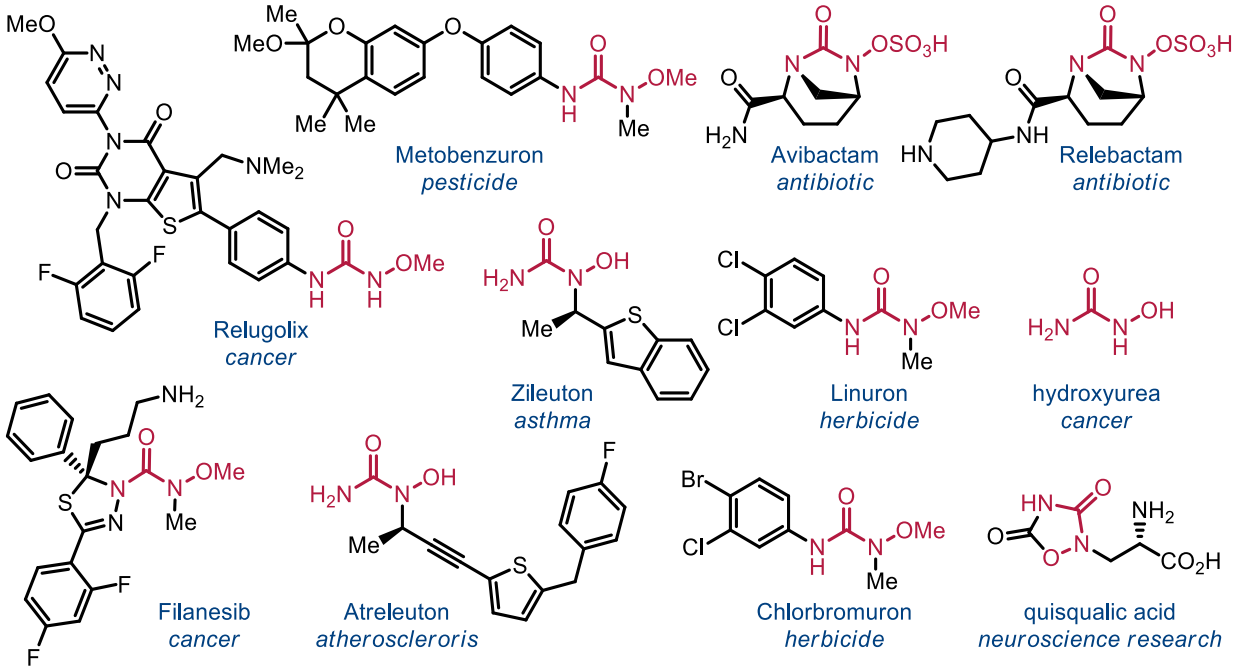
2.1.1 Background on *N*-Oxyureas

2.1.1.1 Uses as Pharmaceuticals and Beyond

Molecules containing *N*-oxyureas have a variety of uses as bioactive compounds. Along with unsubstituted *N*-hydroxyurea, Relugolix and Filanesib are also approved cancer drugs (Figure 2. 1). Several pesticides and herbicides, such as Linuron, include an *N,O*-dimethyloxyurea subunit. These phenyl-substituted N-oxyureas function similarly to other common phenylurea herbicides.[91] Some 5-lipoxygenase inhibitors, such as Zileuton and Atreleuton, include *N*-substituted *N*-oxyureas. These drugs function to relieve the symptoms of asthma by blocking the activity of an enzyme that forms leukotrienes. Avibactam and other related non-β-lactam β-lactamase inhibitors contain a bicyclic *N*-oxyurea, which act as covalent reversible inhibitors via ring opening.[92] Quisqualic acid is a glutamic acid mimic used as a neuron toxin in neuroscience research.[93]

[91] Liu, J. Phenylurea Herbicides. In *Hayes' Handbook of Pesticide Toxicology,* 3rd ed*;* Krieger, R., Eds.; Elsevier, 2010; pp. 1725–1731.
[92] Lahiri, S. D.; Mangani, S.; Durand-Reville, T.; Benvenuti, M.; De Luca, F.; Sanyal, G.; Docquier, J. -D. *Antimicrob. Agents Chemother.* **2013**, *57*, 2496–2505.
[93] Jin, R.; Horning, M.; Mayer, M. L.; Gouaux, E. *Biochemistry* **2002**, *41*, 15635–15643.

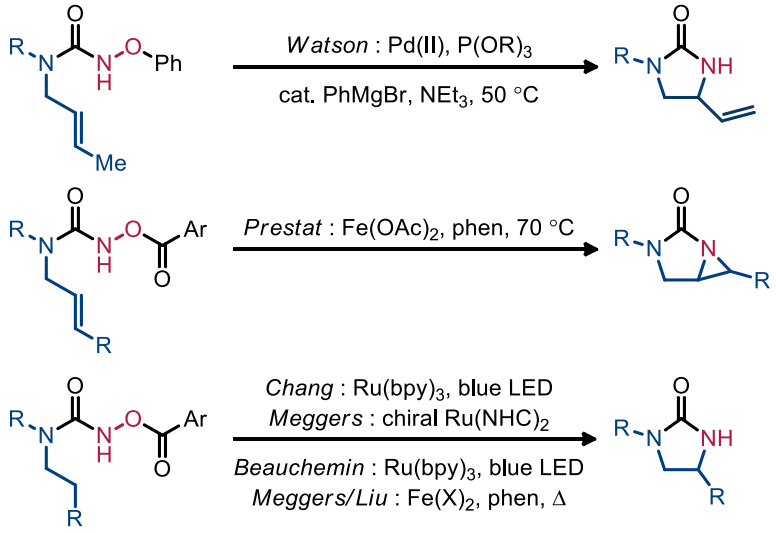
Figure 2. 1 Bioactive molecules contain the N(CO)NO motif



N-Oxyureas are also known reagents for intramolecular aza-Heck reactions, nitrene C-H insertions or aziridination reactions (Scheme 2. 1).[94] These precursors can form nitrenes by organometallic SET processes, photoredox SET activation, or photosensitized triplet energy transfer. In all examples, the N-O bond is cleaved to form the high energy metal-amide or nitrene intermediate. This therefore is aided by an electron-withdrawing substituent (e.g., benzoyl) on oxygen.

[94] (a) Xu, F.; Shuler, S. S.; Watson, D. A. *Angew. Chem. Int. Ed.* **2018**, *57*, 12081-12085. (b) Manick, A. -D.; Aubert, S.; Yalcouye, B.; Prangé, T.; Berhal, F.; Prestat, G. *Chem. Eur. J.* **2018**, *24*, 11485-11492. (c) Jung, H.; Keum, H.; Kweon, J.; Chang, S. *J. Am. Chem. Soc.* **2020**, *142*, 5811−5818. (d) Zijun Zhou, Z.; Tan, Y.; Yamahira, T.; Ivlev, S.; Xie, X.; Riedel, R.; Hemming, M.; Kimura, M.; Meggers, E. *Chem* **2020**, *6*, 2024–2034. (e) Ivanovich, R. A.; Polat, D. E.; Beauchemin, A. M. *Org. Lett.* **2020**, *22*, 6360–6364. (f) Jarrige, L.; Zhou, Z.; Hemming, M.; Meggers, E. *Angew. Chem. Int. Ed.* **2021**, *60*, 6314-6319. (g) Zhong, D.; Wu, L. -Y.; Wang, X. -Z.; Liu, W. -B. *Chin. J. Chem.* **2021**, *39*, 855-858.

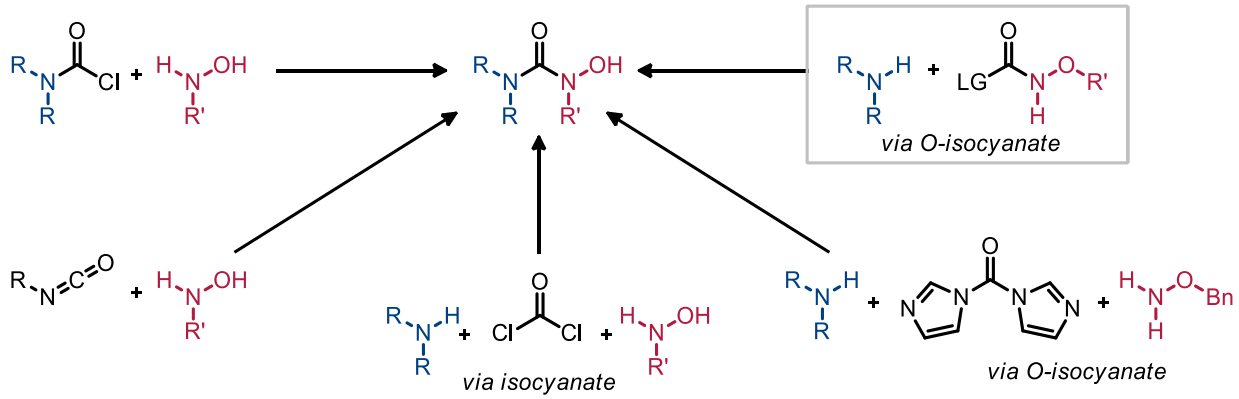
Scheme 2. 1 Examples of *N*-oxyureas as nitrene precursors



2.1.1.2 Known Syntheses

N-Oxyureas are generally synthesized as ureas are, by acylation of a nitrogen nucleophile (Scheme 2. 2). This can be accomplished using a variety of activated electrophiles such as carbamoyl chlorides and isocyanates. Carbamoyl chlorides are not widely commercially available, so in-situ synthesis is more common using phosgene or phosgene equivalents (e.g., triphosgene). Both phosgene and isocyanates are highly toxic and prone to hydrolysis-based degradation, so they are undesirable choices for reagents.

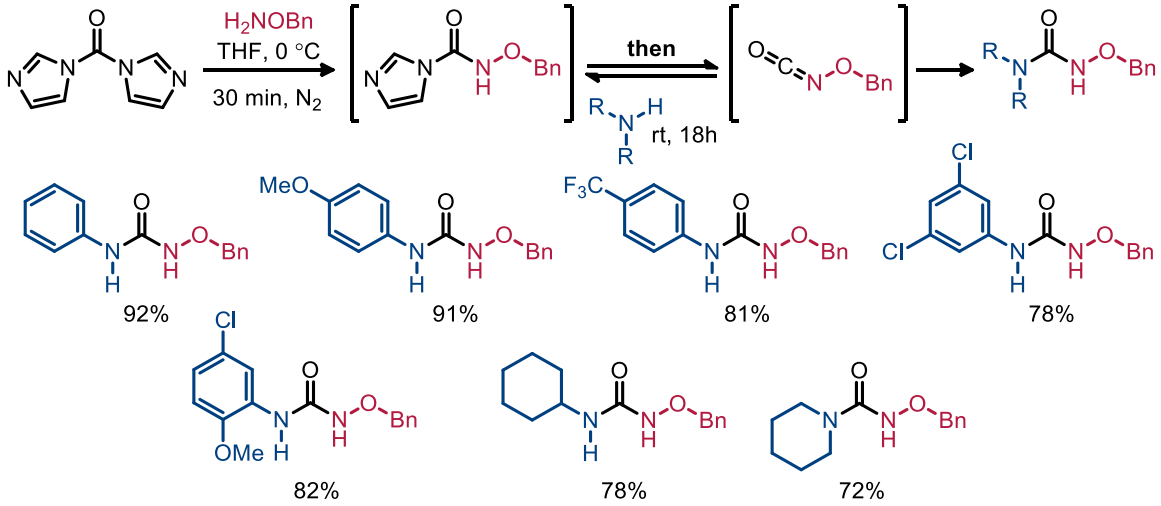
Scheme 2. 2 General strategies for the synthesis of *N*-oxyureas



In 1994, a short communication including the in-situ synthesis and substitution of benzyl-substituted *O*-isocyanates was published by Romine et al (Scheme 2. 3).[27a] The authors use carbonyl diimidazole (CDI) to form an imidazole-blocked isocyanate in-situ, then substitution using various amines produces *N*-oxyureas. Using CDI avoids the use of highly toxic reagents, phosgene or isocyanate. This work relies on

the acylation of amines rather than hydroxylamines, as previously discussed methods do. Five anilines, one primary amine, and one secondary amine were included in the scope, though the stoichiometry for the amine addition step was unclear from the reported data.

Scheme 2. 3 Scope of *N*-oxyureas via in-situ *O*-isocyanate synthesis and substitution *(Romine 1994)*



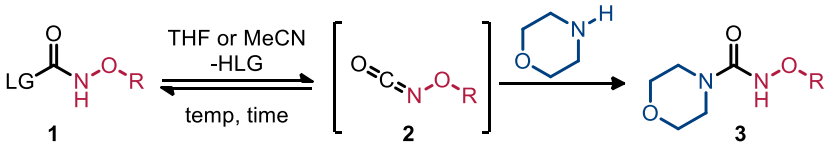
A study of the effects of *O*-substitution on this strategy for *N*-oxyurea synthesis was warranted since only *O*-benzyl substitution was included. An optimization of the leaving group could possibly allow for the development of bench-stable *O*-isocyanate precursors, which is useful because hydroxylamines are prone to degradation when stored as the free base. Recent work using carbamates as *O*-isocyanate precursors for cascade reactions indicated that alcohols may be better blocking groups for amine substitution.[23b,33] With support of the general strategy, tested use of imidazole and some alcohol leaving groups, and minimal exploration of *O*-substitution, we began a more systematic study of *O*-isocyanate substitution.

2.1.2 Optimization of Blocked *O*-Isocyanates as *N*-Oxyurea Precursors

The deblocking equilibrium is affected by the blocking group, base catalyst, and reaction conditions including temperature. We began the optimization of *O*-isocyanate substitution by studying the effects of blocking group modification with various conditions (Table 2. 1). The type of oxygen substituent (H, alkyl, or acyl) affects the reaction outcome for each blocking group (entries 1-3). *p*-Nitrophenol is a relatively good leaving group, however, reactions for different oxygen substituents at rt with base-promoted deblocking (1.0 equiv NEt_3 added) had broadly varying yields (58-99%). Using phenol as the blocking group (entries 4-6) led to a similar range of yields (57-94%) with shorter reaction times. The phenol-blocked precursors were also notably much more stable to long-term storage than *p*-nitrophenol variants,

meaning phenyl carbamates were more suitable substrates. Using worse leaving groups (OEt, N*i*-Pr_2, OBn, OCH_2CF_3, and O*t*-Bu) led to significantly reduced observed substitution product under similar reaction conditions (entries 7-12). The synthesis of these *O*-isocyanate precursors is often more difficult due to the less crystalline nature of the carbamates, leading to worse purification via recrystallization.

Table 2. 1 *O*-Isocyanate substitution: blocking group investigation[a]



1 2 3

Entry	LG	R	Temp (°C)	Time (h)	Yield of 3 (%)[b]
1	*p*-NO_2PhO[c]	H	rt	16	58
2	*p*-NO_2PhO[c]	Et	rt	16	99
3	*p*-NO_2PhO[c]	Bz	rt	16	87
4	PhO	H	70	16	71
5	PhO	Et	120	0.5	94
6	PhO	Bz	120	2	57
7	EtO	H	120[d]	16	0[e]
8	EtO	Et	120	4	60
9	*i*-Pr_2N	H	70	16	74
10	BnO	H	120[d]	16	8[e]
11	CF_3CH_2O	H	120[d]	16	4[e]
12	*t*-BuO	H	120[d]	16	0[e]

(a) Conditions: for R = H: precursor (1.1 equiv), morpholine (1.0 equiv), Et_3N (0.2 equiv) in THF (0.3 M), stir in oil bath, 16 h. For R = Et: carbamate (1.1 equiv) and morpholine (1.0 equiv) in MeCN (0.2 M), µW. For R = Bz: carbamate (1.0 equiv), morpholine (1.05 equiv), imidazole (0.1 equiv) in THF (0.2 M), µW. (b) Isolated yield. (c) Carbamate (1.0 equiv), morpholine (1.0 equiv), NEt_3 (1.0 equiv) in DCM (0.08 M), stir at rt, 16 h. (d) Reactions at 70 and 100 °C also result in no formation of product. (e) ^{1}H NMR yield of **3** using 1,3,5-trimethoxybenzene as an internal standard.

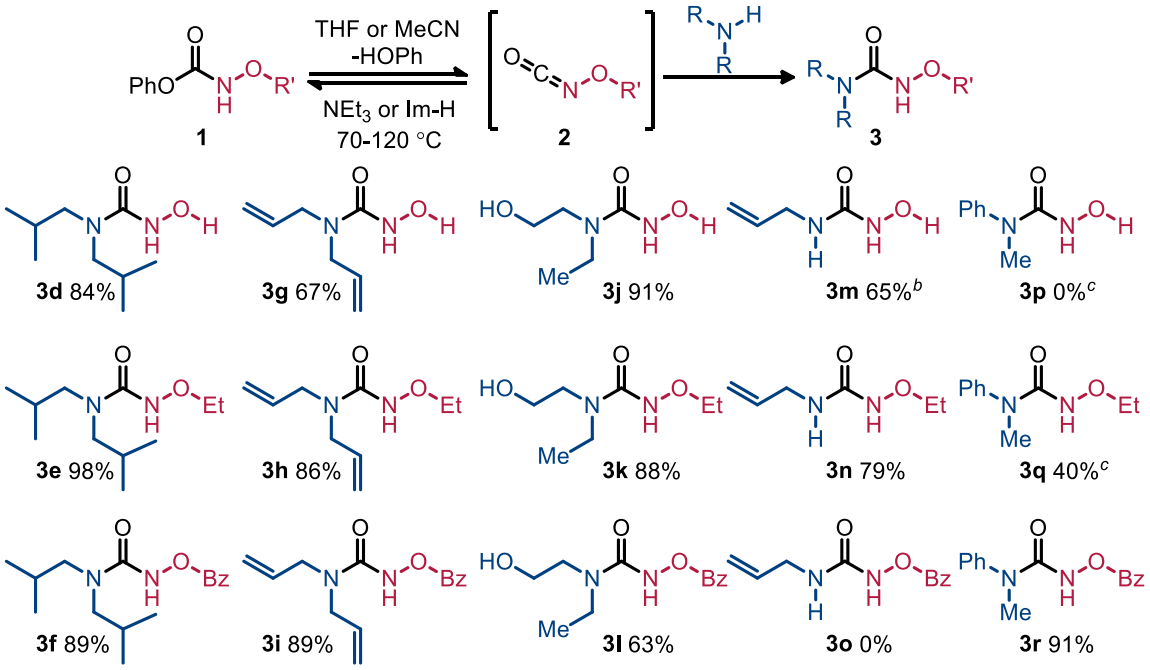
Phenol was therefore used as the optimal blocking group for the substitution reaction of hydroxy-, alkoxy, and acyloxycarbamate *O*-isocyanate precursors **1**. The scope of the reaction could then be determined using a variety of amine nucleophiles and carbamates.

2.1.3 Scope of *N*-Oxyureas

The scope of amine nucleophiles was evaluated first using the optimized reaction conditions (Scheme 2. 4). *This work was largely conducted by Dilan Polat.* Other dialkylamines were also found to be well tolerated for H, Et, and Bz substitution (**3d**-**3i**). Aminoalcohols also led to high yields of the corresponding *N*-oxyureas (**3j**-**3l**). Primary amine nucleophiles only led to similar yields of *N*-oxyurea when excess was used (**3m**-**3n**). Although, no correct substitution product was obtained when using *O*-benzoyl carbamate as only benzoylation of the allylamine and decomposition products were observed. Anilines also served

as suitable nucleophiles for the alkyl and acyloxy-carbamates when additional base (NEt_3) was added, likely to catalyze the deblocking (**3q**-**3r**). Overall, these representative examples serve to demonstrate the similar reactivity of various amine nucleophiles in the reported substitution methodology.

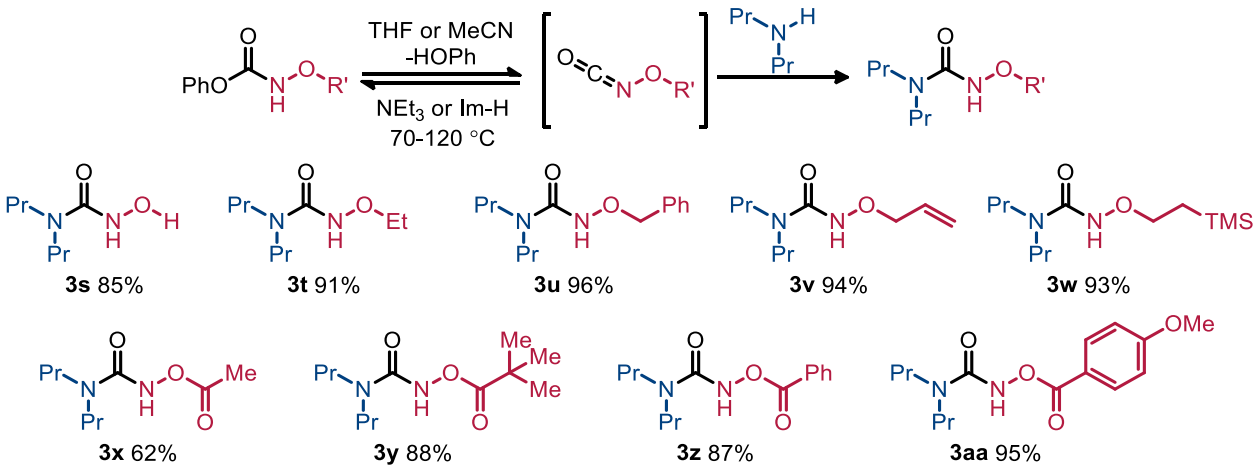
Scheme 2. 4 *O*-Isocyanate substitution: amine scope[a]



(a) Conditions for R' = H: Hydroxy-carbamate (1.1 equiv), NEt_3 (0.2 equiv) added, stirred at 70 °C in oil bath overnight. Conditions for R' = Et: oxy-carbamate (1.05 equiv), n-Pr_2NH (1.0 equiv) in MeCN (0.2 M), heat to 120 °C in μW for 30 min. Conditions for R' = Bz: Acyloxy-carbamate (1.0 equiv), amine (1.05 equiv), imidazole (0.1 equiv) in THF (0.2 M), heat to 100 °C in μW for 1–3 h. (b) Five equiv of allylamine used. (c) One equiv of NEt_3 used.

The scope of *O*-substitution was then explored using various carbamate *O*-isocyanate precursors **1** and dipropylamine (Scheme 2. 5). *This work was largely conducted by Ryan Ivanovich.* Again, distinct conditions were required for hydroxy-, alkoxy-, and acyloxy-carbamates. H-Substitution and alkyl-substitution led to high yields of the corresponding *N*-oxyureas (**3s**-**3w**). This also included various group (Bn, allyl, CH_2CH_2TMS) that can act as protecting groups as well. Acyloxy-carbamates, substituted with alkyl or aryl groups, were also found to be suitable reagents for substitution (**3x**-**3aa**).

Scheme 2. 5 *O*-Isocyanate substitution: oxy-carbamate scope[a]

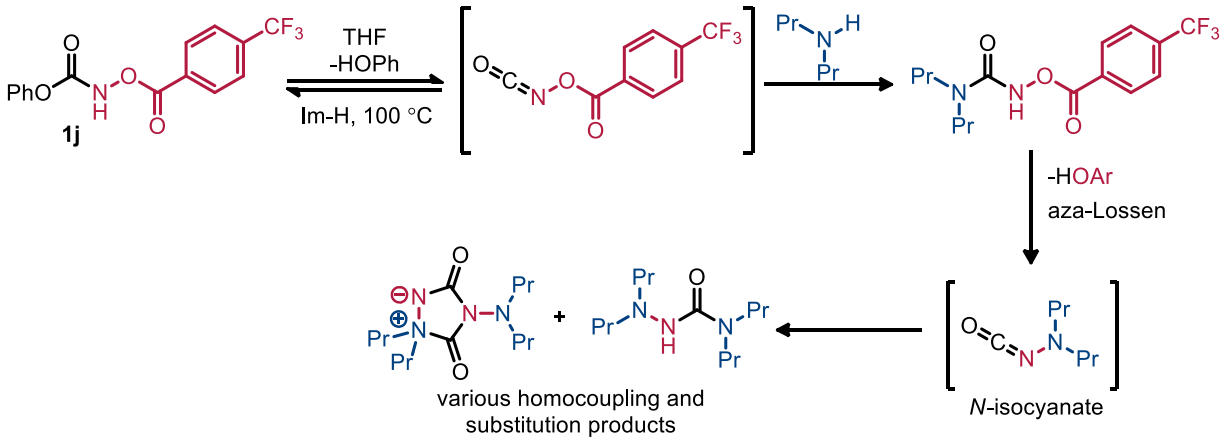


(a) Conditions for R' = H: Hydroxy-carbamate (1.1 equiv), NEt_3 (0.2 equiv) added, stirred at 70 °C in oil bath overnight. Conditions for R' = alkyl: oxy-carbamate (1.05 equiv), n-Pr_2NH (1.0 equiv) in MeCN (0.2 M), heat to 120 °C in μW for 30 min. Conditions for R' = (CO)R: Acyloxy-carbamate (1.0 equiv), amine (1.05 equiv), imidazole (0.1 equiv) in THF (0.2 M), heat to 100 °C in μW for 1–3 h.

2.1.4 Lossen Rearrangement as a Side-Reaction

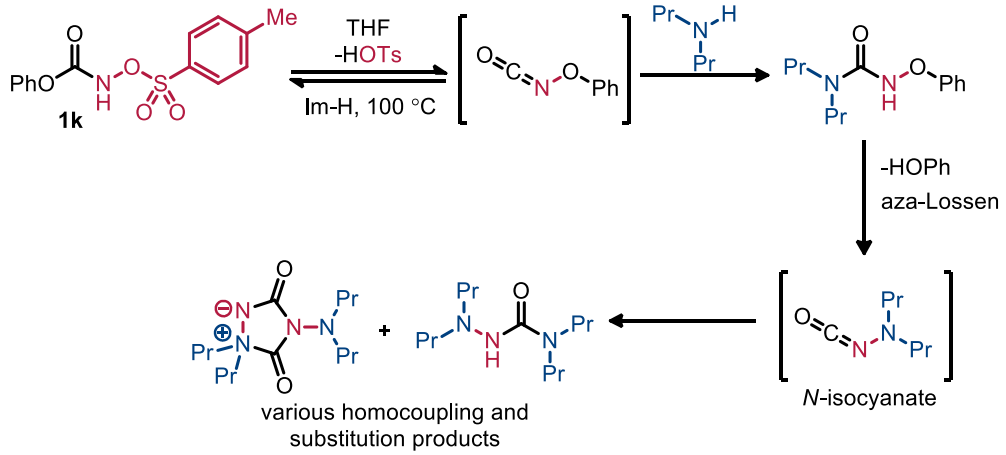
It was observed, however, that electron poor acyl-oxy-carbamates and tosyl-substituted carbamates (**1j**, **1k**) did not lead to the desired products under the optimized reaction conditions. Both types of reagents could undergo Lossen-type rearrangements leading to degradation since electron-poor acyl and tosyl substitution stabilize an oxygen-based leaving group. This could lead to more N-O bond cleavage-based products. Specifically, *N*-isocyanate based products appear to form based on ^{1}H NMR and TLC analysis showing consumption of the amine and multiple new amine signals. *N*-Isocyanates could form via the aza-Lossen of the desired *N*-oxyurea products (Scheme 2. 6).

Scheme 2. 6 Possible aza-Lossen rearrangement of *O*-acyloxyurea products



Another possible pathway to form *N*-isocyanate derived products could begin with an oxa-Lossen, where OPh migrates, then substitution, followed by aza-Lossen rearrangement (Scheme 2. 7).

Scheme 2. 7 Possible oxa-Lossen induced aza-Lossen rearrangement of *O*-phenoxyurea product



In either mechanistic scenario, a wide distribution of amine and carbonyl-containing products would be formed, such as semi-carbazides or cyclic ylides. While this rearrangement was undesired for this project, a PhD candidate, Dilan Polat, optimized the aza-Lossen rearrangement of *N*-oxyureas for the modular synthesis of semi-carbazides.[95] This work also importantly served to improve the understanding of *O*-isocyanate deblocking, which was then applied to studies of the cascade cycloaddition reactivity of *O*-isocyanates as 1,3-dipole equivalents.

2.2 [3+2] Cycloaddition

2.2.1 Background on Dipolar Cycloaddition

2.2.1.1 Charged 1,3-Dipoles

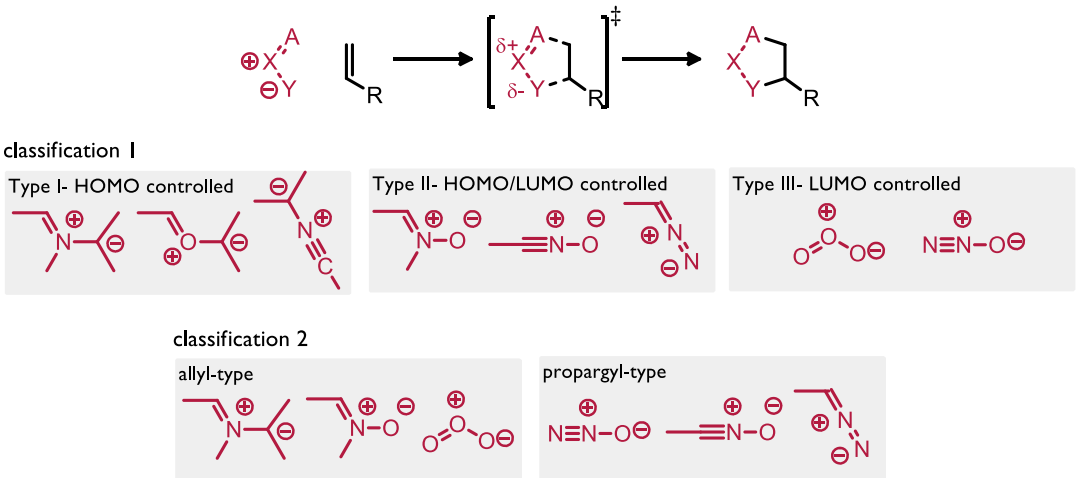
Cycloaddition reactions are an attractive type of pericyclic reaction since two new sigma bonds are formed in a concerted manner, leading to *syn* addition. Five-membered rings can be formed efficiently via [3+2] cycloadditions, often termed “dipolar cycloadditions” (Scheme 2. 8).[96] 1,3-Dipoles can be classified in two ways based on electronics or geometry. First, type I 1,3-dipoles, such as azomethine imines, have a high

[95] Polat, D. E.; Brzezinski, D. D; Beauchemin, A. M. *Org. Lett.* **2019**, *21*, 4849–4852.

[96] (a) Huisgen, R. *Angew. Chem. Int. Ed.* **1963**, *2*, 565-598. (b) Huisgen, R. *J. Org. Chem.* **1968**, *33*, 2291-2297. For a review of intramolecular 1,3-dipolar cycloadditions, see: (c) Padwa, A. *Angew. Chem. Int. Ed.* **1976**, *15*, 123-136. For a recent review of asymmetric 1,3-dipolar cycloadditions, see: (d) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2015**, *115*, 5366-5412.

energy HOMO, leading to a HOMO-controlled cycloaddition.[97] Type II 1,3-dipoles, like nitrones, can undergo HOMO or LUMO controlled cycloadditions depending on the electronics of the substituents and the dipolarophile. Lastly, type III 1,3-dipoles have a low energy LUMO, leading to a LUMO-controlled cycloaddition with more electron-rich dipolarophiles. Type III 1,3-dipoles undergo LUMO controlled cycloadditions and are exceedingly rare, limited to ozone and nitrous oxide only, and the resulting cycloadducts are notably unstable intermediates.

Scheme 2. 8 Dipolar cycloaddition using 1,3-dipoles



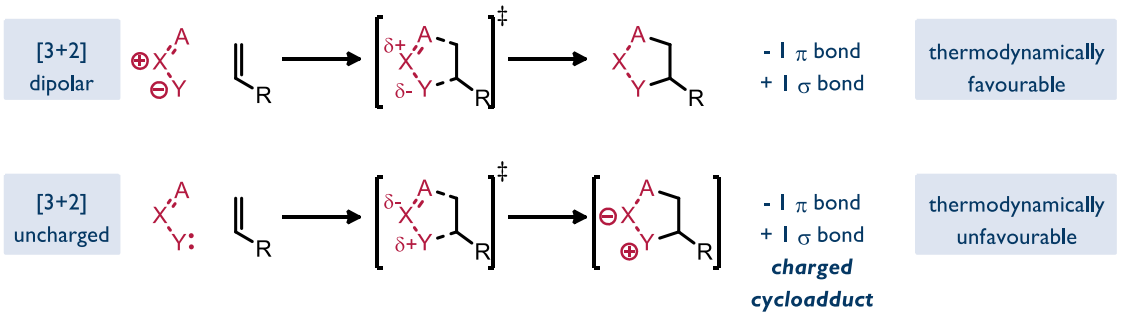
1,3-Dipoles can also be classified as bent allyl-anion type dipoles or linear propargyl anion type dipoles. These classifications lead to varying distortion of the dipole prior to the transition state and different shape of the 5-membered structures at the transition state (planar and envelope respectively).[98]

While conventional 1,3-dipoles tend to undergo thermodynamically favourable cycloaddition reactions with alkenes or alkyne dipolarophiles, their uncharged counterparts (*without any formal charges in their most stable form*) are more likely to be endothermic (Scheme 2. 9). The uncharged variants are rarely reported in the literature, in large part, due to the instability of the resulting charged cycloadduct (*containing two formal charges in its most stable form - zwitterionic*). The above defined *charged* and *uncharged* nomenclature will be used in subsequent discussions of cycloaddition reactivity.

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[97] Sustmann, R. *Pure Appl. Chem.* **1974**, *40*, 569-593.
[98] (a) Ess, D. H. and Houk, K. N. *J. Am. Chem. Soc.* **2007**, *129*, 10646–10647. (b) Ess, D. H. and Houk, K. N. *J. Am. Chem. Soc.* **2008**, *130*, 10187-10198. (c) Xu, L.; Doubleday, C. E.; Houk, K. N. *J. Am. Chem. Soc.* **2010**, *132*, 3029–3037.

Scheme 2. 9 Cycloaddition reactivity of charged 1,3-dipoles vs. uncharged 1,3-dipole equivalents



2.2.1.2 Uncharged 1,3-Dipole Equivalents

Rare examples of 1,3-dipole equivalents have been reported to make charged cycloadducts (Scheme 2. 10). When *N*-isocyanates undergo cycloaddition, the resulting cycloadduct can be stable (e.g., azomethine imine) or reactive.[23a] Azines exclusively form reactive cycloadducts, which can then be trapped via an additional [3+2] cycloaddition with various dipolarophiles.[99] Sulfur based 1,3-dipole equivalents, such as thiones, undergo [3+2] cycloadditions with benzynes or alkynes, forming reactive cycloadducts as well.[100] These charged cycloadducts can undergo elimination or 1,2-rearrangements to form neutral products.

Most recently, the Gagosz research group has reported that both ynamides and alkynyl sulfides can undergo intramolecular [3+2] cycloaddition with alkynes to form fused pyrroles and thiophenes after elimination or 1,2-shift of the unstable cycloadduct generally.[101] Yoshida also described the cycloaddition reactivity of alkynyl sulfides, instead using benzyne as the dipolarophile, and forming benzothiophenes following elimination of ethylene.[102] Analogously, Studer had reported the concerted [3+2] cycloaddition

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[99] (a) Bailey, J. R.; Moore, M. H. *J. Am. Chem. Soc.* **1917**, *39*, 279–291. (b) Schantl, J. G.; Gstach, H.; Hebeisen, P.; Lanznaster, N. *Tetrahedron* **1985**, *41*, 5525-5528. (c) Schantl, J. G.; Nadenik, P. *Synlett* **1998**, 786-788. (d) Cremlyn, R. J.; Ellam, R. M.; Farouk, S. Phosphorus, Sulfur Silicon Relat. Elem. **2000**, *161*, 213-238. (e) Verner, J.; Taraba, J.; Potacek, M. *Tetrahedron Lett.* **2002**, *43*, 4833-4836. (f) Zachova, H.; Man, S.; Necas, M.; Potáček, M. *Eur. J. Org. Chem.* **2005**, 2548-2557. (g) Burger, K.; Hennig, L.; Zeika, O.; Lux, A. *Heterocycles* **2006**, *67*, 443-460. (h) Verner, J.; Potáček, M. *Molecules* **2006**, *11*, 34-42. (i) Man, S.; Nečas, M.; Bouillon, J.-P.; Portella, C.; Potáček, M. *Eur. J. Org. Chem.* **2006**, 3473-3478.

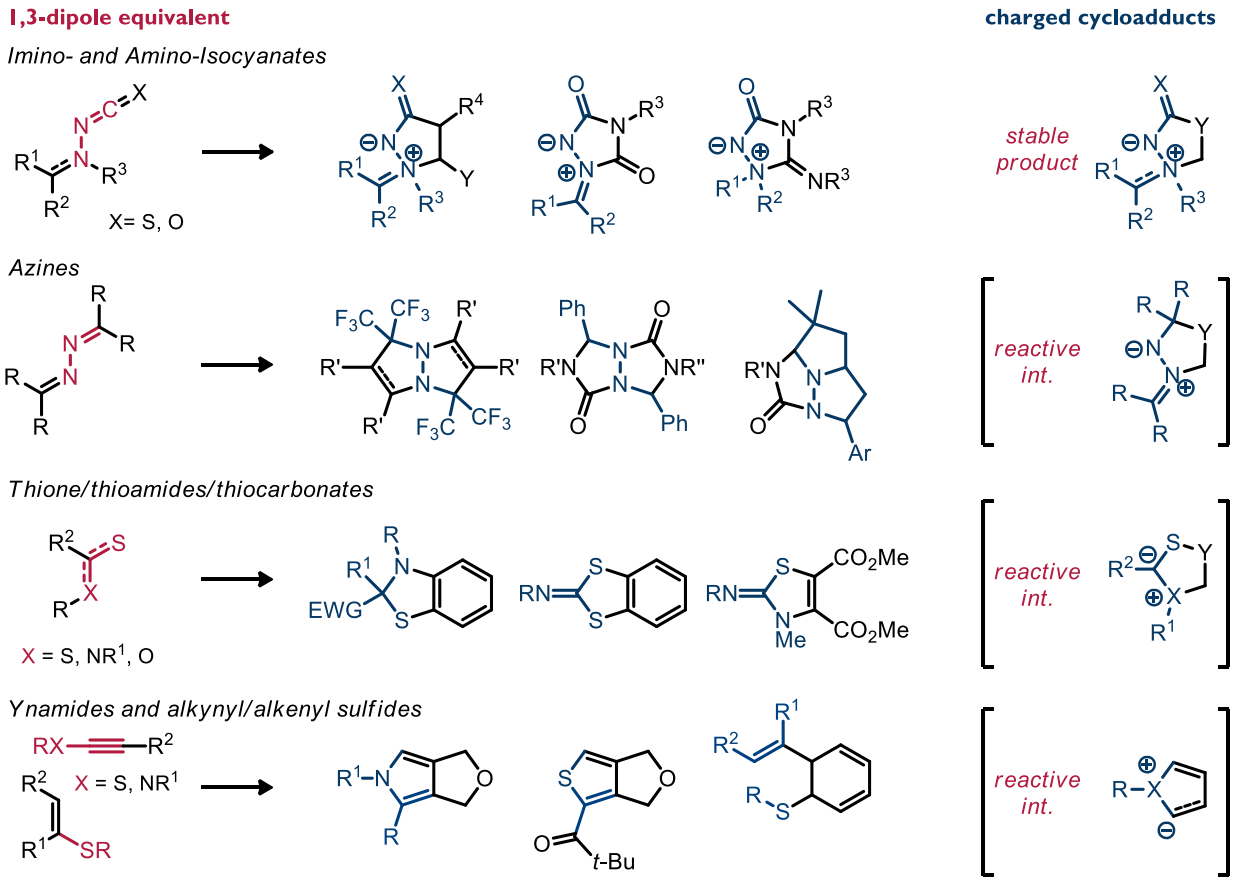
[100] (a) Easton, D. B. J.; Leaver, D. *Chem. Commun. (London)* **1965**, *22*, 585-586. (b) O'Connor, B. R.; Jones, F. N. *J. Org. Chem.* **1970**, *35*, 2002-2005. (c) Oliver, J. E.; Brown, R. T. *J. Org. Chem.* **1974**, *39*, 2228-2233. (d) Lakshmikantham, M. V.; Cava, M. P. *J. Org. Chem*. **1976**, *41*, 879-881. (e) Nakayama, J.; Kimata, A.; Taniguchi, H.; Takahashi, F. *Chem. Commun.* **1996**, 205-206. (f) Hwu, J. R.; Hsu, Y. C. *Chem. Eur. J.* **2011**, *17*, 4727-4731. (g) Zhang, J.; Page, A. C. S.; Palani, V.; Chen, J.; Hoye, T. R. *Org. Lett.* **2018**, *20*, 5550-5553.

[101] (a) Campeau, D.; Pommainville, A.; Gagosz, F. *J. Am. Chem. Soc.* **2021**, *143*, 9601–9611. (b) Pommainville, A.; Campeau, D.; Gagosz, F. *Angew. Chem. Int. Ed.* **2022**, *61*, e202205963.

[102] Matsuzawa, T.; Hosoya, T.; Yoshida, S. *Chem. Sci.* **2020**, *11*, 9691-9696.

reactivity of vinyl sulfides with benzynes earlier in 2016.[103] The zwitterionic cycloadduct here also undergoes elimination to form substituted styrene products.

Scheme 2. 10 Cycloaddition reactivity of known 1,3-dipole equivalents



The rare examples of known uncharged 1,3-dipole reactivity suggest that the development of other 1,3-dipoles could lead to other reactive intermediates via cycloaddition. It is possible that the use of an unstable heterocumulene, like *O*-isocyanates, may lead to thermodynamically feasible [3+2] cycloaddition, which can be diverged into multiple modes of reactivity from the reactive charged cycloadduct.

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[103] (a) Li, Y.; Mück-Lichtenfield, C. Studer, A. *Angew. Chem. Int. Ed.* **2016**, *55*, 14435–14438. For related work involving vinyl sulfide cycloaddition, see: (b) Xiao, P.; Su, S.; Wang, W.; Cao, W.; Chen, J.; Li, J.; Chen, Y. *RSC Adv.* **2019**, *9*, 39119-39123.

2.2.2 Intramolecular *O*-Isocyanate Cycloadditions

2.2.2.1 General Reaction Design

The reaction design to test the cycloaddition reactivity of *O*-isocyanates began with similar intramolecular reagents as explored for amino-isocyanates. Phenol-blocked carbamates were used as *O*-isocyanate precursors due to several beneficial factors (as discussed in section 2.1). It was originally unclear if *O*-isocyanates would proceed through [2+2] cycloaddition, like carbon-substituted isocyanates, or [3+2] cycloaddition, like *N*-isocyanates.[104] Alkenyl substituents that would lead to four- to seven-membered rings via [2+2] or [3+2] mechanisms were therefore tested.

2.2.2.2 Optimization

Using thermal deblocking conditions, carbamates **1l**-**1n** were subjected to microwave irradiation at high temperatures (Table 2. 2, entries 1-3). From these entries, no β-lactam products **A** were observed. Instead, only products derived from cycloadduct **B** from **1m** were observed. The products included three bicyclic lactam isomers and one oxadiazole (Scheme 2. 11), which could all feasibly form the aza-oxonium ylide **4a** followed by acyl nitrene **5a**. To our knowledge, the proposed aza-oxonium ylide is a novel intermediate.[105] In line with regular reactivity trends of nitrene C-H insertions, the most activated C-H bond, α to oxygen, leads to the major product **6a**.[106] The minor lactam products (**7a**, **8a**) result from the other two C-H insertions possible. X-Ray crystal structures were obtained to further support the structural assignment of the lactams originally completed by 1D and 2D NMR spectroscopy. The free acyl nitrene **5a** surprisingly does not require stabilization as a metal-nitrene to avoid 1,2-rearrangement to the corresponding isocyanate.[107] The combined yield of these cycloaddition derived products using MeCN as a solvent at 180 °C was already excellent (90%), however further entries were completed to evaluate solvent, temperature, and base effects.

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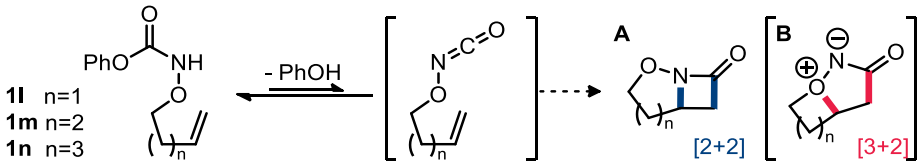
[104] (a) Rasmussen, J. K.; Hassner, A. *Chem. Rev.* **1976**, *76*, 389-408. (b) Cossio, F. P.; Roa, G.; Lecea, B.; Ugalde, J. S. *J. Am. Chem. Soc.* **1995**, *117*, 12306-12313.

[105] To our knowledge there are two examples of structurally distinct aza-oxonium ylides postulated as potential intermediates, though in each case they were discounted as unlikely pathways in the reactions studied. (a) Ochiai, M.; Yamane, S.; Hoque, M. M.; Saito, M.; Miyamoto, K. *Chem. Commun.* **2012**, *48*, 5280-5282. (b) Escudero, J.; Bellosta, V.; Cossy, J. *Angew. Chem. Int. Ed.* **2018**, *57*, 574-578. Attempts to study pentafluorophenylnitrene in neat THF via laser flash photolysis (LFP) resulted in tentative structural assignment of a structurally distinct aza-oxonium ylide: Poe, R.; Schnapp, K.; Young, M. J. T.; Grayzar, J.; Platz, M. S. *J. Am. Chem. Soc.* **1992**, *114*, 5054-5067.

[106] For a review of free nitrene reactions, see: Abramovitch, R. A.; Davies, B. A. *Chem. Rev.* **1964**, *64*, 149-185.

[107] Hong, S. Y.; Park, Y.; Hwang, Y.; Kim, Y. B.; Baik, M.-H.; Chang, S. *Science* **2018**, *359*, 1016-1021.

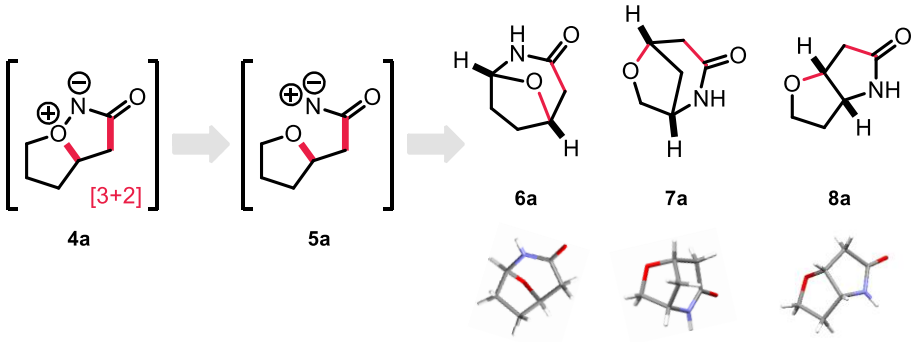
Table 2. 2 *O*-Isocyanate Intramolecular Cycloaddition Optimization[a]



Entry	Carbamate	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	1l	MeCN	180	2	0
2	1m	MeCN	180	2	90 (B)
3	1n	MeCN	180	2	0
4	1m	DMSO	180	2	0
5	1m	DMF	180	2	0
6	1m	$PhCF_3$	180	2	47[c] (B)
7	1m	toluene	180	2	0
8	1m	MeCN	120	6	0
9	1m	MeCN	150	4	5 (B)
10[d]	1m	MeCN	120	2	36[e] (B)

(a) Carbamate **1l**-**1n** (1.0 equiv., 0.1-0.2 mmol) in solvent (0.05 M), under Ar, and heated in a microwave reactor. (b) ^{1}H NMR yield for cycloaddition products **A** or products derived from intermediate **B** using 1,3,5-trimethoxybenzene as an internal standard (identity of the product- *A or B* - noted in parentheses). (c) 20% SM remaining. (d) 20 mol% *i*-Pr_2NEt added. (e) 50% SM remaining.

Scheme 2. 11 Mixture of observed intramolecular *O*-isocyanate cycloaddition products



When other highly polar and aprotic solvents were used (DMSO, DMF), no desired cycloaddition products were observed (entries 4-5). However, using less polar $PhCF_3$, reduced reactivity was observed along with significant degradation (entry 6). Using even less polar solvents (toluene) led to none of the desired reactivity (entry 7). Reducing the reaction temperature led to significantly slower reactivity, with only trace products **6**-**8a** forming after 4 h at 150 °C (entries 8-9). Lastly, using base catalysis to promote isocyanate deblocking at 120 °C did improve the observed yield of cycloaddition-derived products, however, the 2 h reaction only went to 50% conversion and 14% of the starting material appeared to degrade (entry 10). Therefore, thermal conditions in MeCN were chosen for this reaction going forward (entry 2).

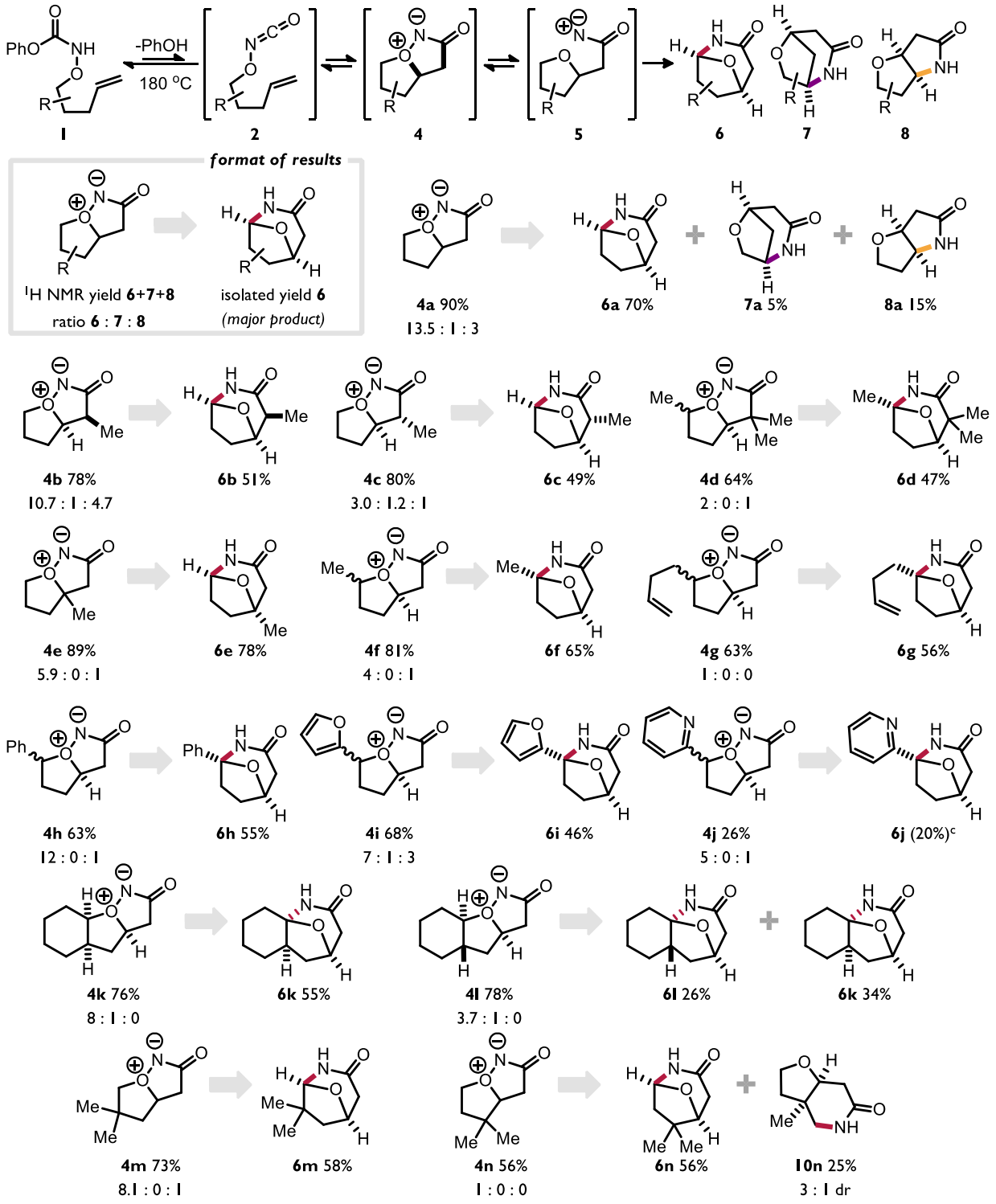
2.2.2.3 Results and Limitations

Next, the scope of intramolecular *O*-isocyanate cycloaddition was assessed, including varying alkyl and alkene substitution (Scheme 2. 12). *This work was completed and evenly divided with Ryan Ivanovich.* The scope of the [3+2] cycloaddition was evaluated using the isolated yield of major lactam **6** and the inferred yield of cycloadduct intermediates **4** using the combined ^{1}H NMR yield of all lactam isomers **6**-**8** which have diagnostic signals. Substitution on the alkene was generally well tolerated (**4a**-**4e**). Terminal alkene substitution led to high yields of the corresponding cycloadducts (**4b**, **4c**). The *cis* and *trans* methyl-substituted *O*-isocyanates underwent stereospecific cycloadditions to form the corresponding *syn* and *anti* C-H insertion products (**6b**, **6c**) respectively, providing strong evidence that the cycloaddition is indeed concerted. Terminal disubstitution of the alkene led to somewhat lower yield (**4d**), while proximal alkene substitution was well tolerated (**4e**).

Substitution alpha to the oxygen atom was well tolerated for alkyl or aromatic substituents (**4f**-**4i**), though basic substituents led to lower yields (**4j**). Both the *syn* and *anti* 2-allyl cyclohexyl substrates underwent cycloaddition readily leading to tricyclic products (**6k**, **6l**). Two substrates with geminal dimethyl substitution in the alkyl tether were also tested and led to lower yields relative to the unsubstituted alkyl chain (**4m**, **4n**). One additional methyl C-H insertion product was also observed (**10n**). In the analogous intramolecular alkene cycloaddition of *N*-isocyanates, substrates with a Thorpe-Ingold bias reacted much faster than those without. High yields of the *N*-isocyanate products could be obtained as low as 50 °C with catalytic base, whereas unbiased substrates reacted best at 120-200 °C.[108] However, no benefit from a Thorpe-Ingold effect was observed for *O*-isocyanate cycloaddition, and lower temperatures lead to no product formation with these biased substrates (**4m**, **4n**). The mechanistic implication is that the cycloaddition is likely not the rate determining step of this intramolecular reaction sequence.

[108] Ivanovich, R. A.; Clavette, C.; Vincent-Rocan, J.-F.; Roveda, J.-G.; Gorelsky, S. I.; Beauchemin, A. M. *Chem. Eur. J.* **2016**, *22*, 7906 – 7916.

Scheme 2. 12 Scope of intramolecular *O*-isocyanate cycloaddition[a] and yield derived from common aza-oxonium intermediate **4**[b]

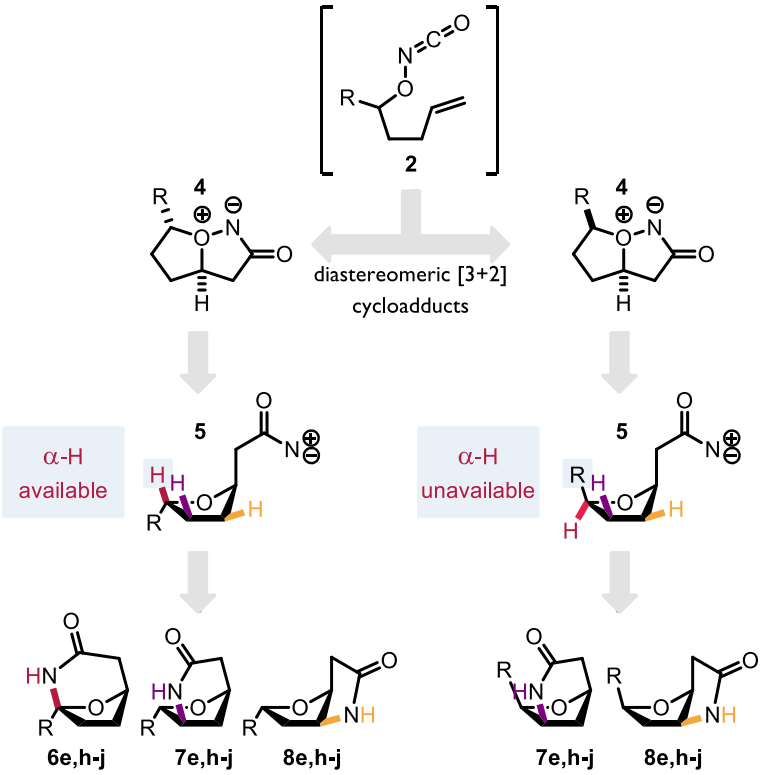


(a) Carbamate (1.0 equiv., 0.38-1.0 mmol) and MeCN (0.05 M), under Ar, μW 180 °C, 4-10 h.(b) ^{1}H NMR yield using 1,3,5-trimethoxybenzene as an internal standard for the inferred yield of common intermediate **4** based on the sum of ^{1}H NMR yields

of products 6, 7, 8 (ratio 6:7:8 shown below). The major product **6** was isolated for each entry (isolated yield shown). (c) ^{1}H NMR yield of product **6j** shown in parentheses. 17% of starting material formed O-isocyanate trimer.

For several substrates, diastereomers of some lactam isomers were also observed. Diastereomers are only observed for the minor lactam products for α-substituted O-isocyanates (**7d,f-j, 8d,f-j)**, although expectedly, not for the major lactam product **6d,f-j** based on the geometry of the acyl nitrene intermediate (Scheme 2. 13).

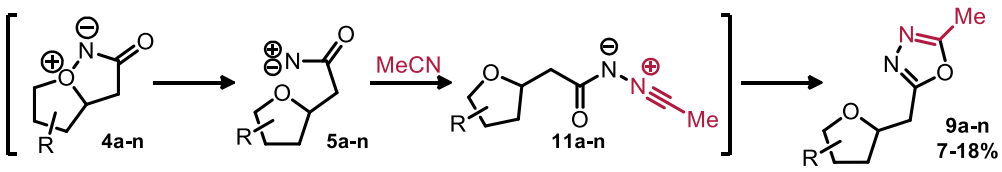
Scheme 2. 13 Rationale for observed diastereomers for minor lactam products



In addition to the three lactam isomer products, oxadiazole **9** also formed for most carbamates (Scheme 2. 14). The proposed mechanism of formation involves the attack of the acyl nitrene by the solvent, MeCN. Cyclization of this ylide adduct **11** then forms aromatic oxadiazole **9**. This process has been previously reported for various acyl nitrenes forming analogous oxadiazole products.[109]

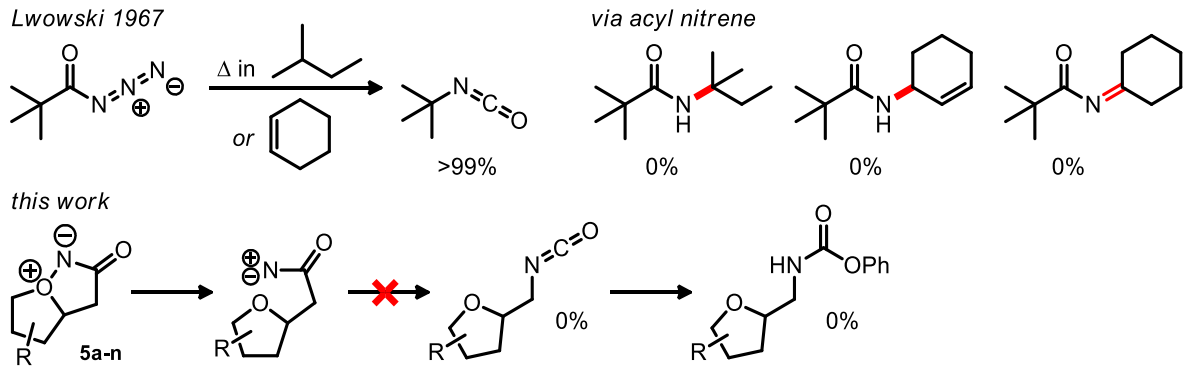
[109] (a) Lwowski, W.; Hartenstein, A.; deVita, C.; Smick, R. L. *Tetrahedron Lett.* **1964**, *5*, 2497-2501. (b) Eibler, E.; Sauer, J. *Tetrahedron Lett.* **1974**, *15*, 2569-2572. (c) Clauss, K. -U.; Buck, K.; Abraham, W. *Tetrahedron* **1995**, *51*, 7181-7192. (d) Pritchina, E. A.; Gritsan, N. P.; Maltsev, A.; Bally, T.; Autrey, T.; Liu, Y.; Wang, Y.; Toscano. J. P. *Phys. Chem. Chem. Phys.* **2003**, *5*, 1010-1018. (e) Desikan, V.; Liu, Y.; Toscano, J. P.; Jenks, W. S. *J. Org. Chem.* **2007**, *72*, 6848-6859.

Scheme 2. 14 Proposed oxadiazole formation via acyl nitrene intermediate



Toscano and Jenks report that photolytically formed benzoyl nitrene is trapped with MeCN at a rate of 1.5 x 10^5 $M^{-1}s^{-1}$ and the subsequent cyclization then occurs at a rate of 3 x 10^4 s^{-1} using time-resolved IR.[109e] They specifically note the absence of isocyanate-derived products when the photolysis is conducted in MeCN-containing solutions. Instead, oxadiazole (and C-H insertion products when 10% cyclohexane is added) are observed. Though these photolysis experiments do not directly correlate with the thermal conditions that allow the formation of acyl nitrenes in this work, both conditions lead to no observable isocyanate formation. The lack of Curtius-style rearrangement of the acyl nitrene to form an isocyanate is probable due to the reported short lifetime of acyl nitrenes.[110] Lwowski reported that thermolysis of azides in hydrocarbon solvents leads to no nitrene C-H insertion products, providing evidence that the Curtius rearrangement is a concerted process from the acyl azide without an acyl nitrene intermediate (Scheme 2. 15), though this topic has come conflicting conclusions from various publications.[111]

Scheme 2. 15 Curtius rearrangement without acyl nitrene intermediate (*Lwowski 1967*) and this work without isocyanate formation

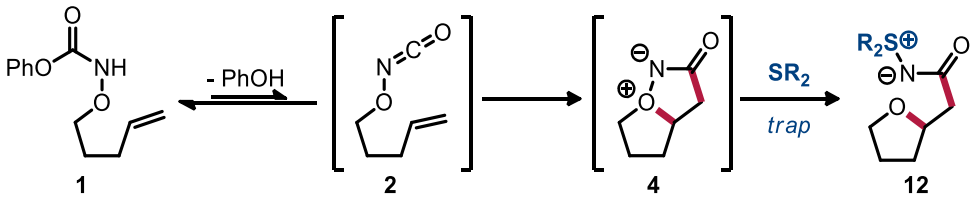


[110] (a) Tisue, G. T.; Linke, S.; Lwowski, W. *J. Am. Chem. Soc.* **1967**, *89*, 6303–6307. (b) Linke, S. Tisue, G. T.; Lwowski, W. *J. Am. Chem. Soc.* **1967**, *89*, 6308–6310. (c) Liu, J.; Mandel, S.; Hadad, C. M.; Platz, M. S. *J. Org. Chem.* **2004**, *69*, 8583-8593. (d) Wentrup, C.; Bornemann, H. *Eur. J. Org. Chem.* **2005**, 4521–4524. (e) Tarwade, V.; Dmitrenko O.; Bach, R. D.; Fox, J. M. *J. Org. Chem.* **2008**, *73*, 8189–8197.

[111] Abu-Eittah, R. H.; Mohamed, A. A.; Al-Omar, A. M. *Int. J. Quantum Chem.* **2006**, *106*, 863-875.

Considering the C-H insertion selectivity issue, trapping the acyl nitrene **5** more efficiently could lead to a more synthetically valuable reaction (Scheme 2. 16). This method of cycloaddition-induced nitrene synthesis via aza-oxonium ylide would be a novel route towards acyl nitrenes.[112]

Scheme 2. 16 Proposed *O*-isocyanate cycloaddition/acyl nitrene trapping



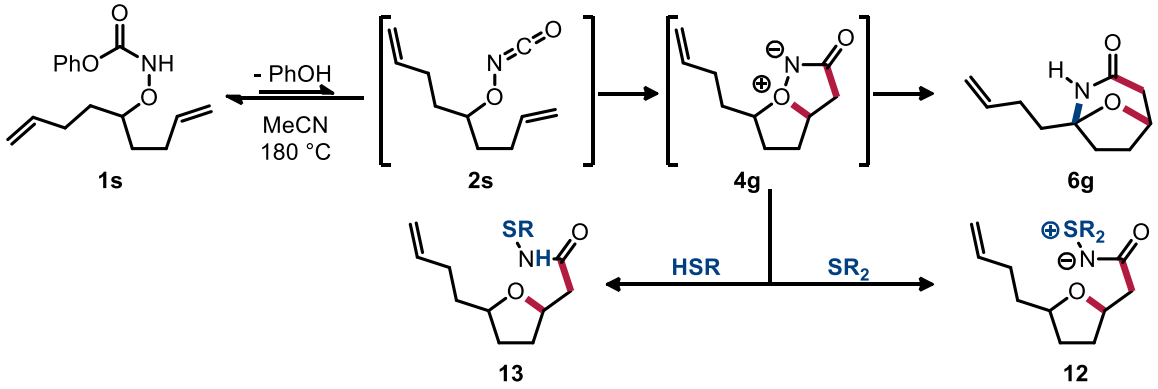
2.2.2.4 Attempts to Trap Acyl Nitrene Intermediates

Using *O*-isocyanate precursor **1**, several sulfur-based nitrene traps were tested (Table 2. 3). Thiols could trap the nitrene via S-H insertion, however, sulfides would form a stable ylide adduct **12**, which could both be detected by ^{1}H NMR analysis of the crude reaction mixture.[109e] The conversion of the starting material to phenol and the yield of the normal C-H insertion product could also be determined by ^{1}H NMR analysis. The dialkenyl carbamate **1s** was used since no detectable amount of minor lactam isomers were formed under optimized conditions, allowing for a simpler evaluation of the reaction mixture (Scheme 2. 12). After a reaction time of 2 h at 180 °C, 62% of lactam **6g** is formed without any additives (entry 1). The addition of *i*-PrSH leads to reduced conversion to phenol and lower yields of the lactam, however, no trapped acyl nitrene is observed (entries 2-3). Dialkylsulfide additives (SMe_2, THT) have minimal impact on the conversion of carbamate to phenol, though the yield of lactam **6g** is reduced significantly (entries 4-5). Though these results suggest possible alternative reaction pathways for the unstable *O*-isocyanate or acyl nitrene intermediate, no trapped acyl nitrene was observed by ^{1}H NMR. Using diphenylsulfide, reduced conversion and yield of the lactam were observed, however, no adduct **12** was observed again

[112] For examples of carbamate nitrenoid precursors, see: (a) Lebel, H.; Huard, K.; Lectard, S. *J. Am. Chem. Soc.* **2005**, *127*, 14198-14199. (b) Peddy, R. P.; Davies, H. M. L. *Org. Lett.* **2006**, *8*, 5013-5016. For examples of sulfamide nitrenoid precursors, see: (c) Breslow, R.; Gellman, S. H. *J. Chem. Soc., Chem. Commun.* **1982**, 1400-1401. (d) Breslow, R.; Gellman, S. H. *J. Am. Chem. Soc.* **1983**, *105*, 6738-6729. For examples of sulfamate ester nitrenoid precursors, see: (e) Cui, Y.; He, C. *Angew. Chem. Int. Ed.* **2004**, *43*, 4210-4212. (f) Milczek, E.; Boudet, N.; Blakey, S. *Angew. Chem. Int. Ed.* **2008**, *47*, 6825-6828. (g) Paradine, S. M.; White, M. C. *J. Am. Chem. Soc.* **2012**, *134*, 2036-2039. (h) Roizen, J. L.; Harvey, M. E.; Du Bois, J. *Acc. Chem. Res.* **2012**, *45*, 911-922. For an example of diaoxazolone nitrenoid precursors, see: (i) Bizet, V.; Buglioni, L.; Bolm, C. *Angew. Chem. Int. Ed.* **2014**, *53*, 5639-5642. For an example of sulfimine nitrenoid precursors, see: (j) Liang, C.; Robert-Peillard, F.; Fruit, C.; Muller, P.; Dodd, R. H.; Dauban, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 4641-4644.

(entry 6). The low stability of the proposed adducts (**12**, **13**) under the high temperature reaction conditions (180 °C) may be a contributing factor to the lack of observed products.

Table 2. 3 Attempts to trap acyl nitrene for intramolecular *O*-isocyanate cycloaddition reactions[a]



Entry	Additive (equiv)	Conv. to PhOH (%)[b]	Yield lactam 6g (%)[b]	Yield of 12 or 13 (%)[b]
1	none	88	62	0
2	*i*-PrSH (1)	47	31	0
3	*i*-PrSH (5)	23	13	0
4	SMe_2 (5)	84	49	0
5	THT (5)	80	38	0
6	SPh_2 (5)	60	35	0

(a) Conditions: alkoxycarbamate **1s** (1.0 equiv) in MeCN (0.05 M) at 180 °C via microwave irradiation for 2h. (b) ^{1}H NMR yield using 1,3,5-trimethoxybenzene as an internal standard. THT = tetrahydrothiophene.

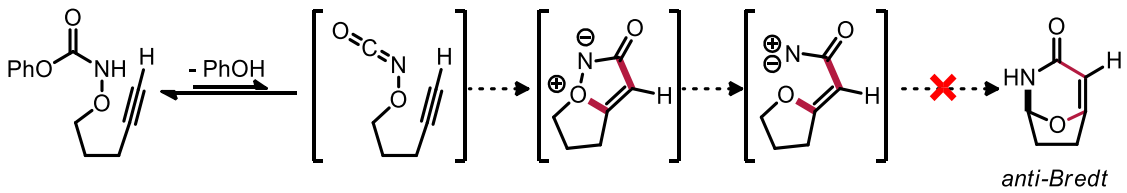
2.2.2.5 Intramolecular *O*-Isocyanate Cycloaddition with Alkynes

Lastly, the cycloaddition reactivity of *O*-isocyanates with alkynes was evaluated. Previous work with *N*-isocyanates demonstrated the efficient intermolecular [3+2] cycloaddition of imino- and amino-isocyanates with alkynes, however, no intramolecular examples have been reported.[113] One challenge specifically for a potential *O*-isocyanate/alkyne cycloaddition is the 3D geometry of the acyl nitrene C-H insertion product (Scheme 2. 17). Any lactam product, typically observed for the analogous alkene cycloaddition cascade, would include an anti-Bredt double bond at a bridgehead position, making these structures unlikely to form.[114]

[113] (a) Heep, U. *Tetrahedron* **1975**, *31*, 77-80. (b) Jones, D. W. J. *Chem. Soc., Chem. Commun.* **1982**, 766-768. (c) Lockley, W. J. S.; Lwowski, W. *Tetrahedron Lett.* **1974**, 4263-4266.

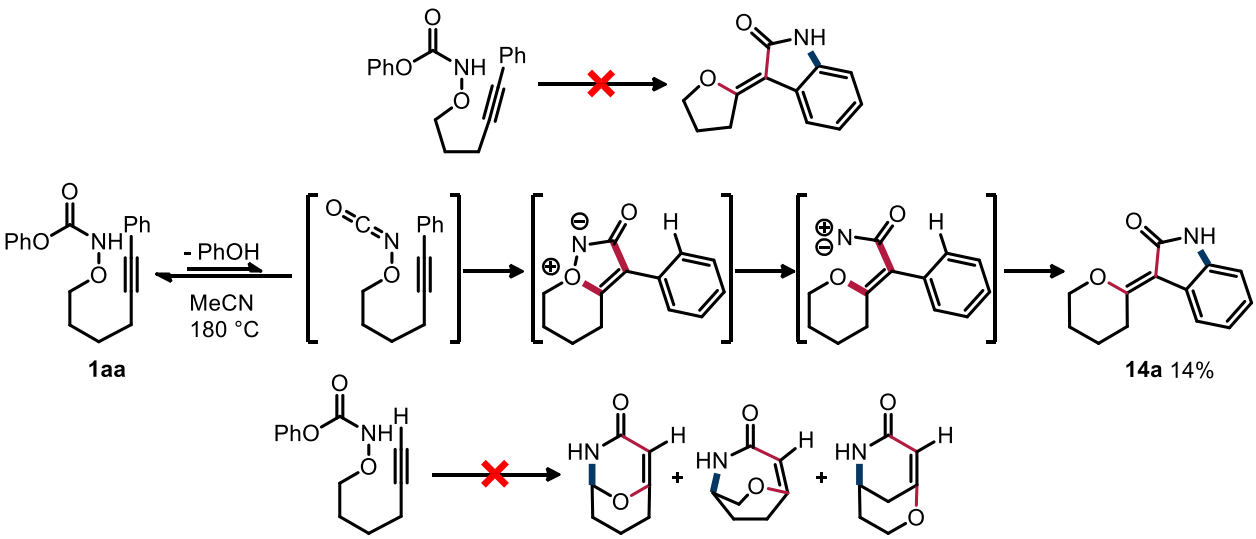
[114] (a) Bredt, J. *Justus Liebigs Ann. Chem.* **1924**, *437*, 1–13. (b) Fawcett, F. S. *Chem. Rev.* **1950**, *47*, 219–274. (c) Köbrich, G. *Angew. Chem. Int. Ed.* **1973**, *12*, 464–473.

Scheme 2. 17 Anti-Bredt type product of terminal alkyne O-isocyanate cycloaddition



In order to avoid this problem, substituted alkyne-tethered carbamates were synthesized that would allow for other C-H insertion products to form. Tether lengths for both 5- and 6-membered ether ring were used because the ideal geometry for intramolecular alkyne cycloaddition is unknown. While the shorter tether led to no observed product, carbamate **1aa** led to a low yield of the C(sp^2)-H insertion product **14a** (Scheme 2. 18). When a terminal alkyne was used with the same 4-methylene tether, no lactam products were observed, as expected.

Scheme 2. 18 Intramolecular *O*-isocyanate cycloaddition with alkynes



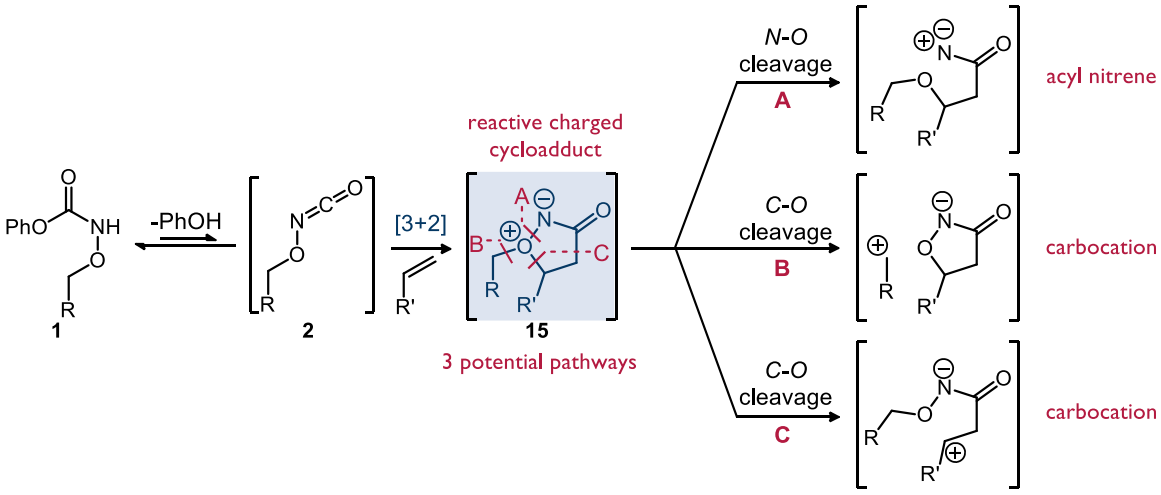
The low yield and substrate limitations of alkyne cycloaddition observed demonstrated that C(sp^2)-H insertion was possible for acyl nitrenes formed under these cycloaddition-induced conditions, however, further optimization was not performed. Instead, efforts toward exploring alternate aza-oxonium ylide reactivity were undertaken by assessing various intermolecular *O*-isocyanate cycloadditions.

2.2.3 Intermolecular *O*-Isocyanate Cycloadditions

2.2.3.1 General Reaction Design

Upon cycloaddition, intramolecular variants of the aza-oxonium ylide (**4**) undergo N-O bond cleavage exclusively to form the observed products, the three lactam isomers (**6**-**8**) and the oxadiazole by-product (**9**). It was hypothesized, however, that alternate pathways were possible from the aza-oxonium cycloadduct formed via intermolecular cycloaddition **15** (Scheme 2. 19). Alleviating the positive charge on oxygen can occur in three ways: (A) N-O bond cleavage to form the acyl nitrene as previously studied, (B) C-O bond cleavage to form a carbocation of the oxy-carbamate *O*-substituent, or (C) the other possible C-O bond cleavage to form a carbocation at the β-carbon relative to the carbonyl.

Scheme 2. 19 Potential reaction pathways of aza-oxonium ylide **15**



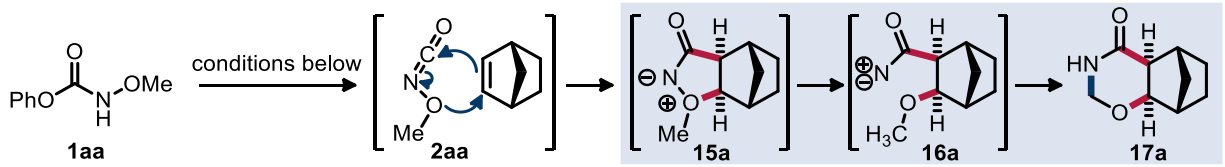
The observation of products derived from these three pathways depended on several factors. First, the cycloaddition itself must be favourable enough to proceed to aza-oxonium ylide **15**. Unactivated alkenes were observed to react previously, though this was part of an intramolecular system, so some substrate limitations might emerge. Selectivity for one of the three paths (A-C) could also potentially be low, so judicious choice of substrates might help to increase path selectivity.

2.2.3.2 Optimization of Nitrene Pathway

It was important to evaluate path A, including acyl nitrene formation and C-H insertion, for an intermolecular variant initially. *This optimization was largely completed by Ryan Ivanovich. O*-Isocyanate precursors were first heated with the strained alkene, norbornene, due to successful *N*-isocyanate

cycloadditions with this substrate previously reported (Table 2. 4).[115] At 120 °C with or without base catalyst, only trace product **17a** and minimal conversion were observed (entries 1-2). Increasing the temperature to 150 °C, then 180 °C led to increased formation of oxazinanone **17a** (entries 3-4). Structural determination could then be conducted with more certainty using 1D and 2D NMR spectroscopy to support the oxazinanone predicted structure presumably formed via C-H insertion of the acyl nitrene into an methoxy C-H bond. Using a common solvent for *N*-isocyanate cycloaddition reactions, $PhCF_3$, reduced conversion and yield were observed (entry 5), so MeCN was used for the remainder of the optimization. Increasing the already excess norbornene from 10 equiv to 30 then 50 equiv led to large increases in yield (entries 6-7). Although 50 equiv of alkene was not ideal, the excess norbornene was removed upon evaporation.

Table 2. 4 *O*-Isocyanate [3+2] cycloaddition optimization with norbornene[a]



Entry	Solvent	Temp (°C)	Time (h)	Equiv Alkene	Base (equiv)	Yield of 17a (%)[b]	1aa remaining (%)[b]
1	MeCN	120	3	10	-	4	82
2	MeCN	120	3	10	*i*-Pr_2NEt (0.05)	4	63
3	MeCN	150	3	10	-	32	24
4	MeCN	180	2	10	-	38	0
5	$PhCF_3$	150	3	10	-	10	75
6	MeCN	180	2	30	-	73	0
7	**MeCN**	**180**	**2**	**50**	**-**	**87**[c]	**0**

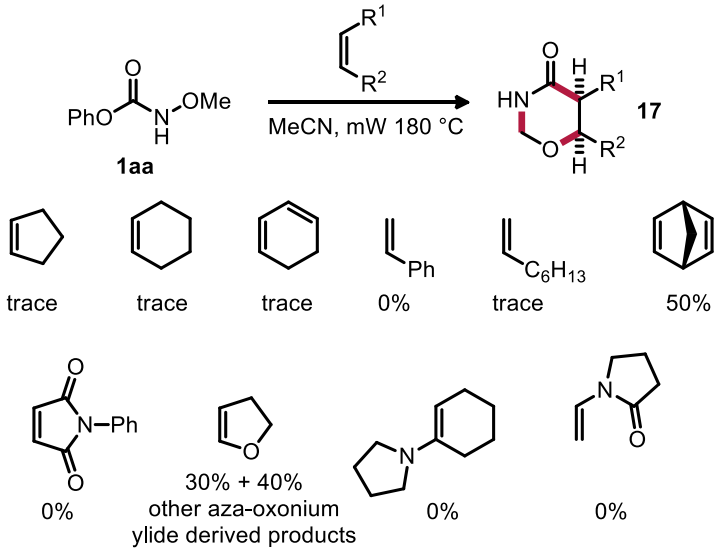
(a) Conditions: alkoxycarbamate **1aa** (1.0 equiv), norbornene (10-50 equiv) in solvent (0.2 M) at 120-180 °C via microwave irradiation for given time. (b) ^1H NMR yield using 1,3,5-trimethoxybenzene as an internal standard. (c) Isolated yield.

With the successful intermolecular cycloaddition and nitrene C-H insertion reaction sequence observed for norbornene, other alkene substrates were tested under similar conditions (Scheme 2. 20). Less strained alkenes, such as cyclopentene or cyclohexene, led to only trace oxazinanone product (**17**). While norbornadiene led to an analogous oxazinanone with an unoptimized yield of 50%, almost no

[115] (a) Clavette, C.; Gan, W.; Bongers, A.; Markiewicz, T.; Toderian, A.; Gorelsky, S. I.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2012**, *134*, 16111-16114. (b) Gan, W.; Moon, P.; Clavette, C.; DasNeves, N.; Markiewicz, T.; Toderian, A.; Beauchemin, A. M. *Org. Lett.* **2013**, *15*, 1890-1893.

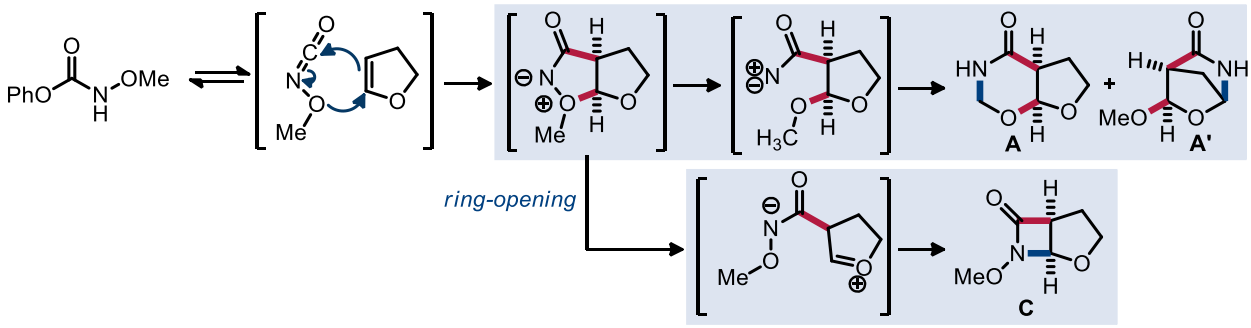
electronically bias alkenes led to observable desired reactivity. Only enol ethers, previously reported to react with imino-isocyanates efficiently, led to a mixture of products.[116]

Scheme 2. 20 Attempts to use other alkene substrates



The resulting product mixture from the reaction of *O*-isocyanate prescursors with dihydrofuran enol ether can be rationalized using two main reaction pathways from the aza-onomium ylide (Scheme 2. 21). The first is the previously observed N-O bond cleavage, which for this dipolarophile, leads to two C-H insertion products (A and A'). The β-lactam product (C) could be formed by ring-opening of the aza-oxonium ylide, follwed by four-membered ring-closure.

Scheme 2. 21 Mechanistic proposal for enol ether product mixture



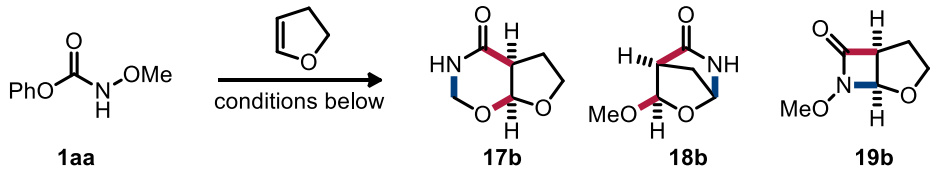
[116] Lavergne, K.; Bongers, A.; Betit, L.; Beauchemin, A. M. *Org. Lett.* **2015**, *17*, 3612–3615.

While this product mixture successfully demonstrates the divergent reactivity of the aza-oxonium ylide, the low selectivity observed is undesirable. An optimization to favour the novel ring-opening pathway was therefore undertaken (Table 2. 5).

2.2.3.3 Optimization of Alternative Oxonium Ylide Pathways

Analysis of the product mixture from the reaction of methoxy-isocyanate precursor **1aa** with dihydrofuran revealed that the nitrene pathway from the aza-oxonium ylide cycloadduct led to most of the observed products (60% **17b** + **18b**) (entry 1). Only 10% of the β-lactam product **19b** was formed. Evaluating other less polar solvents (DCE and $PhCF_3$) led to significantly less productive cycloaddition reactivity of any kind (entries 2-3). Incomplete conversion and significant degradation were observed instead. Reducing the reaction temperature to 150 °C with MeCN as a solvent showed encouraging complete selectivity and good yields of the β-lactam product (C), although this was dependent on a large excess of alkene being used (entries 4-6). Reducing the temperature further to 120 °C or 90 °C significantly reduced the conversion of starting material **1aa** (entries 7-8). It was possible that *O*-isocyanate formation was rate-limiting as 90 or 120 °C, so a base catalyst (*i*-Pr_2NEt) was added to aid in deblocking (entries 9-10). Gratifyingly, the yields of β-lactam improved drastically with added base and the high selectivity of β-lactam formation was maintained. In fact, quantitative yields of lactam **19b** were observed when base catalysis was used at 120 °C. Modifying the heating conditions from microwave irradiation to conventional oil bath heating led to somewhat reduced yields (entry 11) along with much longer reaction times, so microwave heating was used for the optimized conditions. *This optimization was largely completed by Ryan Ivanovich.*

Table 2. 5 β-lactam synthesis through enol ether cycloaddition reaction optimization[a]



1aa 17b 18b 19b

Entry	Solvent	Temp (°C)	Time (h)	Equiv Alkene	Base (equiv)	Yield of 17b (%)[b]	Yield of 18b (%)[b]	Yield of 19b (%)[b]
1	MeCN	180	2	30	-	30	30	10
2	DCE	180	2	30	-	0	0	0
3	$PhCF_3$	180	2	30	-	2	0	0
4	MeCN	150	2	30	-	0	0	70
5	MeCN	150	2	20	-	0	0	55
6	MeCN	150	2	10	-	0	0	30
7	MeCN	120	2	30	-	0	0	15
8	MeCN	90	2	30	-	0	0	0
9	MeCN	120	2	30	*i*-Pr_2NEt (0.2)	0	0	99
10	MeCN	90	2	30	*i*-Pr_2NEt (0.2)	0	0	35
11	MeCN	120[c]	20	30	*i*-Pr_2NEt (0.2)	0	0	90

(a) Conditions: alkoxycarbamate **1aa** (1.0 equiv), alkene (10-30 equiv), base (if applicable), in solvent (0.2 M) at given temperature and time via microwave irradiation. (b) ^{1}H NMR yield using 1,3,5-trimethoxybenzene as an internal standard. (c) Oil bath was used. DCE = 1,2-dichloroethane.

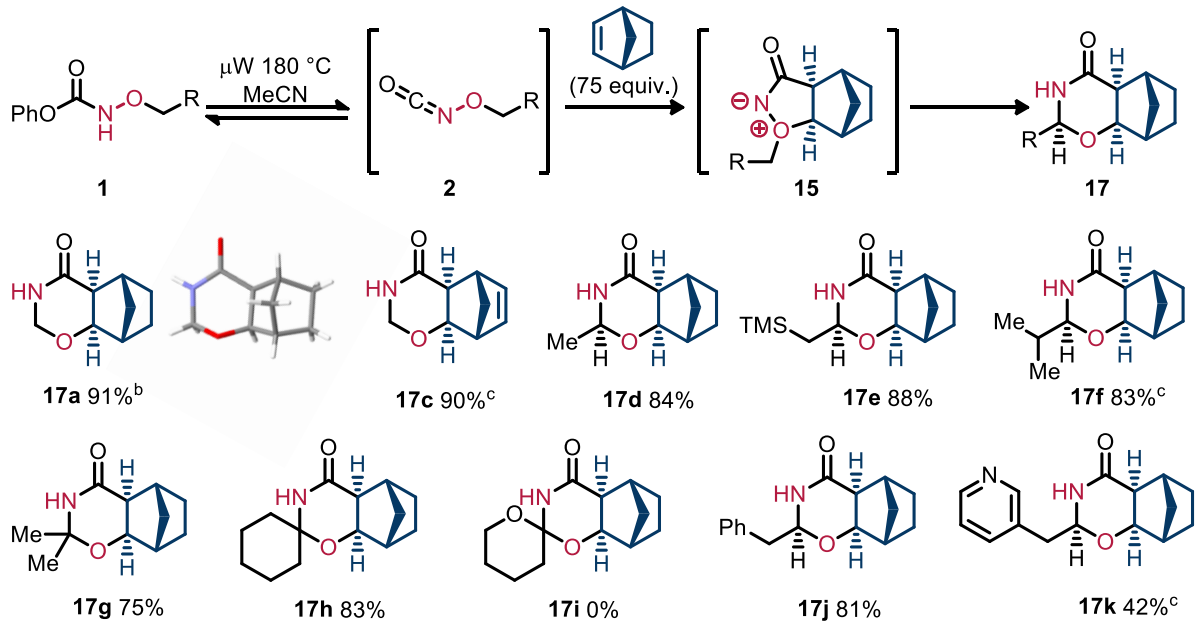
With these optimized conditions along with the cycloaddition/nitrene insertion cascade (Table 2. 4), the scope of each reaction pathway was evaluated by modification of the carbamate and dipolarophile substrate.

2.2.3.4 Results and Limitations

To assess the effect of *O*-substitution on cycloaddition, a variety of carbamates were heated with excess norbornene to produce the corresponding oxazinanones **17** (Scheme 2. 22). *This portion of the scope was largely completed by Ryan Ivanovich.* Methoxycarbamate precursor (**1aa**) led to an excellent yield of the corresponding oxazinanones with both norbornene and norbornadiene (**17a**, **17c**). Ethyl, 2-(trimethylsilyl)ethanol, and isobutyl substituted carbamates also led to high yields of C-H insertion products (**17d**-**17f**). Isopropyl- and cyclohexyl-derived oxazinanones (**17g, 17h**) were obtained in only slightly reduced 75% and 83% yields respectively, suggesting that the cycloaddition is not significantly sensitive to steric hindrance. Conversely, the tetrahydropyran-substituted carbamate led to no formation on oxazinanone **17i** after full conversion of the substrate. Homo-benzylic substitution was well tolerated (**17j**), though inclusion of a basic pyridine functional group led to a significantly reduced yield (**17k**, 42%).

Basic functional groups can affect the deblocking equilibrium, so modified reaction conditions would likely be required for improved results.

Scheme 2. 22 *O*-Isocyanate [3+2] cycloaddition/nitrene insertion cascade scope[a]

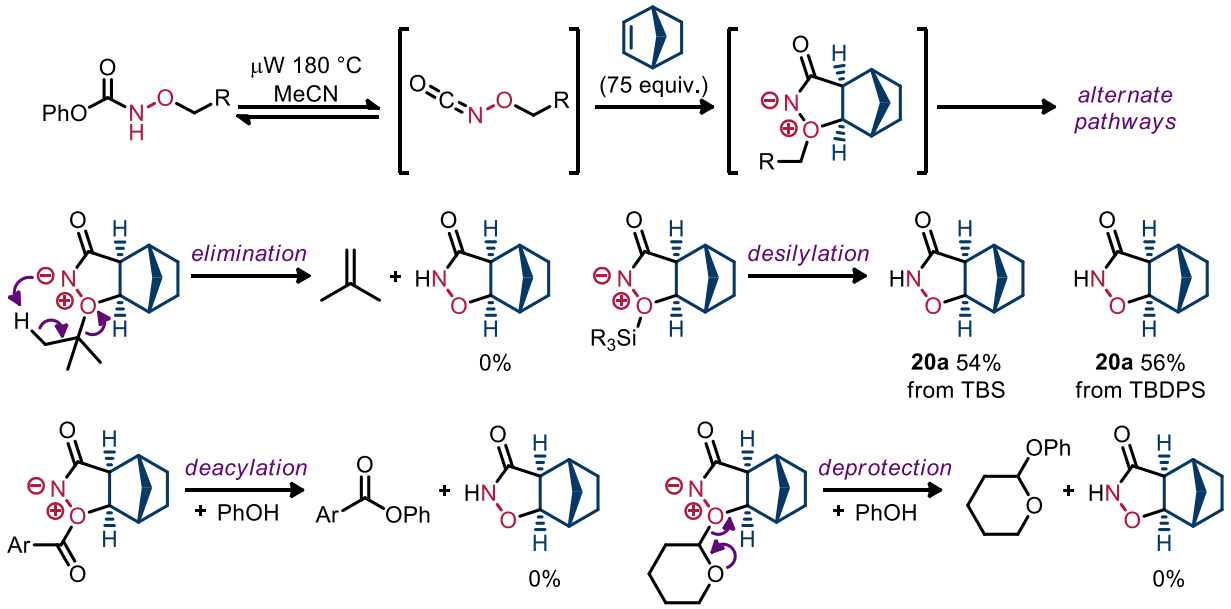


(a) Conditions: alkoxycarbamate **1** (1.0 equiv), alkene (50 equiv) in MeCN (0.2 M), μW 180 °C, 2 h. Major diastereomer shown (d.r. by ^{1}H NMR are typically ~10:1, see SI for exact values). (b) 30 equiv alkene used. (c) ^{1}H NMR yield using 1,3,5-trimethoxybenzene as an internal standard.

Several starting materials potentially leading to alternate reaction pathways were tested in attempts to allow for path B to be favoured, forming isoxazolidinone products **20** (Scheme 2. 23). *Tert*-Butyl substituted *O*-isocyanate precursors were tested as substrates due to the potential elimination reaction of 2-methylpropene. Under a variety of conditions, this process or any other cycloaddition-based process was not observed by crude ^{1}H NMR analysis. It seemed feasible that *O*-silyl derivatives could selectively react via pathway B, either through O−Si bond cleavage of the aza-oxonium ylide, or perhaps [1,2]-silyl shift and subsequent N−Si cleavage. In either mechanistic scenario, it is likely that phenol would participate in the silyl deprotection step. Silyl-derived *O*-isocyanate precursors (**1ab**-**1ac**) provided the same isoxazolidinone product **20a** in good yield. Importantly, these *O*-silyl substrates allow for selective and direct synthesis of N−H unprotected isoxazolidinones via concerted cycloaddition. Unfortunately, the *O*-silyl isocyanate cycloaddition reactions are limited by the reliance on strained alkenes, such as norbornene, as reaction partners. Acyl-substituted carbamates were used in attempt to allow deacylation of the aza-oxonium ylide intermediate, though no cycloaddition-based products were ever observed using

acyl-substituted precursors. Lastly, tetrahydropyran-linked carbamate also led to no oxazinanone product through the anticipated deacetylation mechanism.

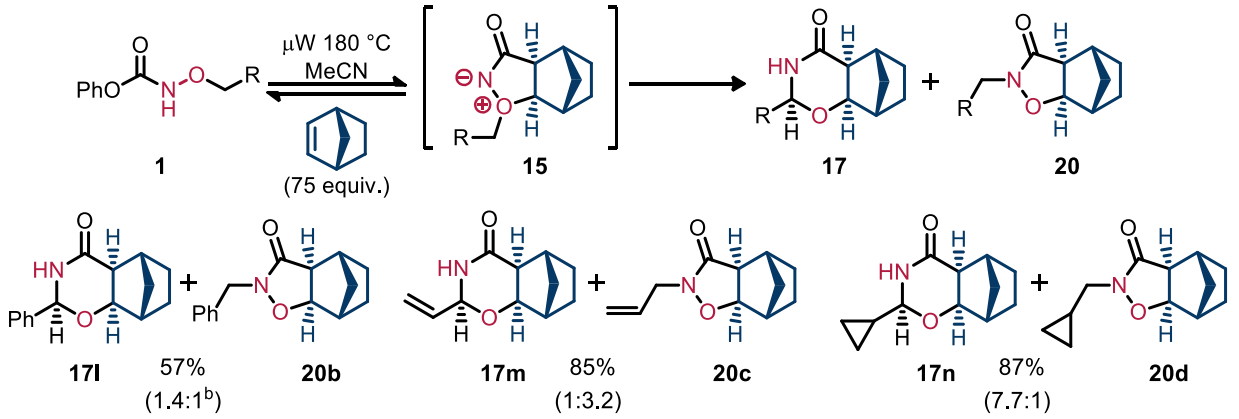
Scheme 2. 23 *O*-Isocyanate [3+2] cycloaddition/alternate pathway cascades



Next, rearrangement-based C-O bond cleavage was evaluated to promote path B-type reactivity of the aza-oxonium ylide (Scheme 2. 24). *This work was completed and evenly divided with Ryan Ivanovich.* Previous work with *N*-isocyanates demonstrates that 1,2-Steven's shifts or 2,3-Meisenheimer rearrangements were accessible pathways for related ylide reactivity.[117] Both *O*-benzyl (**1c**) and *O*-allyl (**1d**) substrates were found to undergo analogous reactions of the ylide cycloadduct, though not with complete selectivity over the nitrene C-H insertion pathway. These rearrangement products (**20**) provided experimental evidence that N−O bond cleavage or C−H amination could be rate limiting, and that these rearrangements offer lower-energy pathways from the aza-oxonium ylide **15**.

[117] Ivanovich, R. A. Quartus, J. Q.; Das Neves, N.; Loiseau, F.; Raymond, M.; Beauchemin, A. M. *J. Org. Chem.* **2019**, *84*, 9792-9800.

Scheme 2. 24 *O*-Isocyanate [3+2] cycloaddition/nitrene insertion or 1,2/2,3-shift cascade[a]

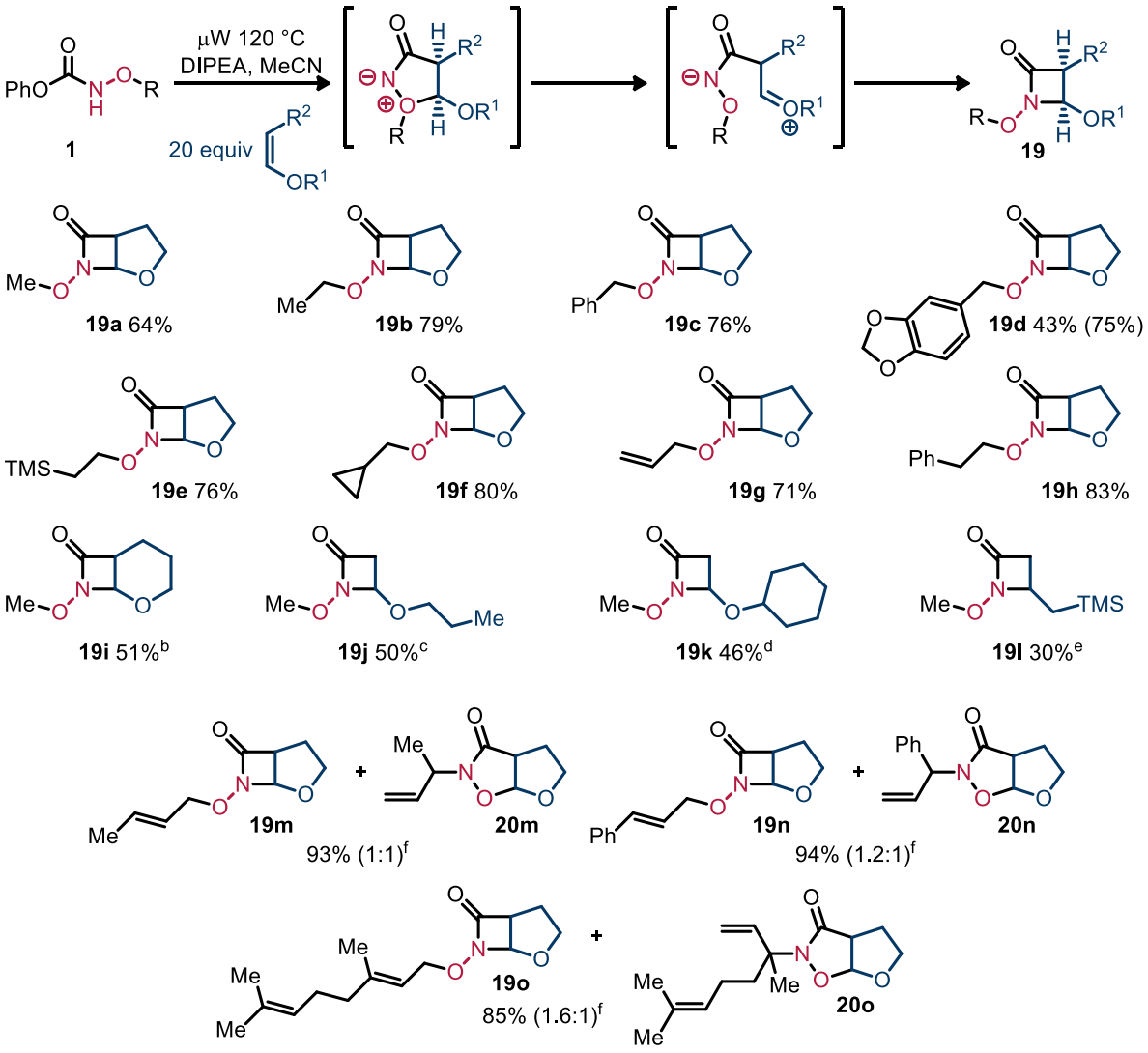


(a) Conditions: alkoxycarbamate **1** (1.0 equiv), alkene (50 equiv) in MeCN (0.2 M), μW 180 °C, 2 h. (b) ^{1}H NMR yield and ratio using 1,3,5-trimethoxybenzene as an internal standard.

With conditions that could enable pathway A (Scheme 2. 22) and B (Scheme 2. 24), efforts were directed to evaluating the scope of pathway C-derived products, the β-lactams (**19**). We hypothesized that the ability to selectively achieve pathway C hinged on stabilizing the carbocation formed as a result of O−C1 cleavage. Efficient and selective generation of β-lactams was optimized at a lower temperature (120 °C) using catalytic *i*-Pr_2NEt (Table 2. 5). Complete suppression of N−O bond cleavage (pathway A), and [2,3]-sigmatropic rearrangement / 1,2-shift (pathway B) was achieved and high yields of β-lactams were obtained (Scheme 2. 25). These products could be used as antibiotic pharmacophores or synthetic building blocks.[118] β-Lactam products were formed in similar yields irrespective of the *O*-isocyanate precursors used (**19a**-**19h**). Larger cyclic enol ethers were also competent reaction partners in higher alkene loadings (**19i**) and cyclic enol ethers can form β-lactams in modest yields (**19j**-**19k**). Preliminary results with allylsilane (30% **19l**) are encouraging for the expansion of this reactivity beyond enol ethers-type substrates. *This portion of the scope was largely completed by me.*

[118] (a) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Rev.* **2007**, *107*, 4437–4492. (b) D'hooghe, M.; Dekeukeleire, S.; Leemans, E.; De Kimpe, N. *Pure Appl. Chem.* **2010**, *82*, 1749-1759. (c) Ombito, J. O.; Singh. G. S. *Mini-Reviews in Organic Chemistry* **2019**, *16*, 544-567.

Scheme 2. 25 *O*-Isocyanate [3+2] cycloaddition/ring opening cascade[a]



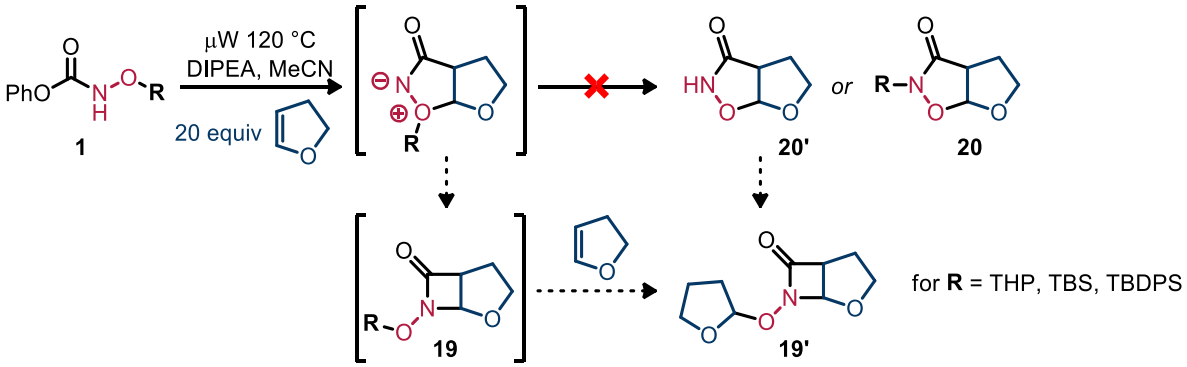
(a) Conditions: alkoxycarbamate **1** (1.0 equiv), alkene (20 equiv), *i*-Pr_2NEt (0.20 equiv) in MeCN (0.2 M), μW 120 °C, 2.5 h. (b) 100 equiv alkene used. (c) 30 equiv alkene used. (d) 10 equiv alkene used. (e) 75 equiv alkene used at 150 °C. (f) ^1H NMR yield using 1,3,5-trimethoxybenzene as an internal standard.

β-Lactams can be formed by [2+2] cycloadditions of isocyanates and enol ethers or enol esters, so it became important to provide evidence for either a [3+2] or [2+2] reaction pathway.[119] In an effort to establish if these reactions operate via thermal [3+2] cycloaddition / ring opening and closing sequence,

[119] a) Łysek, R.; Furman, B.; Cierpucha, M.; Grzeszczyk, B.; Matyjasek, Ł.; Chmielewski, M. *Eur. J. Org. Chem.* **2002**, 2377–2384. (b) Chmielewski, M.; Kałuża, Z.; Furman, B. *Chem. Commun.* **1996**, 2689–2696. (c) Kałuza, Z.; Fudong, W.; Bełzecki, C.; Chmielewski, M. *Tetrahedron Lett.* **1989**, *30*, 5171–5172. (d) De Bernardo, S.; Tengi, J. P.; Sasso, G. J.; Weigele, M. *J. Org. Chem.* **1985**, *50*, 3457–3462.

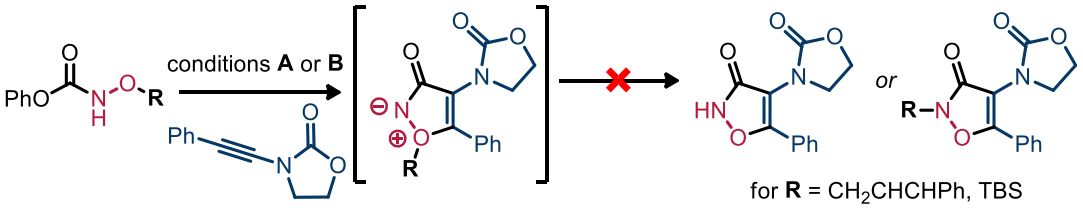
the substrates were modified to undergo rearrangements from the proposed aza-oxonium ylide more readily. Substrates bearing substituted allyl substituents provided mixtures of the [2,3]-sigmatropic rearrangement products (**20**) and β-lactam products (**19**) in an approximately equal ratio, supporting that these reactions likely operate via [3+2] cycloaddition.

Scheme 2. 26 Incompatible R groups for β-lactam synthesis form carbamates



Lastly, silyl- and THP-substituted *O*-isocyanate precursors (**1**) were also used for intermolecular cycloaddition reactions with enol ethers (Scheme 2. 26). Instead of the desilylative isoxazolidinone synthesis observed for norbornene as a dipolarophile or lack of cycloaddition reactivity observed for the THP derivative, all substrates led to a β-lactam **19'**. Interestingly, each reaction formed the β-lactam product that was substituted with dihydrofuran after the optimized 2 h reaction time. This product could be formed via an isoxazolidinone **20'** or β-lactam **19** as shown above.

Scheme 2. 27 Attempts to expand the dipolarophile scope using path B carbamate substrates



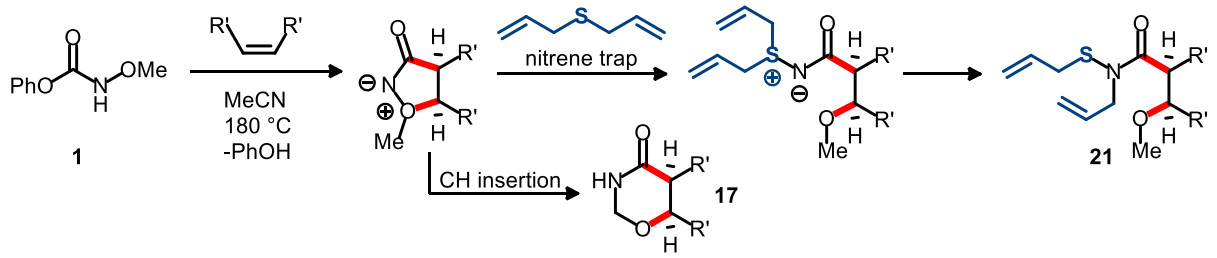
In an attempt to expand the dipolarophiles that could be used for *O*-isocyanate [3+2] cycloaddition, carbamates which had demonstrated the capacity to undergo path B-type reactivity of the aza-oxonium ylide were heated with alkyne-substituted oxazolidinones (Scheme 2. 27). If the acyl nitrene formation and/or C-H insertion were the RDS, then path B reactivity of the aza-oxonium ylide avoids these two steps,

perhaps allowing less favourable cycloaddition reactions to proceed. However, no aromatic product was observed under the above conditions A or B, suggesting that the cycloaddition is still disfavoured.

2.2.3.5 Attempts to Trap Acyl Nitrene Intermediates

Once again for the intermolecular system, an *O*-isocyanate precursor **1aa** was allowed to react with dipolarophiles in the presence of a diallylsulfide nitrene trap (Table 2. 6). When allyl is a substituent of the sulfide trap, a [2,3]-sigmatropic rearrangement could occur to form neutral product **21**.[120] This irreversible intramolecular reaction could feasibly outcompete the intramolecular C-H insertion if the trapping step is fast enough. Unfortunately, however, reactions with 2 or 10 equiv excess of the diallylsulfide trap led to no observed formation of *N*-allyl-*N*-(thio)amide **21** when using norbornene or dihydrofuran as the dipolarophile (entries 1-4).

Table 2. 6 Attempts to trap acyl nitrene for intermolecular *O*-isocyanate cycloaddition reactions[a]



Entry	Alkene (equiv)	Additive equiv	Yield of 21 (%)[b]
1	Norbornene (75)	2	0
2	Norbornene (75)	10	0
3	Dihydrofuran (30)	2	0
9	Dihydrofuran (30)	10	0

(a) Conditions: alkoxycarbamate **1aa** (1.0 equiv), norbornene (75 equiv) in MeCN (0.05 M), μW 180 °C, 2 h or alkoxycarbamate (1.0 equiv), dihydrofuran (30 equiv), *i*-Pr_2NEt (0.20 equiv) in MeCN (0.2 M), μW 120 °C, 2.5 h. (b) ^{1}H NMR yield using 1,3,5-trimethoxybenzene as an internal standard.

Though sulfides and thiols appear to be non-functional acyl nitrene traps for the intramolecular or intermolecular systems, further work using phosphorous of iodine-based traps could be effective. Ideally,

[120] (a) Zhang, Y.; Wang, J. *Coord. Chem. Rev.* **2010**, *254*, 941−953. (b) Armstrong, A.; Challinor, L.; Moir, J. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 5369−5372. (c) Armstrong, A.; Deacon, N.; Donald, C. *Synlett* **2011**, *2011*, 2347−2350. (d) Armstrong, A.; Emmerson, D. P. G.; Milner, H. J.; Sheppard, R. J. *J. Org. Chem.* **2014**, *79*, 3895−3907. (e) Armstrong, A.; Emmerson, D. P. G. *Org. Lett.* **2009**, *11*, 1547−1550. (f) Armstrong, A.; Emmerson, D. P. G. *Org. Lett.* **2011**, *13*, 1040−1043. (g) Armstrong, A.; Challinor, L.; Cooke, R. S.; Moir, J. H.; Treweeke, N. R. *J. Org. Chem.* **2006**, *71*, 4028−4030. (h) Zhang, X.; Lin, B.; Chen, J.; Chen, J.; Luo, Y.; Xoa, Y. *Org. Lett.* **2021**, *23*, 819−825.

a carbamate and/or dipolarophile with some bias against intramolecular C-H insertion reactivity (e.g., phenoxy-carbamate, Scheme 2. 23) could be used to assess this nitrene formation strategy.

2.2.4 Computational Results

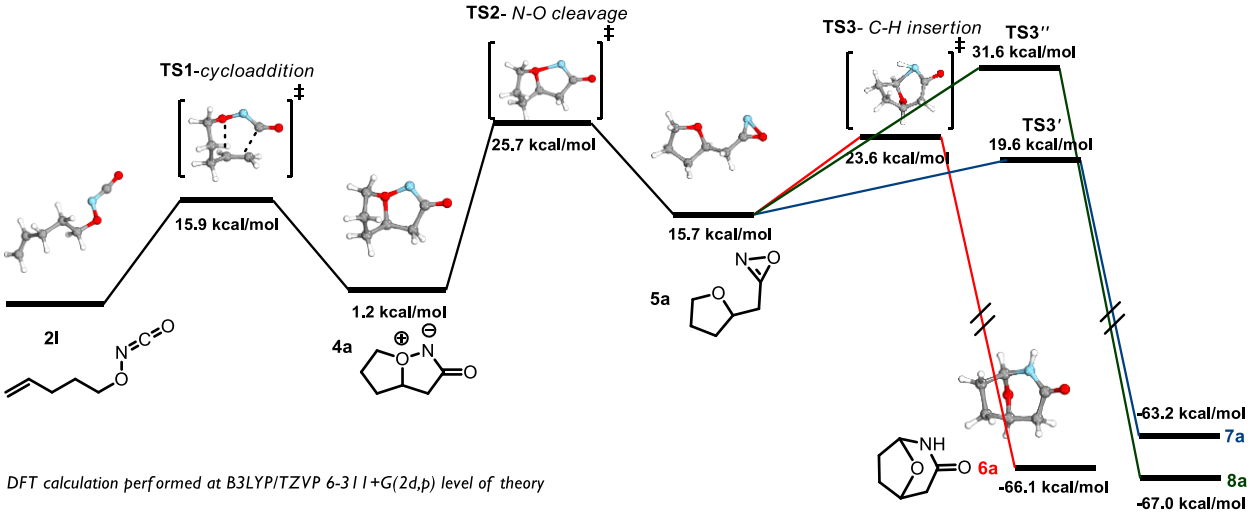
To gain further insight into this reactivity, the [3+2] cycloaddition of *O*-isocyanates was studied by density functional theory (DFT) calculations, largely for the intramolecular system. *This work was initiated by Ryan Ivanovich, then additional contributions were made by me.* Minimal computational work related to the [3+2] cycloadditions of uncharged 1,3-dipole equivalents has been reported previously, apart from the intramolecular cycloaddition of amino-isocyanates.[121] Initial calculations were aimed at probing the reaction mechanism and studying the nature of the cycloaddition transition state structure. The relative energies of intermediates and products, as well as transition states for each step were calculated using the B3LYP functional and the 6-311+G(2d,p) basis set (Figure 2. 2). The B3LYP functional has been previously found to produce results in accordance with experimental trends of *N*-isocyanates.[121]

The deblocking mechanism of the carbamate **1l** was not modelled, though it was determined to be endergonic by 9.1 kcalmol^{-1}. The remainder of the DFT energies listed are relative to the energy of *O*-isocyanate **2l**, not including the PhOH present from deblocking. It is also expected that the stability of several intermediates would also benefit from hydrogen bonding, but this was not explored computationally. The cycloaddition was found to have a transition state energy of +15.9 kcalmol^{-1} (**TS1**). Interestingly, the expectedly unstable aza-oxonium ylide cycloadduct **2a** is only +1.2 kcalmol^{-1}, likely owing to the instability of *O*-isocyanates, highlighting the importance of controlled in-situ formation from blocked precursors. On a broader scale, it can be reasoned that the use of an unstable heterocumulene allows this cycloaddition (**TS1**) to be thermodynamically feasible. The N-O bond cleavage of aza-oxonium ylide **4a** to form the acyl nitrene **5a** (**TS2**) was found to have the highest transition state energy (ΔG‡ = +21.5 kcalmol^{-1}). The nitrene C-H insertion to form the major product requires +23.6 kcalmol^{-1} (**TS3**) and is highly exergonic (-66.1 kcalmol^{-1}). The reason for the product distribution of lactam isomer **6**-**8** remains unclear after DFT analysis of nitrene C-H insertion transition state energies (**TS3**, **TS3'**, **TS3''**). The large differences in all three TS energies (+19.6 kcalmol^{-1}, +23.6 kcalmol^{-1}, and +31.6 kcalmol^{-1}) do not seem to

[121] Roveda, J. G.; Clavette, C.; Hunt, A. D.; Gorelsky, S. I.; Whipp, C. J.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2009**, *131*, 8740-8741.

correspond to the observed experimental ratio of 1:14:3. Further computational optimization is required to determine how to best explain and predict C-H insertion selectivity for various *O*-isocyanate substrates.

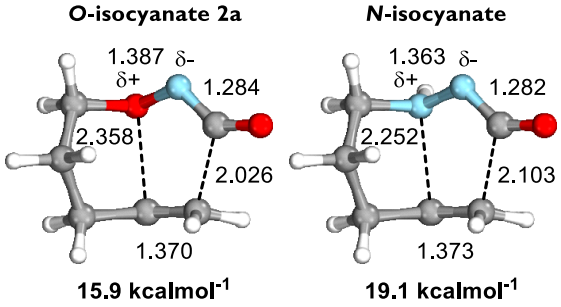
Figure 2. 2 DFT calculations for *O*-isocyanate **2l** intramolecular alkene cycloaddition



The nature of the O-isocyanate cycloaddition transition state structure was then analyzed and compared to known charged and uncharged dipolar cycloadditions. The calculated *O*-isocyanate cycloaddition transition state is highly similar to the analogous structure at the amino-isocyanate cycloaddition transition state (Figure 2. 3).[121] Both cycloadditions are concerted, though asynchronous in favour of C-C bond formation suggesting a LUMO-controlled cycloaddition. The *O*-isocyanate cycloaddition is calculated to be more asynchronous than that of the amino-isocyanate, which could be caused by the more electronegative oxygen atom, lowering the LUMO further. While many conventional charged 1,3- dipoles (e.g. nitrones) have concerted, but asynchronous cycloaddition transition state structures, this feature is exaggerated in the studied heteroatom-substituted isocyanates.[122]

[122] Xu, L.; Doubleday, C. H.; Houk, K. N. *J. Am. Chem. Soc.* **2010**, *132*, 3029-3037.

Figure 2. 3 Cycloaddition transition state structures of *O*-isocyanate **2l** in comparison to *N*-isocyanates (distance in Angstroms, energy vs. free isocyanate)



Overall, *O*-isocyanate [3+2] cycloaddition reactivity appears to be type III (LUMO-controlled).[97] The only other exclusively LUMO-controlled 1,3-dipoles are ozone and nitrous oxide, both of which only under intermolecular cycloadditions, forming unstable intermediates (molozonide and 4,5-dihydro[1,2,3]oxadiazole respectively) while many other 1,3-dipolar cycloaddition cycloadducts are highly stable. This outcome could be caused by the inclusion of weak heteroatom-heteroatom bonds in the starting dipole. It appears that choosing an unstable heterocumulene dipole equivalent with heteroatom-heteroatom bonds, such as an *O*-isocyanate, allowed for a similarly low-lying LUMO and analogous cycloadduct reactivity.

2.3 Attempts for Activation and Catalysis

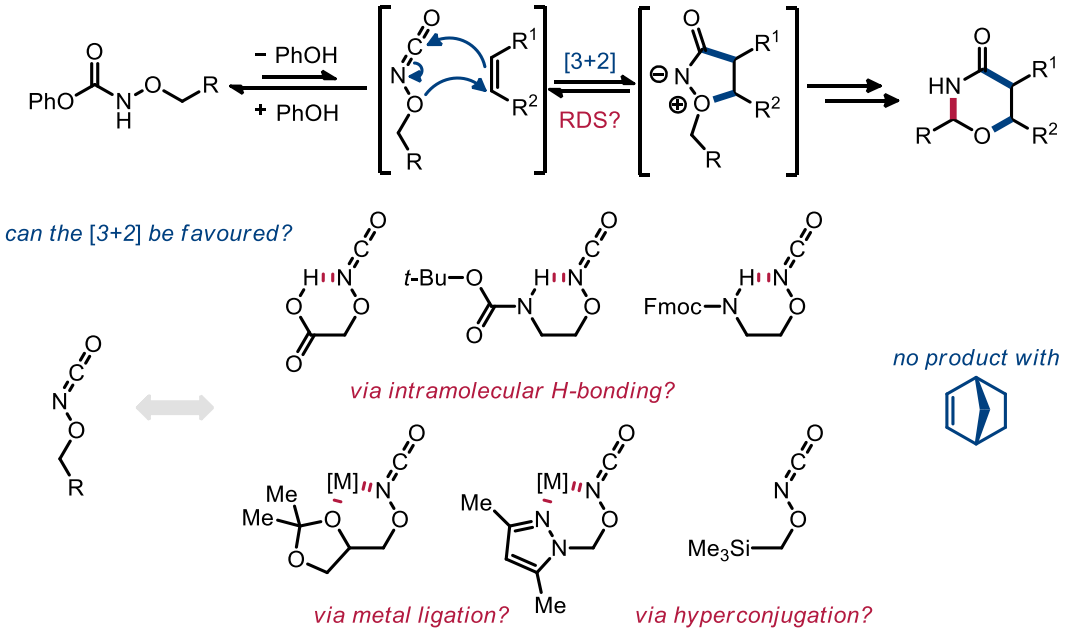
With the cycloaddition reactivity of *O*-isocyanates clearly limited to minimally synthetically applicable examples, alternative modes of activation and catalysis were sought. Intermolecular dipolarophiles were particularly limited, so two main strategies were devised to improve initial cycloaddition reactivity: (1) *O*-isocyanate activation enabled by tethered functional groups and (2) Lewis acid activation.

2.3.1 *O*-Isocyanate Activation

Specific functional groups tethered to the isocyanate could feasibly interact with the isocyanate N enough to stabilize its developing negative charge during the cycloaddition step. These groups could also be electron-withdrawing, potentially decreasing the energy of the LUMO. Activation of *O*-isocyanates via intramolecular H-bonding was first attempted (Scheme 2. 28). Carboxylic acid and carbamates were incorporated accordingly to form a six-membered intramolecular H-bond, however, no cycloaddition products were observed under a variety of reaction conditions with norbornene. It is possible that the increased electron-withdrawing nature of these substituents destabilized the aza-oxonium ylide enough to prevent efficient reactivity. It is also possible that the nitrene formation and C-H insertion, as later

calculated to have energies at either TS, were still too high in energy to be achieved under the attempted conditions.

Scheme 2. 28 Substrates attempted for intramolecular *O*-isocyanate activation



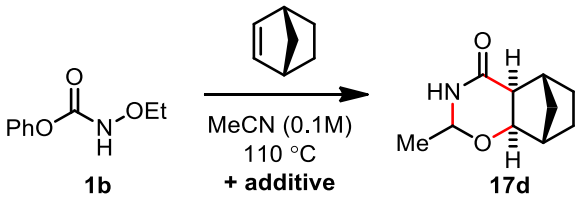
Next, substrates with Lewis basic atoms that could participate in the two-point biding of Lewis acidic metals with the isocyanate nitrogen were also used under several reaction conditions with norbornene as a dipolarophile. Several metals were found to have no effect on the reaction yield or temperature, suggesting that metal ligation was either not occurring or it was not helpful towards the cycloaddition. Lastly, the hyperconjugative stabilization of a β-positive center by silicon was tested by using an appropriate carbamate precursor. While the 2-(trimethylsilyl)ethanol homolog leads to excellent cycloaddition reactivity (Scheme 2. 22, Scheme 2. 25), this (trimethylsilyl)methanol derivative led to no observed cycloaddition products. Substrate modification appeared to have only detrimental effects on [3+2] cycloaddition reactivity, so another strategy, Lewis acid catalysis, was prioritized.

2.3.2 Lewis Acid Catalysis

Efforts to improve and expand the [3+2] cycloaddition reactivity of *O*-isocyanates were also directed towards Lewis acid activation. A Lewis acid could hypothetically decrease the LUMO of the reactive *O*-isocyanate further to allow for less bias alkene or alkyne dipolarophile substrates to react efficiently. This

is a distinct mode of Lewis acid activation in comparison to other [3+2] cycloadditions, which are more commonly HOMO-controlled, so the dipolarophile interacts with the Lewis acid.[123]

Table 2. 7 Additive screening for intermolecular *O*-isocyanate cycloaddition with norbornene[a]



1b **17d**

Entry	Additive (equiv)	Conv. to PhOH (%)[b]	Yield 17d vs. PhOH (%)	Yield 17d vs. TMB (%)[b]
1	None	4	0	-
2	$Al(OTf)_3$ (0.2)	100	15	-
3	$Cu(OTf)_2$ (0.2)	35	0	-
4	$FeCl_3$ $6H_2O$ (0.2)	100	0	-
5	$Mg(OTf)_2$ (0.2)	100	42	-
6	$Sc(OTf)_3$ (0.2)	100	0	-
7	$ZnCl_2$ (0.2)	100	40	-
8	$MgCl_2$-$6H_2O$ (0.2)	62	48	18
9	$Mg(OAc)_2$-$4H_2O$ (0.2)	75	76	20
10	MgI_2 (0.2)	100	0	0
11	$Zn(OAc)_2$ (0.2)	100	39	26
12	$Zn(OTf)_2$ (0.2)	100	14	7
13	$Zn(OH)_2$ (0.2)	77	61	26
14	ZnI_2 (0.2)	53	0	0
15	$ZnSO_4$-$7H_2O$ (0.2)	0	0	0
16	$MgCl_2$-$6H_2O$ (1.1)	27	15	4
17	$Mg(OAc)_2$-$4H_2O$ (1.1)	26	23	6
18	$Zn(OAc)_2$ (1.1)	93	10	8
19	$Zn(OH)_2$ (1.1)	96	26	23
20	$CaCl_2$ (1.1)	36	0	0

(a) Conditions: ethoxycarbamate **1b** in MeCN (0.05 M), then norbornene (75 equiv) added, then additive added, stirred at 110 °C, 16 h. (b) ^{1}H NMR yield using 1,3,5-trimethoxybenzene as an internal standard.

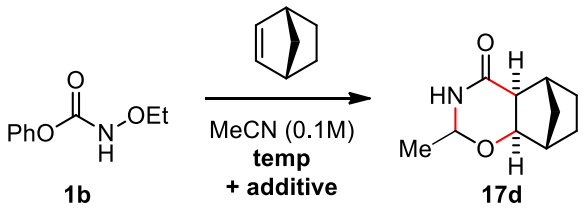
A large screen of Lewis acids demonstrated no beneficial effects related to the Lewis acidity of the additive, but rather likely from the Brønsted basicity or acidity, helping to favour the *O*-isocyanate deblocking equilibrium (Table 2. 7). Both catalytic (entries 2-15) and stoichiometric (entries 16-20) quantities of various Lewis acidic additives led to low yields of oxazinanone **17d** (0-26%).

Further screening of mostly metal oxides led to improved yields (0-55%), though these results were found to be poorly reproducible (Table 2. 8). High conversion of the carbamate to phenol was often observed at

[123] Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2015**, *115*, 5366–5412.

110 ˚C (entries 8-22), however, higher catalyst loading did not lead to improved yields and also led to lower conversion (entries 12, 17-19). This observation does not support the hypothesis that the additive (SiO_2) is catalyzing deblocking since a higher conversion with more degradation would be expected with the addition of more catalyst. The inconsistencies in the screening results may be related to uneven heating in the oil bath.

Table 2. 8 Additional additive screening for intermolecular *O*-isocyanate cycloaddition with norbornene[a]



1b **17d**

Entry	Additive (equiv)	Temp (°C)	Conv. to PhOH (%)[b]	Yield 17d vs. TMB (%)[b]
1	$MgCl_2$-$6H_2O$ (0.2)	90	7	0
2	$Mg(OAc)_2$-$4H_2O$ (0.2)	90	6	0
3	$Mg(OTf)_2$ (0.2)	90	7	0
5	$Zn(OAc)_2$ (0.2)	90	32	2
6	$Zn(OH)_2$ (0.2)	90	38	2
7	$ZnCl_2$ (0.2)	90	86	9
8	MgO (0.2)	110	68	22
9	ZnO (0.2)	110	72	44
10	Mg (0.2)	110	43	26
11	Al_2O_3 (0.2)	110	78	trace
12	SiO_2 (0.2)	110	96	55
13	MnO_2 (0.2)	110	92	46
14	CuO (0.2)	110	65	30
15	CaO (0.2)	110	82	25
16	Cu_2O (0.2)	110	65	14
17	SiO_2 (0.5)	110	13	4
18	SiO_2 (1.0)	110	18	4
19	SiO_2 (5.0)	110	24	0
20	Ag_2O (0.2)	110	47	10
21	FeS (0.2)	110	38	13
22	La_2S_3 (0.2)	110	8	trace
23	S_2W (0.2)	110	trace	0
24	ZnS (0.2)	110	0	0

(a) Conditions: ethoxycarbamate **1b** in MeCN (0.05 M), then norbornene (75 equiv) added, then additive added, stirred at given temp, 16 h. (b) ^{1}H NMR yield using 1,3,5-trimethoxybenzene as an internal standard.

While Lewis acid activation of O-isocyanate cycloaddition does not appear to function under the current conditions, these results do potentially support the use of inorganic base catalysis for isocyanate deblocking.

2.4 Conclusion

The recently discovered [3+2] cycloaddition reactivity of *O*-isocyanates has led to numerous novel reactions of the previously undescribed aza-oxonium ylide cycloadduct. The blocking group strategy described in section 2.1 demonstrates the importance of controlled concentrations of the highly reactive free *O*-isocyanates, deblocked from carbamate precursors. This work also allowed amines to be used as nucleophiles for the substitution of *O*-isocyanates, forming *N*-oxyureas products efficiently and safely. Intramolecular cycloadditions demonstrated the reactivity with simple alkenes and a cascade C-H insertion to form lactam isomers. Intermolecular cycloadditions highlighted the divergent reactivity of the novel aza-oxonium ylide cycloadducts, leading to the formation of three distinct heterocycles: oxazinanones, isoxazolidinones, and β-lactams. Efforts to trap the acyl nitrene intermediate have not yet proved fruitful and various strategies to improve the cycloaddition cascades have failed. Computational results suggest that C-H insertion, rather than cycloaddition or N-O bond cleavage, is the RDS, so further work on acyl nitrene trapping is warranted. The synthetic efficiency of this alkene oxy-carbonylation process would benefit from milder, controlled reactivity of aza-oxonium ylides. DFT results also established that a concerted and asynchronous cycloaddition pathway is likely, as was reported for *N*-isocyanates as well. This research involving charged hydroxylamine-containing intermediates also allowed for the reinvestigation of Cope-type hydroamination of alkenes to begin, starting with *N*-oxyureas as substrates.

Chapter 3 Cope-Type Hydroamination

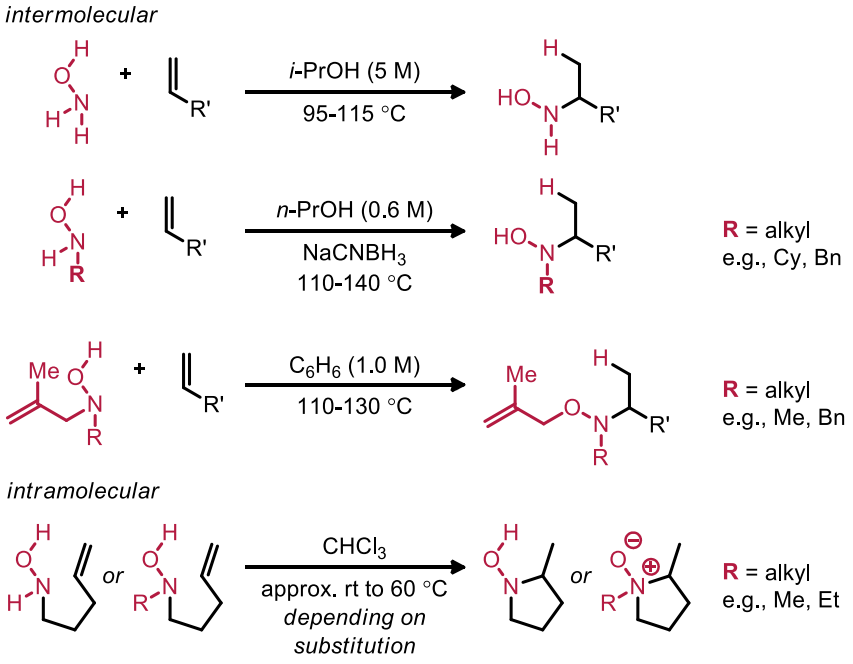
Within this chapter, the discovery and work exploring the Cope-type hydroamination of N-hydroxyureas, the redox-enabled intramolecular hydroamination of alkenes, and significant solvent and substitution effects on the stability of alkyl and enamine N-oxides are disclosed. This chemistry is significant for the synthesis of biologically relevant acyclic amines and pyrrolidines. Literature background, key synthetic findings, and ongoing work are included. The research within this chapter was completed in a collaborative manner with various junior colleagues and Ryan Ivanovich. Refer to Statement of Contributions *for more details.*

3.1 Intramolecular *N*-Oxyurea Hydroamination

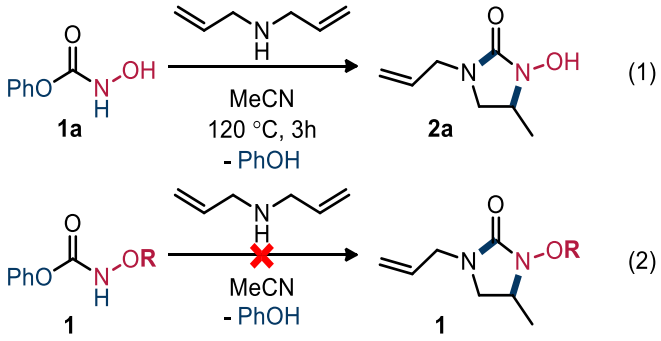
3.1.1 Background

Though a variety of unsubstituted, primary, and alkyl-substituted secondary hydroxylamines have been reported to undergo intermolecular and intramolecular Cope-type hydroamination (see section 1.3.3.3), no *N*-acyl variant had known Cope-type reactivity (Scheme 3. 1). An important FMO interaction for Cope-type hydroamination is the $HOMO_{(hydroxylamine)} \rightarrow LUMO_{(alkene)}$, so reducing the electronic density on nitrogen through resonance into an acyl substituent would likely reduce the reactivity.[87b]

Scheme 3. 1 Reported conditions and hydroxylamine substitution for Cope-type hydroamination

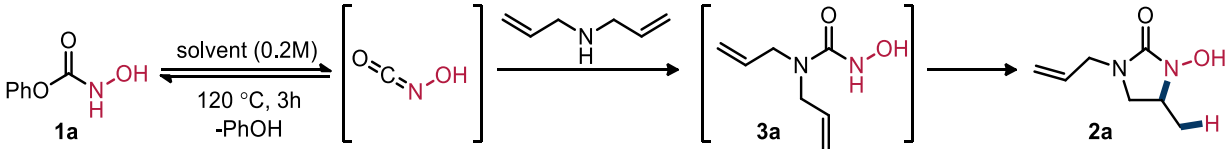


The cascade substitution then cyclization observed by Ryan Ivanovich in 2016 when diallylamine was mixed with hydroxycarbamate **1a** was therefore unexpected (eq 1). After 3 h of microwave irradiation at 120 °C, cyclic *N*-oxyurea **2a** isolated from the reaction mixture. This preliminary finding was considered to proceed though Cope-type hydroamination when it was observed that alkoxycarbamates **1** did not undergo the same reaction (eq 2).



Initial optimization efforts by Ryan Ivanovich focused on solvent effects, which are known to have a large impact on Cope-type hydroamination (Table 3. 1).[87] It was found that polar solvents worked best for the cascade substitution and Cope-type hydroamination process (entries 1-5). Reaction temperatures above the boiling points of the solvents employed could be attained due to the sealed vial used in the microwave apparatus. Further optimization was required at this point to assess the effects of other solvents, temperature, reaction time, and additives.

Table 3. 1 Initial results of cascade substitution/hydroamination from Ryan Ivanovich[a]



Entry	Solvent	Conv. to 2a vs. PhOH (%)[b]
1	$CDCl_3$	29
2	*i*-PrOH	40
3	*t*-BuOH	26
4	MeCN	35
5	$PhCF_3$	12

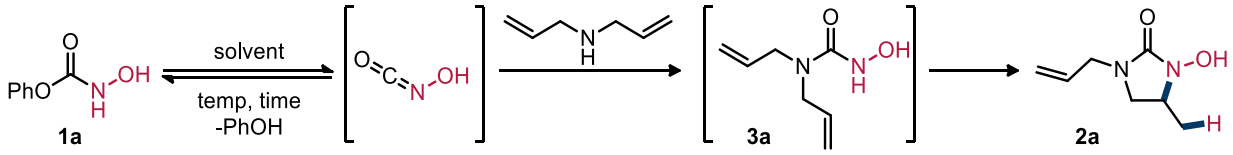
(a) Phenyl *N*-hydroxycarbamate **1a** (1.0 equiv), diallylamine (1.0 equiv) in solvent (0.2 M), μW 120 °C, 3 h. (b) ^{1}H NMR conversion of **2a** using PhOH released from **1a** as an internal standard.

3.1.2 Optimization and Additive Effects

First, the effects of solvent, temperature, time were assessed (Table 3. 2). Increasing the reaction temperature from 120 °C to 140 °C led to a higher yield of cyclic *N*-oxyurea **2a** (entry 1). Increasing the

reaction time from 3 h to 6 h (entry 2) or 9 h (entry 3) also led to higher yields, though with diminishing benefits at 9 h. Lowering the concentration to favour the second intramolecular step had minimal effect on the yield (entry 4), so 0.2 M was used as the concentration going forward. A more hindered alcohol solvent, *t*-BuOH, led to similar observed yields of *N*-oxyurea **2a**. A variety of aprotic solvents were then tried (entries 7-11). High polarity appeared to be important for the desired reactivity, though no aprotic solvent tested worked as well as *i*-PrOH or *t*-BuOH. Heating to 160 °C with *i*-PrOH or *t*-BuOH for 3 h did not have a large impact of the observed yield (entries 12-13). Notably, at temperatures above 140 °C, small amounts of substitution occur with *i*-PrOH as the nucleophile. However, testing polar aprotic EtOAc at this temperature led to an improved 66% yield over just 1 h (entry 14).

Table 3. 2 Initial optimization of solvent, temperature, and reaction time[a]



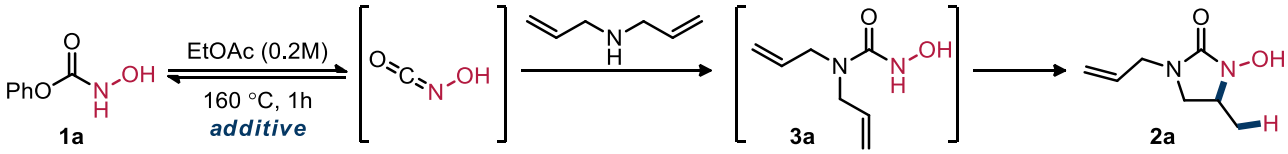
Entry	Solvent (M)	Temp (°C)	Time (h)	Conv. to 2a vs. PhOH (%)[b]
1	*i*-PrOH (0.2)	140	3	49
2	*i*-PrOH (0.2)	140	6	61
3	*i*-PrOH (0.2)	140	9	66
4	*i*-PrOH (0.05)	140	3	46
5	*t*-BuOH (0.2)	140	3	54
6	*t*-BuOH (0.2)	140	6	59
7	THF (0.2)	140	3	39
8	$PhCF_3$ (0.2)	140	3	29
9	MeCN (0.2)	140	3	47
10	benzene (0.2)	140	3	15
11	DCE (0.2)	140	3	34
12	*i*-PrOH (0.2)	160	3	53
13	*t*-BuOH (0.2)	160	3	61
14	EtOAc (0.2)	160	1	66

(a) Phenyl *N*-hydroxycarbamate **1a** (1.0 equiv), *N*,*N*-diallylamine (1.0 equiv) in solvent, μW given temperature and time. (b) ^{1}H NMR conversion of **2a** using PhOH released from **1a** as an internal standard.

Noting the large additive effect previously observed for intermolecular Cope-type hydroamination, a screen of basic, acidic, hydrogen-bonding, and nucleophilic additives was conducted (Table 3. 3).[87a] Basic additives could aid in the deblocking step of the sequence (isocyanate formation), however, no effect was observed when using *i*-Pr_2NEt (entry 2) and negative effects were observed when using the stronger base, DBU (entries 3-4). Hydrogen-bonding or acidic additives could feasibly disrupt the intramolecular hydrogen-bonding of the *N*-hydroxyurea intermediate **3a**.[34] Though, using $NaCHBH_3$ which has been beneficial in earlier hydroamination studies, the desired reactivity was almost completely inhibited (entry

5).[87a] Other hydrogen-bonding additives tried also had neutral or negative effects on the yield of *N*-oxyurea **2a** (entries 6-8). Using 1 equivalent of $TfNH_2$ led to a higher yield of the cascade reaction product **2a** (entry 9). Other equivalents of this additive were tested, and 0.5 equivalents was the lowest amount tested that led to similar reactivity (entries 10-14). This additive could be helping the hydroamination step via hydrogen-bonding or by acid catalysis.

Table 3. 3 Additive survey for cascade substitution/hydroamination[a]

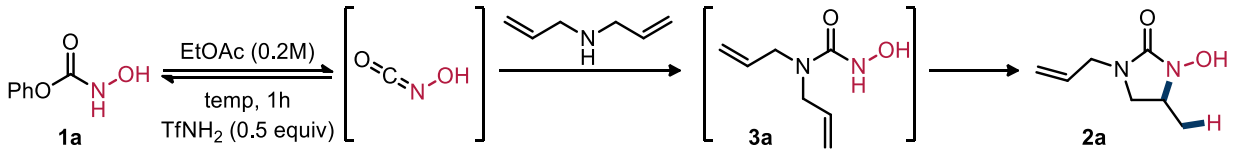


Entry	Additive (equiv)	Conv. to 2a vs. PhOH (%)[b]
1	-	66
2	*i*-Pr_2NEt (0.05)	63
3	DBU (0.25)	6
4	DBU (1.0)	0
5[c]	$NaCNBH_3$ (1.0)	4
6	*N*,*N*-diphenylurea (1.0)	17
7	Tf_2NH (1.0)	18
8	$TsNH_2$ (1.0)	66
9	$TfNH_2$ (1.0)	77
10	$TfNH_2$ (0.1)	71
11	$TfNH_2$ (0.25)	73
12	**$TfNH_2$ (0.5)**	**78**
13	$TfNH_2$ (1.5)	70
14	$TfNH_2$ (2.0)	65
15	Nitroaniline (1.0)	64

(a) Phenyl *N*-hydroxycarbamate **1a** (1.0 equiv), diallylamine (1.0 equiv) in EtOAc (0.2 M), μW 160 °C, 1 h. (b) ^1H NMR conversion to **2a** using PhOH released from **1a** as an internal standard. (c) *i*-PrOH used as solvent. Tf = trifluoromethanesulfonyl; Ts = *p*-toluenesulfonyl.

Nucleophilic additives could be useful in the initial substitution step to reduce the concentration of reactive free isocyanate, as reported in previous related work with amino-isocyanates.[108] In this case, 4-nitroaniline was found to have no effect on the reaction sequence (entry 15). The hydrogen-bonding additive, $TfNH_2$, therefore appeared to be the best option for the desired reactivity, though the required temperature for efficient reactivity was possibly different using this additive, so temperature was revaluated (Table 3. 4). Higher temperatures were still required for adequate substitution reactivity, as suggested by the phenol formation observed (entries 1-5), and 175 °C was optimal for the substitution and Cope-type hydroamination reactivity (entry 5).

Table 3. 4 Temperature requirements for hydroamination[a]

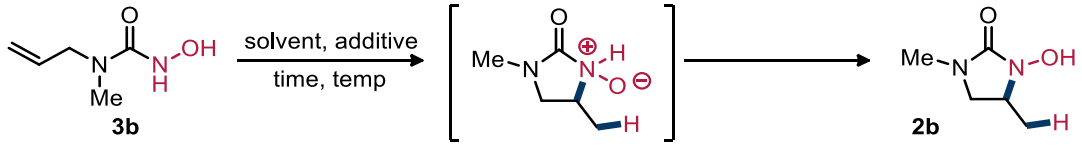


Entry	Temp (°C)	PhOH formation (%)[b]	Yield of 2a (%)[b]
1	75	25	0
2	100	51	0
3	125	86	trace
4	150	100	28
5	175	100	60

(a) Phenyl *N*-hydroxycarbamate **1a** (1.0 equiv), diallylamine (1.0 equiv), $TfNH_2$ (0.5 equiv) in EtOAc (0.2 M), μW given temperature, 1 h. (b) ^1H NMR yield of **2a** using 1,3,5-trimethoxybenzene as an internal standard.

With these conditions optimized for the sequential substitution and elimination, the effects of solvents, temperature, time, and additives on the Cope-type hydroamination step alone were studied (Table 3. 5). Using the substitution product of *N*-methylallylamine and phenyl *N*-hydroxycarbamate **1a**, *i*-PrOH, *t*-BuOH, and EtOAc were tested with and without $TfNH_2$ as an additive (entries 1-6). Interestingly, $TfNH_2$ was found to decrease the yield of cyclic *N*-oxyurea **2b** when using alcohol solvents but increase the yield when using EtOAc. This observation could be explained by the hydrogen-bonding abilities of the alcohol solvents either preferentially interacting with the additive or with the substrate. The addition of one equivalent of phenol, which would presumably be present in the cascade variant of this reaction, led to a similar increase in yield as observed with $TfNH_2$ as an additive (entry 7). A combination of $TfNH_2$ and various substituted phenols was therefore tried (entries 8-13). An increase in yield was observed when these additives were used together (entry 8), however, no additional benefit was observed from increased temperature (entry 9) or phenol (entry 10), or by using substituted phenols (entries 11-13). The use of other alcohols in place of phenol led to similar observed yields (entries 14-15), though thiophenol was not an suitable replacement (entry 16). The alcohols and thiophenol have significantly different steric environments and pK_a values than phenol, though only the alcohols promote the desired reaction. The released blocking group, phenol, might play a role in hydrogen bonding or stabilizing any *O*-isocyanate that reforms under the reaction conditions via nucleophilic attack. Overall, these hydroamination studies using the *N*-oxyurea did not lead to any changes in the conditions used for the cascade reaction.

Table 3. 5 Optimization of conditions for the Cope-type hydroamination of *N*-oxyureas[a]



Entry	Solvent	Additive(s) (equiv)	Temp (°C)	Time (h)	Yield of 2b (%)[b]
1	*i*-PrOH	-	160	3	64
2	*i*-PrOH	$TfNH_2$ (0.5)	160	3	60
3	*t*-BuOH	-	160	3	52
4	*t*-BuOH	$TfNH_2$ (0.5)	160	3	47
5	EtOAc	-	175	1	32
6	EtOAc	$TfNH_2$ (0.5)	175	1	40
7	EtOAc	PhOH (1.0)	175	1	41
8	EtOAc	$TfNH_2$ (0.5), PhOH (1.0)	160	1	54
9	EtOAc	$TfNH_2$ (0.5), PhOH (1.0)	180	1	57
10	EtOAc	$TfNH_2$ (0.5), PhOH (2.0)	160	1	54
11	EtOAc	$TfNH_2$ (0.5), *o*-BrC_6H_4OH (1.0)	160	1	54
12	EtOAc	$TfNH_2$ (0.5), *p*-$CF_3C_6H_4OH$ (1.0)	160	1	44
13	EtOAc	$TfNH_2$ (0.5), BHT (1.0)	160	1	50
14	EtOAc	$TfNH_2$ (0.5), *t*-BuOH, (1.0)	160	1	47
15	EtOAc	$TfNH_2$ (0.5), HFIP (1.0)	160	1	50
16	EtOAc	$TfNH_2$ (0.5), PhSH (1.0)	160	1	29

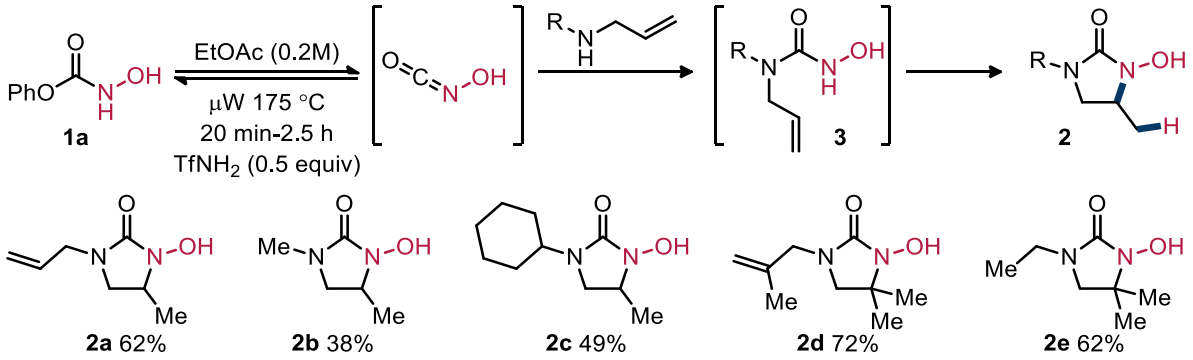
(a) *N*-Oxyurea **3b** (1.0 equiv), additive(s), in solvent (0.2 M), μW given temperature and time. (b) ^{1}H NMR yield of **2b** using 1,3,5-trimethoxybenzene as an internal standard.

3.1.3 Results and Limitations

The scope of this cascade reaction was then evaluated using several allylamines (Scheme 3. 2). The isolated yield of cyclic *N*-oxyurea **2a** after column chromatography using *N*,*N*-diallylamine was good (62%), though it was lower than the ^{1}H NMR yield (78%) due to the product's high affinity to silica gel. Using other substituted allylamines, the yield of *N*-oxyurea isolated was lower (**2b**-**2c**). The methylamine variant (**2b**) likely suffers from a low concentration of the reactive conformer due to hindered rotation of the urea, while the cyclohexylamine variant (**2c**) plausibly has a less favourable amine addition or increased reversibility due to the increased steric bulk of the cyclohexyl substituent.[124] Allylamines with proximal substitution led to improved yields of cyclic *N*-oxyurea product (**2d**-**2e**), as observed in previous Cope-type hydroamination studies.[85]

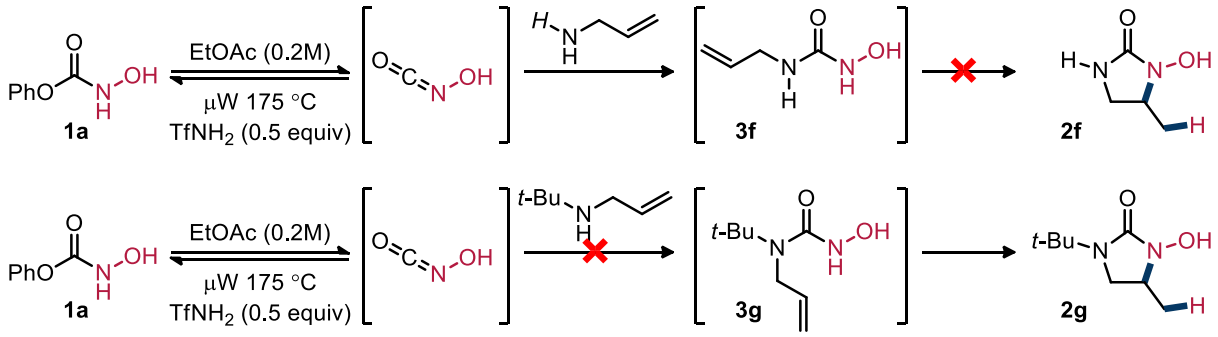
[124] Hutchby, M.; Houlden, C. E.; Haddow, M. F.; Tyler, S. N. G.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *Angew. Chem. Int. Ed.* **2012**, *51*, 548-551.

Scheme 3. 2 Scope of cascade substitution/hydroamination using *O*-isocyanate precursors



Primary allylamine and *t*-butylallylamine did not undergo the desired reaction using the optimized conditions (Scheme 3. 3). While the initial substitution step is feasible for allylamine, the reactive conformer of acyclic *N*-oxyurea **3f** is likely minimally present, again due to hindered rotation of the urea. The large *t*-butyl substituent likely prevents or disfavours the initial substitution step from occurring, leading to degradation of the sample after 1 h at 175 °C.[124]

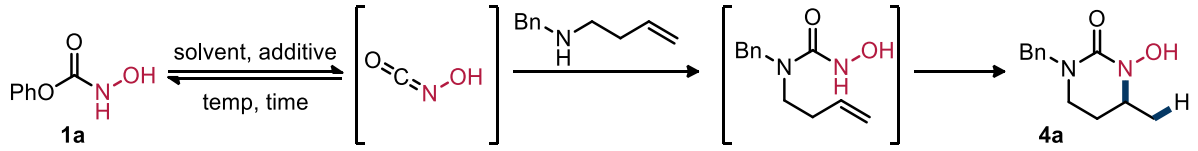
Scheme 3. 3 Reaction scope limitations for the cascade substitution/hydroamination using *O*-isocyanate precursors



After observing some successful reactivity to form 5-membered cyclic *N*-oxyureas **2**, homologous amines were used under similar conditions to form the 6-membered analogues (**4**) (Table 3. 6). Using the previously optimized conditions with *N*-benzyl-3-butenamine, only 19% of the desired product **4a** was observed (entry 1). Using other polar solvents at 160 °C led to no significant change in yield (entries 2-3). Removing the $TfNH_2$ additive also had no effect, forming the same amount of cyclic *N*-oxyurea **4a** after 1 or 3 h (entries 4-5). Lowering the temperature used with EtOAc as the solvent led to a similar yield after 1 h (entry 6), though a higher yield was observed after 3 h (entry 7). Unfortunately, the reaction mixture contained no starting materials after 3 h, so 32% was the maximum possible conversion under these

conditions. The optimization of this process was not continued after these unsuccessful preliminary optimization efforts.

Table 3. 6 Optimization of the cascade substitution/hydroamination using 3-buten-1-amines[a]



Entry	Solvent	Additive (equiv)	Temp (°C)	Time (h)	Yield of 4a (%)[b]
1	EtOAc	$TfNH_2$ (0.5)	175	1	19
2	*i*-PrOH	$TfNH_2$ (0.5)	160	1	24
3	MeCN	$TfNH_2$ (0.5)	160	3	18
4	MeCN	-	160	1	17
5	MeCN	-	160	3	17
6	EtOAc	$TfNH_2$ (0.5)	160	1	21
7	EtOAc	$TfNH_2$ (0.5)	160	3	32

(a) Phenyl *N*-hydroxycarbamate **1a** (1.0 equiv), *N*-benzylbut-3-en-1-amine (1.0 equiv), additive in solvent (0.2 M), μW given temperature and time. (b) ^{1}H NMR yield of **4a** using 1,3,5-trimethoxybenzene as an internal standard.

The studies on cascade *O*-isocyanate substitution and Cope-type hydroamination served to highlight the significant solvent and alkene substitution effects on Cope-type hydroamidation reactivity. Additionally, the high reaction temperatures and amine substitution limitations demonstrate the challenges associated with using *N*-oxyureas, and likely other related *N*-acyl hydroxylamines, for Cope-type hydroamination reactions. The reduced electron density on nitrogen and the hindered rotation both plausibly reduce the hydroamination reactivity. Though hydroxylamine substitution appears to be a limitation for Cope-type hydroamination applicability due to the commercial availability and oxidative degradation of substrates, *N*-acyl substitution of hydroxylamines is not a feasible solution as demonstrated through these studies.

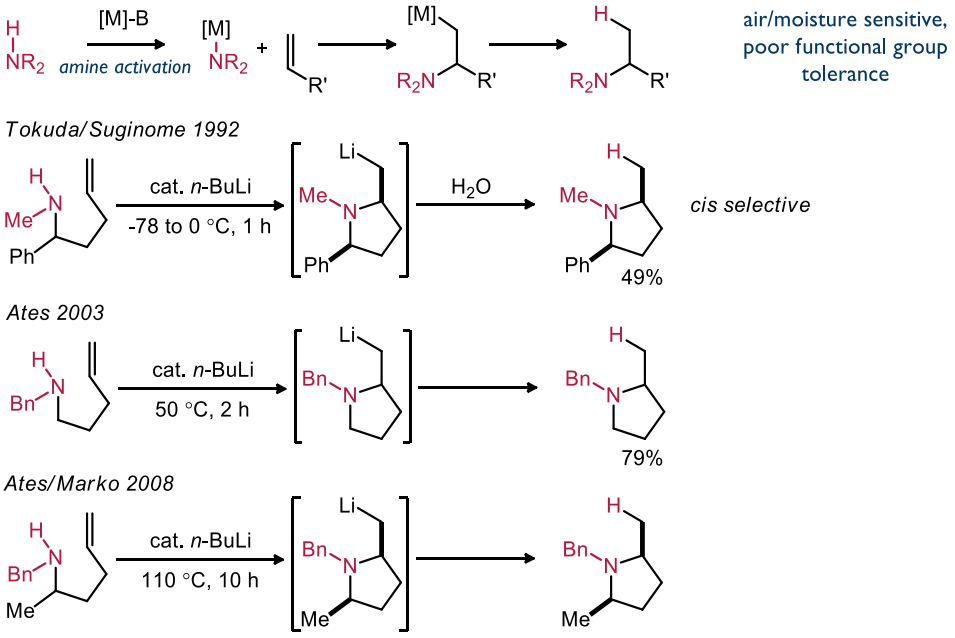
3.2 Intramolecular Redox-Enabled Hydroamination

3.2.1 Reaction Design and Related Methodology

3.2.1.1 Pyrrolidine Synthesis using Catalysis

Pyrrolidines are an important heterocycle for medicinal chemistry and can be synthesize in highly atom economical method by hydroamination.[3] Strong bases can catalyze hydroamination by deprotonation of the amine to the corresponding amide (Scheme 3. 4). After cyclization, the resulting carbanion can then deprotonate another amine, forming a new amide. The first example of base catalysis for the intramolecular hydroamination of non-activated alkenes was reported by Tokuda and Suginome in 1992. Secondary amines and *n*-BuLi are most commonly reported as effective reagents for this method and moderate diastereoselectivity has been reported for 2,5-disubstituted pyrrolidines.[125]

Scheme 3. 4 General mode of base catalyzed hydroamination and examples

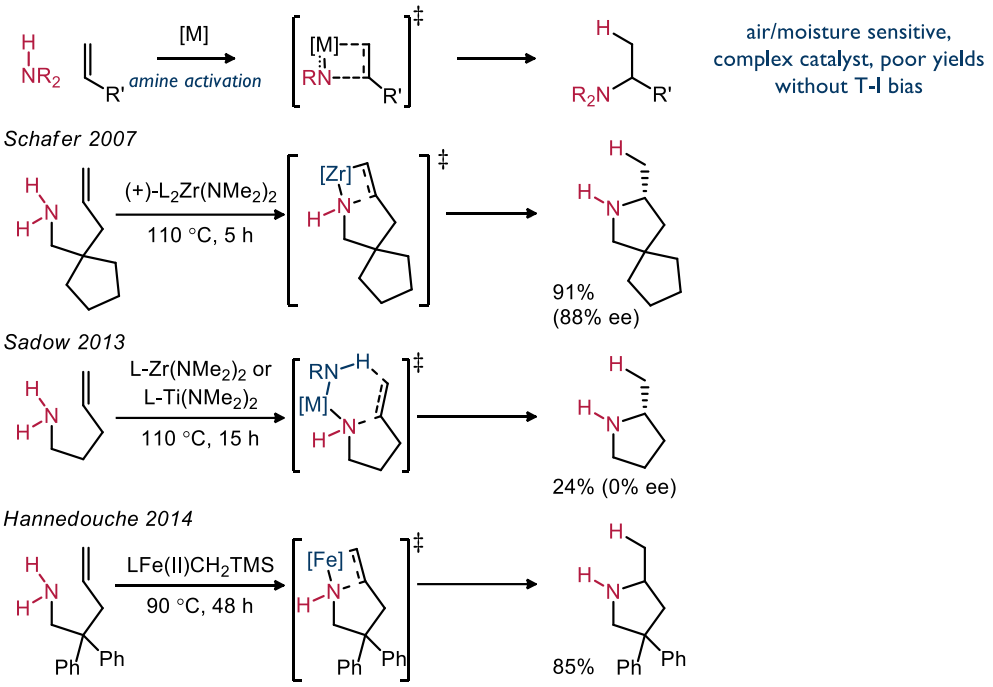


Early transition metals can activate amines towards hydroamination as well, often forming a metal nitrene intermediate (Scheme 3. 5). The alkene can then undergo hydroamination with this organometallic complex via a four or six-membered transition state. Primary amines are more commonly reported as

[125] (a) Fujita, H.; Tokuda, M.; Mitta, M.; Suginome, H. *Tetrahedron Lett.* **1992**, *33*, 6359-6362. (b) Ates, A.; Quinet, C. *Eur. J. Org. Chem.* **2003**, 1623-1626. (c) Quinet, C.; Jourdain, P.; Hermans, C.; Ates, A.; Lucas, I.; Markó, I. E. *Tetrahedron* **2008**, *64*, 1077-1087.

effective reagents for this catalysis, though some secondary amines have been reported to form pyrrolidines in moderate yields.[126] Thorpe-Ingold bias to promote cyclization is often required for this catalytic methodology.

Scheme 3. 5 General mode of early transition metal catalyzed hydroamination and examples



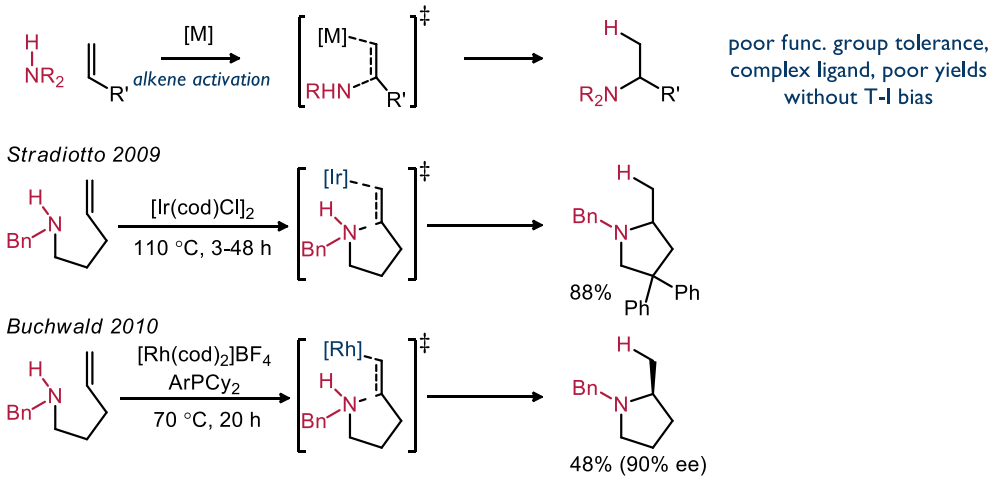
Late transition metal catalysts generally activate the alkene instead to catalyze hydroamination (Scheme 3. 6). In Buchwald's 2010 report of Rh catalysis for enantioselective intramolecular hydroamination, arylamines undergo hydroamination well, though alkylamines and substrates without Thorpe-Ingold bias led to considerably reduced yields of pyrrolidines.[127c] Like other late transition metal catalyzed process, Lewis basic substituents and weak C-X bonds are minimally tolerated.

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[126] (a) Wood, M. C.; Leitch, D. C.; Yeung, C. S.; Sozak, J. A.; Schafer, L. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 354–358. (b) Manna, K.; Everett, W. C.; Schoendorff, G.; Ellern, A.; Windus, T. L.; Sadow, A. D. *J. Am. Chem. Soc.* **2013**, *135*, 7235-7250. (c) Bernoud, E.; Ouli, P.; Guillot, R.; Mellah, M.; Hannedouche, J. *Angew. Chem. Int. Ed.* **2014**, *53*, 4930-4934.

[127] (a) Hesp, K. D.; Stradiotto, M. *Org. Lett.* **2009**, *11*, 1449–1452. (b) Hesp, K. D.; Tobisch, S.; Stradiotto, M. *J. Am. Chem. Soc.* **2010**, *132*, 413–426. (c) Shen, X.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2010**, *49*, 564 –567.

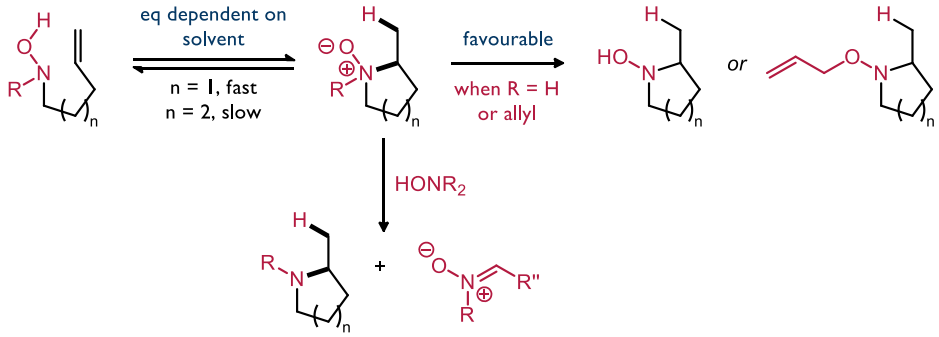
Scheme 3. 6 General mode of late transition metal catalyzed hydroamination and examples



3.2.1.2 Synthetic Limitations of Intramolecular Cope-Type Hydroamination

Cope-type hydroamination is a distinct approach to facilitate hydroamination using an oxidized amine, a hydroxylamine. As discussed briefly in chapter 1, intramolecular Cope-type hydroamination has significant solvent (Table 1. 4) and ring-size effects (Scheme 1. 33). Once hydroamination occurs, irreversible proton transfer or 2,3-Meisenheimer shift allow the overall process to be thermodynamically favourable (Scheme 3. 7).[77,86,128] When these steps cannot occur, the pyrrolidine *N*-oxide can undergo redox degradation involving another molecule of hydroxylamine. This can limit the effectiveness of intramolecular Cope-type hydroamination for secondary hydroxylamines.

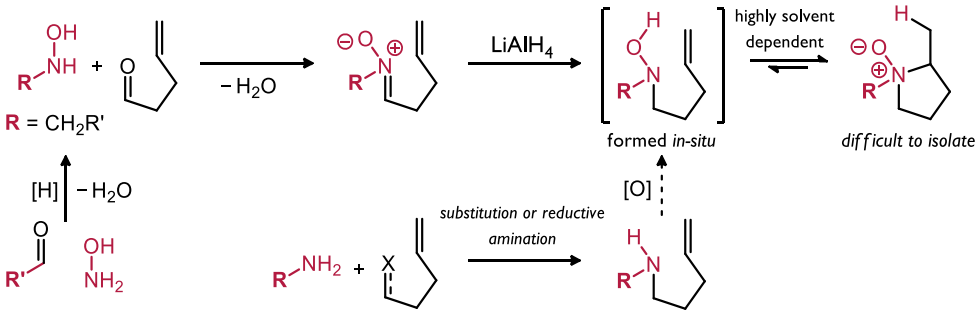
Scheme 3. 7 General intramolecular Cope-type hydroamination reactivity



[128] (a) Ciganek, E.; Read Jr., J. M.; Calabrese, J. C. *J. Org. Chem.* **1995**, *60*, 5795–5802. (b) Bourgeois, J.; Dion, I.; Cebrowski, P. H.; Loiseau, F.; Bédard, A. -C.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2009**, *131*, 874–875. (c) Brown, A. R.; Uyeda, C.; Brotherton, C. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2013**, *135*, 6747–6749.

In addition, the syntheses of secondary hydroxylamines that could be used for pyrrolidine synthesis are limited. Hydroxylamines can be unstable, undergoing oxidative degradation over time. The most common method is therefore an in-situ synthesis involving the addition of hydride or a Grignard nucleophile to a nitrone (Scheme 3. 8). Primary hydroxylamines can also be synthesized by alkylation, then deprotection of bis-Boc-protected hydroxylamines.[128c]

Scheme 3. 8 Synthesis of secondary hydroxylamines for use in intramolecular Cope-type hydroamination



Unfortunately, these methods require the use of a primary hydroxylamine. Primary hydroxylamines are minimally commercially available and are synthesized by reduction of an oxime generally (Figure 1. 9). Overall, the nitrone process involves two equivalents of aldehyde or ketone reagents for alkylation and up to two equivalents of a hydride reductant. Direct single oxidation of the corresponding secondary amine to the hydroxylamine has not yet been reported, though this would be a less wasteful approach to the required secondary hydroxylamine. The pyrrolidine *N*-oxide product is then also difficult to isolate as it is highly hygroscopic and polar (Figure 1. 10), so often the the crude *N*-oxide is reduced in a separate step.[83,129]

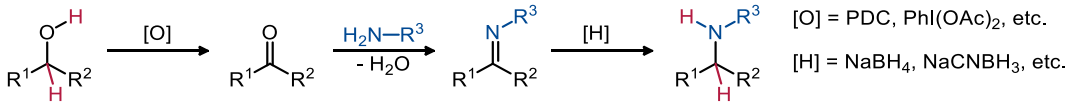
3.2.1.3 Redox-Enabled Methodologies

A redox-enabled methodology can be considered as a chemical process that is facilitated by a temporary modification in oxidization state. A classic stoichiometric example is the synthesis of amines from alcohols (Scheme 3. 9). While direct substitution with an amine nucleophile is difficult, an alcohol can be oxidized, followed by reductive amination to form amine products. This process avoids overalkylation problems common in substitution-based approaches. Importantly, the change in alcohol oxidation state allows for favourable imine condensation to take place, forming the key new N-C bond. Stoichiometric oxidants and

[129] Ciganek, E. *J. Org. Chem.* **1995**, *60,* 5803-5907.

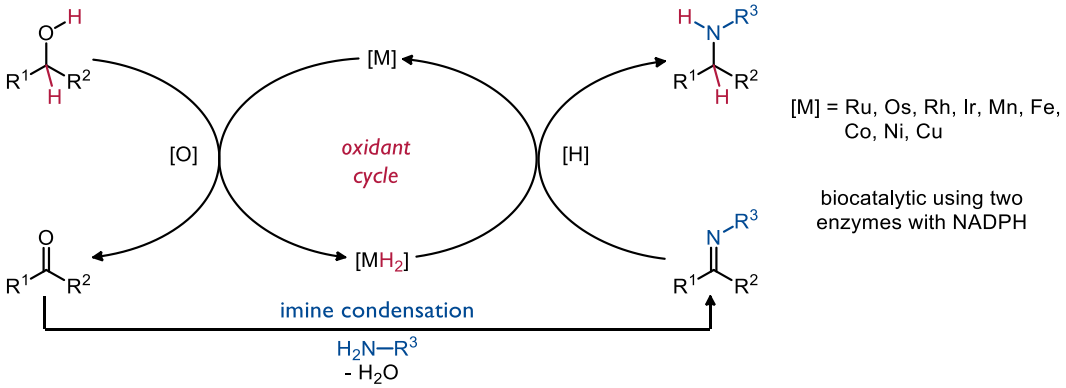
reductants are both required for this process, meaning these steps must be separated and stoichiometric waste is also produced.

Scheme 3. 9 Stoichiometric redox-enabled amination



Grigg and Watanabe reported the first catalytic variants of this amination reactivity using Rh/Ir/Ru catalysis.[130] The role of the metal catalyst is to temporarily remove hydrogen from the alcohol starting material then transfer hydrogen back to the imine after condensation, leading to the name "borrowing hydrogen catalysis" (Scheme 3. 10). Many transition metal complexes and enzymes have been used as catalysts for amination and other borrowing hydrogen reactions.[131] This catalytic process produces no stoichiometric waste apart from water.

Scheme 3. 10 Catalytic redox-enabled amination (borrowing hydrogen)



The deoxygenative functionalization of pyridine also serves as an important example of redox-enabled methodology using *N*-oxidation. In Reissert-type reactivity, pyridine *N*-oxides are activated (using AG-X), then a nucleophile attacks C2 of the pyridine (Scheme 3. 11).[132] Deoxygenative rearomatization then leads to the functionalized product. The nitrogen oxidation state modification essentially allows the activation

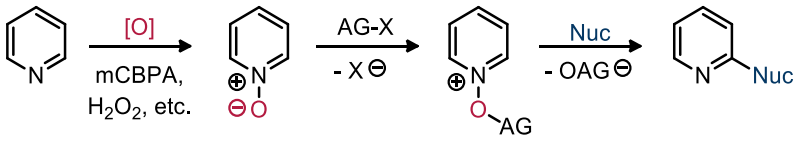
[130] (a) Grigg, R.; Mitchell, T. R. B.; Sutthivaiyakit, S.; Tongpenyai, N. *J. Chem. Soc., Chem. Commun*. **1981**, *12*, 611–612. (b) Watanabe, Y.; Tsuji, Y.; Ohsugi, Y.; Ohta, T. *J. Org. Chem.* **1984**, *49*, 3359–3363. (c) Tsuji, Y.; Huh, H.-T.; Ohsugi, Y.; Watanabe., Y. *J. Org. Chem.* **1985**, *50*, 1365–1370.

[131] Reed-Berendt, B. G.; Latham, D. E.; Dambatta, M. B.; Morrill, L. C. *ACS Cent. Sci.* **2021**, *7*, 570–585.

[132] Reissert, A. *Ber. Dtsch. Chem. Ges.* **1905**, *38*, 3415-3435.

of pyridine towards nucleophilic attack and the deoxygenative rearomatization to become more favourable.

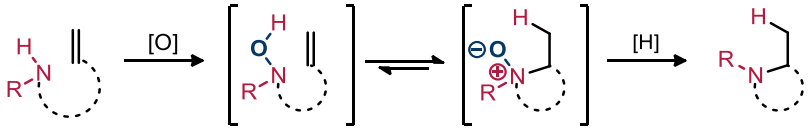
Scheme 3. 11 Reissert-type redox-enabled pyridine functionalization



3.2.1.4 Proposed Redox-Enabled Hydroamination

Appreciating the practical limitations of Cope-type hydroamination and the power of temporary oxidation state modifications as seen in borrowing hydrogen amination methodology, we sought to develop an analogous redox-enabled hydroamination involving Cope-type hydroamination (Scheme 3. 12). This process would allow the hydroamination to occur under the milder conditions of Cope-type hydroamination without the need to synthesize or isolate hydroxylamines, or isolate *N*-oxides. Significant chemoselectivity issues for oxidation and reduction were possible challenges as well as overoxidation of the amine to the nitrone.

Scheme 3. 12 Proposed redox-enabled hydroamination using in-situ oxidation and reduction

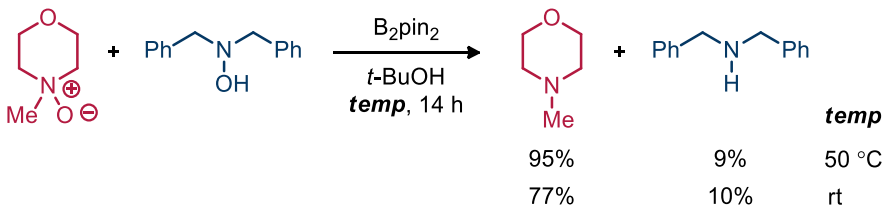


3.2.2 Early Optimization: Acrylonitrile Elimination

To evaluate the viability of the proposed oxygen-transfer based reduction, competition studies were completed (Scheme 3. 13). It is important that the reductant is selective for the *N*-oxide over the hydroxylamine present in the Cope-type hydroamination equilibrium. Using one equivalent of amine *N*-oxide and hydroxylamine each, the ratio of reduced amine products was measured using quantitative ^{1}H NMR yields. Several reports use boron-containing reagents (e.g., boronic acids, diboron) for mild and selective reduction of *N*-oxides.[133] One equivalent of a boron-based reductant, B_2pin_2, was therefore tested at 50 °C and rt.

[133] (a) Köster, R.; Morita, Y. *Justus Liebigs Ann. Chem.* **1967**, *704*, 70-90. (b) Kabalka, G. W.; Hedgecock, H. C. *J. Org. Chem.* **1975**, *40*, 1776-1779. (c) Bae, S.; Laksham, M. K. *J. Org. Chem.* **2008**, *73*, 1311-1319. (d) Kokatla, H. P.; Thomson, P. F.; Doddi V. R.; Lakshman, M. K. *J. Org. Chem.* **2011**, *76*, 7842-7848. (e) Zhu, C.; Wang R.; Falck, J. R. *Org.*

Scheme 3. 13 Competition study of *N*-oxide vs. hydroxylamine reduction



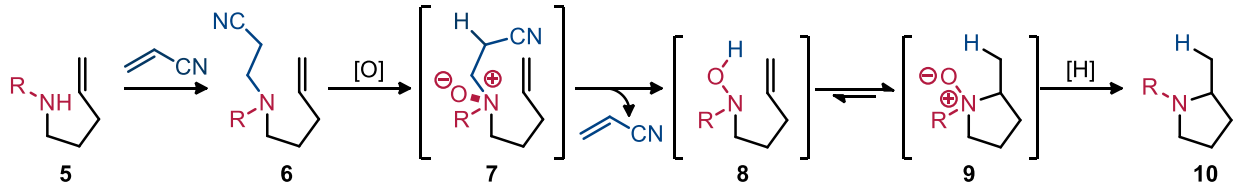
While some selectivity was observed for the reduction of *N*-oxides over hydroxylamines, either reduction could not selectively occur in the presence of an oxidant such as mCBPA or peroxide. Therefore, the oxidation step must be complete prior to the addition of a boron reductant. The oxidation step itself is a challenge considering the lack of reported methodologies that do not lead to over-oxidation of amines to nitrones.[34]

Propionitrile-substituted tertiary amines have been used as hydroxylamine precursors, undergoing Cope-elimination of acrylonitrile after oxidation.[134] This method importantly avoids overoxidation since the tertiary amine can only be oxidized once. The propionitrile-substituted reagents (**6**) can be made simply and quantitatively from Michael addition of the corresponding secondary amine **5** with acrylonitrile (Scheme 3. 14). Once the initial *N*-oxide (**7**) is formed, Cope elimination forms hydroxylamine **8**, which can then undergo intramolecular Cope-type hydroamination to form the second *N*-oxide (**9**). A reductant can then reduce *N*-oxide **9** to pyrrolidine **10**. The required selectivity of reduction for the proposed cascade reaction includes two *N*-oxides (**7** and **9**) and one hydroxylamine (**8**) if the reductant is added after the initial oxidation is complete.

Lett. **2012**, *14*, 3494-3497. (f) Londregan, A. L.; Piotrowski D. W.; Xiao, J. *Synlett* **2013**, *24*, 2695-2700. (g) Kim, J.; Bertozzi, C. R. *Angew. Chem. Int. Ed.* **2015**, *54*, 15777-15781. (h) Gurram, V.; Akula, H. K.; Garlapati, R.; Pottabathini, N.; Lakshman, M. K. *Adv. Synth. Catal.* **2015**, *357*, 451-462. (i) Gupta, S.; Sureshbabu, P.; Singh, A. K.; Sabiah S.; Kandasamy, J. *Tetrahedron Lett.* **2018**, *59*, 909-913. (j) Xie, Q.; Dong, G. *J. Am. Chem. Soc.* **2022**, *144*, 8498–8503.

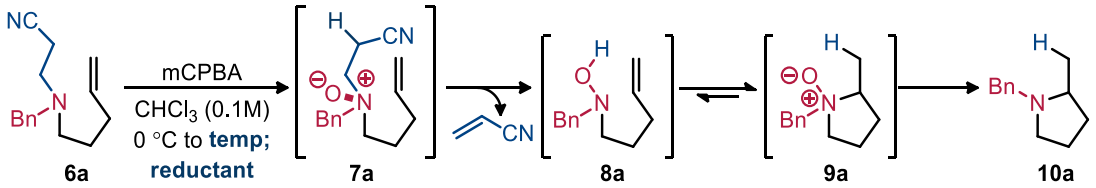
[134] (a) O'Neil, I. A.; Cleator, E.; Ramos, V. E.; Chorlton, A. P.; Tapolczay, D. J. *Tetrahedron Lett.* **2004**, *45*, 3655–3658. (b) O'Neil, I. A.; Ramos, V. E.; Ellis, G. L.; Cleator, E.; Chorlton, A. P.; Tapolczay, D. J.; Kalindjian, S. B. *Tetrahedron Lett.* **2004**, *45*, 3659–3661.

Scheme 3. 14 Hydroamination employing oxidation/Cope elimination for hydroxylamine synthesis



For the initial reaction optimization, *N*-benzylamine **6a** was oxidized using mCPBA (Table 3. 7). After oxidation was complete within 30 minutes (0 °C to rt), the reductant was added, and the reaction was heated. Heat should promote both the elimination of acrylonitrile and the reduction of pyrrolidine *N*-oxide **9a**. First, control reactions without reductant at 70 °C and 50 °C showed higher yields of *N*-oxide (**9a**) at lower temperature (entries 1-2). Comparing a diboron reductant to a weaker arylboronic acid reductant (Figure 3. 1), a higher combined yield of *N*-oxide **9a** and reduced pyrrolidine **10a** was observed with significantly less degradation using the boronic acid (entries 3-4). This result suggests that B_2pin_2 is likely unselective for pyrrolidine *N*-oxide **10a** reduction under these conditions. Notably, the incomplete reduction of pyrrolidine *N*-oxide using arylboronic acid **A** (entry 4) included remaining reductant, so only a longer reaction time was presumed to be needed. Using mCPBA in excess led to a reduced combined yield of pyrrolidine **10a** and remaining *N*-oxide **9a**, even with additional equivalents of reductant added (entry 5-7). The oxidant was therefore used as the limiting reagent in additional optimization.

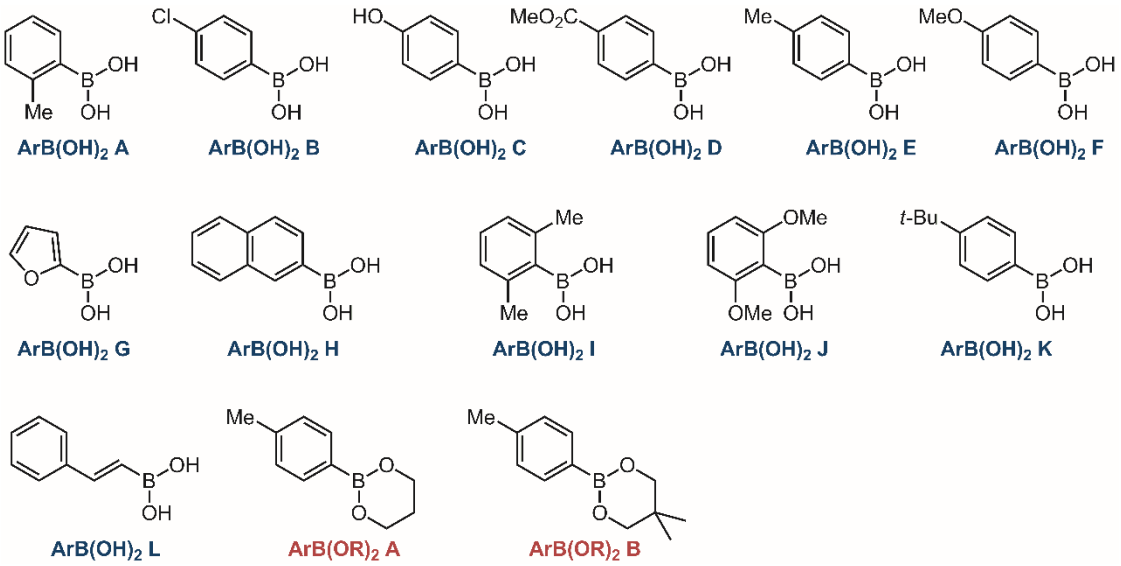
Table 3. 7 Optimization of hydroamination cascade from tertiary amines[a]



Entry	Equiv 6a	Equiv mCPBA	Boron Reductant (equiv)	Temp (°C)	Yield 9a (%)[b]	Yield 10a (%)[b]
1	1.1	1.0	none	70	75	0
2	1.1	1.0	none	50	93	0
3	1.1	1.0	B_2pin_2 (1.1)	50	0	34
4	1.1	1.0	$ArB(OH)_2$ **A** (1.1)	50	46	52
5	1.0	1.1	$ArB(OH)_2$ **A** (1.1)	50	25	39
6	1.0	1.1	$ArB(OH)_2$ **A** (1.5)	50	17	45
7	1.0	1.5	$ArB(OH)_2$ **A** (1.5)	50	8	23

(a) Conditions: amine **6a** in $CHCl_3$ (0.1 M), then mCPBA added, stirred at 0 °C, 30 min. Reductant then added, stirred at given temperature, 4 h. (b) ^1H NMR yield of **9a** and **10a** using 1,3,5-trimethoxybenzene as an internal standard. Bpin = $B(O_2C_2(CH_3)_4)$.

Figure 3. 1 Boronic acids and boronic esters used in reaction optimization

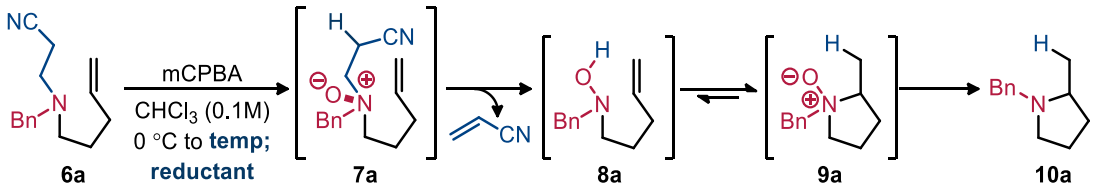


3.2.2.1 Reductant Optimization

The steric and electronic effects of the boronic acid reductant were then surveyed to determine if a more efficient reaction could be observed using other commercially available boronic acids **A**-**L** (Figure 3. 1). *This optimization was completed with the help of Geneviève O'Keefe.* Boronic acid **A** was found to be the most efficient reductant (entry 1-12). Interestingly, this *o*-methyl substituted boronic acid performed better than the less hindered *p*-methyl variant (entry 5), but also the more hindered *o*,*o*-dimethyl variant (entry 9). While it is possible that there is an optimal intermediate steric hindrance required for selective *N*-oxide reduction, steric hindrance could also affect the condensation of boronic acids into the corresponding boroxines.[135] The ratio of boronic acid to boroxine, which is difficult to accurately determine, could also be affecting the outcome of this reaction. Electron-poor (**B**, **D**) or electron-rich (**C**, **F**, **G**, **J**) arylboronic acids all led to minimal reduction (entries 2, 3, 4, 6, 7, 10). Only alkyl-substituted arylboronic acids were therefore used in subsequent optimization.

[135] Kua, J.; Fletcher, M. N.; Iovine, P. M. *J. Phys. Chem. A* **2006**, *110*, 8158–8166.

Table 3. 8 Boron reductant scan for hydroamination using tertiary amine staring materials[a]



Entry	Reductant	Temp (°C)	Time (h)	Yield 9a (%)[b]	Yield 10a (%)[b]
1	$ArB(OH)_2$ **A**	50	4	44	52
2	$ArB(OH)_2$ **B**	50	4	73	22
3	$ArB(OH)_2$ **C**	50	24	100	trace
4	$ArB(OH)_2$ **D**	50	24	100	trace
5	$ArB(OH)_2$ **E**	50	4	75	25
6	$ArB(OH)_2$ **F**	50	4	83	10
7	$ArB(OH)_2$ **G**	50	4	95	0
8	$ArB(OH)_2$ **H**	50	4	55	36
9	$ArB(OH)_2$ **I**	50	4	69	19
10	$ArB(OH)_2$ **J**	50	4	98	trace
11	$ArB(OH)_2$ **K**	50	24	99	trace
12	$ArB(OH)_2$ **L**	50	24	58	30
13	$ArB(OR)_2$ **A**	50	24	100	trace
14	$ArB(OR)_2$ **B**	50	24	100	trace
15	$B(C_6F_5)_3$	50	4	0	0
16	$B(C_6F_5)_3$	rt	4	0	13
17	$HOB(tol)_2$	50	4	0	8
18	$HOB(tol)_2$	rt	4	20	0
19	$Et_3SiBpin$	rt	4	12	20
20	$Et_3SiBpin$	50	4	30	43

(a) Conditions: amine **6a** (1.2 equiv) in $CHCl_3$ (0.1 M), then mCPBA (1.0 equiv), 0°C, 30 min. Reductant then added (1.2 equiv), stirred at given temperature, 4 – 24 h. (b) ^1H NMR yield of **9a** and **10a** using 1,3,5-trimethoxybenzene as an internal standard.

Arylboronic acid alternatives were then tested mainly to assess the effects of modified Lewis acidity. The effects of using arylboronic esters were surprisingly drastic (entries 13-14). Both boronic esters tested led to no reduction even after 24 h in contrast to the slow reactivity observed for the analogous boronic acid after 4 h (entry 5).[136] Using a more Lewis acidic boron reductant, $B(C_6F_5)_3$, led to minimal hydroamination products at 50 °C or rt and degradation of the reductant (entries 15-16).[137] Diarylborinic acid, also more Lewis acidic than boronic acids, similarly led to minimal observed hydroamination products and degradation of the reductant (entries 17-18). Lastly, silylborane was found to have improved results in

[136] Lennox, A. J. J.; Lloyd-Jones, G. C. *Chem. Soc. Rev.* **2014**, *43*, 412-443.

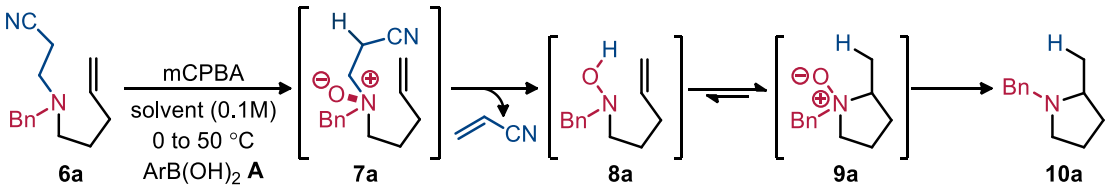
[137] (a) *Stereodirected Synthesis with Organoboranes;* Matteson, D. S., Ed.; Springer: Berlin, Heidelberg, New York, 1995 and references therein. (b) Ishihara, K.; Kurihara, H.; Yamamoto, H. *J. Org. Chem.* **1997**, *62,* 5664–5665. (c) Ishihara, K.; Kurihara, H.; Yamamoto, H. *Synlett* **1997**, 597-599. (d) Taylor, M. S. *Acc. Chem. Res.* **2015**, *48*, 295–305. (e) Sivaev, I.; B.; Bregadze. Z. I. *Coord. Chem. Rev.* **2014**, *270-271*, 75-88.

comparison to the other boronic acid alternatives, though still led to worse overall hydroamination yields than arylboronic acid **A** (entries 19-20). Arylboronic acid **A** was therefore used for additional solvent optimization.

3.2.2.2 Solvent Effects

Since Cope elimination and Cope-type hydroamination have large known solvent effects (Table 1. 4), a solvent scan was an important study (Table 3. 9). *This optimization was completed with the help of Geneviève O'Keefe.* While chloroform appeared to be an effective solvent choice for the cascade reaction (entry 1), MeCN and *t*-BuOH led to reduced yields of pyrrolidine and increased degradation products (entries 2-3). Both MeCN and *t*-BuOH are effective solvents for Cope-type hydroamination, so another part of this process must be significantly negatively affected. Cyclohexane led to no observed hydroamination products (**9a** or **10a**), though mCPBA was minimally soluble, perhaps contributing to the poor reactivity observed (entry 4). DCE, a chlorinated polar aprotic solvent similar to chloroform, led to similar results to chloroform (entry 5). Other polar aprotic solvents ($PhCF_3$ and dioxane) led to reduced yields of hydroamination products (entries 6-7). Chloroform was used as the solvent for further studies of nitrogen substitution for this cascade reaction rather than DCE due to the lower boiling point and improved environmental profile.

Table 3. 9 Solvent scan for hydroamination using tertiary amine starting materials[a]



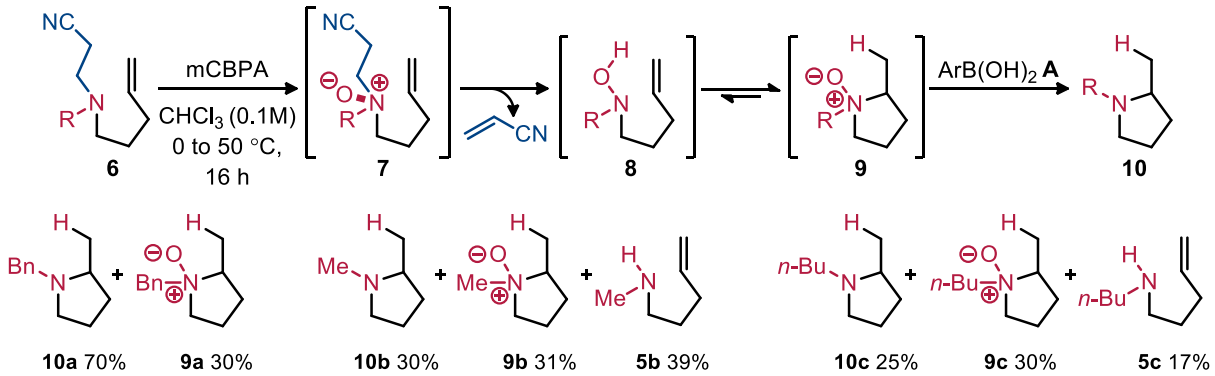
Entry	Solvent	Yield 9a (%)[b]	Yield 10a (%)[b]
1	$CDCl_3$	40	42
2	MeCN	47	13
3	*t*-BuOH	6	trace
4	Cyclohexane	0	0
5	DCE	43	40
6	$PhCF_3$	34	23
7	Dioxane	22	19

(a) Conditions: amine **6a** (1.2 equiv) in solvent (0.1 M), then mCPBA (1.0 equiv) added, stirred at 0 °C, 30 min. 2-Methylphenyl boronic acid ($ArB(OH)_2$ **A**) then added (1.2 equiv), stirred at 50 °C, 4 h. (b) ^1H NMR yield of **9a** and **10a** using 1,3,5-trimethoxybenzene as an internal standard.

Unfortunately, when other amine substrates were tested under the optimized reaction conditions with a longer reaction time (16 h), an unexpected and undesirable mixture of products was obtained as observed

by ^{1}H NMR yields (Scheme 3. 15). Both *N*-methyl (**6b**) and *N*-butylamine (**6c**) starting materials formed a mixture of pyrrolidine **10**, pyrrolidine *N*-oxide **9** and secondary amine **5**, presumably formed via hydroxylamine reduction. The non-generalizable optimized conditions could not be carried forward for this project, so another strategy for redox-enabled hydroamination was prioritized.

Scheme 3. 15 Scope limitations using tertiary amine starting materials (**6**) and optimized conditions



3.2.3 Secondary Optimization: Direct Oxidation to Hydroxylamine

In order to simplify the cascade hydroamination process, a secondary amine starting material was targeted for optimization. The major challenge of this modification is the potential for over-oxidation of the amine to the nitrone, meaning a new oxidation procedure needed to be developed. Mild oxidation conditions would be required that allowed for rapid and favourable intramolecular Cope-type hydroamination to occur, preventing over-oxidation.

3.2.3.1 Oxidant and Solvent Optimization

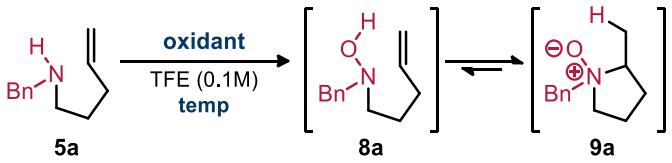
Related sulfur oxidation and alkene epoxidation methodology inspired the use of fluorinated alcohols to activate peroxide for amine oxidation.[138,139] These conditions have not been reported for hydroxylamine synthesis, however, tetrahydroquinoline has been submitted to oxidative conditions with HFIP, though

[138] For examples of sulfide oxidation using fluorinated alcohols and peroxide, see: (a) Ravikumar, K. S.; Begue, J. P.; Bonnet-Delpon, D. *Tetrahedron Lett.* **1998**, *39*, 3141-3144. (b) Ravikumar, K. S.; Zhang, Y. M.; Begue, J. P.; Bonnet-Delpon, D. *Eur. J. Org. Chem.* **1998**, 2937-2940.

[139] For examples of epoxidation using fluorinated alcohols and peroxide, see: (a) Van Vliet, M. C. A.; Arends I. W. C. E.; Sheldon, R. A. *Synlett* **2001**, 248. (b) Neimann K.; Neumann, R. *Org. Lett.* **2000**, *2*, 2861-2863. (c) Legros, J.; Crousse, B.; Bonnet-Delphon, D.; Bégué, J. -P. *Eur. J. Org. Chem.* **2002**, 3290-3293. (d) Berkessel, A.; Adrio, J. A. J. *Am. Chem. Soc.* **2006**, *128*, 13412-13420. For an example of imine oxidation using these conditions, see: (e) Llopis, N.; Gisbert P.; Baeza, A. *J. Org. Chem.* **2020**, *85*, 11072-11079.

the corresponding nitrone is the sole reported product via a proposed hydroxylamine intermediate.[140] The optimization of the redox-enabled Cope-type hydroamination began with peroxide and fluorinated solvents for the initial oxidation and hydroamination steps (Table 3. 10). The required reduction step could in theory be completed quantitatively by the sequential addition of a diboron reductant, so this step was not evaluated within this optimization. Using aqueous peroxide and TFE, secondary amine **5a** successfully forms *N*-oxide **9a** after 16 h at 50 °C (entry 1). Increasing the peroxide equivalents to a larger excess leads to good yield of 84% (entry 2). It is apparent that the oxidation conditions are compatible with an efficient cyclization as minimal overoxidation of the amine is observed. Importantly, TFE also functions to stabilize *N*-oxide product **9a**, allowing the product of the Cope-type hydroamination equilibrium to be more favoured.[141] Using a solid source of peroxide instead, UHP, the oxidation/hydroamination reaction sequence works well at 50 °C (entries 3-4).

Table 3. 10 Optimization of the oxidant for the cascade oxidation and hydroamination of secondary amines[a]



Entry	Oxidant (equiv)	Temp (°C)	Yield 9a (%)[b]
1	30% aq. H_2O_2 (1.2)	50	42
2	30% aq. H_2O_2 (1.5)	50	84
3	UHP (1.2)	50	92
4	UHP (1.2)	rt	33

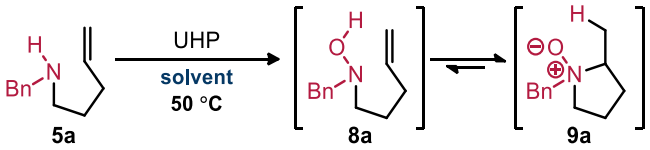
(a) Amine **5a** (1.0 equiv) in TFE (0.1M), then oxidant added, given temperature, 16 h. (b) ^{1}H NMR yield of **9a** using 1,3,5-trimethoxybenzene as an internal standard. UHP = urea hydrogen peroxide adduct; TFE = 2,2,2-trifluoroethanol.

A study of various fluorinated and non-fluorinated solvent mixtures was then conducted to assess the role of solvent and further optimize this procedure (Table 3. 11). Low concentrations of TFE worked well for the desired reactivity (entries 1-2). All non-fluorinated alcohol solvents led to significantly lower yields of pyrrolidine *N*-oxide **9a** (entries 3-6). Using the more acidic fluorinated alcohol HFIP, the yield of *N*-oxide **9a** was lower with no observed amine **5a** remaining (entry 7). While HFIP could activate peroxide, the observed lower yield at complete conversion suggests that the amine is over-oxidizing under these

[140] Granato, Á. S.; Amarante, G. W.; Adrio, J. *J. Org. Chem.* **2021**, *86*, 13817–13823.
[141] Mucsi, Z.; Szabó, A.; Hermecz, I.; Kucsman, A.; Csizmadia, I. G. *J. Am. Chem. Soc.* **2005**, *127*, 7615-7631.

conditions, leading to degradation products. Since TFE has some toxicity risks, mixtures of MeOH and HFIP were used, though these entries led to reduced yields (entries 8-9). Trying mixtures of *i*-PrOH with TFE or HFIP also led to reduced yields (entries 10-11). TFE was therefore used as the optimal solvent for the one-pot redox-enabled hydroamination cascade. The optimization of the reduction and isolation steps could then become the focus.

Table 3. 11 Optimization of the solvent for the cascade oxidation and hydroamination of secondary amines



5a **8a** **9a**

Entry	Solvent (M)	Yield 9a (%)[b]
1	TFE (0.1)	92
2	TFE (0.2)	91
3	MeOH (0.1)	30
4	EtOH (0.1)	22
5	*i*-PrOH (0.1)	16
6	*t*-BuOH (0.1)	18
7	HFIP (0.1)	70
8	MeOH/HFIP 3:1 (0.1)	52
9	MeOH/HFIP 1:1 (0.1)	79
10	*i*-PrOH/TFE 10:1 (0.1)	27
11	*i*-PrOH/HFIP 10:1 (0.1)	36

(a) Amine **5a** (1.0 equiv) in solvent, then UHP (1.2 equiv) added, stirred at 50 °C, 16 h. (b) ^{1}H NMR yield of **9a** using 1,3,5-trimethoxybenzene as an internal standard. UHP = urea hydrogen peroxide adduct; TFE = 2,2,2-trifluoroethanol; HFIP = 1,1,1,3,3,3-hexafluoroisopropanol.

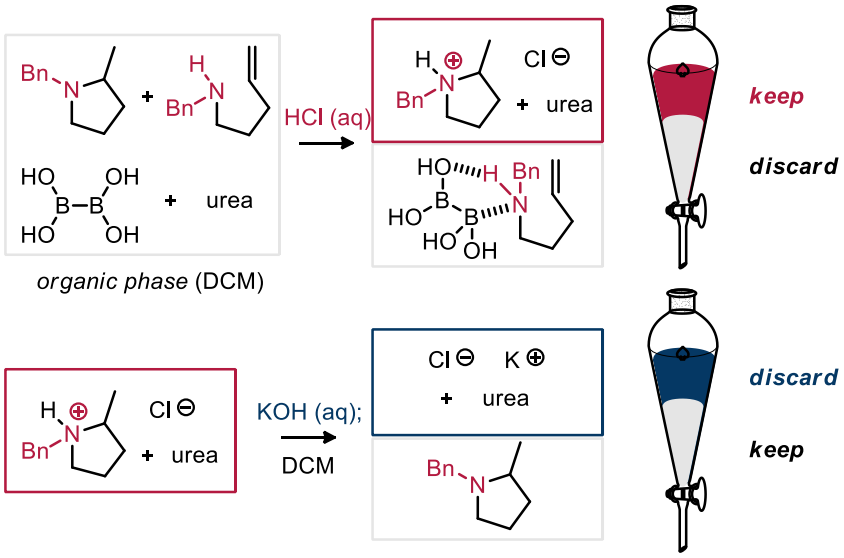
3.2.3.2 Purification Process

As expected, a diboron reductant (B_2pin_2) was found to effectively reduce the pyrrolidine *N*-oxide **9** after stirring at rt for 30 minutes.[133] The purification of the reduced pyrrolidine products **10** was originally optimized as concentration, followed by flash column chromatography, then HCl salt formation due to the volatility of most intended scope entries. Common impurities found after column chromatography include the secondary amine reagent and some form of pinacol. Difficulties arose while forming HCl salts of different *N*-substituted pyrrolidines because this process was not as generalizable as expected.

Therefore, a different purification strategy was developed. Using $B_2(OH)_4$ as the reductant instead, only inorganic reduction by-products would be formed, allowing for simpler chromatography. Serendipitously, the use of $B_2(OH)_4$ also allowed for an aqueous extraction alone to separate the pyrrolidine **10** from remaining secondary amine **5**. Though the exact mode of action is unclear, it appears as though the

diboron interacts with the secondary amine selectively to prevent its protonation by aqueous HCl, allowing only the pyrrolidine to dissolve in the acidic aqueous phase (Figure 3. 2). Upon addition of excess 1M KOH, the basic aqueous phase is extracted. The resulting organic phase then contains pure pyrrolidine product. Both B_2pin_2 and oxidized $B_2(OH)_4$ as additives were not found to cause effective separation.

Figure 3. 2 Aqueous extraction purification for pyrrolidines



To our knowledge, this extraction procedure using $B_2(OH)_4$ is a novel method for the separation of secondary and tertiary amines, which can otherwise be difficult by conventional extraction or chromatography techniques for small scale.[142] This $B_2(OH)_4$ enabled separation is therefore being optimized for other applications by Rosemary Karn, an undergraduate student, for her Honour's thesis project. Studies on solvent effects, boron additives, and extraction conditions will be completed.

3.2.4 Methodology Evaluation

3.2.4.1 Scope

With an optimized simple isolation procedure in hand, the scope of this one-pot hydroamination sequence was evaluated (Scheme 3. 16). *This scope was completed and evenly divided with Huy Minh Ly.* Various *N*-alkyl substituted secondary amines formed the corresponding pyrrolidine in good yields (**10a**, **10d**-**10i**).

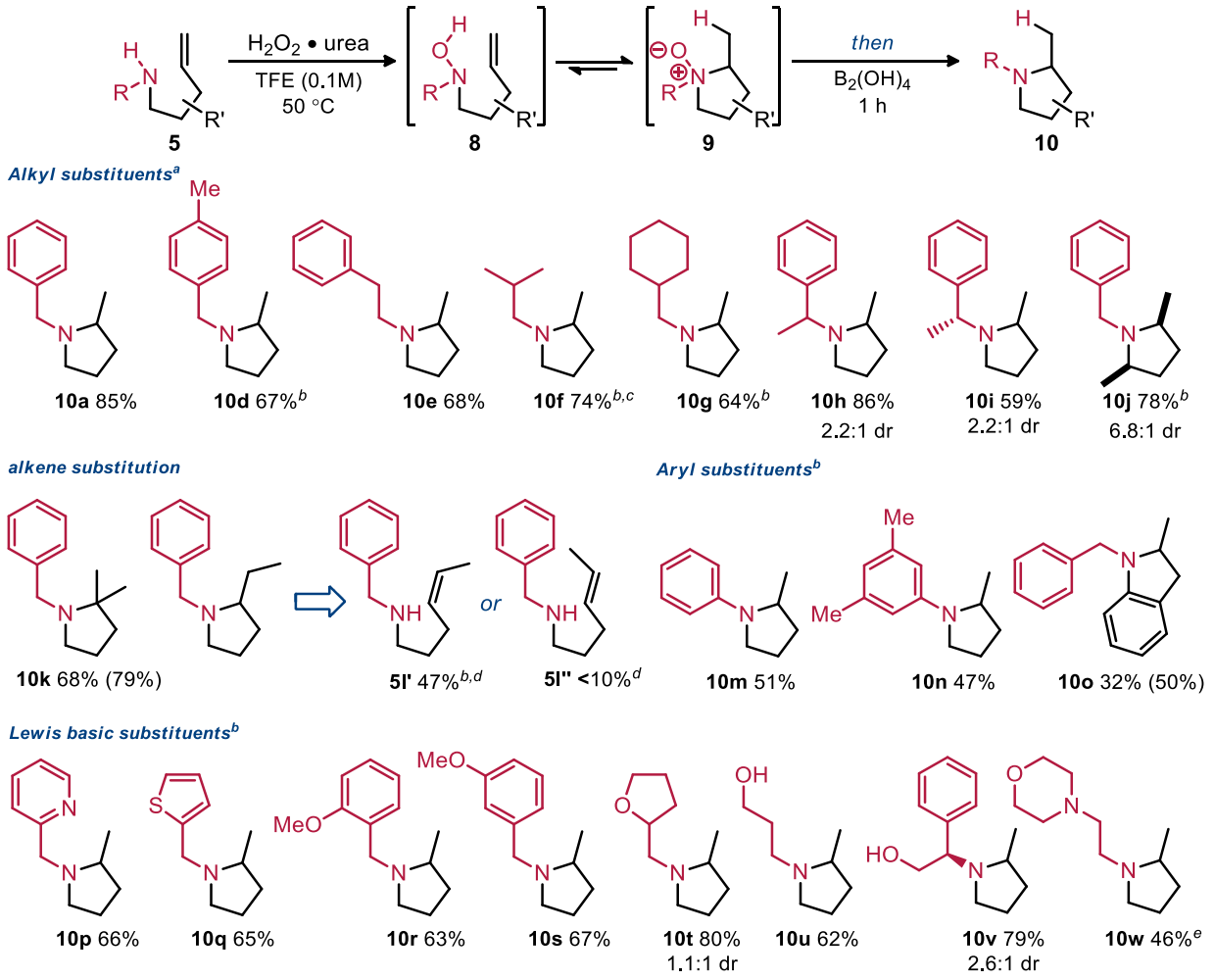
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[142] (a) Chartoire, A.; Claver, C.; Corpet, M.; Krinsky, J.; Mayen, J.; Nelson, D.; Nolan, S. P.; Peñafiel, I.; Woodward, R.; Meadows, R. E. *Org. Process Res. Dev.* **2016**, *20*, 551−557. (b) Falß, S.; Tomaiuolo, G.; Perazzo, A.; Hodgson, P.; Yaseneva, P.; Zakrzewski, J.; Guido, S.; Lapkin, A.; Woodward, R.; Meadows, R. E. *Org. Process Res. Dev.* **2016**, *20*, 558−567 (c) Ashworth, I. A.; Meadows, R. E. *J. Org. Chem.* **2018**, *83*, 4270−4274.

Conformational bias promoting ring closure using alkyl-substituents is often required for other methodologies, with geminal disubstitution (Thorpe-Ingold bias) being most common. However, high yields of cyclized product without Thorpe-Ingold bias were obtained for this reaction sequence. A 2,5-dimethyl substituted pyrrolidine (**10j**) was also isolated in good yields with notably higher diastereoselectivity (6.8:1) than 2-methylbenzylamine derivatives (**10h**, **10i**). Related *n*-BuLi catalyzed hydroamination reactivity has reported similar diastereoselectivity for the synthesis of pyrrolidine **10j** (3.5:1 or 5.7:1).[143] The difference in isolated yield between products **10h** and **10i** cannot currently be rationalized, so resynthesis and retesting of the corresponding amine substrates would be recommended.

[143] (a) Ates, A.; Quinet, C. *Eur. J. Org. Chem.* **2003**, 1623-1626. (b) Quinet, C.; Jourdain, P.; Hermans, C.; Ates, A.; Lucas, I.; Markó, I. E. *Tetrahedron* **2008**, *64*, 1077-1087.

Scheme 3. 16 Scope of pyrrolidines formed via redox-enabled hydroamination

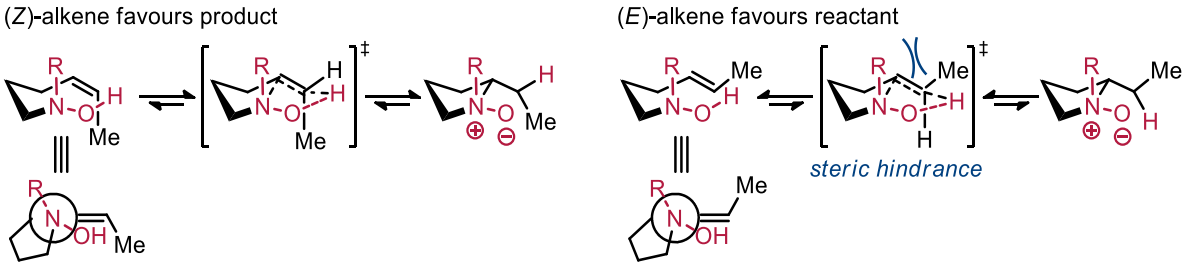


(a) Conditions: amine **5** (1.0 equiv) in TFE (0.1M), then UHP (1.2 equiv) added, stirred at 50 °C, 16 h. $B_2(OH)_4$ (1.2 equiv) then added, stirred at 50 °C, 1 h. Isolated yields shown with ^{1}H NMR yields using 1,3,5-trimethoxybenzene as an internal standard shown in parentheses. (b) 2.2 Equiv of $B_2(OH)_4$ was added; (c) isolated as the HCl salt; (d) at 60 °C; (e) 2.2 Equiv of UHP and 3.2 equiv of $B_2(OH)_4$ were added. UHP = urea hydrogen peroxide adduct; TFE = 2,2,2-trifluoroethanol.

Alkene substitution is known to greatly affect Cope-type hydroamination (section 1.3.3.3). When a proximal methyl group is included on the alkene (**5k**), the one-pot reaction proceeds similarly to the mono-substituted variant (**5a**) as expected. Terminal alkene substitution had a significant effect on the observed reactivity. The (*Z*)-alkene precursor (**5l'**) led to a moderate isolated yield of pyrrolidine (**10l**) at 60 °C, however, the (*E*)-alkene **5l''** only led to trace product and degradation products. This effect of alkene geometry has not yet been studied thoroughly in the Cope-type hydroamination literature.[85b] A possible explanation for the difference in reactivity is the additional steric interaction present for the hydroamination of the (*E*)-alkene between the R group and methyl (Scheme 3. 17). Another possible

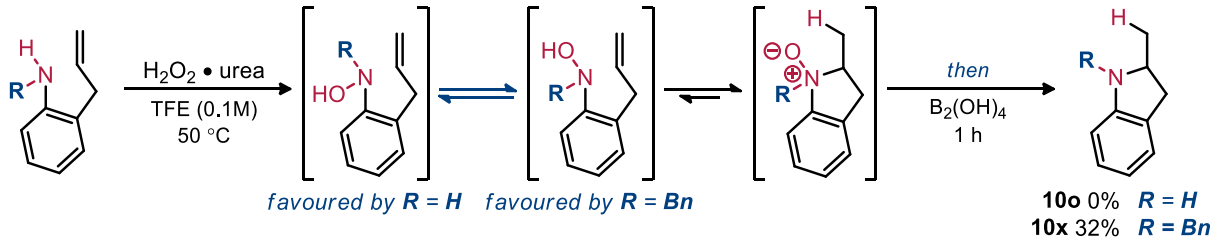
explanation is the decreased stability of (*Z*)-alkenes relative to (*E*)-alkenes. Further optimization of the oxidation and hydroamination step of this process is likely required to improve the reactivity of the slower hydroamination for terminally substituted alkenes. More similar rates of oxidation and hydroamination would allow a lower concentration of hydroxylamine to be present, likely lowering the amount of degradation observed for these entries.

Scheme 3. 17 Possible effects of alkene geometry on intramolecular Cope-type hydroamination



Gratifyingly, aryl-substituted amines underwent oxidation and Cope-type hydroamination under the optimized reaction conditions (**5m**-**5o**). Due to the rapid degradation pathways applicable to aryl hydroxylamines, further optimization is likely required to increase the yields of the corresponding hydroamination product of arylamines.[144] Additionally, due to the higher pKa of protonated arylamines, a modified isolation procedure involving chromatography was required for products **10n** and **10o**. No conformational effects were observed for this hydroamination process except for the indoline precursors **5o** and **5x** (Scheme 3. 18). While the *N*-benzyl substituted aniline **5o** formed the corresponding indoline **10o** in moderate yields under optimized reaction conditions (50% ^{1}H NMR yield, 32% isolated), the primary aniline **5x** did not cyclize after successful oxidation to the corresponding hydroxylamine.

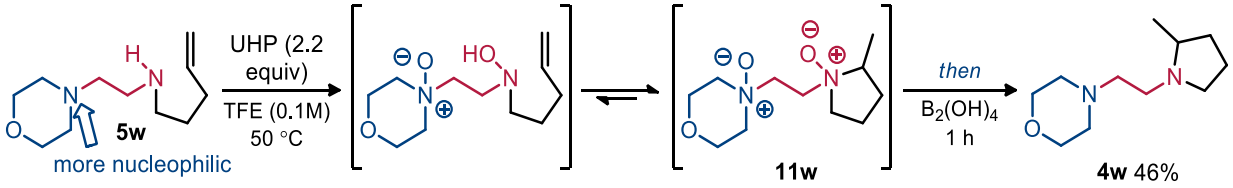
Scheme 3. 18 Indolines formed via redox-enabled hydroamination and the conformational effects



[144] Bagley, M. C.; Tovey, J. *Tetrahedron Lett.* **2001**, *42*, 351.

The functional group tolerance of this process was then evaluated. Related intramolecular hydroamination processes catalyzed by acid, base, and early or late transition metals have significant Lewis base substitution limitations. However, pyridine, thiophene, and ethers were all well tolerated for the redox-enabled methodology (**10p**-**10t**). Unprotected alcohols were also well tolerated under the optimized conditions (**10u**, **10v**). Amine-containing substituents were originally not tolerated when using 1.2 equivalents of the oxidant. Although, when 2.2 equivalents of UHP were used, along with an excess of $B_2(OH)_4$, the pyrrolidine product **10w** was formed in moderate yield (46%). Analysis of the reaction mixtures prior to reduction showed that morpholine was selectively oxidized with 1.2 equivalents of UHP, though the bis-*N*-oxide **11w** was formed when 2.2 equivalents were used (Scheme 3. 19).

Scheme 3. 19 Oxidation of amine containing hydroamination substrates



3.2.4.2 Robustness Screen

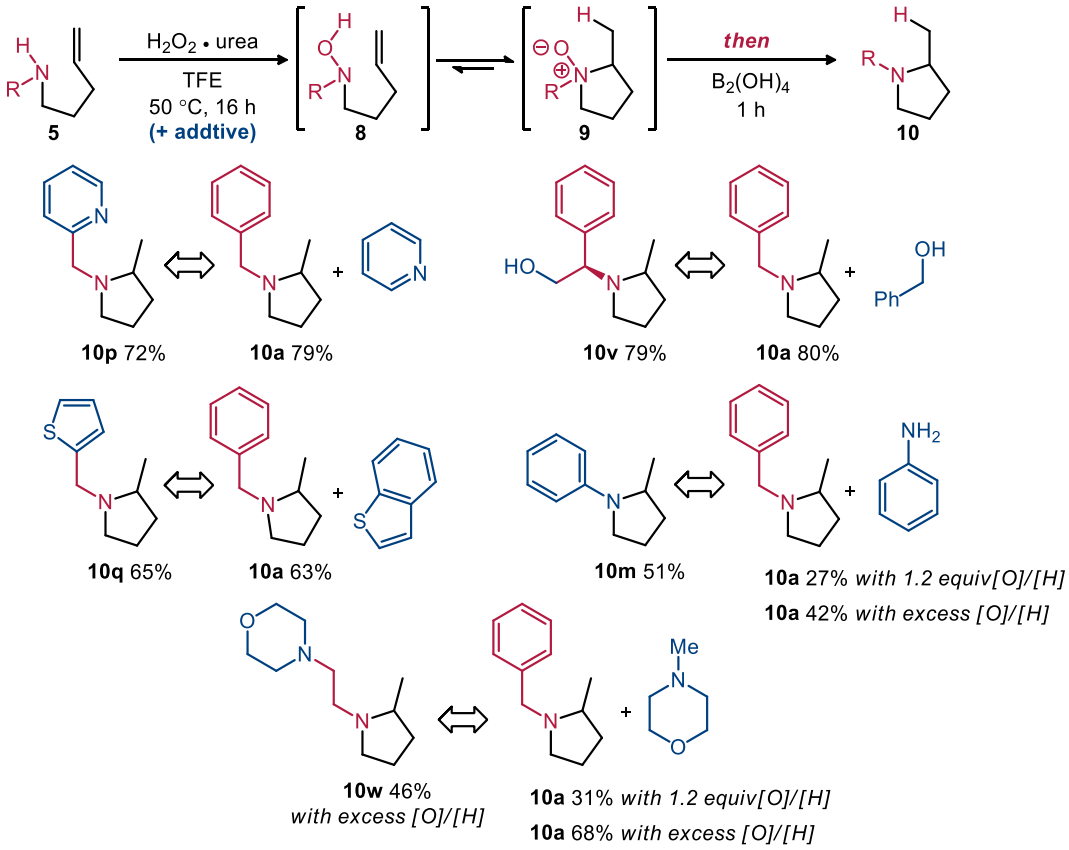
To gain a better appreciation for the functional group tolerance of this one-pot hydroamination, a robustness screen was performed.[145] This would allow a broader array of functional group tests without independent syntheses of alkenylamines. To our knowledge, there are no previously reported examples of the evaluation of hydroamination reactions using a robustness screen. *This screen was completed and evenly divided with Huy Minh Ly.*

Comparing the yield of substrates containing Lewis basic functional groups with the yield of the pyrrolidine **10a** when the corresponding additive was included, good parallels were observed (Scheme 3. 20). For example, adding a pyridine additive led to an ^{1}H NMR yield of 79% of the *N*-benzylpyrrolidine **10a**, whereas including pyridine in the nitrogen substituent (**10p**) led to an isolated yield of 72%. The results of aniline (**10m**) or alkylamine (**10w**) substitution and the corresponding additives were less comparable. However, since the reaction involves nitrogen oxidation and reduction, other reactive amines can lead to a variety

[145] Collins, K. D.; Glorius, F. *Nat. Chem.* **2013**, *5*, 597-601.

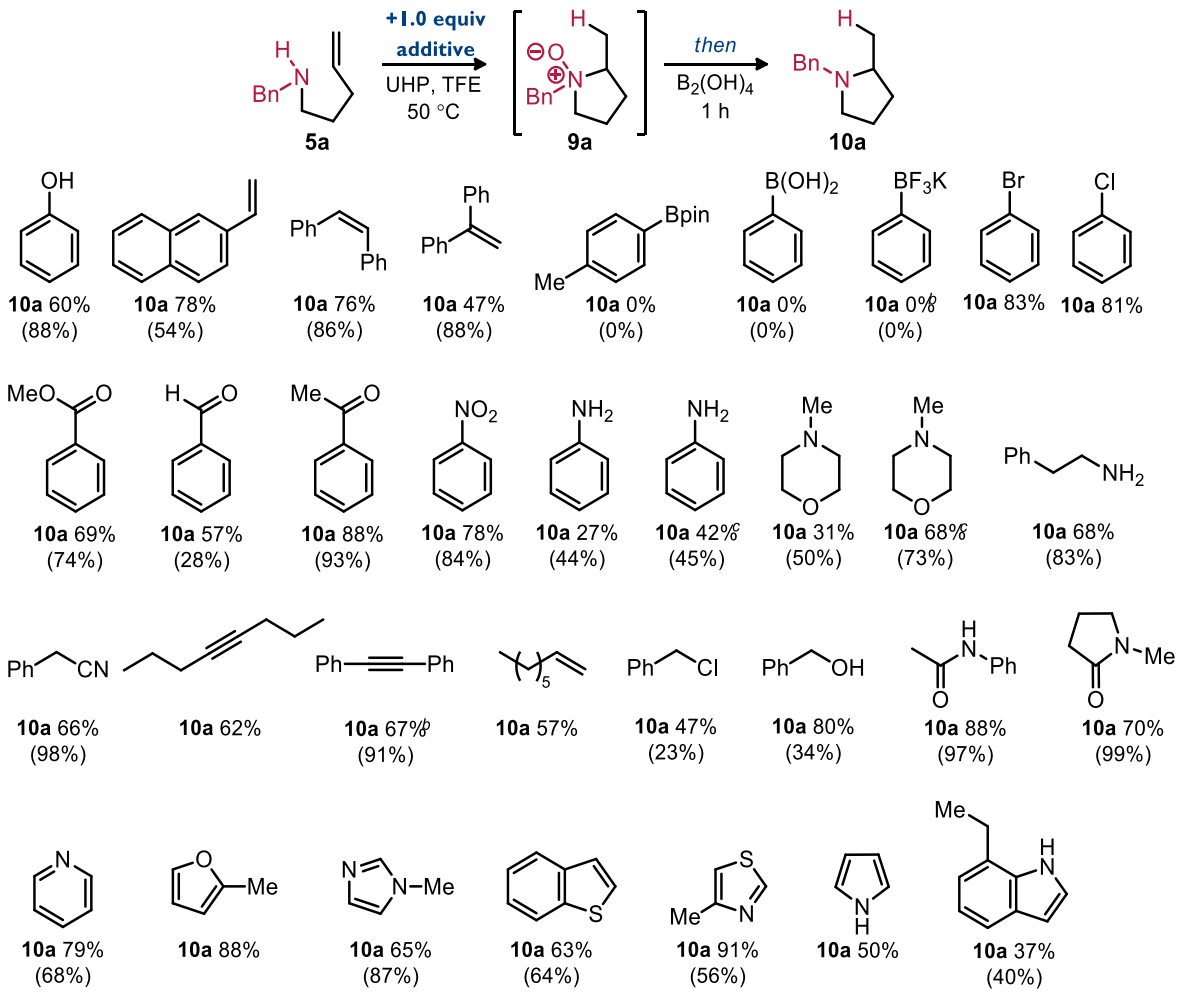
of side reactions that could lead to a less predictable robustness screen outcome. Overall, the validity of the robustness screen using non-amine additives can be demonstrated using these examples.

Scheme 3. 20 Validity of the robustness screen for Lewis basic substitution and additives



A wide variety of other additives were screened and were found to be generally well tolerated (Scheme 3. 21). Specifically, aryl halides, which would likely be not tolerated for transition metal catalyzed processes, were very well tolerated (83 and 81%). Using aniline or a morpholine as additives led to minimal observed product, however, when the 2.2 equivalents of oxidant and reductant were used, the product was again observed in higher yields. When excess oxidant is used, both the nitrogen atoms of the additive and substrate can be oxidized, leading to improved observed yield of the cyclized product. Lower yields were also observed when *N*-alkylation (e.g., benzyl chloride), or other oxidation (e.g., pyrrole) could occur readily. The only substrates which led to complete inhibition of the desired reactivity were the boronic acid, boronic ester, and trifluoroborate salt. For these additives, the oxidant reacted with the boron faster than nitrogen, leading to complete oxidation of the additive and 0% yield of the pyrrolidine.

Scheme 3. 21 Robustness screen for redox-enabled hydroamination[a]



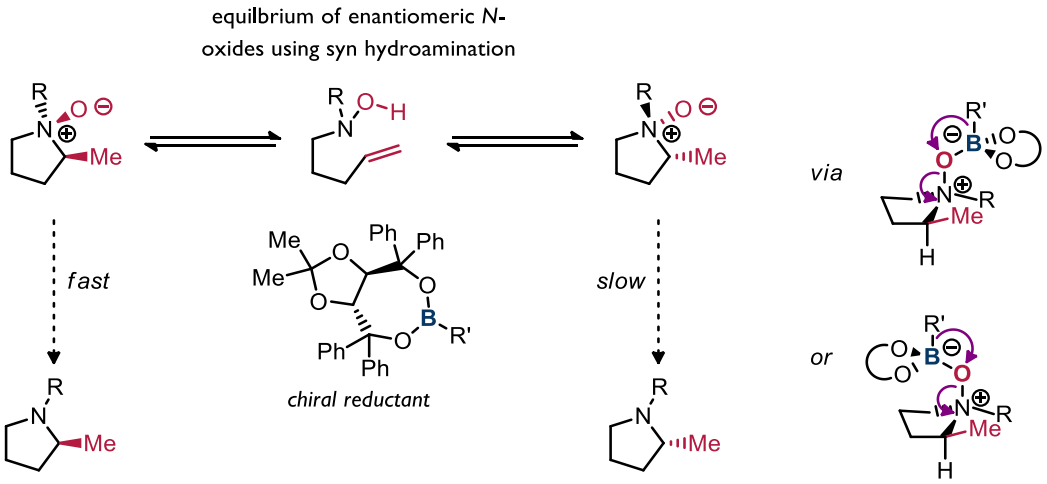
(a) Amine **5a** (1.0 equiv) in solvent, then UHP (1.2 equiv) added, then additive added (1.0 equiv), stirred at 50 °C, 16 h. $B_2(OH)_4$ (1.2 equiv) then added, stirred at 50 °C, 1 h. ^{1}H NMR yield of pyrrolidine **10a** using 1,3,5-trimethoxybenzene as an internal standard (additive remaining in parentheses – value not included for volatile additives). (b) partial solubility of additive. (c) 2.2 Equiv of UHP and $B_2(OH)_4$ were used. UHP = urea hydrogen peroxide adduct; TFE = 2,2,2-trifluoroethanol.

3.2.5 Initial Studies Towards Stereoselective Reduction

The *syn* addition of the intramolecular Cope-type hydroamination step of this one-pot sequence was only exploited by several diastereoselective examples. To further capitalize on this selectivity, it was hypothesized that if the Cope-type hydroamination was in an appropriate equilibrium between the hydroxylamine and the two enantiomeric forms of the pyrrolidine *N*-oxide, then a chiral reductant could feasibly reduce one enantiomer faster than the other (Scheme 3. 22). This process would then function as a dynamic kinetic resolution. Additionally, a kinetic resolution would also be possible if enantiospecific

reduction could occur without the Cope hydroamination/elimination equilibrium occurring to a significant degree. Diboron reagents were known to be too reactive at room temperature or above to allow for a reversible Cope-type hydroamination to occur, so boronic esters were tested as potential chiral reductants.

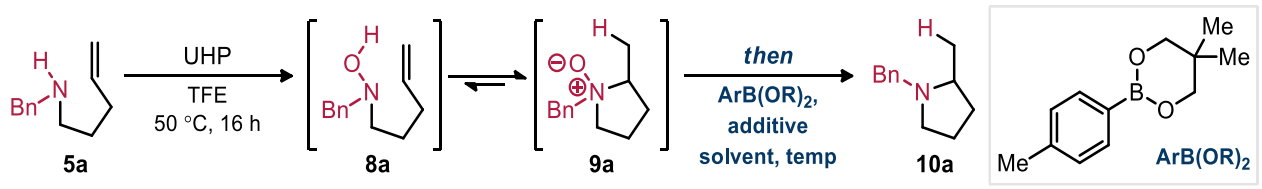
Scheme 3. 22 Proposed dynamic kinetic resolution of 1,2-dialkylpyrrolidines



Preliminary experiments to test the conditions necessary for boronic esters to be used as effective reductants showed minimal reactivity at 50-80 °C (Table 3. 12). Using TFE as a solvent, no reduction was observed at 80 °C using neopentyl glycol arylboronic ester as a model boronic ester (entry 1). The Hall and Ishiyama research groups have shown that Lewis acid activation of boronic esters via coordination to oxygen can improve the reactivity of pinacol boronic esters for allylboration.[146] This interaction could possibly also help improve the reduction of *N*-oxides using boronic esters. However, no improved reactivity was observed when $Sc(OTf)_3$ was added in catalytic amounts (entries 2-4). It was plausible that TFE might stabilize pyrrolidine *N*-oxide **9a** too much for boronic esters to act as reductants, so other solvents were tried along with a variety of Lewis acids. Using $CHCl_3$, trace reduced pyrrolidine **10a** was observed, however, the addition of Lewis acids led to no reduction (entries 5-10). Using the a less polar solvent, toluene, analogous results were obtained with the screened Lewis acids (entries 11-16). Again, Lewis acids were found to have a detrimental effect on the desired reaction.

[146] (a) Kennedy, J. W.; Hall, D. G. *J. Am. Chem. Soc.* **2002**, *124*, 11586–11587. (b) Ishiyama, T.; Ahiko, T.; Miyaura, N. *J. Am. Chem. Soc.* **2002**, *124*, 12414-12415. (c) Kennedy, J. W.; Hall, D. G. *J. Org. Chem.* **2004**, *69*, 4412–4428. (d) Rauniyar, V.; Zhai, H.; Hall, D. G. *J. Am. Chem. Soc.* **2008**, *130*, 8481–8490.

Table 3. 12 Optimization of tandem Cope-type hydroamination and reduction using boronic esters



Entry	Additive (mol %)	Solvent	Temp (°C)	Yield 10a (%)[b]
1	-	TFE	80	0
2	$Sc(OTf)_3$ (10)	TFE	80	0
3	$Sc(OTf)_3$ (20)	TFE	80	0
4	$Sc(OTf)_3$ (50)	TFE	80	0
5	-	$CHCl_3$	50	7
6	$BF_3{\cdot}OEt_2$ (10)	$CHCl_3$	50	0
7	$Al(OTf)_3$ (10)	$CHCl_3$	50	0
8	$Mg(OTf)_2$ (10)	$CHCl_3$	50	0
9	$Sc(OTf)_3$ (10)	$CHCl_3$	50	0
10	$SnCl_2{\cdot}H_2O$ (10)	$CHCl_3$	50	0
11	-	Toluene	50	12
12	$BF_3{\cdot}OEt_2$ (10)	Toluene	50	0
13	$Al(OTf)_3$ (10)	Toluene	50	0
14	$Mg(OTf)_2$ (10)	Toluene	50	0
15	$Sc(OTf)_3$ (10)	Toluene	50	0
16	$SnCl_2{\cdot}H_2O$ (10)	Toluene	50	0

(a) Amine **5a** (1.0 equiv) in TFE (0.1 M), then UHP (1.2 equiv) added, stirred at 50 °C, 16 h. Concentrate, then add solvent (0.1 M), boronic ester $ArB(OH)_2$ (1.5 equiv), and additive. Stir at given temperature, 16 h. (b) ^1H NMR yield of **10a** using 1,3,5-trimethoxybenzene as an internal standard. UHP = urea hydrogen peroxide adduct; TFE = 2,2,2-trifluoroethanol.

Observing this inefficient reduction reactivity with or without Lewis acids, the optimization of this reduction with boronic esters was discontinued. The proposed kinetic resolution could be reassessed if an improved activating system for boronic ester reductions was optimized or another potential enantiospecific *N*-oxide reductant was identified.[147] Terminal substitution of the alkene, increasing the size of the C2-subsitutent, may also improve enantiospecificity if reduction can be accomplished.

3.2.6 Application of Oxidation Conditions to Hydroxylamine Synthesis

Observing the success of the developed oxidation conditions for intramolecular hydroamination, we sought to test if the UHP/TFE combination could also be used for amine oxidative hydroxylamine synthesis. The direct oxidative synthesis of hydroxylamines from amines is a desirable route, however,

[147] For a potential molybdenum-based biocatalytic approach, see: (a) Abo, M.; Tachibana, M.; Okubo, A.; Yamazaki, S. *Bioorg. Med. Chem.* **1995**, *3*, 109-112. (b) Simala-Grant, J. L.; Weiner, J. H. *Microbiology* **1996**, *142*, 3221-3239. (c) Anselmi, A.; Aggarwal, N.; Moody, T. S.; Castagnolo, D. *ChemBioChem* **2021**, *22*, 298-307.

there are minimal examples currently reported (Scheme 3. 23). Biloski first reported the use of benzoyl peroxide (BPO) for the oxidation of amines to *O*-benzoylhydroxylamines.[148] Further reports since then have modified the reaction conditions and provided reliable deacylation methods. Murray reported the oxidation of amines using a solution of DMDO in acetone in 1989.[149] This methodology includes the general drawbacks associated with the use of DMDO, such as the requirement for DMDO titration and difficult storage. Kropp reported a similar process in 2000 using oxone as the oxidant with silica gel in refluxing benzene.[150] Using a Cope elimination strategy, Kurth and O'Neil separately reported the synthesis of dialkylhydroxylamines by Michael addition, followed by oxidation, which triggers Cope elimination.[35] Most recently, Crich has reported the use of dialkylperoxide species as oxidants for amines.[151] There are three main limitations with the currently available methodology: (1) multistep synthesis with low atom economy, (2) use of oxidants that are not commercially available and/or (3) inconsistent results, as noted by Yamamoto recently.[148c] If a UHP/TFE oxidation system could work efficiently, then atom economy and commercial availability could be greatly improved for hydroxylamine synthesis.

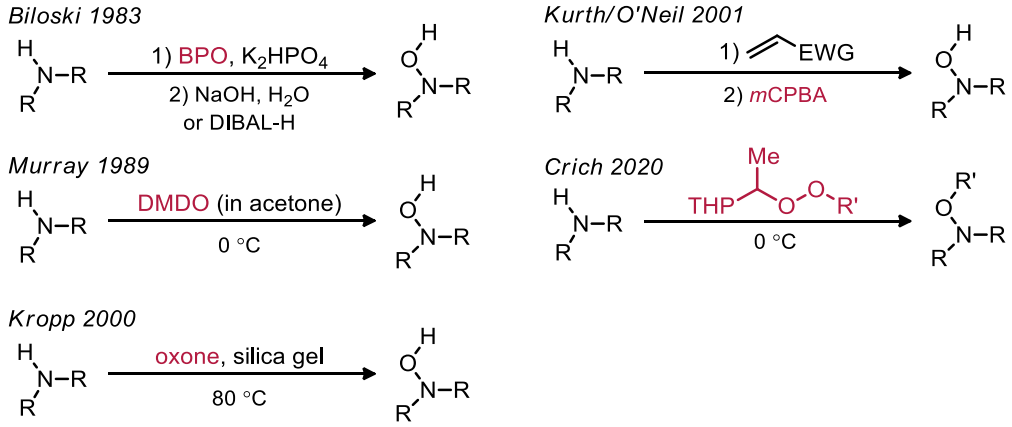
[148] (a) Biloski, A. L.; Ganem, B. *Synth. Commun.* **1983**, *7*, 537-538. (b) Berman, A. M.; Johnson, J. S. *J. Org. Chem.* **2006**, *71*, 219-224. (c) Banerjee, A.; Yamamoto, H. *Chem. Sci.* **2019**, *10*, 2124-2129.

[149] Murray, R. W.; Singh, M. *Synthetic Commun.* **1989**, *19*, 3509-3522.

[150] Fields, J. D.; Kropp, P. J. *J. Org. Chem.* **2000**, *65*, 5937-5941.

[151] (a) Hill, J.; Hettikankanamalage, A. A.; Crich, D. *J. Am. Chem. Soc.* **2020**, *142*, 14820-14825. (b) Hill, J.; Crich, D. *Org. Lett.* **2021**, *23*, 6396–6400 (c) Upadhyaya, K.; David Crich, D. *Org. Lett.* **2022**, *24*, 9, 1833–1836. For related reactivity, see: (d) Adam, W.; Heil, M. *J. Am. Chem. Soc.* **1992**, *114*, 5591−5598. (e) (32) Adam, W.; Stoessel, R.; Treiber, A. *J. Org. Chem.* **1995**, *60*, 2879−2884. (f) Kelly, D. R.; Bansal, H.; Morgan, J. J. G. *Tetrahedron Lett.* **2002**, *43*, 9331−9333.

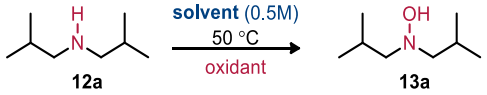
Scheme 3. 23 Reported methods for the oxidative synthesis of hydroxylamines from amines



We began the optimization using UHP in trifluoroethanol, as optimized previously (section 3.2.3), with diisobutylamine (**12a**) (Table 3. 13). Using an excess of the amine led to a good yield of hydroxylamine **13a** and a low yield of the over-oxidation product, nitrone (entry 1). Notably, the similar structures of the amine reagent and hydroxylamine product led to difficult ^{1}H NMR analysis, though it was determined that diethyl ether was an appropriate NMR solvent choice to allow for distinction between related signals. Using HFIP, a similar fluorinated alcohol also known to activate peroxide, led to a significantly reduced yield of hydroxylamine **13a** (entry 2). HFIP is also more acidic than TFE (pKa = 9.3 vs. 12.8), so the reduced nucleophilicity of protonated diisobutylamine may be the cause of the lower yield.[152] Increasing the excess of amine to 5 equivalents led to a quantitative yield of hydroxylamine using TFE (entry 3). Again, using HFIP was detrimental to the reaction (entry 4), as was methanol (entry 5). Attempts to reduce the reaction temperature (entry 6) or time (entry 7) led to reduced yields, therefore the 50 °C temperature and 16 h time were used for further experiments.

[152] Dyatkin, B. L.; Mochalina, E. P.; Knunyants, I. L. *Tetrahedron* **1965**, *21*, 2991-2995.

Table 3. 13 Optimization for the oxidative synthesis of secondary hydroxylamines

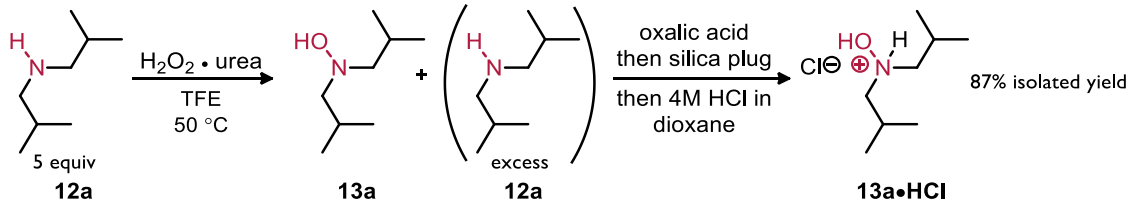


Entry	Equiv UHP	Equiv amine	Solvent	Yield 13a (%)[b]
1	1.0	3.0	TFE	86
2	1.0	3.0	HFIP	36
3	**1.0**	**5.0**	**TFE**	**99**
4	1.0	5.0	HFIP	56
5	1.0	5.0	MeOH	38
6[c]	1.0	5.0	TFE	74
7[d]	1.0	5.0	TFE	86

(a) UHP is dissolved in the solvent (0.5M), then amine **12a** was added, 50 °C, 16 h. (b) ^{1}H NMR yield of **13a** using 1,3,5-trimethoxybenzene as an internal standard. (c) rt instead of 50 °C. (d) 6 h instead of 16 h.

With optimized conditions in hand, the scope could be explored, however, the isolation of hydroxylamines from the reaction mixture proved challenging. The hydroxylamine **13** and its parent amine **12** present in excess have very similar properties, such as solubility and acidity/basicity, and they likely form strong hydrogen-bonds with each other in solution. Extensive trial and error of various aqueous workups and chromatography failed to provide adequate isolated yields and purity of hydroxylamine product. However, the lower pK_a of protonated amines offered an opportunity to selectivity form the solid oxalic salt of the excess amine reagent and remove it via filtration. *This purification optimization was completed with the help of Myroslava Volosheniuk.*

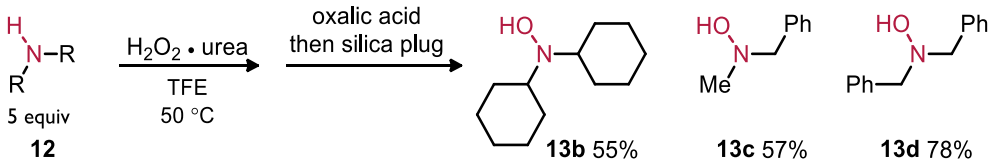
Scheme 3. 24 Reaction procedure for the synthesis and isolation of secondary hydroxylamines



This optimized method then involved a short silica plug for purification, which allowed large scale synthesis to function similarly. The silica plug allows the separation of the hydroxylamine from any over-oxidized nitrone product. Volatile hydroxylamines, such as *N*,*N*-diisobutylhydroxylamine, could be protonated to form a solid HCl salt to improve stability and ease of isolation (Scheme 3. 24). This method relies on the accurate addition of 1 equivalent of oxalic acid relative to the remaining amine reagent, as determined by ^{1}H NMR analysis. If insufficient oxalic acid is added, the remaining free amine reduces the

isolated yield on hydroxylamine, likely via strong hydrogen bonding interactions, interfering with silica plug separation.

Scheme 3. 25 Preliminary scope of secondary hydroxylamine synthesis



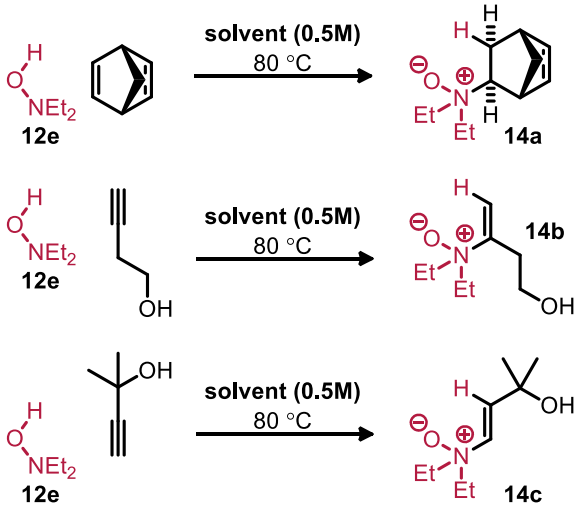
With the optimized isolation method, good yields of several hydroxylamines can be obtained (**13b**-**13d**) (Scheme 3. 25). The excess amine used can also be recovered as the oxalic acid salt. This work was then taken over by undergraduate student, Daniel Barriault, as an Honour's project to further generalize the purification and determine the scope of the reaction.

3.3 Reinvestigating Intermolecular Hydroamination

3.3.1 Solvent Effects using TFE

Throughout other Cope-type hydroamination studies, it became clear that TFE had a particularly beneficial effect on reactivity. TFE had not previously been investigated as a solvent for Cope-type hydroamination. The relative reactivity of activated alkenes and alkynes was therefore assessed using MeCN, EtOH, and TFE (Table 3. 14). While no hydroamination product **14a**-**c** was observed when MeCN was used as a solvent, modest yields were obtained when using EtOH at 80 °C. These results align well with previous intermolecular Cope-type hydroamination studies.[87] Using TFE, all hydroamination yields increase considerably, demonstrating significant solvent effects.

Table 3. 14 Solvent effects for intermolecular Cope-type hydroamination[a]

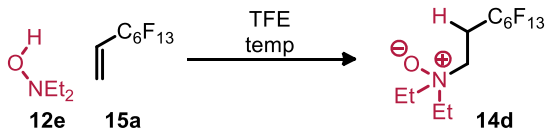


product	Yield with MeCN (%)[b]	Yield with EtOH (%)[b]	Yield with TFE (%)[b]
14a	0	36	78
14b	0	12	36
14c	0	30	66

(a) Conditions: hydroxylamine **12e** (1.0 equiv) in solvent (0.5M), then alkene or alkyne (10 equiv) added, stirred at 80 °C, 16 h. (b) ^{1}H NMR yield of **14** using 1,3,5-trimethoxybenzene as an internal standard. TFE = 2,2,2-trifluoroethanol.

Using an electronically activated alkene with a perfluorinated hexyl substituent, hydroamination proceeds well forming *N*-oxide **14d** in excellent yields with a small excess of alkene (Table 3. 15, entries 1-2). This reaction evens proceeds well at 50 °C during a 22 h reaction time (entry 3), which is significantly lower than all other intermolecular hydroamination reactions reported at this time (95-150 °C).[87]

Table 3. 15 Cope-type hydroamination of polyfluorinated alkenes in TFE[a]

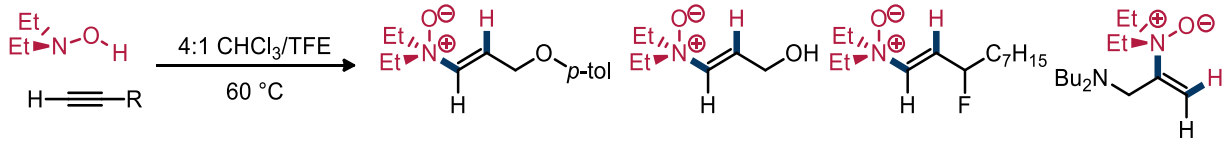


Entry	Equiv 1:6a	Temp (°C)	Yield of 14d (%)[b]
1	1:5	80	92
2	1:3	80	88
3	1:5	50	92

a) Conditions: *N*,*N*-diethylhydroxylamine **12e** in TFE (1 M), then alkene **15a** added, stirred at given temperature for 22 h. (b) ^{1}H NMR yield of **14a** using 1,3,5-trimethoxybenzene as an internal standard. TFE = 2,2,2-trifluoroethanol.

Within the time of the solvent effect studies using TFE, Justin Kim's research group reported that TFE mitigates the degradation of enamine *N*-oxides formed via Cope-type hydroamination of alkynes (Scheme 3. 26).[153] The authors report an optimized solvent mixture of 4:1 $CHCl_3$/TFE to balance reaction rate considerations with *N*-oxide stability. The reaction times remained quite long (up to 240 h) at 60 °C for substrates without strong electron withdrawing groups. This work was undertaken to allow simpler synthetic access to enamine *N*-oxides for use as hypoxia-responsive prodrugs and imaging agents, therefore the requirement for electronic activation by inductive effects was acceptable. TFE, however, was not an acceptable solvent choice for later bioorthogonal applications due to toxicity, so other activating modifications to the alkyne substrate were made.[154]

Scheme 3. 26 Selected examples of the hydroamination of alkynes using *N*,*N*-diethylhydroxylamine (*Kim 2021*)



3.3.2 Attempts towards Intermolecular Redox-Driven Hydroamination

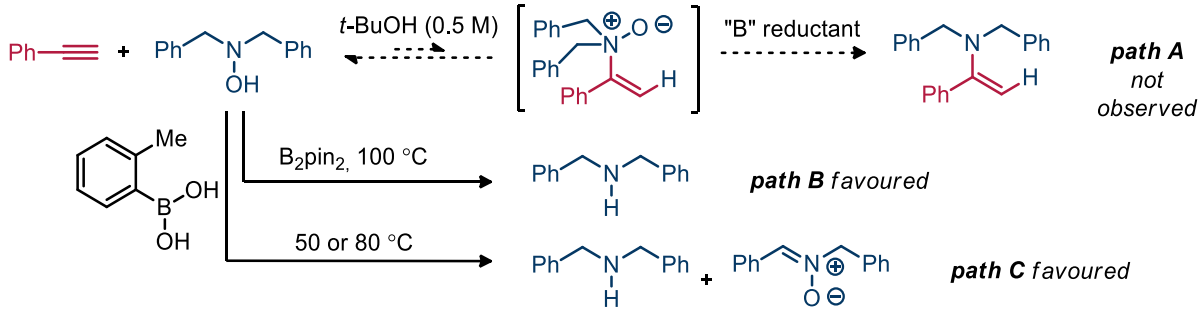
Given the improved Cope-type hydroamination reactivity in TFE as a solvent and the observed chemoselectivity for *N*-oxide over hydroxylamine reduction (Scheme 3. 13), in-situ reduction of the *N*-

[153] Kang, D.; Cheung, S. T.; Wong-Rolle, A.; Kim, J. *ACS Cent. Sci.* **2021**, *7*, 631-640.
[154] (a) Kang, D.; Kim, J. *J. Am. Chem. Soc.* **2021**, *143*, 5616–5623. (b) Kang, D.; Cheung, S. T.; Kim, J. *Angew. Chem. Int. Ed.* **2021**, *60*, 16947–16952. (c) Kang, D.; Lee, S.; Lim, J. *Chem* **2022**, doi.org/10.1016/j.chempr.2022.05.018

oxide product of hydroamination is plausible using a boron-based reductant. An in-situ reduction could help push the hydroamination equilibrium towards the product side, allowing improved yields of tertiary amine products via Cope-type hydroamination.

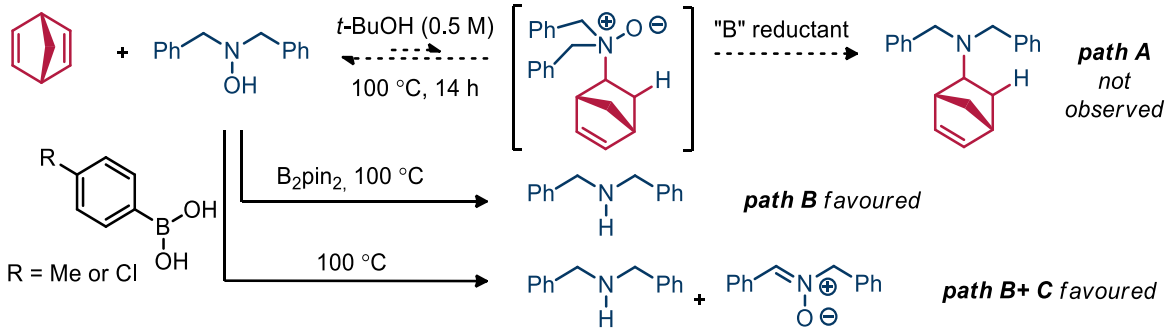
Using phenylacetylene and dibenzylhydroxylamine, B_2pin_2 and boronic acid were both tested as possible reductants for the desired enamine *N*-oxide intermediate (Scheme 3. 27). When B_2pin_2 was used, premature reduction of the hydroxylamine was the only observed product (path B). When boronic acid was used at lower temperatures, both the amine and nitrone derived from dibenzylhydroxylamine were observed. The presence of amine and nitrone is indicative of the redox-based degradation of hydroxylamine (path C).

Scheme 3. 27 Attempted reduction-enabled Cope-type hydroamination of phenylacetylene



Using a strain activated alkene, norbornadiene, to further promote the initial Cope-type hydroamination, similar results were obtained (Scheme 3. 28). Path B was favoured when B_2pin_2 was used as a reductant, and paths C and possibly B were likely involved when a boronic acid was used.

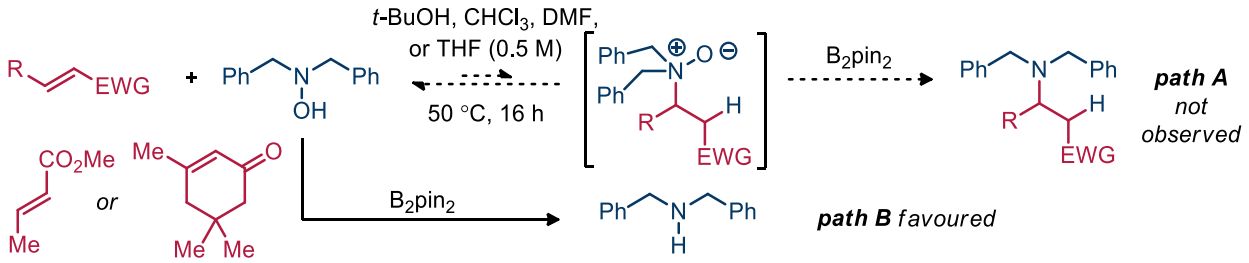
Scheme 3. 28 Attempted reduction-enabled Cope-type hydroamination of norbornadiene



As strain release was not observed to help promote the desired reactivity, electronically activated alkenes were tried under similar reaction conditions (Scheme 3. 29). Michael acceptors have been previously reported as effective reagents for Cope-type hydroamination with primary hydroxylamines at lower

temperatures than unactivated species.[155] However, only hydroxylamine reduction (path B) was observed again using a variety of solvents with B_2pin_2 as a reductant.

Scheme 3. 29 Attempted reduction-enabled Cope-type hydroamination of Michael acceptors



It appears as though the chemoselectivity of *N*-oxide reduction by diboron or boronic acids is inadequate for the desired redox-enabled Cope-type hydroamination process. Fortunately, ongoing work from PhD candidate, Huy Minh Ly, can potentially solve this chemoselectivity problem using an osmium-based reductant.

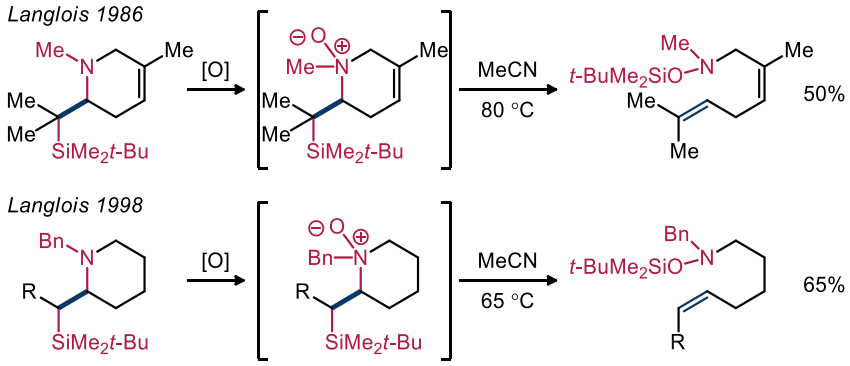
3.3.3 Activating Effects of Silicon Substitution

Along with the newly studied beneficial solvent effects of TFE, additional activating effects of silicon substitution on alkenes and alkynes were studied. Sila-Cope elimination has already been reported (Scheme 3. 30), so it was important to consider the potential elimination of the desired *N*-oxide products.[156] Two examples of the Cope-type hydroamination of a vinylsilane have been reported by the Beauchemin research group previously (Scheme 3. 31).[87b,128b]

[155] (a) Niu, D.; Zhao, K. *J. Am. Chem. Soc.* **1999**, *121*, 2456-2459. (b) Moglioni, A. G.; Muray, E.; Castillo, J. A.; Álvarez-Larena, Á.; Moltrasio, G. Y.; Branchadell, V.; Ortuño, R. M. *J. Org. Chem.* **2002**, *67*, 2402-2410.

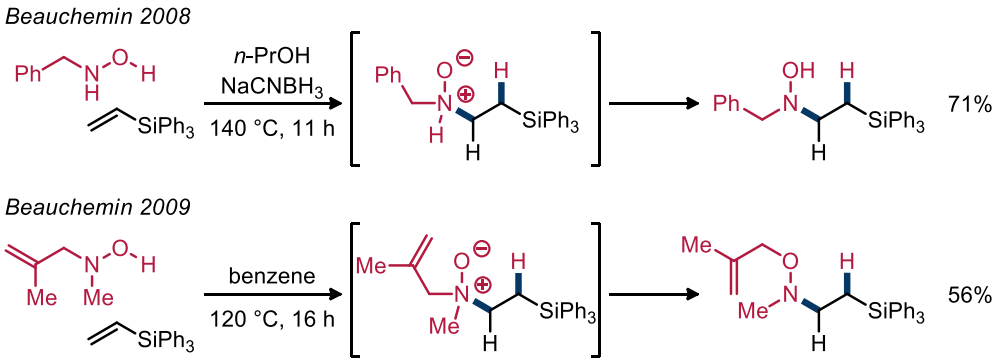
[156] (a) Fall, Y.; Van Bac, N.; Langlois, Y. *Tetrahedron Lett.* **1986**, *27*, 3611-3614. (b) Vidal, T.; Magnier, E.; Langlois, Y. *Tetrahedron* **1998**, *54*, 5959-5966.

Scheme 3. 30 Known examples of sila-Cope elimination



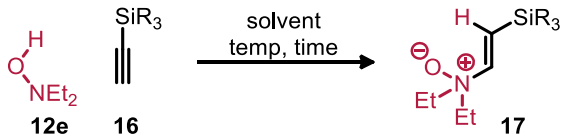
The previously reported yields for triphenylvinylsilane hydroamination are similar (71% and 56%) to those observed for styrenes in these reports (36-79% and 28-50% respectively), although vastly improved anti-Markovnikov regioselectivity is observed. Overall, the α-negative and β-positive stabilization from silicon substitution appears to improve both reactivity and regioselectivity.

Scheme 3. 31 Previous examples of Cope-type hydroamination of vinylsilanes



Further exploration of silicon-substituted alkenes and alkynes was warranted, especially with the added beneficial solvent effects of TFE. *This work was completed with the help of Mei Xi Chen.* Silyl-substituted alkynes were used first since the trans orientation of the enamine *N*-oxide would prohibit sila-Cope elimination (Table 3. 16). When *N*,*N*-diethylhydroxylamine was mixed with excess triisopropylacetylene in TFE, a good yield of the hydroamination product, enamine *N*-oxide **16a**, was observed (entry 1). Using a smaller excess of acetylene also led to good yields (entries 2-3). Using the $CHCl_3$/TFE solvent mixture and equivalents reported by Kim's research group (Scheme 3. 26), enamine *N*-oxide was observed in high yields after 18 h reaction time (entries 4-7).

Table 3. 16 Cope-Type Hydroamination of silyl-substituted acetylene[a]



12e **16** **17**

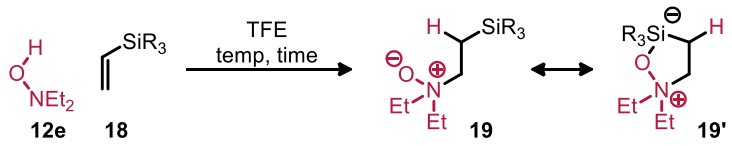
Entry	SiR_3	Solvent (M)	Equiv 12e:16	Temp (°C)	Time (h)	Yield of 17 (%)[b]
1	Si(*i*-Pr)$_3$	TFE (0.2 M)	1:10	80	20	80
2	Si(*i*-Pr)$_3$	TFE (0.5 M)	1:5	80	15	86
3	Si(*i*-Pr)$_3$	TFE (1.0 M)	1:2	80	15	73
4	Si(*i*-Pr)$_3$	TFE/$CHCl_3$ 1:4 (0.2 M)	5:1	60	1	11
5	Si(*i*-Pr)$_3$	TFE/$CHCl_3$ 1:4 (0.2 M)	5:1	60	2	31
6	Si(*i*-Pr)$_3$	TFE/$CHCl_3$ 1:4 (0.2 M)	5:1	60	3	47
7	Si(*i*-Pr)$_3$	TFE/$CHCl_3$ 1:4 (0.2 M)	5:1	60	18	68
8	$SiMe_3$	TFE (0.2 M)	1:10	80	20	82
9	$SiMe_3$	TFE (1.0 M)	1:5	80	15	76
10	$SiMe_3$	TFE (1.0 M)	1:2	80	15	10
11	$SiMe_3$	TFE/MeCN 1:1 (0.1 M)	1:10	80	18	30

(a) Conditions: *N*,*N*-diethylhydroxylamine in solvent, then acetylene **16** added, stirred at given temperature for given time. (b) ^{1}H NMR yield of **17** using 1,3,5-trimethoxybenzene as an internal standard. TFE = 2,2,2-trifluoroethanol.

Unfortunately, the isolation of these charged products (**17**) proved difficult by recrystallization and flash column chromatography, and no similar zwitterionic structures with silicon substitution have been reported to date to help guide isolation methods. Attempts to reduce *N*-oxide **17** then isolate the silyl-substituted enamine also proved unsuccessful. These enamines could hydrolyze on silica, so vinylsilanes (**18**) were used in place of the acetylenes in order to obtain more stable derivatization products (Table 3. 17).

The reaction of *N*,*N*-diethylhydroxylamine with triphenylvinylsilane proceeded well at high concentrations of TFE (0.5-1 M) with excess alkene (entries 1-6). The crude ^{1}H NMR of this hydroamination product corresponds well with the zwitterionic structures **19a** or **19a'**. Dimethylphenylvinlysilane was more reactive at lower concentration (entries 7-8) than the triphenylvinylsilane (entries 1-2). Higher concentrations of TFE allowed for lower equivalents of alkene to be used (entries 9-10). Again, using the conditions reported by Kim's research group, a good yield of the hydroamination product could be observed after 18 h (entry 11). The isolation of hydroamination products **19** and their reduced forms also proved difficult, so further isolation optimization is required.

Table 3. 17 Cope-Type Hydroamination of Vinylsilanes[a]



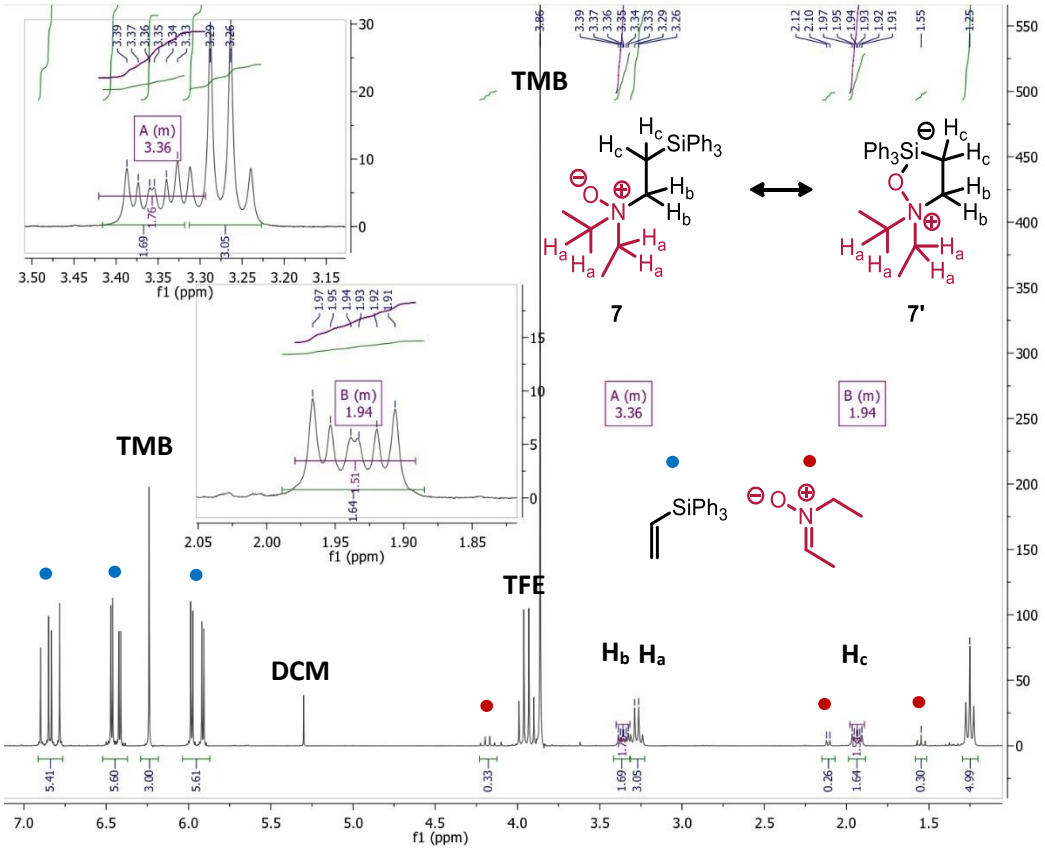
Entry	SiR_3	Solvent (M)	Equiv 12e:18	Temp (°C)	Time (h)	Yield of 19 (%)[b]
1	$SiPh_3$	TFE (0.2 M)	1:5	80	18	51
2	$SiPh_3$	TFE (0.2 M)	1:10	80	18	82
3	$SiPh_3$	TFE (0.5 M)	1:10	80	17	79
4	$SiPh_3$	TFE (0.5 M)	1:2	80	17	89
5	$SiPh_3$	TFE (0.5 M)	1:5	80	17	89
6	$SiPh_3$	TFE (1.0 M)	1:2	80	17	88
7	$SiMe_2Ph$	TFE (0.2 M)	1:5	80	18	89
8	$SiMe_2Ph$	TFE (0.2 M)	1:10	80	18	93
9	$SiMe_2Ph$	TFE (0.5 M)	1:2	80	19	88
10	$SiMe_2Ph$	TFE (1.0 M)	1:2	80	15	87
11	$SiMe_2Ph$	TFE/$CHCl_3$ 1:4 (0.2 M)	5:1	60	18	74

a) Conditions: *N*,*N*-diethylhydroxylamine in solvent, then alkene **18** added, stirred at given temperature for given time. (b) ^{1}H NMR yield of **19** using 1,3,5-trimethoxybenzene as an internal standard. TFE = 2,2,2-trifluoroethanol.

The presence of virtual coupling in the ^{1}H NMR spectra of these products is a distinct feature supporting the zwitterionic structure proposed for *N*-oxide **19** (Figure 3. 3). Virtual coupling occurs when the chemical shift between two coupled protons, which are isolated in space from other protons, is the same order as the coupling constant.[157] This leads to false coupling information with complex, non-first order multiplet structures. The signal at 3.36 ppm is second-order due to the small chemical shift difference between the methylenes of the ethyl groups (H_a) and the other methylene attached to the nitrogen (H_b). The complicated nature of the resonance of the methylene protons alpha to the silicon (H_c) at 1.94 ppm is also a result of the extensive coupling and close proximity to the other methylene resonances at 3.3 ppm. These virtual couplings are indicative of a hydroamination product since H_a/H_b must be close in space for virtual coupling to occur, which suggests new N-C bond formation. The high chemical shift of the methylene signals also suggests a positively charged nitrogen species.

[157] Musher, J. I., Corey, E. J. *Tetrahedron* **1962**, *18*, 791-809.

Figure 3. 3 Crude ^{1}H NMR spectrum of amine *N*-oxide **19a** with virtual coupling (1.0-7.0 ppm)



While the structural determination of these hydroamination products is likely correct based on literature precedent of uncharged species, further work is required to isolate or derivatize and isolate these zwitterionic silylamines.[158] In future work, reverse phase chromatography could aid in isolation of the *N*-oxides **17** or **19**. Alternatively, further work to optimize the reduction and isolation of silylamines could also be completed, since related silylamines have previously been isolated with silica gel column chromatography or simply aqueous extraction.[158]

[158] Zhu, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **2014**, *136*, 15913−15916.

3.4 Conclusion

The new era of Cope-type hydroamination research within the Beauchemin research group has led to a variety of new amination methodology. The redox-enabled intramolecular hydroamination procedure described in section 3.2 demonstrates the novel stoichiometric variant of an "oxygen-transfer" methodology. This work allows secondary amines to be used directly as substrates, under mild conditions, with broad functional group tolerance, and does not require column chromatography for the isolation of most pyrrolidine products. The stoichiometric studies described above allow for further development towards catalytic oxygen-transfer methodology. The oxidation conditions developed for this work can also be applied to the direct oxidative synthesis of secondary hydroxylamines using excess amine reagents. The strong solvent effects of TFE and the activating and stabilizing effects of silicon substitution demonstrate new directions for the application of Cope-type hydroamination. *N*-Oxyureas were also found to be suitable substrates for Cope-type hydroamination at high temperatures. The stability of the amine *N*-oxides formed for several of the intermolecular reactions described was still problematic, so further studies on the Cope-type hydroamination of vinylboronates was conducted (Chapter 4). The O-B intramolecular Lewis interactions, similar to those proposed for vinylsilanes, could also greatly improve the stability for the products of vinylboronate hydroamination.

Chapter 4 Hydroamination with Boron-Containing Species

Within this chapter, the recent discovery and work exploring the hydroamination of vinylboronate species and related reactivity with alkenes and alkynes is disclosed. This chemistry is significant for the synthesis of biologically relevant aminoboronic acids and related amphoteric compounds. Literature background, key synthetic findings, computational details (in collaboration with the Schwan research group), and ongoing work are included. The research within this chapter was completed in a collaborative manner with Myroslava Volosheniuk and Eric Nicol (University of Guelph). Refer to Statement of Contributions *for more details.*

4.1 Aminoboronic Acid Derivatives and Boron Heterocycles

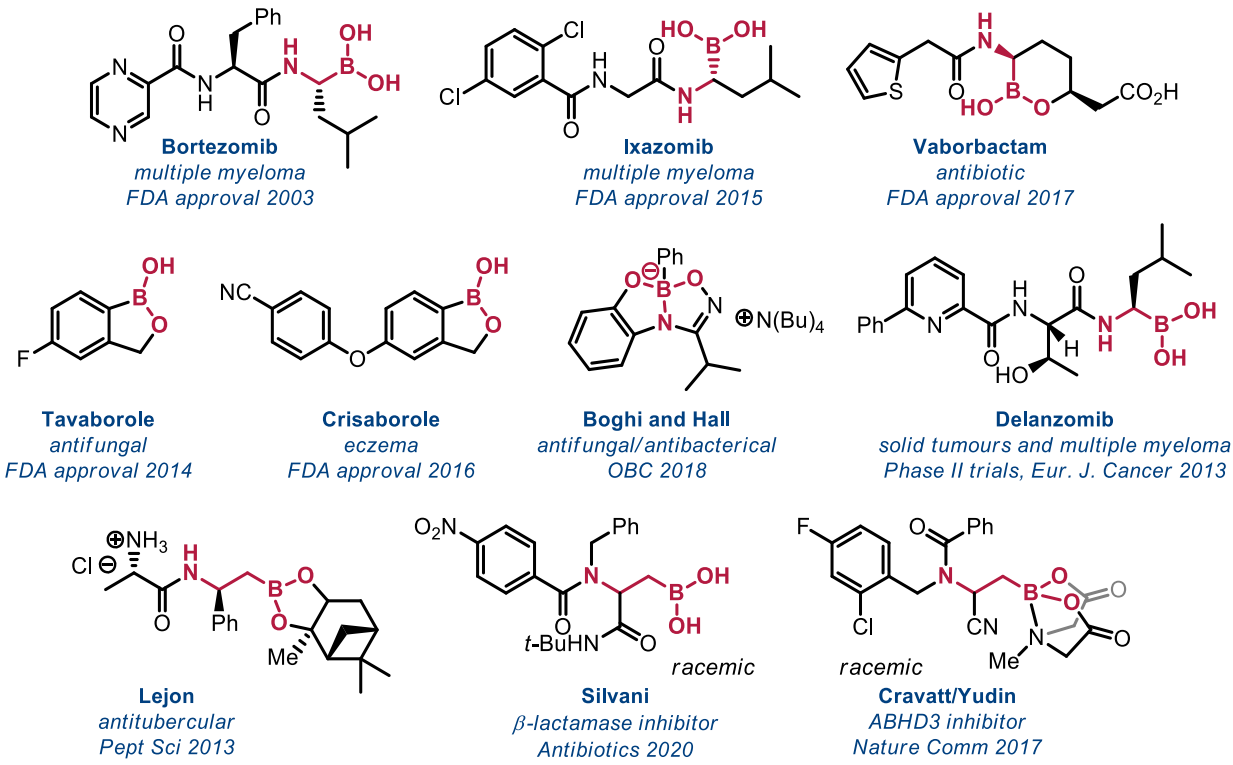
4.1.1 Biological Relevance

Boron-containing species have recently garnered attention as possible pharmaceuticals (Figure 4. 1). Specifically, boronic acid derivatives, such as aminoboronic acids, have the potential to act as unnatural amino acids and transition state analogues to block enzymatic activity of various proteases.[159] Proteases catalyze the hydrolysis of peptide bonds, which is important for many physiological processes, and are therefore implicated in a broad array of diseases. Anticancer, antibiotic, antifungal, and eczema drugs have been recently approved by the Food and Drug Administration (FDA) in the USA. Academic drug discovery has also been underway for and α- and β-aminoboronic acids among other boron-containing structures.[160]

[159] (a) Touchet, S.; Carreaux, F.; Carboni, B.; Bouillon, A.; Boucher, J. -L. *Chem. Soc. Rev.* **2011**, *40*, 3895–3914. (b) Smoum, R.; Rubinstein, A.; Dembitsky, V. M.; Srebnik, M. *Chem. Rev.* **2012**, *112*, 4156–4220.

[160] (a) Boghi, M.; Hall, D. G. *Org. Biomol. Chem.* **2018**, *16*, 4849-4856. (b) Gallerani, E.; Zucchetti, M.; Brunelli, D.; Marangon, E.; Noberasco, C.; Hess, D.; Delmonte, A.; Martinelli, G.; Böhm, S.; Driessen, C.; De Braud, F.; Marsoni, S.; Cereda, R.; Sala, F.; D'Incalci, M.; Sessa, C. *Eur. J. Cancer* **2013**, *49*, 290-296. (c) Gorovoy, A. S.; Gozhina, O.; Svendsen, J. -S.; Tetz, G. V.; Domorad, A.; Tetz, V. V.; Lejon, T. *J. Pept. Sci.* **2013**, *19*, 613-618. (d) Bassini, E.; Gazzotti, S.; Sannio, F.; Lo Presti, L.; Sgrignani, J.; Docquier, J. -D.; Grazioso, G.; Silvani, A. *Antibiotics* **2020**, *9*, 249-270. (e) Tan, J.; Cognetta III, A. B.; Diaz, D. B.; Lum, K. M.; Adachi, S.; Kundu, S.; Cravatt, B. F.; Yudin, A. K. *Nat. Commun.* **2017**, *8*, 1760-1768.

Figure 4. 1 Bioactive molecules containing boron



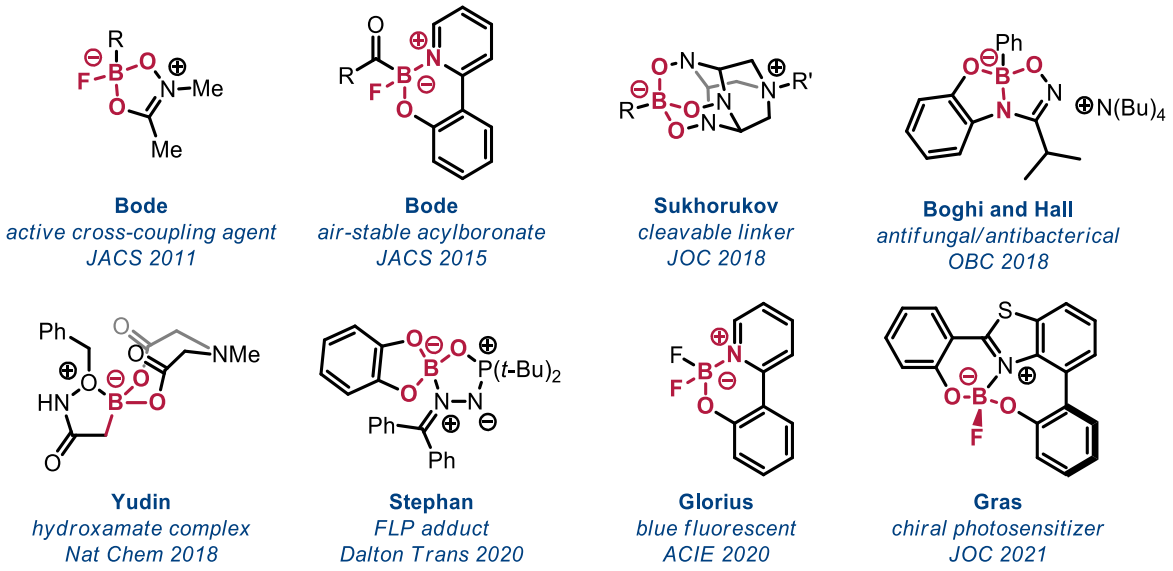
4.1.2 NOB-Containing Heterocycles

Hydroxylamine-containing species and boron-containing species can be combined into various forms of heterocyclic structures that have different applications (Figure 4. 2). Several variations of boronic acids serve as bioorthogonal probes for site-selective labeling of proteins.[161] Hydroxamic acids or nitrones/oximes among other functional groups can coordinate reversibly or irreversibly to aryl boronic acids in biological conditions.[162] When bound, these functional groups form NOB-containing heterocycles with varying stability. Several of these heterocycles have also been studied as pharmaceuticals.[160a] NOB-

[161] Akgun, B.; Hall, D. G. *Angew. Chem. Int. Ed.* **2018**, *57*, 13028-13044.
[162] Golovanov, I. S.; Mazeina, G. S.; Nelyubina, Y. V.; Novikov, R. A.; Mazur, A. S.; Britvin, S. N.; Tartakovsky, V. A.; Ioffe, S. L.; Sukhorukov, A. Y. *J. Org. Chem.* **2018**, *83*, 9756-9773.

Containing heterocycles have also found use as synthetic intermediates, like cross-coupling agents, or more recently as photoactive species.[163,164]

Figure 4. 2 Recent examples of NOB-containing heterocycles



4.1.3 Previous Synthetic Strategies

4.1.3.1 α-Aminoboronic Acid Derivatives

The first boron-containing drug to be approved by the American FDA was an α-aminoboronic acid, Bortezomib, in 2003. Since then, numerous aminoboronic acid and esters have been studied as potential pharmaceuticals and several have been approved for clinical use (Ixazomib, Vaborbactam). As such, much attention has been paid to the synthesis of these structures and was thoroughly reviewed recently by Yudin and Marder.[165] The first reported synthesis of α-aminoboronic acids by Matteson used diastereoselective homologation via 1,2-shift to make α-chloroboronates, which could then react with a

[163] (a) Vo, C. -V. T.; Mitchell, A.; Bode, J. W. *J. Am. Chem. Soc.* **2011**, *133*, 14082-14089. (b) Noda, H.; Bode, J. W. *J. Am. Chem. Soc.* **2015**, *137*, 3958-3966. (c) Lee, C. F.; Diaz, D. B.; Holownia, A.; Kaldas, S. J.; Liew, S. K.; Garrett, G. E.; Dudding T.; Yudin, A. K. *Nat. Chem.* **2018**, *10*, 1062-1070. (d) Zhu, D.; Qu, Z. -W.; Stephan, D. W. *Dalton Trans.* **2020**, *49*, 901-910.

[164] (a) Tan, G.; Schrader, M. L.; Daniliuc, C.; Strieth-Kalthoff, F.; Glorius, F. *Angew. Chem. Int. Ed.* **2020**, *59*, 21541-21545. (b) Sadek, O.; Galán, L. A.; Gendron, F.; Baguenard, B.; Guy, S.; Bensalah-Ledoux, A.; Le Guennic, B.; Maury, O.; Perrin, D. M.; Gras, E. *J. Org. Chem.* **2021**, *86*, 11482–11491.

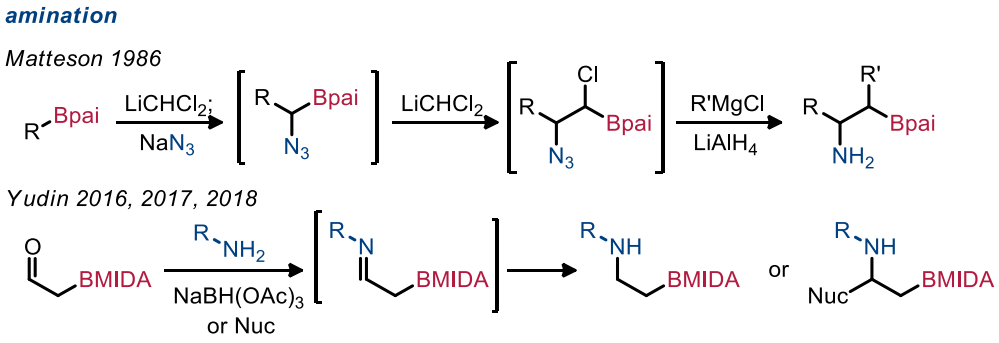
[165] Ming, W.; Soor, H. S.; Liu, X.; Trofimova, A.; Yudin, A. K.; Marder, T. B. *Chem. Soc. Rev.* **2021**, *50*, 12151–12188.

nitrogen source.[166] The functionally dense structures can also be further elaborated by metal catalyzed C-C coupling.[167]

4.1.3.2 β-Aminoboronic Acid Derivatives

There are similar reported methods to form β-aminoboronic acid derivatives. Amination-based methods include Matteson homologation using azides as nitrogen sources and several reactions developed by Yudin's research group using α-borylaldehydes (Scheme 4. 1).[168] Borylative methods rely on nucleophilic sources of boron reacting with aziridines or sulfinamides (Scheme 4. 2).[169] Examples of bora-amination generally use metal-catalysis and alkenes as substrates, however, Dong's research lab recently published an aza-Matteson method to form β-aminoboronic esters in-situ as well (Scheme 4. 3).[170]

Scheme 4. 1 Known methods for β-aminoboronic acid synthesis via amination



[166] (a) Matteson, D. S.; Cheng, T.-C. *J. Organomet. Chem.* **1966**, *6*, 100–101. (b) Matteson, D. S.; Cheng, T.-C. *J. Org. Chem.* **1968**, *33*, 3055–3060.

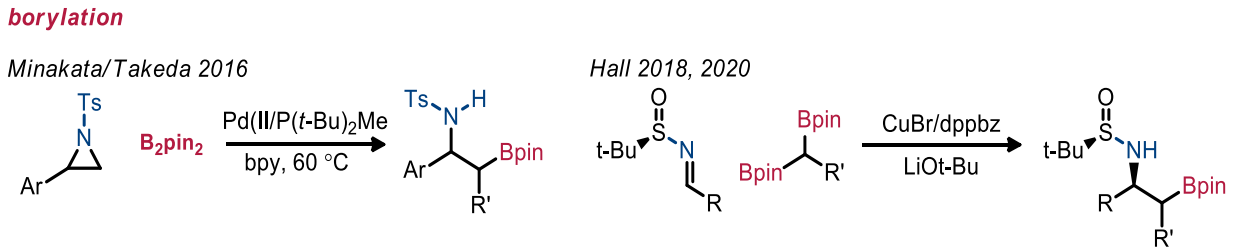
[167] For an early example, see: Molander, G. A.; Sandrock, D. L. *Org. Lett.* **2007**, *9*, 1597–1600.

[168] (a) Matteson, D. S.; Sadhu, K. M.; Peterson, M. L. *J. Am. Chem. Soc.* **1986**, *108*, 810–819. (b) Diaz, D. B.; Scully, C. C. G.; Liew, S. K.; Adachi, S.; Trinchera, P.; St Denis, J. D.; Yudin, A. K. *Angew. Chem. Int. Ed.* **2016**, *55*, 12659–12663. (c) Tan, J.; Cognetta III, A. B.; Diaz, D. B.; Lum, K. M.; Adachi, S.; Kundu, S.; Cravatt, B.; Yudin, A. K. *Nat. Commun.* **2017**, 8, 1760-1768. (d) Kaldas, S. J.; Rogova, T.; Nenajdenko, V. G.; Yudin, A. K. *J. Org. Chem.* **2018**, *83*, 7296–7302.

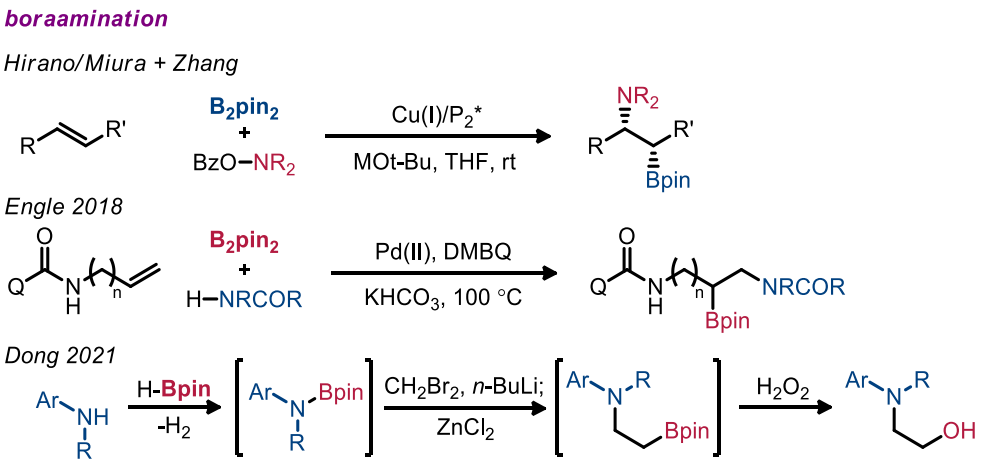
[169] (a) Takeda, Y.; Kuroda, A.; Sameera, W. M. C.; Morokuma, K.; Minakata, S. *Chem. Sci.* **2016**, *7*, 6141–6152. (b) Li, X.; Hall, D. G. *Angew. Chem. Int. Ed.* **2018**, *57*, 10304-10308. (c) Li, X.; Hall, D. G. *J. Am. Chem. Soc.* **2020**, *142*, 9063–9069.

[170] (a) Matsuda, N.; Hirano, K.; Satoh, T.; Masahiro Miura, M. *J. Am. Chem. Soc.* **2013**, *135*, 4934-4937. (b) Liu, Z.; Ni, H. Q.; Zeng, T.; Engle, K. M. *J. Am. Chem. Soc.* **2018**, *140*, 3223-3227. (c) Xie, Q.; Dong, G. *J. Am. Chem. Soc.* **2021**, *143*, 14422-14427.

Scheme 4. 2 Known methods for β-aminoboronic acid synthesis via borylation

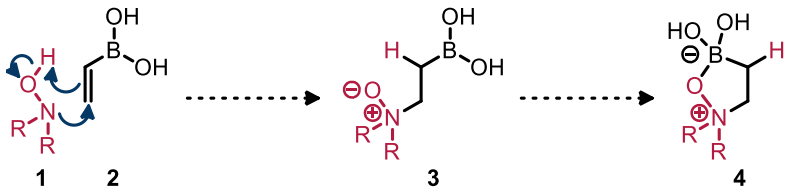


Scheme 4. 3 Known methods for β-aminoboronic acid synthesis via bora-amination



It seemed feasible that Cope-type hydroamination could serve a distinct aminative path towards β-aminoboronic acid derivatives **4** (Scheme 4. 4). Using hydroxylamines **1** and vinylboronic acids **2**, this would be a novel disconnection for the synthesis of these compounds if the hydroamination could occur regioselectively. Boron substitution of alkenes or alkynes has yet to be explored for Cope-type hydroamination reactivity, however, the Beauchemin lab among others have previously studied in detail intermolecular hydroamination reactions with carbon-substituted alkenes.

Scheme 4. 4 Proposed Cope-type hydroamination of vinylboronic acids for the synthesis of β-aminoboronic acids

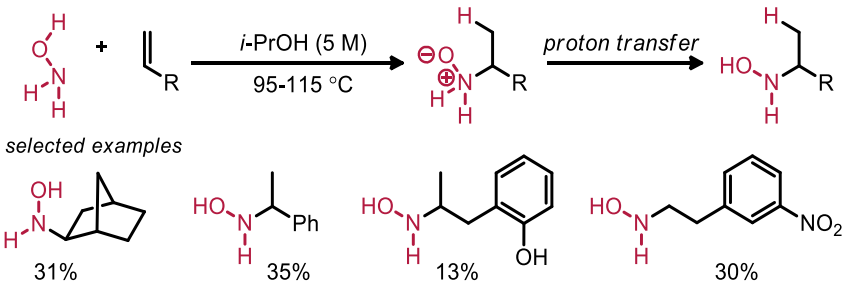


4.2 Cope-Type Hydroamination with Vinylboronates

4.2.1 Related Works with Carbon-Substituted Alkenes

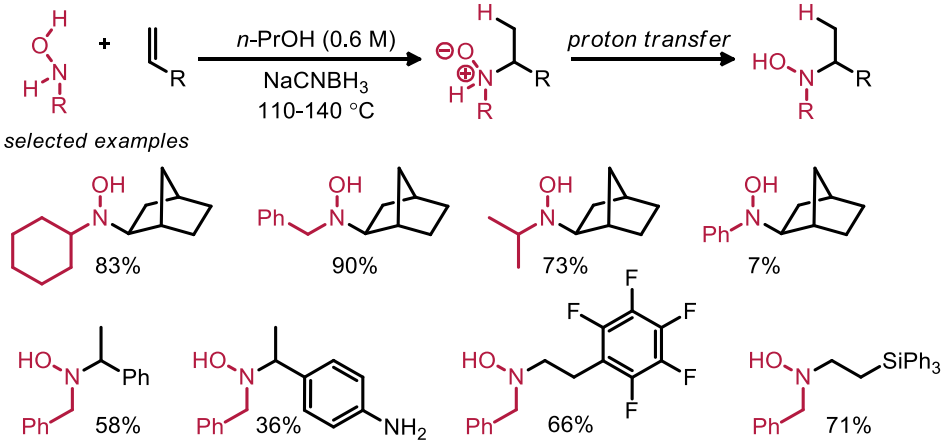
Previous work from the Beauchemin lab explored the use of solvents effects, hydrogen bonding additives, and Meisenheimer rearrangements to promote the Cope-type hydroamination of alkenes. With aqueous hydroxylamine, reactions in concentrated *i*-PrOH at 95-115 °C proceeded forming a mixture of regioisomers and mono-/diamination products (Scheme 4. 5).[87b,171] Markovnikov selectivity was generally favoured, however, alkenes with electron-poor substituents led to more anti-Markovnikov products after proton transfer. Using *N*-alkylhydroxylamines, reactions in *n*-PrOH at 110-140 °C proceeded well using $NaCNBH_3$ as an additive, which is postulated to help reduce the negative effects of hydroxylamine hydrogen-bonding dimers (Scheme 4. 6).[87b] Regioselectivity remained an issue for the alkyl-substituted hydroxylamines.

Scheme 4. 5 Previously reported intermolecular Cope-type hydroamination with hydroxylamine



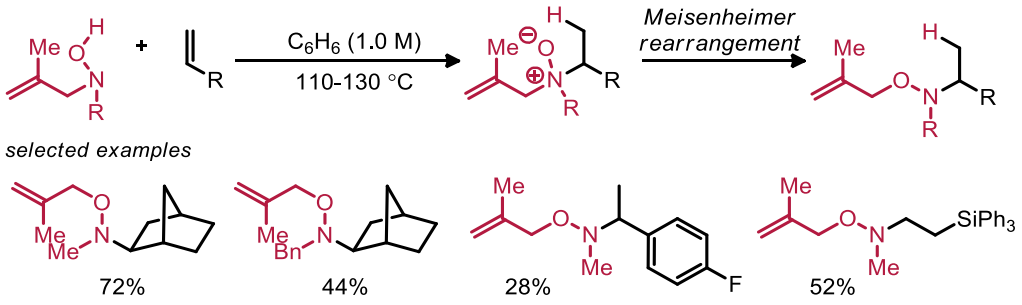
[171] Beauchemin, A. M.; Moran, J.; Lebrun, M. -E.; Séguin, C.; Dimitrijevic, E.; Zhang, L.; Gorelsky S. I. *Angew. Chem. Int. Ed.* **2008**, *47*, 1410 –1413.

Scheme 4. 6 Previously reported intermolecular Cope-type hydroamination with *N*-alkylhydroxylamines



N-Allyl substitution on *N*,*N*-dialkylhydroxylamines allowed thermodynamically unfavourable hydroamination reaction to proceed followed by a 2,3-Meisenheimer rearrangement to form a neutral product (Scheme 4. 7).[128b] Optimal conditions included benzene as a solvent and high reaction temperatures (110-130 °C). Similar low regioselectivities to mono-alkylhydroxylamines were observed. All of these examples include significant synthetic limitations related to the mixture of products formed and the high reaction temperatures, which are particularly problematic for concentrated solutions of potentially explosive hydroxylamines. Each reaction is also driven by the consumption of the *N*-oxide product by proton or allyl shift to the oxygen.

Scheme 4. 7 Previously reported intermolecular Cope-type hydroamination with *N*-allyl-*N*-alkylhydroxylamines

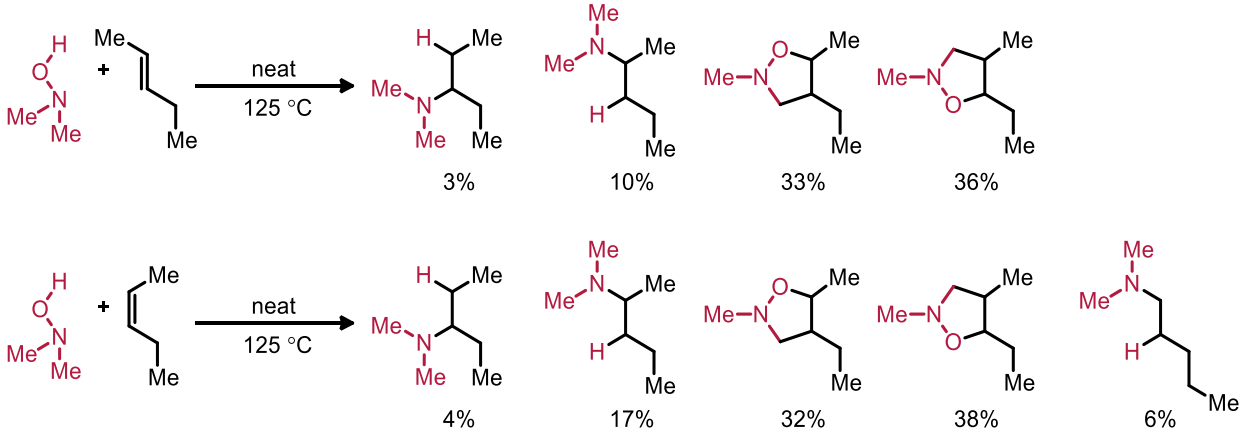


Minimal work has been reported on the Cope-type hydroamination of reactivity of dialkylhydroxylamines due to the instability of the *N*-oxide product as described by Laughlin in 1973 (Scheme 4. 8).[172] Laughlin's

[172] Laughlin, R. G. *J. Am. Chem. Soc.* **1973**, *95*, 3295-3299.

work focused on the redox reactivity of *N*,*N*-dimethylhydroxylamine in the presence of alkenes, and was therefore unoptimized with regards to the Cope-type hydroamination reactivity, however, it provides clear examples of the variety of degradation products for amine *N*-oxides. Tertiary amines result from reduction of *N*-oxide products using hydroxylamines as the reductant. This forms nitrones that can then undergo [3+2] cycloaddition to form isoxazolidines. The presence of a 1-pentene derived isoxazolidine from the reaction with *cis*-2-pentene highlights the reversible nature of the Cope-type hydroamination as well. Therefore, in addition to the expected unfavourable equilibrium of Cope-type hydroamination using dialkylhydroxylamines, redox-based degradation is also possible. This report is, however, a rare example of metal-free intermolecular amination.

Scheme 4. 8 Laughlin's study of the Cope-type hydroamination of alkenes using *N*,*N*-dimethyl-hydroxylamine



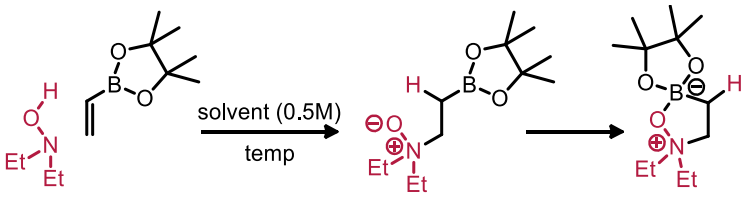
With the harsh reaction temperatures reported and the substitution and regioselectivity limitations known for carbon-substituted alkenes, activation and intramolecular stabilization by boron leading to improved hydroamination reactivity was desired. Primary and secondary hydroxylamines were both reagents of interest to explore this new subset of Cope-type hydroamination.

4.2.2 Optimization and Solvent Effects

The optimization began using *N*,*N*-diethylhydroxylamine **1a** and pinacol vinylboronate **2a**, both of which are commercially available, with TFE as a solvent (Table 4. 1). TFE had recently been found to be an optimal solvent for intramolecular and intermolecular Cope-type hydroamination (see section 3.3.1). With an excess of vinylboronate at 50 °C, good yields of oxazaborolidine **4a** were obtained (entries 1-2). Reducing the reaction temperature to rt even with a larger excess of the alkene led to a significantly reduced yield (entry 3). Using an excess of the hydroxylamine reagent instead at 50 °C led to excellent yields (entries 4-

5), though there was no improvement for a 1.5 to 5 equivalent excess. Reducing the reaction temperature to rt again led to a reduced yield (entry 6). Switching to another fluorinated alcohol solvent, HFIP, also led to an excellent yield (entry 7). Methanol was also an adequate solvent substitute, with only slightly reduced yields (entry 8), however, the bulkier *t*-BuOH was considerably worse (entry 9). Polar aprotic solvent, THF, and non-polar solvent, toluene, did not lead to any observed product (entries 10-11). TFE was chosen as the optimal solvent due to the high yield observed and lower cost than the similarly performing HFIP.

Table 4. 1 Optimization of the hydroamination of pinacol vinylboronic ester[a]



1a **2a** **3a** **4a**

Entry	Equiv 1a	Equiv 2a	Solvent	Temp (°C)	Yield 4a (%)[b]
1	1.0	1.2	TFE	50	71
2	1.0	1.5	TFE	50	88
3	1.0	3.0	TFE	rt	42
4	1.5	1.0	TFE	50	93
5	5.0	1.0	TFE	50	86
6	1.5	1.0	TFE	rt	74
7	1.5	1.0	HFIP	50	91
8	1.5	1.0	MeOH	50	82
9	1.5	1.0	*t*-BuOH	50	47
10	1.5	1.0	THF	50	0
11	1.5	1.0	toluene	50	0

(a) Pinacol vinylboronate **2a** in solvent (0.5M), Et_2NOH added, 50 °C, 16 h; (b) 1H NMR yield of **4a** using 1,3,5-trimethoxybenzene as an internal standard. TFE = 2,2,2-trifluoroethanol. HFIP = 1,1,1,3,3,3-hexafluoroisopropanol.

4.2.3 Scope and Limitations of Hydroamination

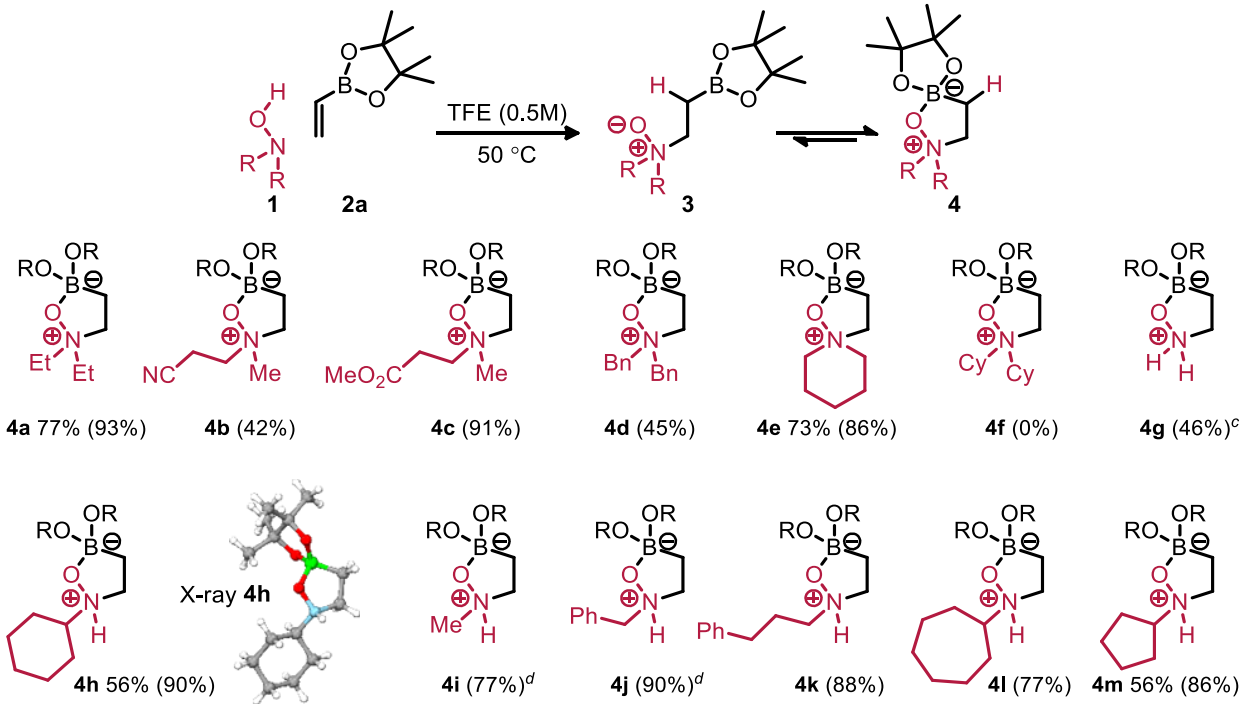
4.2.3.1 Scope of Hydroxylamines

Using the optimized conditions (Table 4. 1, entry 4), we then explored the scope of this novel reactivity (Scheme 4. 9). *This scope was completed and evenly divided with Myroslava Volosheniuk.* A variety of dialkylhydroxylamines **1** underwent hydroamination with pinacol vinylboronate **2a** in good yields (**4a**-**4e**, 42-93%). Small electronic effects were observed when using electron poor hydroxylamines, likely due to the greater ease of Cope-type elimination degradation of reagent **1b** and its corresponding reaction

intermediates and product (**4b**). Sterically hindered substituents decreased the yield of oxazaborolidine (**4d**) or led to no reaction (**4f**). Unsubstituted hydroxylamine could be used as an aqueous solution to form the oxazaborolidine in a moderate yield (**4g**).

Primary hydroxylamines were also able to form the zwitterionic oxazaborolidines in good yields (**4h**-**4m**, 77-90%) under the same conditions when using the free base or with added DIPEA when the hydroxylamine salt was used. Interestingly, zwitterionic heterocycle **4** was the favoured structure even with a possible proton shift leading to a neutral species, as indicated by the NMR data and the obtained X-ray structure (**4h**).

Scheme 4. 9 Scope of hydroamination reaction with pinacol vinylboronate ester[a]



(a) Pinacol vinylboronate (1.0 equiv) in solvent (0.5M), hydroxylamine **1** (1.5 equiv) added, 50 °C, 16 h; (b) Isolated yield, ^{1}H NMR yield of **4** using 1,3,5-trimethoxybenzene as an internal standard shown in parentheses; (c) Aqueous hydroxylamine solution (50%) used (1.5 equiv); (d) Hydroxylamine HCl salt (1.5 equiv) used and DIPEA added (1.5 equiv). TFE = 2,2,2-trifluoroethanol.

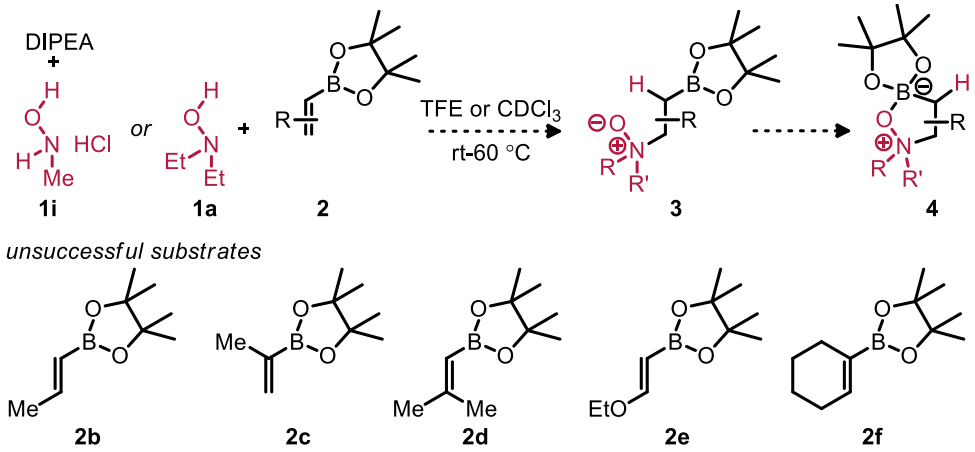
The isolation of these zwitterionic products was a significant challenge for this methodology. The secondary hydroxylamine derived products (**4a**-**4e**) could be isolated in reduced yields using flash column chromatography with silica gel and highly polar eluent. The primary hydroxylamine derived products (**4h**-**4m**) were too polar to be isolated using silica gel, though could be isolated by recrystallization, again in reduced yields. Another issue was the inconsistency of efficient isolation procedures among similar substrates, so no general procedure could be achieved. Isolation could allow for improved data for

structural determination but was not a reliable method to find an accurate yield of the reaction. We therefore decided to use various derivatization reactions to further verify the ^{1}H NMR yields and structure (see section 4.2.4).

4.2.3.2 Alkene Substitution Limitations

With a generally good scope of *N*-substitution tolerated under the optimized reaction conditions, alkene substitution was then explored. Simple commercially available substituted vinylboronic esters (**2b**-**2f**) were subjected to similar hydroamination conditions (Scheme 4. 10). While no oxazaborolidines could be observed, the products of the consumed vinylboronate could not be determined using NMR spectroscopy, possibly due to the volatility of some by-products.

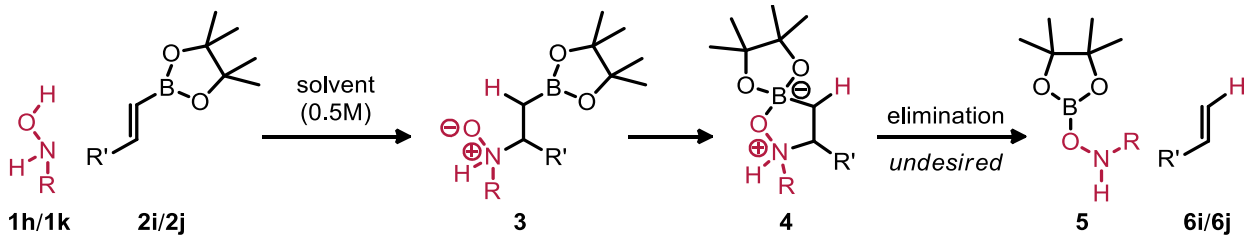
Scheme 4. 10 Attempted hydroamination of substituted vinylboronates



Higher molecular weight substrates were synthesized and tested in order to better follow the outcome of the reaction (Table 4. 2). When mono-alkylhydroxylamines (**1h** or **1k**) were reacted at rt or 50 °C with styrylboronic ester, no oxazaborolidine zwitterion **4** was observed (entries 1-4). Instead, the elimination product, styrene (**6i**), was formed exclusively. This result suggests that the previous vinylboronates (Scheme 4. 10) were likely producing volatile alkene products, which is why the analysis of their reaction outcome was inconclusive. This result also suggests that carbon substitution likely affects the stability of this zwitterion, or the energy needed for elimination. Notably, when reactions were performed at rt (entries 2/4), they were incomplete at 16h, with both boronic ester starting material **2i** and alkene **6i** observed by ^{1}H NMR. These results suggest that the intermediate oxazaborolidine zwitterion **4** is immediately consumed as it is formed under the tested reaction conditions. Changing the reaction solvent to aprotic solvents, led to only recovered starting materials (entries 5-8), suggesting TFE was required for

the initial hydroamination. It was hypothesized that the conjugation of elimination product **6i** was perhaps leading to a more favourable elimination, so alkyl-substituted vinylboronic ester **2j** was used (entries 9-10). However, the alkene elimination product **6j** was still exclusively formed at rt and 50 °C.

Table 4. 2 Attempted optimization of the hydroaminations of substituted vinylboronates[a]



Entry	Solvent	R	R'	Temp (°C)	Time (h)	Yield 4 (%)[b]	Yield 6 (%)[b]
1	TFE	$(CH_2)_3Ph$	Ph	50	16	0	71
2	TFE	$(CH_2)_3Ph$	Ph	rt	16	0	54
3	TFE	Cy	Ph	50	16	0	87
4	TFE	Cy	Ph	rt	16	0	72
5	DCM	Cy	Ph	rt	17	0	0
6	THF	Cy	Ph	rt	17	0	0
7	MeCN	Cy	Ph	rt	17	0	0
8	$PhCF_3$	Cy	Ph	rt	17	0	0
9	TFE	Cy	C_3H_6Cl	50	16	0	71
10	TFE	Cy	C_3H_6Cl	rt	16	0	31

(a) Vinylboronate **2i** or **2j** (1.0 equiv) in solvent (0.5M), hydroxylamine **1h** or **1k** (1.5 equiv) added, given temperature, time; (b) ^{1}H NMR yield of **4** or **6** using 1,3,5-trimethoxybenzene as an internal standard. TFE = 2,2,2-trifluoroethanol.

A stable hydroamination adduct appeared to be restricted to unsubstituted pinacol vinylboronic esters. Following this finding, the effects of different substitution at boron were important to assess for both unsubstituted and substituted alkenes. Modifying the Lewis acidity at boron or the steric bulk around boron could increase the stability of oxazaborolidines derived from substituted vinylboronates.

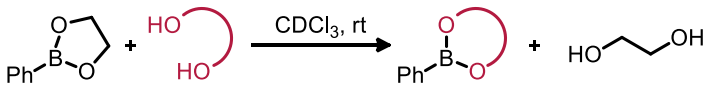
4.2.3.3 Boron Substitution Effects

Pinacol esters are the most common boronic ester and the most commercially available. The five-membered cyclic structure leads to small differences stability relative to similar six-membered boronic esters. The relative thermodynamic stability of several boronic esters was reported by Brown in 2007.[173]

[173] (a) Roy, C. D.; Brown, H. C. *J. Organomet. Chem.* **2007**, *692*, 784–790. (b) Roy, C. D. Brown, H.C.; *Monatsh. Chem.* **2007**, *138*, 879–887.

Boronic esters were compared using the equilibrium composition of products in the transesterification of 2-(phenyl)-1,3,2-dioxaborolane with diols. In these studies, six-membered boronic esters were found to be more thermodynamically stable than five-membered esters (Table 4. 3). In addition, two α-alkyl substituents on diols (entries 3 and 7) slow down the transesterification but still form more thermodynamically stable boronic esters. Overall, these results on stability suggest that a change in diol could influence the Lewis acid/base interaction of the *N*-oxide with the chosen boronic ester. When the boronic ester was modified from pinacol (**2a**) to neopentyl glycol, the yield of oxazaborolidine zwitterion was unsurprisingly similarly excellent (Table 4. 4, entry 1). As the yield and the reaction time were not significantly changed, larger modifications to the boron center were tested.

Table 4. 3 Boronic ester stability assessed by time to and percent maximum transesterification *(Brown 2007)*



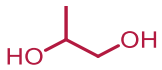
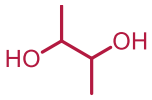
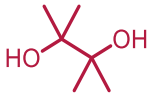
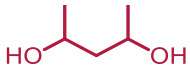
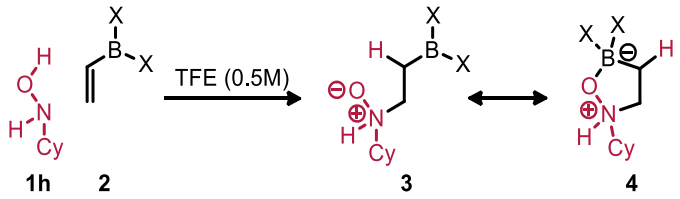
Entry	Diol structure	Time to maximum (h)	Maximum Transesterification (%)
1		0.1	68.6
2		0.1	74.7
3		94	87.8
4		0.1	88.5
5		0.1	98
6		0.1	85
7		67	91

Table 4. 4 Effects of boron ligands on the hydroamination of vinylboronate with *N*-cyclohexyl-hydroxylamine[a]



1h **2** **3** **4**

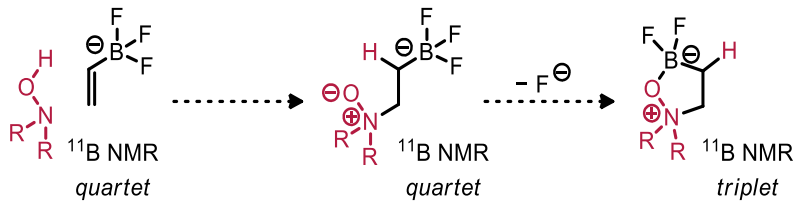
Entry	BX_2	Temp (°C)	Yield (%)[b]
1	Bneop	50	quan
2	BF_3K	50	*
3	Bdan	rt	0
4	Bdan	50	0
5	Bdan	80	trace
6[c]	Bdan	rt	0
7[c]	Bdan	50	0

(a) Vinylboronate **2** (1.0 equiv) in solvent (0.5M), hydroxylamine (**1h**) (1.5 equiv) added, given temperature, 16 h; (b) ^{1}H NMR yield of **4** using 1,3,5-trimethoxybenzene as an internal standard; (c) reaction solvent is 1:1 TFE:$CDCl_3$ (0.25M). TFE = 2,2,2-trifluoroethanol; neop = neopentyl glycol; dan = 1,8-diaminonapthalene; quan = quantitative. * Low solubility complex mix of products, which may contain product.

Changing to non-oxygen-based ligands also modifies the Lewis acidity among other properties. Potassium trifluoroborate salts are very stable due to the tetracoordinate boron center and the 3 strong B-F bonds. Although some productive reactivity appeared to be taking place with potassium vinyltrifluoroborate, the poor solubility of the complex reaction mixture did not allow for in depth analysis by ^{1}H, ^{13}C, ^{11}C, or ^{19}F NMR (Table 4. 4, entry 2). However, a triplet observed in the crude ^{11}B NMR spectrum (1.97 or 1.75 ppm in TFE/acetone-d_6) suggests hydroamination and displacement of one fluoride from boron may have occurred (Scheme 4. 11). Further work is required to improve the isolation procedure for structural elucidation. Amino groups, such as 1,8-diaminonapthlene, are known to reduce the Lewis acidity of boron by donation of the N_{LP}.[174] Conditions using this ligand for boron (**2l**) led to no significant amount of observed hydroamination products at rt, 50 °C, or 80 °C (entries 3-5). Modifying the solvent to a mixture of TFE/$CDCl_3$ to improve solubility led to no hydroamination products as well (entries 6,7). With no improvements observed for mono-substituted hydroxylamines using alternative boron ligands, disubstituted hydroxylamines were then scanned using the same modifications.

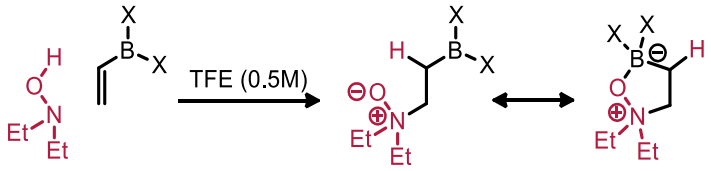
[174] (a) Hall, D. In *Boronic Acid*; Hall, D., Ed.; Wiley: Weinheim, Germany, 2005; p 1. (b) Noguchi, H.; Hojo, K.; Suginome, M. *J. Am. Chem. Soc.* **2007**, *129*, 758–759.

Scheme 4. 11 Potential hydroamination and fluoride displacement reaction using potassium vinyltrifluoroborate



Similarly to cyclohexylhydroxylamine **1h**, hydroamination reactions using diethylhydroxylamine **1a** with other boron ligands showed minimal improvement relative to pinacol vinylboronic ester **2a** (Table 4. 5). At 50 °C, however, small yields of cyclic zwitterionic structure **4** were observed by crude ^{1}H NMR using alkene **2l** (entries 4 and 6). The observed difference in reactivity may be related to two factors. (1) Disubstituted hydroxylamines are more nucleophilic than mono-substituted hydroxylamines, leading to more efficient Cope-type hydroamination.[87a] (2) Disubstituted hydroxylamines do not have an N-H bond to participate in hydrogen bonding with the solvent or other reagents, thereby increasing their probability to react productively.[89a] The reactivity was, however, still less efficient than when using pinacol esters, so a larger modification was tried.

Table 4. 5 Effects of boron ligands on the hydroamination of vinylboronate with *N*,*N*-diethyl-hydroxylamine[a]



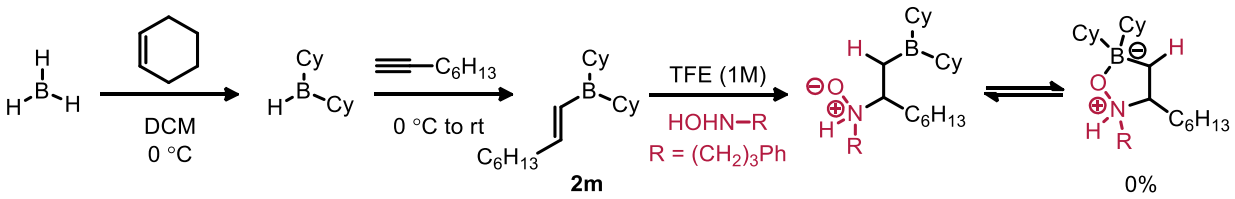
1a **2** **3** **4**

Entry	BX_2	Temp (°C)	Yield (%)[b]
1	Bneop	50	quan
2	BF_3K	50	*
3	Bdan	rt	0
4	Bdan	50	23
5[c]	Bdan	rt	0
6[c]	Bdan	50	10

(a) Vinylboronate **2** (1.0 equiv) in solvent (0.5M), hydroxylamine (**1a**) (1.5 equiv) added, given temperature, 16 h; (b) ^{1}H NMR yield of **4** using 1,3,5-trimethoxybenzene as an internal standard; (c) reaction solvent is 1:1 TFE:$CDCl_3$ (0.25M). TFE = 2,2,2-trifluoroethanol; neop = neopentyl glycol; dan = 1,8-diaminonapthalene; quan = quantitative. * Low solubility complex mix of products, which may contain product.

To evaluate the effects of a significantly more Lewis acidic boron center, dicyclohexylvinylborane **2m** was made in-situ via sequential hydroboration reactions with BH_3-THF (Scheme 4. 12). A solution of hydroxylamine (**1k**) in TFE was then added to the dry reaction mixture and allowed to stir at rt. No oxazaborolidine product was observed. Hydrolysis of the vinylborane was determined to be a possible undesirable side reaction when using TFE, so hydroxylamine **1k** was instead added as a solution in dry THF. Again, no oxazaborolidine was observed.

Scheme 4. 12 Attempted hydroamination of dicyclohexylvinylborane

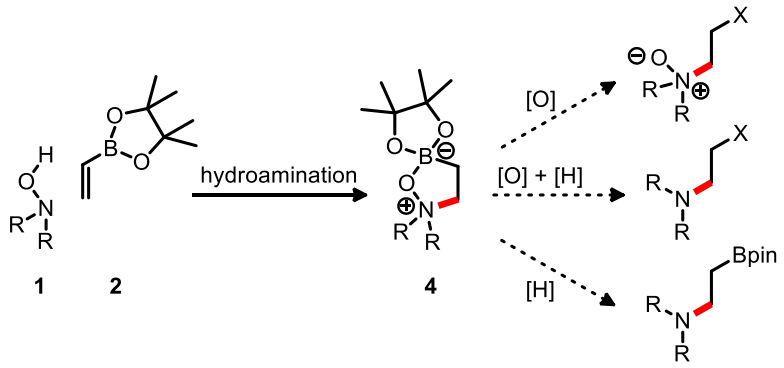


It was clear that pinacol was the best boron ligand for the desired hydroamination reactivity at the time, so isolation of zwitterionic oxazaborolidine products **4** was attempted next. Various column chromatography methods and eluent systems were tried along with several different aqueous workups. In general, these zwitterions proved too polar, too unstable or too water-soluble for every attempted isolation method. Column chromatography can work for some of the products derived from secondary hydroxylamines but is plagued by co-elution of excess hydroxylamine and lower yields. Column chromatography using silica gel will not work for the products derived from primary hydroxylamines, but isolation with some success has been demonstrated using recrystallization.

4.2.4 Derivatization of Oxazaborolidines

Since the isolation of the polar zwitterionic products of vinylboronic ester hydroamination proved difficult, derivatization could serve as a method to support the structures assigned and yields determined by ^{1}H NMR, and to demonstrate synthetic utility. Due to the amphoteric nature of the *N*-oxide and boronic ester moieties of the heterocycles formed, oxidative or reductive approaches to derivatization can be employed as well as redox-neutral approaches (Scheme 4. 13). *This work was completed with Myroslava Volosheniuk.*

Scheme 4. 13 Proposed derivatization reactions of zwitterionic oxazaborolidines

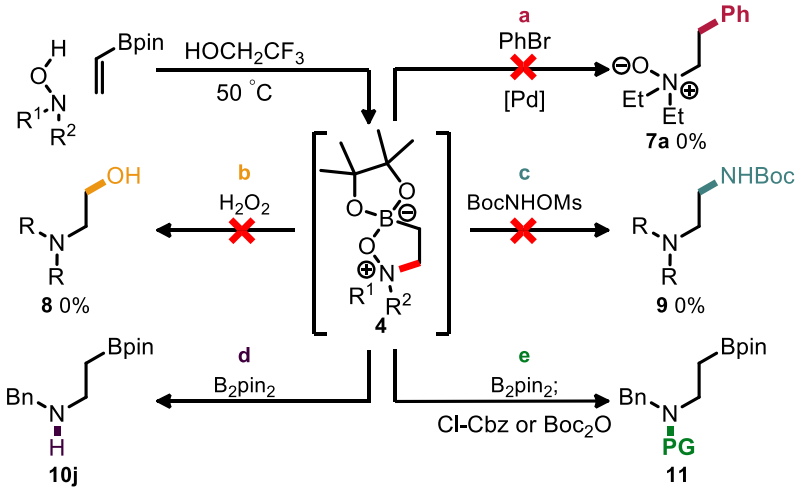


4.2.4.1 Oxidative or Reductive Approaches

Oxidation of the carbon-boron bond of the zwitterionic oxazaborolidine could form amine, amino-alcohol, or diamine derivatives. Under all conditions tested, however, no reaction took place, and all starting material was recovered (Scheme 4. 14 a-c). The zwitterionic heterocycle is impressively stable towards oxidative conditions.[175] This is potentially due to the requirement for an empty p orbital on boron in most oxidative reactions of boronic acids or esters. The *N*-oxide intramolecular donation to the boronic ester is strong as seen by the X-ray O-B bond length (1.537 Å). Reduction of the *N*-oxide forms β-aminoboronic ester **10j** well, though these products were difficult to purify (Scheme 4. 14 d). The isolation of the reduced compounds after protection with Cbz or Boc (**11**) still proved difficult, so further work is required to optimize the isolation procedure (Scheme 4. 14, e).

[175] Graham, B. J.; Windsor, I. W.; Golda, B.; Raines, R. T. *Proc. Natl. Acad. Sci. U.S.A.* **2021**, *118*, e2013691118.

Scheme 4. 14 Oxidative or reductive derivatization of zwitterionic oxazaborolidines

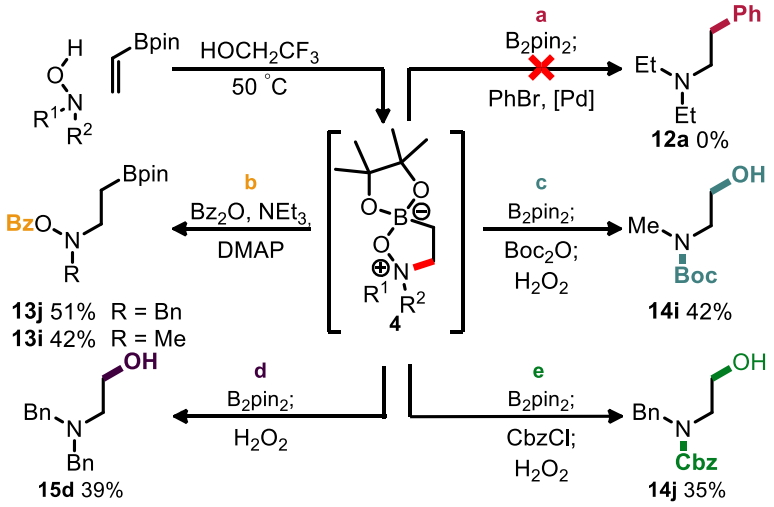


4.2.4.2 Redox-Neutral Approaches

When metal-catalyzed cross coupling was attempted after first reducing the *N*-oxide, no product was obtained yet again (Scheme 4. 15 a). The amine is likely too basic to be tolerated under cross-coupling conditions. Dong's cross-coupling of aminoboronic esters used arylamines, which are much better tolerated in transition-metal catalysis.[170c] Trialkylamines are not present in any reported metal-catalyzed coupling of aminoboronic acid derivatives to our knowledge.[176] If primary hydroxylamines are used for the hydroamination reaction, then protection of the oxygen could yield *O*-acyl-β-hydroxylamine boronic acids **13** in moderate yields over three steps (Scheme 4. 15 b). When reduction then oxidation conditions are used in sequence, amino alcohols **14** or **15** are obtained in moderate yields over three or four steps (Scheme 4. 15 c-e) (*completed by Myroslava Volosheniuk*). These isolated derivatives served to further reinforce the validity of the ^{1}H NMR yields obtained (Scheme 4. 9) and of the proposed structures.

[176] For examples of aryl- or acyl-substituted aminoboronic acid derivatives undergoing cross-coupling, see: (a) Molander, G. A.; Vargas, F. *Org. Lett.* **2007**, *9*, 203–206. (b) Pietruska, J.; Solduga, G. *Eur. J. Org. Chem.* **2009**, *34*, 5998-6008. (c) St. Denis, J. D.; Zajdlik, A.; Tan, J.; Trinchera, P.; Lee, C. F.; He, Z.; Adachi, S.; Yudin, A. K. *J. Am. Chem. Soc.* **2014**, *136*, 17669–17673. (d) Kong, D.; Han, S.; Zi, G.; Hou, G.; Zhang, J. *J. Org. Chem.* **2018**, *83*, 1924–1932. (e) Wang, J. -W.; Li, Y.; Nie, W.; Chang, Z.; Yu, Z. -A.; Zhao, Y. -F.; Lu, X.; Fu, Y. *Nat. Commun.* **2021**, *12*, 1313-1323. (f) Jones, C. C. V.; Patel, J.; Jansen-van Vuuren, R. D.; Ross, G. M.; Keller, B. O.; Sauriol, F.; Schatte, G.; Johnson, E. R.; Snieckus, V. *Org. Lett.* **2021**, *23*, 1966−1973.

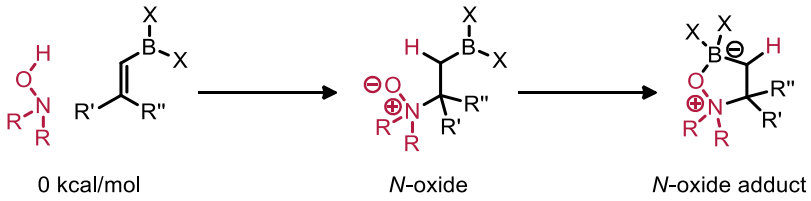
Scheme 4. 15 Redox-neutral derivatization of zwitterionic oxazaborolidines



4.2.5 Computational Results

The effects of nitrogen, alkene, and boron substitution on the observed hydroamination reactivity were studied computationally using DFT with the desire to expand the limited substrate scope. Initial DFT calculations suggested that mono-alkylhydroxylamines formed a more stable *N*-oxide adduct that dialkylhydroxylamines (Table 4. 6, entries 1-2). Alkene substitution was calculated to raise the energy of the *N*-oxide and the adduct relative to the unsubstituted pinacol vinylboronate, which was expected based on the increased steric hindrance (entries 1,3,4). The *cis*-propenylboronate was calculated to have a more favourable reaction than the *trans*-propenylboronate. Modifying boron substitution to increase Lewis acidity led to considerably more favourable *N*-oxide adducts (entries 1,5,6). These results supported our attempts to use the highly Lewis acidic dicyclohexylvinylboranes as reagents (Scheme 4. 12). Although, in all entries, a reasonable transition state could not be found. As TFE was crucial for much of the observed experimental results, a concern for the DFT calculations was the absence of TFE solvent interactions to stabilize charges and hydrogen-bond.

Table 4. 6 Preliminary DFT calculations for the Cope-type hydroamination of vinylboronates (B3LYP/6-31G(d) in MeOH)



Entry	R_2NOH	R'/R''	BX_2	*N*-oxide	*N*-oxide adduct
1	MeNHOH	H/H	Bpin	+ 4.13 kcal/mol	- 6.56 kcal/mol
2	Me_2NOH	H/H	Bpin	*not calculated*	- 3.79 kcal/mol
3	MeNHOH	Me/H	Bpin	+ 9.14 kcal/mol	- 4.22 kcal/mol
4	MeNHOH	H/Me	Bpin	+ 7.51 kcal/mol	- 5.85 kcal/mol
5	MeNHOH	H/H	B(OCHCHO)	*not calculated*	- 9.54 kcal/mol
6	MeNHOH	H/H	BMe_2	*not calculated*	- 16.45 kcal/mol

Serendipitously, a computational collaboration was initiated during this time at the virtual 2021 CSC conference with Eric Nicol, a PhD candidate in the lab of Prof. Adrian Schwan at the University of Guelph, due to the beneficial overlap in related computational work that was already underway in the Schwan lab. Indeed, this student had presented results on the elimination reactivity of related sulfur-containing borane heterocycles. Initial collaborative DFT studies included mapping the potential energy surface of the hydroamination of pinacol vinylboronate with mono- and dialkylhydroxylamines. Studying the activation energies and the nature of the transition states was important to rationalize the mild reaction conditions relative to analogous carbon-substituted alkene reactivity.

Eric Nicol performed the DFT calculations below with guiding parameters from me and Prof. Beauchemin. Eric also developed the basis set combination described below. The analysis of the potential energy surfaces from Eric and their relation to observed experimental results included below was completed by me. The analysis of natural bond order results and their relation to observed experimental results included below was completed by Eric and me.

Each system was thus optimized using DFT methods (B3LYP-D3/def2-TZVP) with dispersion corrections in TFE via CPCM. These optimized geometries were then submitted for a gas phase electronic single point

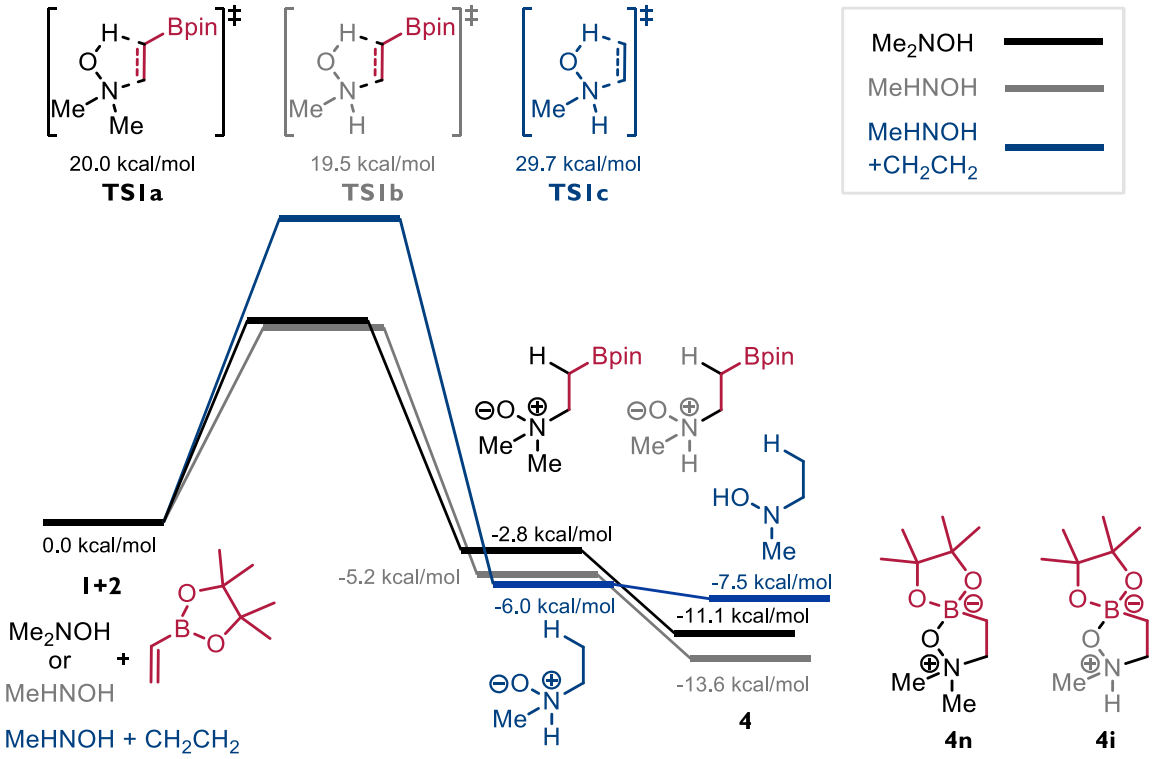
energy using ORCA's DLPNO-CCSD(T) method with a complete basis set extrapolation.[177] A solvated electronic free energy was then calculated for each molecule by using the SMD model for TFE with B3LYP/def2-tzvp and was added to the CBS-DLPNO-CCSD(T) results.

4.2.5.1 Potential Energy Surface

The computational results suggest that the initial hydroamination step is thermodynamically favourable for both mono- and dialkylhydroxylamines (ΔG = –2.8 kcal/mol and –5.2 respectively for the methyl variants) (Figure 4. 3). Once bond rotation occurs to allow the Lewis interaction between oxygen and boron for the *N*-oxide adduct, this product is significantly more favourable (ΔG = –11.1 and –13.6 kcal/mol respectively) and its formation is likely irreversible under the reaction conditions. The calculated activation energies for the hydroamination step ($\Delta G^{\ddagger}$) are +20.0 kcal/mol for Me_2NOH (**TS1a**) and +19.5 kcal/mol for MeNHOH (**TS1b**). For MeNHOH, only the most favorable pathway is shown in Figure 4. 3, with the N-Me and C-B bonds oriented *anti* relative to each other (for *anti* pathway: $\Delta G^{\ddagger}$ = +19.5 kcal/mol and ΔG = –5.2 kcal/mol and for *syn* pathway: $\Delta G^{\ddagger}$ = +20.0 kcal/mol and ΔG = –4.2 kcal/mol). The calculated activation energies are considerably lower than those calculated for carbon-substituted alkenes ($\Delta G^{\ddagger}$ for the hydroamination of ethylene with MeNHOH is +29.7 kcal/mol (**TS1c**)), which is aligned with the observation that the Bpin substituent lowers the reaction temperature requirements from 95-140 °C in previous experimental studies to 50 °C for the boron-substituted alkenes.[87b]

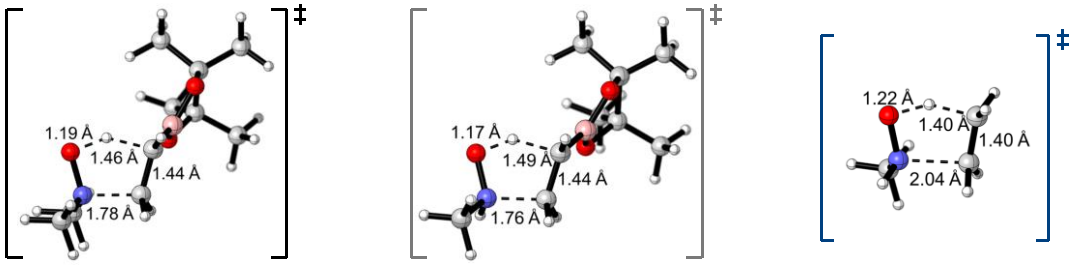
[177] Plumley, J. A.; Evanseck, J. D. *J. Phys. Chem. A* **2009**, *113*, 5985–5992.

Figure 4. 3 Potential energy surface for Cope-type hydroamination of pinacol vinylboronate and ethylene *(results from Eric Nicol)*



The calculated structures at the hydroamination transition state highlight differences that may rationalize the observed changes for the boron-substituted alkene reactivity (Figure 4. 4). As expected from prior studies, the structures at the transition states are concerted and asynchronous.[12a] Notably, the C-N bond is considerably shorter at the vinylboronate transition state (1.76 vs. 2.04 Å), though the proton transfer from oxygen to carbon is calculated to be similarly progressed according to the similar O-H (1.17 vs. 1.22 Å) and C-H (1.49 vs. 1.40 Å) bond lengths. More thorough computational studies were required to elucidate possible reasons for these changes.

Figure 4. 4 Structures at the transition state for the Cope-type hydroamination of pinacol vinylboronate and ethylene *(results from Eric Nicol)*

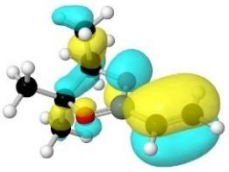
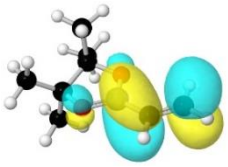
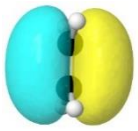
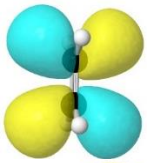
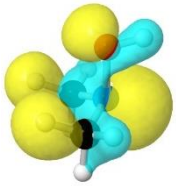
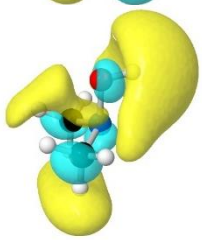


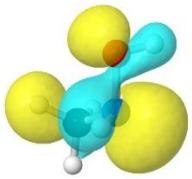
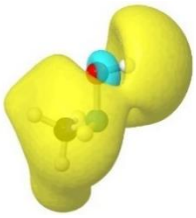
Me_2NOH + $CH_2CHBpin$ (TS1a) | MeHNOH + $CH_2CHBpin$ (**TS1b**) | MeHNOH + CH_2CH_2 (**TS1c**)

4.2.5.2 Effects of Boronic Ester Substitution

Natural bond order is a program to analyze wavefunctions and electron densities calculated by DFT. It is helpful for understanding the distribution of electron density, hyperconjugation effects and to measure an intermolecular or intramolecular interaction. In the ground state, substitution of a boronic ester onto ethylene results in a lower LUMO by 0.84 eV, but only slightly raises the energy of the HOMO (0.06 eV) (Table 4. 7). Therefore $HOMO_{(MeHNOH)}$-$LUMO_{(vinylboronate)}$= 5.87 eV or 5.54 eV for Me_2NOH, whereas the $HOMO_{(MeHNOH)}$-$LUMO_{(ethylene)}$= 6.38 eV or 6.71 eV for Me_2NOH. This significant reduction to the HOMO-LUMO energy gap would allow faster reactions with boronic ester substituted alkenes.

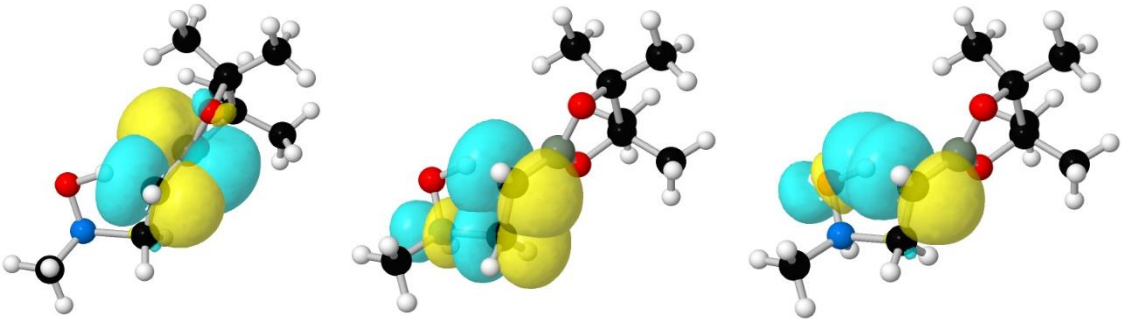
Table 4. 7 Natural Bond Orbital (NBO) computational results for ground state species *(results from Eric Nicol)*

Compound	HOMO energy (eV)	Orbital Structure	LUMO energy (eV)	Orbital Structure
Pinacol vinylboronate	-7.66		-1.04	
Ethylene	-7.72		-0.20	
Me_2NOH	-6.58		0.90	

MeNHOH	-6.91		0.97	

The effects of boronic ester substitution can also be analyzed at the transition state. Boron substitution favours a molecular orbital interaction for N-C1 (C1 = carbon distal to boron), while it minimally changes proton transfer. This can be determined using the NBO analysis at the transition state for hydroamination with pinacol vinylboronate (Figure 4. 5) vs. ethylene (Figure 4. 6). Additionally, in the reaction with vinylboronate, the C1-C2 π bond has completely broken at transition state, the new lone pair on C2 (C2 = carbon proximal to boron) is delocalized into O-H σ*, B-O π*, and N-C1 σ*. In contrast, the O-H σ bond completely breaks at ethylene transition state, and the new lone pair on oxygen is delocalized almost completely into the C2-H σ*. The increased stabilization of the O lone pair leads to increase asynchronicity and a lower kinetic barrier to hydroamination for boronic ester substituted alkenes.

Figure 4. 5 NBO analysis of MeNHOH hydroamination TS with pinacol vinylboronate *(results from Eric Nicol)*

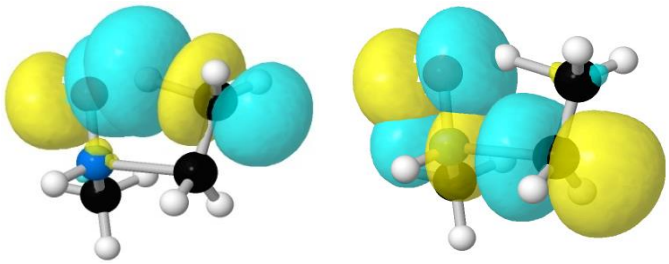


LP(C) → B-O π*
65.6 kcal/mol

LP(C) → N-C σ*
58.9 kcal/mol

LP(C) → O-H σ*
121.5 kcal/mol

Figure 4. 6 NBO analysis of MeNHOH hydroamination TS with ethylene *(results from Eric Nicol)*



LP(O) → C-H σ*
131.2 kcal/mol

LP(O) → N-C σ*
8.79 kcal/mol

Boronate substitution therefore seemingly affects hydroamination in two significant ways; (1) lowering the $HOMO_{(MeNHOH)}$-$LUMO_{(ALKENE)}$ gap and (2) stabilizing the increased electron density at carbon with the B-O π* orbital. Overall, these changes lead to lower energetic barriers to hydroamination for vinylboronate vs. ethylene. These kinetic effects are in addition to the improved thermodynamic stability offered by the intramolecular dative bonding between the *N*-oxide and boronic ester (B-O). These computational results demonstrate the combined beneficial effects of boron substitution for Cope-type hydroamination.

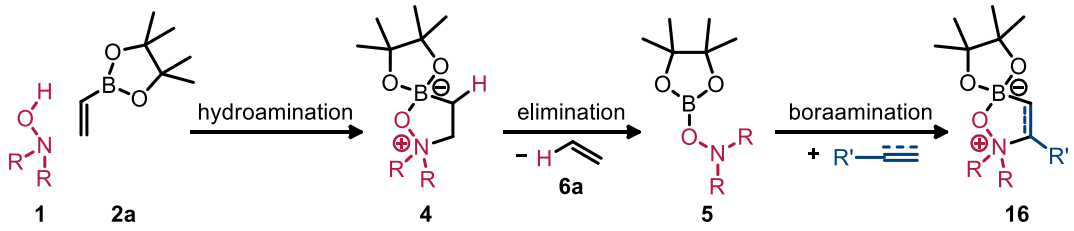
4.3 Attempts for Bora-Amination Cascades

4.3.1 Conceptual Framework and Related Work

4.3.1.1 Reaction Proposal

With the observed bora-Cope elimination reactivity, seemingly forming *O*-borylhydroxylamines **5**, the possibility to use these novel hydroxylamines in bora-amination reactivity was intriguing. By choosing a vinylboronate (**2a**) that would produce a volatile alkene (**6a**) upon elimination, a subsequent bora-amination could occur without a significant equilibrium between the two zwitterions (**4**/**16**) (Scheme 4. 16Scheme 4. 16 Proposed bora-amination reaction using in-situ generation of *O-borylhydroxylamine*).

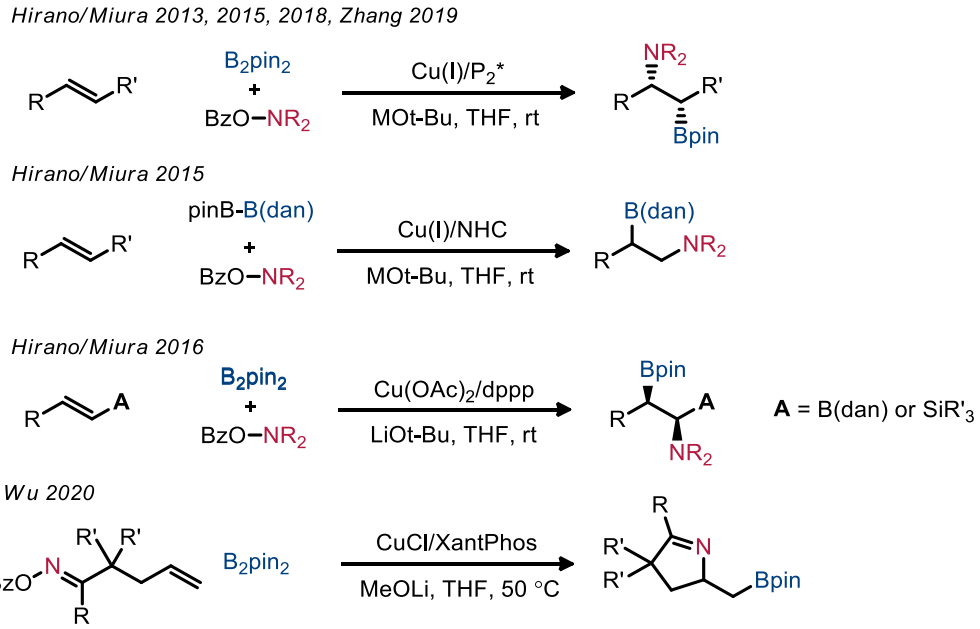
Scheme 4. 16 Proposed bora-amination reaction using in-situ generation of *O*-borylhydroxylamine



4.3.1.2 Related Bora-amination Methodology

Bora-amination has been previously reported using metal catalysis, Lewis acid catalysis and photoredox methods. Bora-amination of alkenes has been well-studied using copper catalysis by Hirano and Miura (Scheme 4. 17). They use pinacol diboronic ester (B_2pin_2) as a boron source and *O*-acylhydroxylamines as nitrogen sources.[178] The same strategy can be applied to vinylboronate or vinylsilane species.[179] Intramolecular bora-amination can be accomplished using copper catalysis as well, forming dihydropyrrole products.[180]

Scheme 4. 17 Previously reported alkene bora-amination methods using copper catalysis with *O*-acylhydroxylamines



Non-copper catalyzed methods for bora-amination include several reports of indole syntheses via cyclization (Scheme 4. 18).[181] In these examples, boron or a metal act as a Lewis acid to promote nitrogen

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[178] (a) Matsuda, N.; Hirano, K.; Satoh, T.; Masahiro Miura, M. *J. Am. Chem. Soc.* **2013**, *135*, 4934–4937. (b) Sakae, R.; Hirano, K.; Miura, M. *J. Am. Chem. Soc.* **2015**, *137*, 6460–6463. (c) Sakae, R.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem. Int. Ed.* **2015**, *54*, 613-617. (d) Kato, K.; Hirano, K.; Miura, M. *Chem. Eur. J.* **2018**, *24*, 5775-5778. (e) Wu, L.; Zatolochnaya, O.; Qu, B.; Wu, L.; Wells, L. A.; Kozlowski, M. C.; Senanayake, C. H.; Song, J. J.; Zhang, Y. *Org. Lett.* **2019**, *21*, 8952–8956.

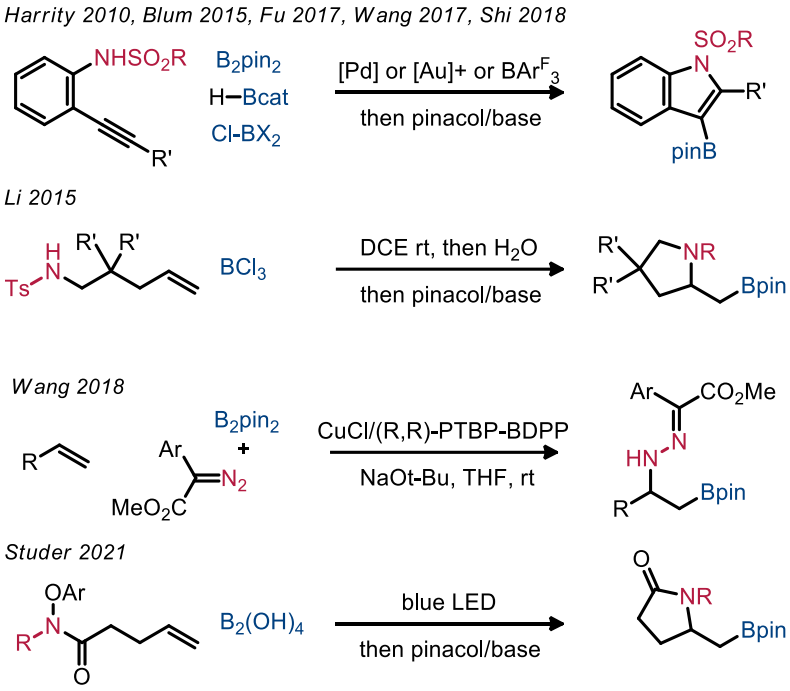
[179] (a) Nishikawa, D.; Hirano, K.; Miura, M. *Org. Lett.* **2016**, *18*, 4856–4859. (b) Kato, K.; Hirano, K.; Miura, M. *Angew. Chem. Int. Ed.* **2016**, *55*, 14400-14404.

[180] Zhang, Y.; Wu, X. -F. *Org. Chem. Front.* **2020**, *7*, 3382-3386.

[181] (a) Huang, J. -H.; Macdonald, S. J. F.; J. P. A. Harrity, J. P. A. *Chem. Commun.* **2010**, *46*, 8770-8772. (b) Chong, E.; Blum, S. A. *J. Am. Chem. Soc.* **2015**, *137*, 10144−10147. (c) Jiang, J.; Zhang, Z.; Fu, Y. *Asian J. Org. Chem.* **2017**, *6*, 282-

endo-cyclization. Pyrrolidines have been formed by a similar method using BCl_3 and *N*-tosylpentenylamines.[182] Alternatively, copper catalysis can be used for bora-amination using B_2pin_2 and a diazo species.[183] Photocatalysis has also recently been applied to the synthesis of boronic acid-substituted lactams.[184] In all of these examples, two separate reagents are required for N-C and B-C bond formation, however, the proposed reaction with *O*-borylhydroxylamines **5** would use a single reagent, offering diastereoselectivity from a concerted process.

Scheme 4. 18 Previously reported alkene/alkyne bora-amination methods using other modes of activation



4.3.1.3 Reported examples of bora-Cope elimination

While Cope-type bora-amination has yet to be reported, the microscopic reverse reaction, a bora-Cope elimination, has been reported prior to these studies, albeit minimally explored. Brown first reported an alkene synthesis via a sequential hydroboration/oxidation/elimination of enamines in 1987, then reported

289. (d) Yuan, K.; Wang, S. *Org. Lett.* **2017**, 19, 1462-1465. (e) Lv, J.; Zhao, B.; Liu, L.; Han, Y.; Yuan, Y.; Chi, Z. *Adv. Synth. Catal.* **2018**, *360*, 4054–4059.

[182] Yang, C. -H.; Zhang, Y.-S.; Fan, W. -W.; Liu, G. -Q.; Li, Y. -M. *Angew. Chem. Int. Ed.* **2015**, *54*, 12636–12639.

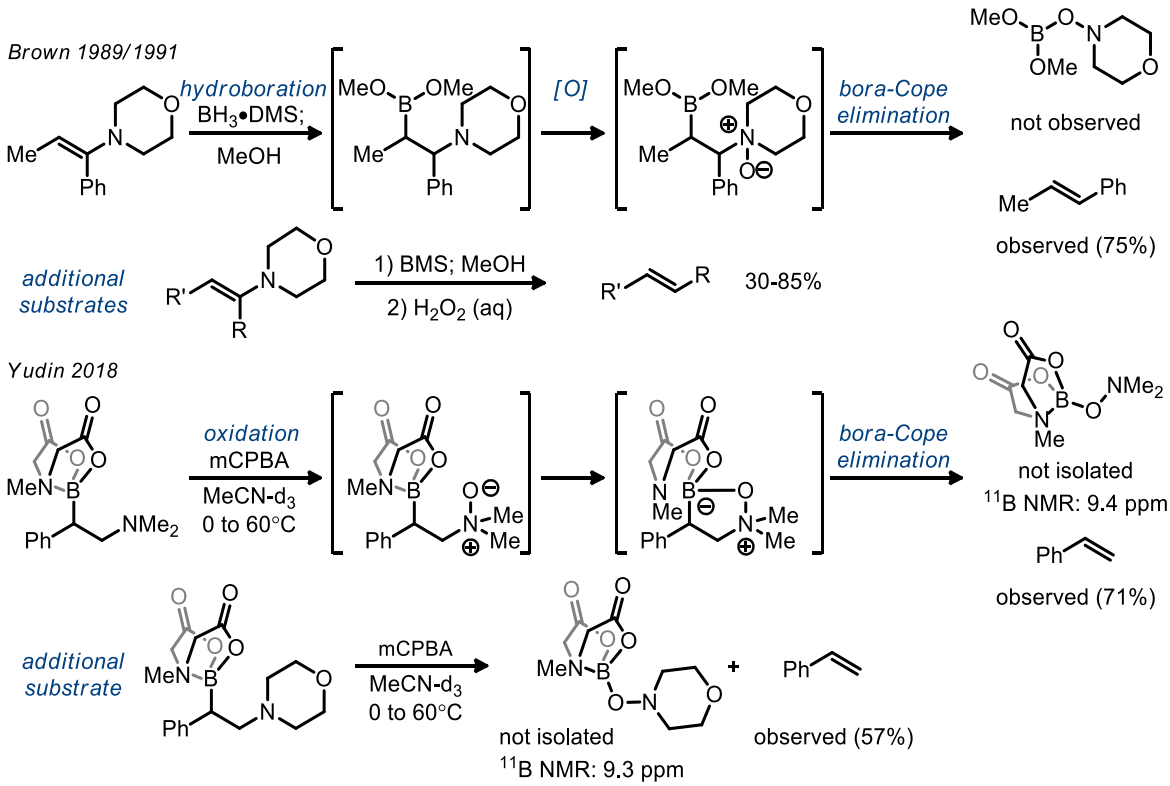
[183] Huo, J.; Xue, Y.; Wang, J. *Chem. Commun.* **2018**, *54*, 12266-12269.

[184] Zheng, D.; Jana, K.; Alasmary, F. A.; Daniliuc, C. G.; Studer, A. *Org. Lett.* **2021**, *23*, 7688–7692.

more detailed studies in 1989 and 1991 (Scheme 4. 19).[185] A bora-Cope elimination mechanism was proposed to account for the *E*-alkene selectivity, however, the *O*-borylhydroxylamine by-product was not discussed or observed by the authors in any of the publications. Within an extensive article describing various modes of amino MIDA boronate reactivity in 2018, Yudin and Dudding reported an oxidation/elimination of β-amino MIDA boronates to form *O*-borylhydroxylamine and styrene.[163c] They observe the formation of styrene as evidence supporting a bora-Cope elimination reaction as well as a new ^{11}B NMR peak believed to correspond to an *O*-MIDA boronate-substituted hydroxylamine, however, they were unable to isolate the hydroxylamine species for further structural elucidation. Both of these examples include valid mechanistic assumptions, though are missing important characterization of the boron-containing product, the *O*-borylhydroxylamine. Significantly for the proposed bora-amination reaction, *O*-borylhydroxylamine is likely extremely unstable as implied by these reports, though the mechanism of degradation is ambiguous.

[185] (a) Goralski, C. T.; Singaram, B.; Brown, H. C. *J. Org. Chem.* **1987**, *52*, 4014-4019. (b) Singaram, B.; Goralski, C. T.; Rangaishenvi, M. V.; Brown, H. C. *J. Am. Chem. Soc.* **1989**, *111*, 386-388. (c) Singaram, B.; Rangaishenvi, M. V.; Brown, H. C. Goralski, C. T.; Hasha, D. L. *J. Org. Chem.* **1991**, *56*, 1543-1549.

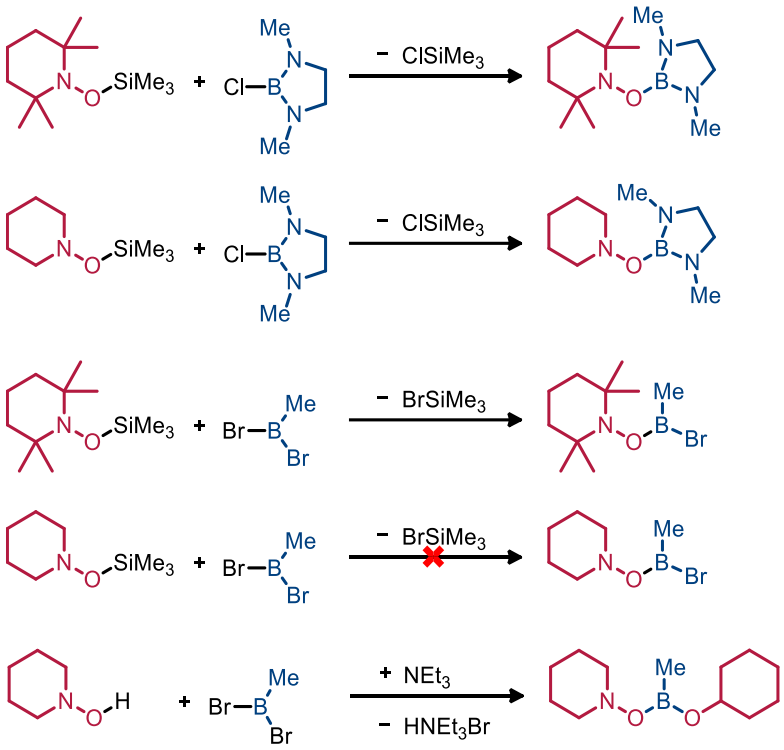
Scheme 4. 19 Reported Examples of bora-Cope elimination and observed products



In fact, *O*-borylhydroxylamines have been reported very rarely in any previous literature. Examples using TEMPO as the hydroxylamine source are most common as they form sterically hindered products and are therefore more stable. Meller and co-authors reported the formation of TEMPO and 1-hydroxypiperidine derived *O*-borylhydroxylamines in 1985 (Scheme 4. 20).[186] While silylated TEMPO and 1-hydroxypiperidine react similarly with 2-chloro-diazaborolidine, when multiple halides can be displaced, TEMPO will only undergo one substitution reaction, whereas the less sterically hindered 1-hydroxypiperidine will undergo two substitutions. In fact, the authors noted that the mono-substituted product was subject to degradation under the attempted reaction conditions with silylated 1-hydroxypiperidine. It therefore seems as though steric bulk on both nitrogen and boron affect the stability of *O*-borylhydroxylamines.

[186] (a) Armbrecht, M.; Maringgle, W.; Meller, A.; Noltemeyer, M.; Sheldrick, G. M. *Naturforsch*. **1985**, *40b*, 1113-1122. For one later example using TEMPO and BBr_3, see: (b) Wright, A. M.; Page, J. S.; Scepaniak, J. J.; Wu, G.; Hayton, T. W. *Eur. J. Inorg. Chem.* **2013**, 3817–3820.

Scheme 4. 20 Known syntheses of *O*-borylhydroxylamines *(Meller 1985)*



With the examples of the microscopic reverse reaction and noted caution related to the potential instability of the *O*-borylhydroxylamine, various conditions using a large excess of alkene or alkyne reagents were tested. Pinacol esters of the boron reagent were used due to steric bulk and high availability of related precursors.

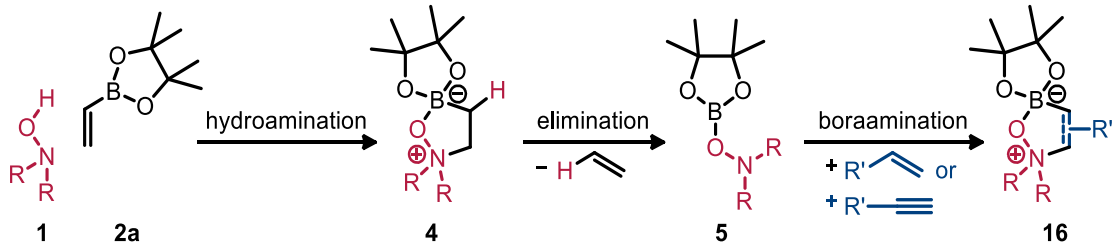
4.3.2 Bora-Cope Elimination Cascade

4.3.2.1 Attempts for Cascade Cope Reactivity

With a proposed Cope-type hydroamination/bora-Cope elimination sequence to form the *O*-borylhydroxylamine **5** for bora-amination in-situ, we used unsubstituted vinylboronate **2a** in order to form volatile ethylene gas (**6a**), preventing reformation of the first zwitterion **4** (Table 4. 8). We began by using TFE as a solvent to help stabilize the desired zwitterionic product **16**. A large excess of electronically activated silyl alkene (entry 1) or alkyne (entry 2) was chosen to promote the final step, bora-amination. Using simultaneous addition conditions, the intermediate zwitterion **4** was formed, though none of the desired zwitterion **16** was observed (entries 1-2). Using crude oxazaborolidine zwitterions **4a** as the starting material instead to simplify the reaction sequence, no bora-amination of alkynes (entries 3-4) or alkenes (entries 5-6) was observed. TFE was potentially stabilizing zwitterion **4** too much for the bora-

Cope elimination to occur, so $PhCF_3$ was tried as a solvent instead. Using the isolated *N*-cyclohexylhydroxylamine derived oxazaborolidine **4h** with $PhCF_3$, no bora-amination was observed for several alkynes either (entries 7-9). In some entries using activated alkenes or alkynes, some Cope-type hydroamination products with no boron included were observed, suggesting degradation to $HONR_2$. To gain a better understanding of why this reaction sequence may not proceed as proposed, further computational work was completed in collaboration with the Schwan lab.

Table 4. 8 Attempted optimization of the elimination cascade bora-amination of alkenes or alkynes[a]



Entry	R	Alkene or alkyne trap (equiv)	Solvent (M)	Temp (°C)	Yield of **4** (%)[b]	Yield of **16** (%)[b]
1	H/$(CH_2)_3Ph$	$CH_2CHSiMe_2Ph$ (5)	TFE (0.5)	50	67	0
2	H/$(CH_2)_3Ph$	HCCSi(*i*-Pr)$_3$ (5)	TFE (0.5)	50	60	0
3[c]	Et-Et	HCCSi(*i*-Pr)$_3$ (10)	TFE (0.5)	80	-	0
4[c]	Et-Et	$HCC(CH_3)_5CH_3$ (10)	TFE (0.5)	80	-	0
5[c]	Et/Et	Norbornadiene (10)	TFE (0.5)	80	-	0
6	Et/Et	Cyclopentene (10)	TFE (0.5)	80	-	0
7[d]	H/Cy	$HCC(CH_3)_2OH$ (10)	$PhCF_3$ (0.2)	100	-	0
8[d]	H/Cy	$HCC(CH_3)_5CH_3$ (10)	$PhCF_3$ (0.2)	100	-	0
9[d]	H/Cy	HCCPh (10)	$PhCF_3$ (0.2)	100	-	0

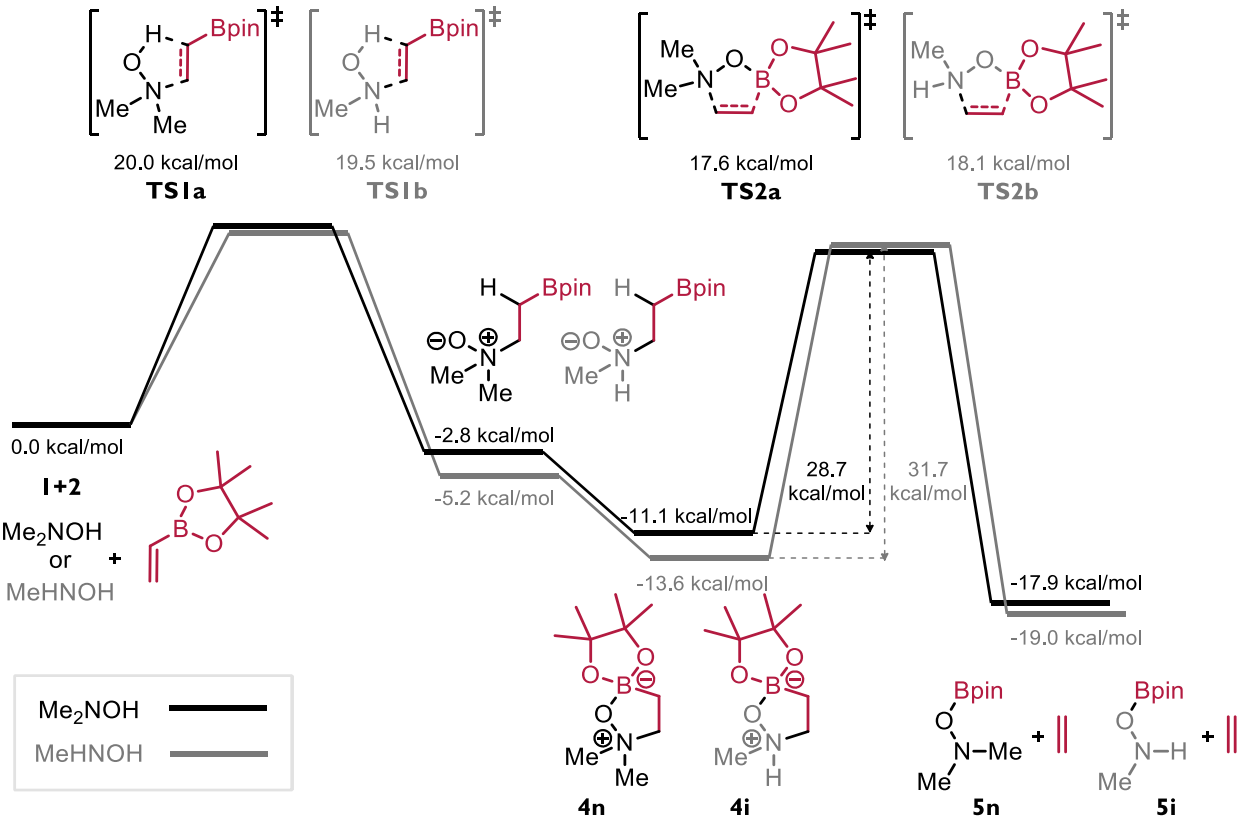
(a) Vinylboronate **2a** (1.0 equiv) in solvent, hydroxylamine **1** (1.0 equiv) added, given alkene/alkyne added, given temperature, 16h; (b) ^1H NMR yield of **4** or **16** using 1,3,5-trimethoxybenzene as an internal standard; (c) Using crude oxazaborolidine zwitterion; (d) Using isolated oxazaborolidine zwitterion; TFE = 2,2,2-trifluoroethanol.

4.3.2.2 Computational Results

Continuing the previous computational study of the Cope-type hydroamination of pinacol vinylboronate, the solvated electronic free energy was then calculated for the bora-Cope elimination step using the SMD model for TFE with B3LYP/def2-tzvp + CBS-DLPNO-CCSD(T) (Figure 4. 7). While the bora-Cope elimination was calculated to be thermodynamically favourable (ΔG = –6.8 kcal/mol or –5.4 kcal/mol from the zwitterion of Me_2NOH and MeNHOH respectively), the activation energies were calculated to be relatively high. The energy at both transition states (**TS2**) was found to be significantly higher ($\Delta G^{\ddagger}$ = + 28.7 kcal/mol or + 31.7 kcal/mol) from the lowest energy intermediate, the oxazaborolidine zwitterion, than the first

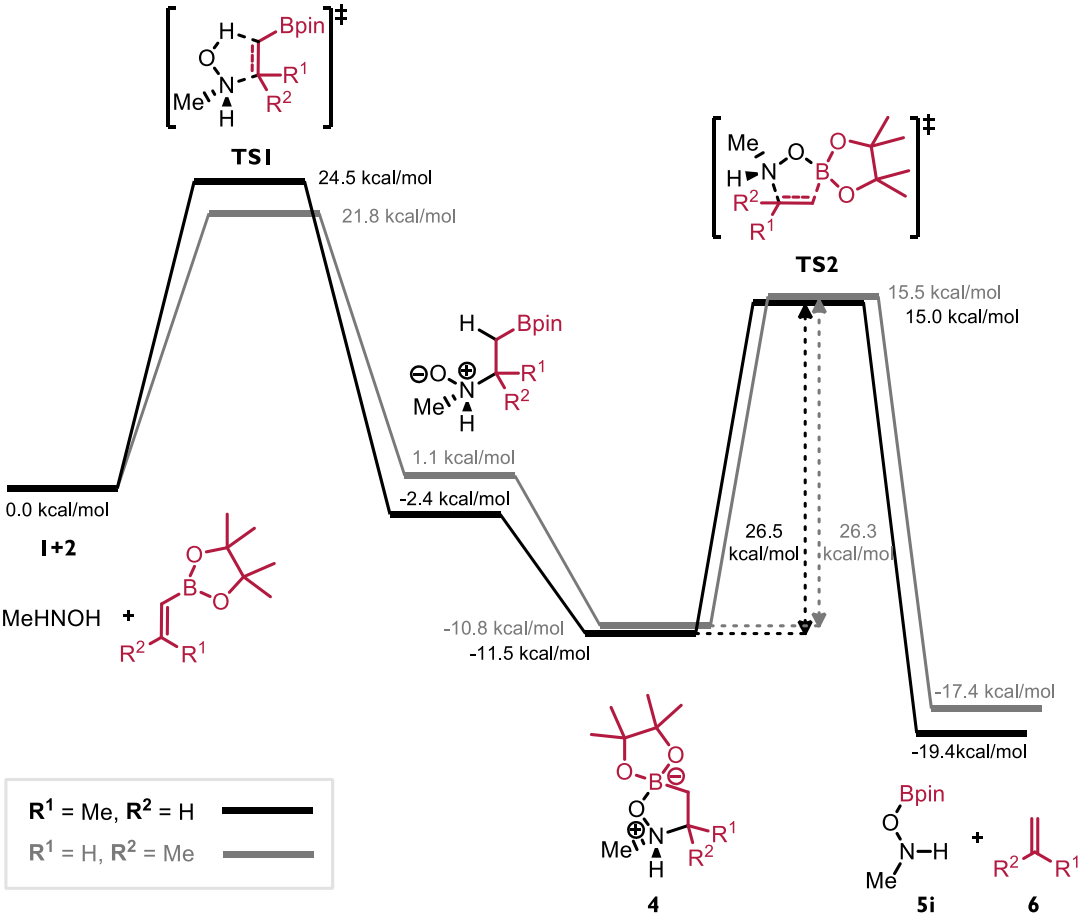
transition state energy (**TS1**) ($\Delta G^{\ddagger}$ = + 20.0 kcal/mol or + 19.5 kcal/mol). The bora-Cope elimination is therefore likely kinetically inaccessible under the reaction conditions when using unsubstituted pinacol vinylboronate. This result aligns well with the experimentally observed stable oxazolidines for unstabilized pinacol vinylboronate.

Figure 4. 7 Potential energy surface for Cope-type hydroamination/Bora-Cope elimination sequence for pinacol vinylboronate with Me_2NOH and MeNHOH *(results from Eric Nicol)*



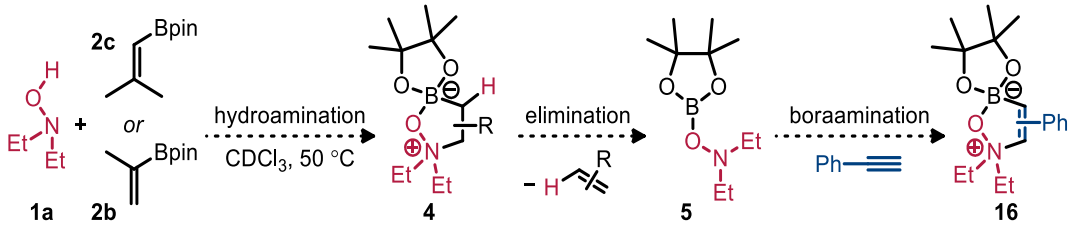
The bora-Cope elimination products are exclusively observed, however, when using substituted vinylboronates for Cope-type hydroamination (Table 4. 2). The computational results for *cis*- and *trans*-propenylboronate show similar activation energies for the initial hydroamination (**TS1**) and the bora-Cope elimination (**TS2**) steps for both alkene geometries (Figure 4. 8), so the bora-Cope elimination is more likely to also occur. These results help to rationalize the changes in reaction selectivity observed when using substituted vinylboronates.

Figure 4. 8 Potential energy surface for Cope-type hydroamination/Bora-Cope elimination sequence for pinacol *cis*- and *trans*-propenylboronate with MeNHOH *(results from Eric Nicol)*



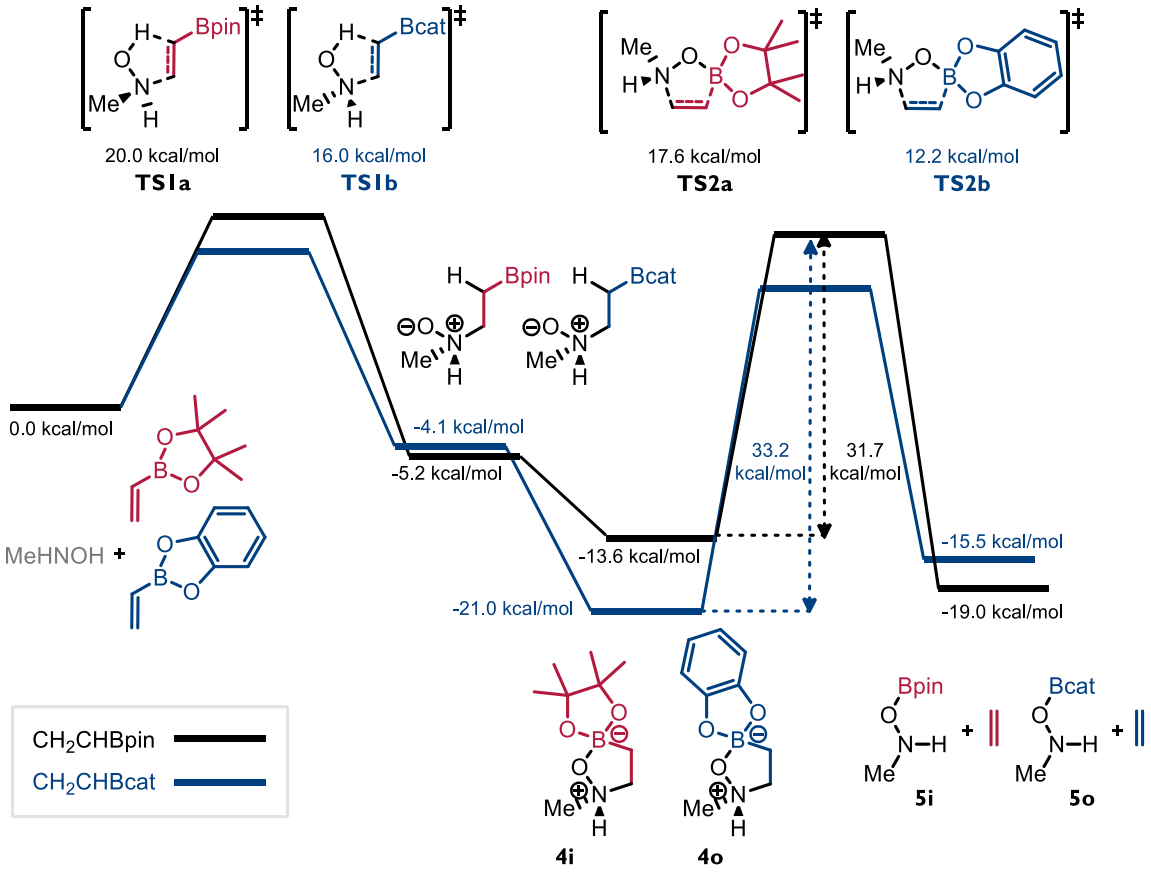
Unfortunately, when substituted pinacol vinylboronates (**2b**, **2c**) were then used for the proposed cascade bora-amination reaction sequence, which requires elimination to occur, no product (**16**) was observed (Scheme 4. 21). ^{1}H and ^{11}B NMR data suggests some starting boronic ester remained and only decomposition products were formed. These results are likely related to the low stability of the *O*-borylhydroxylamines **5**.

Scheme 4. 21 Attempted cascade bora-amination of phenylacetylene



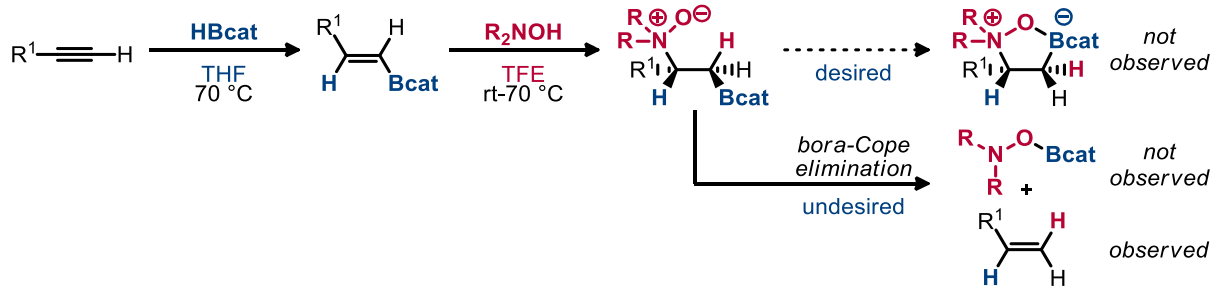
The effects of boronic ester identity were studied by calculating the difference in the potential energy surfaces of pinacol and catechol vinylboronate hydroamination/bora-Cope elimination (Figure 4. 9). As predicted and initially calculated (Table 4. 6), increasing Lewis acidity at boron led to considerably more stable *N*-oxide adducts. The bora-Cope elimination reaction is also calculated to be unfavourable for catechol vinylborane (ΔG = + 5.5 kcal/mol), potentially allowing for selectivity for hydroamination without bora-Cope elimination.

Figure 4. 9 Potential energy surface for Cope-type hydroamination/Bora-Cope elimination sequence for pinacol and catechol vinylboronate with MeNHOH *(results from Eric Nicol)*



Initial experimental results forming substituted catechol vinylboronates in-situ, then allowing them to react with various hydroxylamines formed alkenes derived from bora-Cope elimination exclusively (Scheme 4. 22). While this was a surprising result based on the computed high **TS2** in comparison to **TS1** (Figure 4. 9), this more Lewis acidic *O*-borylhydroxylamine was considered a good option for the cascade bora-amination. Unfortunately, work performed by a colleague, Myroslava Volosheniuk, also led to no observed bora-amination using similar conditions to previous attempts (Table 4. 8, Scheme 4. 21).

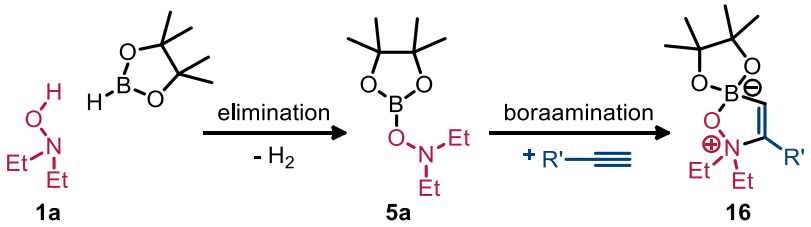
Scheme 4. 22 Attempted Cope-type hydroamination of catechol vinylboronates



4.3.3 Dehydrogenative Coupling

Another possible route towards *O*-borylhydroxylamine **5** needed for the desired bora-amination reactivity is through dehydrogenative coupling. The loss of hydrogen gas is rapid for related arylamines and pinacol borane.[170c] Attempts to form the *O*-borylhydroxylamine in-situ by mixing *N*,*N*-diethylhydroxylamine and pinacol borane, followed by the addition of alkynes for bora-amination led to no observable desired product **16** (Table 4. 9). The first dehydrogenation step visibly forms gas immediately upon mixing. Using dry polar aprotic solvents, MeCN or $PhCF_3$, with mono-substituted alkynes, no zwitterion **16** was formed as determined by the lack of sp^2 C-H signal in the crude ^1H NMR spectrum. Notably, all ^{11}B NMR signals observed for each entry are significantly higher than that expected for a zwitterionic $RB(OR)_3$ product. The desired product is likely to have a ^{11}B chemical shift lower than that of the related oxazaborolidine zwitterions **4** discussed in section 4.2 (approximately 13 ppm) due to the Csp^2 substituent. Additionally, no *O*-borylhydroxylamine **5a** was observed by NMR spectroscopy using this method either.

Table 4. 9 Attempted optimization of the dehydrogenative cascade bora-amination of alkenes[a]



Entry	Equiv HBpin	Alkyne (equiv)	Solvent (M)	^{11}B NMR signals (ppm)	Yield 16 (%)[b]
1	1.1	-	MeCN (3)	24.6, 23.1, 21.8	-
2	1.1	$HCC(CH_3)_2OH$ (10)	MeCN (3)	23.9, 22.4, 21.7	0
3	1.1	$HCC(CH_2)_5CH_3$ (10)	MeCN (3)	23.9, 22.6, 21.2	0
4	1.1	-	$PhCF_3$ (3)	24.2, 21.8	-
5	1.1	$HCC(CH_3)_2OH$ (10)	$PhCF_3$ (3)	23.8, 22.5, 21.7	0
6	1.1	$HCC(CH_2)_5CH_3$ (10)	$PhCF_3$ (3)	24.0, 22.7, 21.3	0
7[c]	1.1	$HCC(CH_2)_3CH_3$ (10)	MeCN (3)	24.0, 22.5	0
8[c]	1.1	$HCC(CH_2)_5CH_3$ (2)	MeCN (3)	23.8, 22.1	0
9[c]	1.1	$HCC(CH_2)_5CH_3$ (5)	MeCN (3)	24.0, 22.4	0
10[c]	1.0	$HCC(CH_2)_5CH_3$ (5)	MeCN (3)	23.9, 22.2	0
11[c]	3.0	$HCC(CH_2)_5CH_3$ (5)	MeCN (3)	22.3	0
12[c]	10	$HCC(CH_2)_5CH_3$ (5)	MeCN (3)	28.3, 23.8, 21.2	0

(a) HBpin in solvent (0.5M), Et_2NOH (1.0 equiv) added, 30 min, then alkene added, rt, 2h; (b) ^{1}H NMR yield of **16** using 1,3,5-trimethoxybenzene as an internal standard; (c) order of addition is modified to hydroxylamine, solvent, and alkyne added first, then HBpin added, stir rt, 1h.

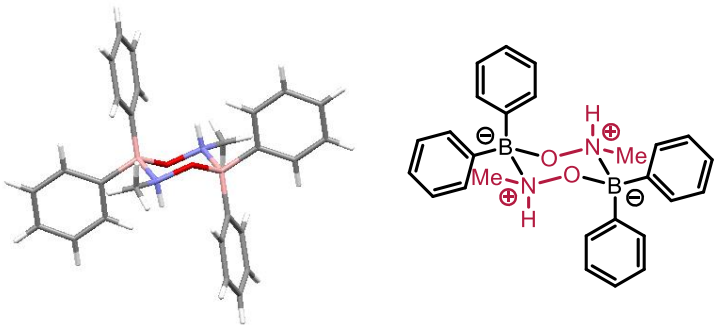
4.4 Lessons Learned and Ongoing Work

4.4.1 Future Bora-Amination Work

The fate of the expected *O*-borylhydroxylamine intermediate **5** in both the cascade bora-Cope elimination (Table 4. 8) and dehydrogenation reactions (Table 4. 9) is unclear from the current studies. The limitations of ^{1}H NMR and ^{11}B NMR as the main tools for analysis of these reactions include the minimal distinct coupling of NMR active nuclei and the minimal changes in spectra associated with various heteroatom-substitution boronic ester species. It is possible that TFE may play role in the degradation of boronic ester reagents via alcoholysis. No conclusions regarding the degradation products can be drawn based on NMR alone for these reactions, however Raman or IR spectroscopy may be useful tools. Specifically, in-situ reaction monitoring may be able to detect short-lived reactive species and differentiate related boron-containing species. Future work towards bora-amination could focus on intramolecular bora-amination, as this would increase the rate of bora-animation potentially beyond that of degradation.

A potential strategy to use *O*-borylhydroxylamines effectively for bora-animation is to use a dimeric species as a stable precursor. The monomeric species could be released in a controlled equilibrium, or the open dimer could react, similar to the strategy used to control the reactivity of amphoteric α-aziridine aldehydes by Yudin.[187] Dimeric species (BONBON) have been synthesized form borinic acids and their crystal structures have reported by the Trotter lab (Figure 4. 10).[188]

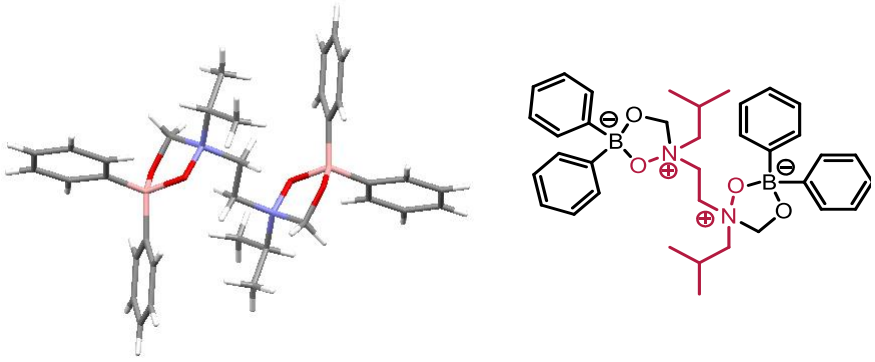
Figure 4. 10 Dimeric X-ray crystal structure of BONBON dimeric heterocycles *(Trotter 2001)*



The Trotter lab also reported X-ray crystal structures of BON/carbonyl adducts.[189] This heterocycle forms by the reaction of a hydroxylamine, borinic acid (or anhydride) and an aldehyde. In an example from 2002, the C-O bond from formaldehyde has a bond length of 1.360 Å in the zwitterionic heterocycle and has considerable double-bond character (25%) (Figure 4. 11). This stronger C-O bond may suggest a reversible formation of the cyclic structure.

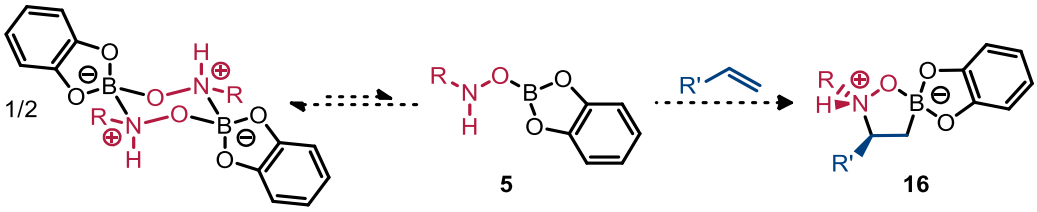
[187] Assem, N.; Hili, R.; He, Z.; Kasahara, T.; Inman, B. L.; Decker, S.; Yudin, A. K. *J. Org. Chem.* **2012**, *77*, 15613–5623.
[188] (a) Kuhn, L. P.; Inatome, M. *J. Am. Chem. Soc.* **1963**, *85*, 1206–1207. (b) Kliegel, W.; Nanninga, D.; Riebe, U.; Rettig, S. J.; Trotter, J. *Can. J. Chem.* **1994**, *72*, 1735-1740. (c) Kliegel, W.; Preu, L.; Riebe, U.; Patrick, B. O.; Rettig, S. J.; Trotter, J. *Acta Cryst.* **2001**, *E57*, 943-944.
[189] (a) Kliegel, W.; Riebe, U.; Rettig, S. J.; Trotter, J. *Can. J. Chem.* **1995**, *73*, 835-845. (b) Kliegel, W.; Amt, H.; Patrick, B. O.; Rettig, S. J.; Trotter, J. *Acta Cryst*. **2002**, *E58*, o473-o475.

Figure 4. 11 X-Ray crystal structures of BON/carbonyl adduct heterocycles *(Trotter 2002)*



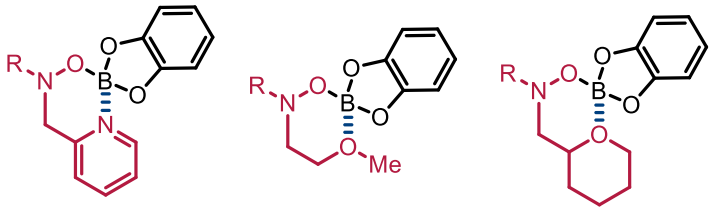
Overall, either of these precursors could potentially release *O*-borylhydroxylamine **5** in a controlled manner for bora-amination with an alkene or alkyne. The proposed reactivity resembles a deblocking equilibrium, as discussed in detail within chapter 1 for isocyanates (Scheme 4. 23).

Scheme 4. 23 Proposed bora-amination reactivity using blocked *O*-borylhydroxylamines



A distinct approach to improve the stability of the *O*-borylhydroxylamine reagents would be to include a Lewis base in one or both substituents on nitrogen (Figure 4. 12). This functional group would need to be easily displaced and the nitrogen of the hydroxylamine functional group would need to remain adequately electron rich for the intended reaction to occur. Several variants with different Lewis bases are proposed and the steric bulk near the Lewis basic atom could also be tuned.

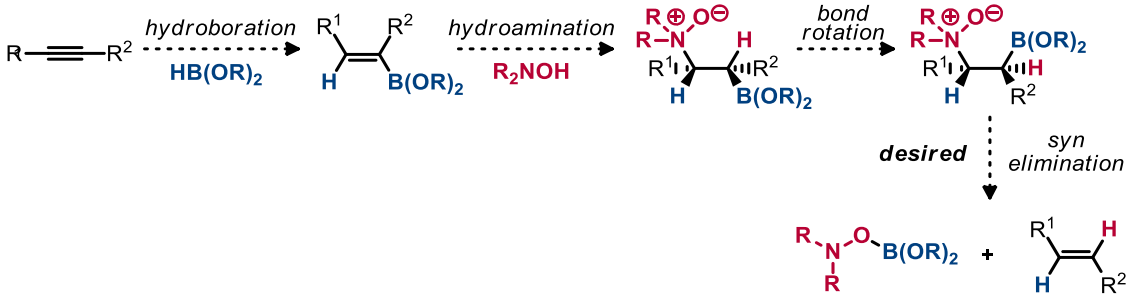
Figure 4. 12 Several examples of *O*-borylhydroxylamines potentially stabilized by Lewis bases



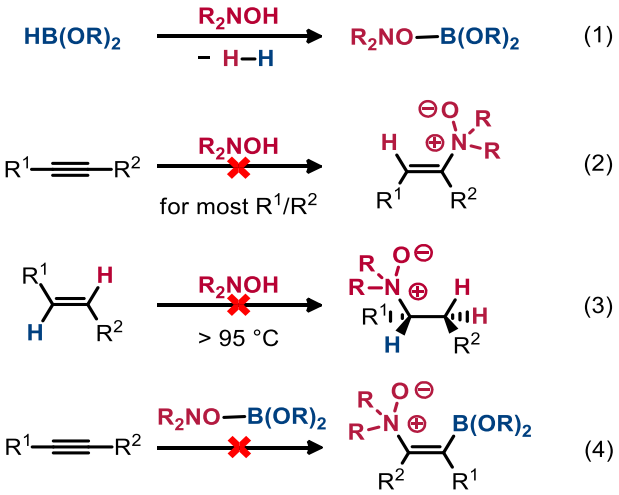
4.4.2 Alkene Synthesis from Alkynes

Avoiding bora-Cope elimination reactivity appeared to be difficult under the tested bora-amination conditions. An opportunity to take advantage of this favoured reaction pathway to form alkenes seemed plausible (Scheme 4. 22). In fact, from alkyne reagents, a reaction sequence of (1) syn-hydroboration, (2) syn-hydroamination, then (3) bond rotation for (4) syn-elimination could form alkenes with *E* geometry selectively (Scheme 4. 24). The syn-elimination to allow for *(E)*-alkene selectivity is inspired by Brown's work with enamines (Scheme 4. 19).[185]

Scheme 4. 24 Proposed *(E)*-alkene synthesis via hydroboration/hydroamination/elimination cascade



Several key potential side reactions were already well understood. It was known that rapid dehydrogenation occurs when hydroboranes and hydroxylamines are mixed (eq 1), so these reagents must be added sequentially. *N*,*N*-Dialkylhydroxylamines do not significantly react with alkynes (eq 2) or alkenes (eq 3) at temperatures below 95 °C, so these hydroaminations were not considered major possible side-reactions. Both experimental and computational data discussed in section 4.2 suggest that vinylboronic esters undergo hydroamination at much lower temperatures with hydroxylamines than hydrogen- and carbon-substituted alkenes do (<50 °C vs. >95 °C). Bora-amination had also proven difficult using the synthesis of *O*-borylhydroxylamines via elimination (4.3.2) or dehydrogenation (4.3.3), so this was also not expected to be a significant side-reaction, likely due to the instability of *O*-borylhydroxylamines (eq 4).



While hydroboration-based methods have been reported for alkyne semi-hydrogenation, they are largely limited to (*Z*)-selectivity.[190] This proposed (*E*)-selective methodology is in contrast with related work by Brown, which reports the synthesis of (*Z*)-alkenes by hydroboration/protodeboration of alkynes using refluxing acetic acid (Scheme 4. 25).[191] The overall proposed reaction is equivalent to a metal- and hydrogen gas-free trans hydrogenation of alkynes. Common issues of reductive syntheses of alkenes including overreduction, high pressures of hydrogen gas, functional group tolerance, and *E* vs. *Z* selectivity, are all precluded by the proposed one-pot reaction design.[192]

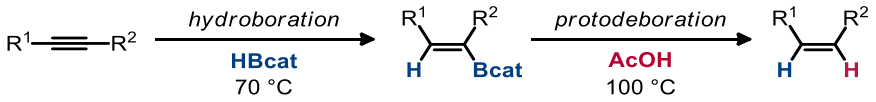
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[190] (a) Liu, Y.; Hu, L.; Chen, H.; Du, H. *Chem. Eur. J.* **2015**, *21*, 3495-3501. (b) Chernichenko, K.; Madarász, A.; Pápai, I.; Nieger, M.; Leskelä, M.; Repo, T. *Nat. Chem.* **2013**, *5*, 718-723. (c) Wech, F.; Hasenbeck, M.; Gellrich, U. *Chem. Eur. J.* **2020**, *26*, 13445-13450.

[191] (a) Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1975**, *97*, 5249-5255. For milder protodeboration conditions using dialkylboranes, see: (b) Brown, H. C.; Molander, G. A. *J. Org. Chem.* **1986**, *51*, 4512-4514. For recent examples of catalyzed protodeboration, see: (c) Liu, C.; Li, X.; Wu, Y.; Qiu, J. *RSC Adv.* **2014**, *4*, 54307-54311; (d) Liu, C.; Li, X.; Wu, Y. *RSC Adv.* **2015**, *5*, 15354-15358; (e) Barker, G.; Webster, S.; Johnson, D. G.; Curley, R.; Andrews, M.; Young, P. C.; Macgregor, S. A.; Lee, A. L. *J. Org. Chem.* **2015**, *80*, 9807-9816; (f) Kallepalli, V. A.; Gore, K. A.; Shi, F.; Sanchez, L.; Chotana, G. A.; Miller, S. L.; Maleczka, R. E., Jr.; Smith, M. R., III *J. Org. Chem.* **2015**, *80*, 8341-8353; (g) Shen, F.; Tyagarajan, S.; Perera, D.; Krska, S. W.; Maligres, P. E.; Smith, M. R., III; Maleczka, R. E., Jr. *Org. Lett.* **2016**, *18*, 1554-1557; (h) Li, N.; Xiong, F.; Gao, K. *J. Org. Chem.* **2021**, *86*, 2, 1972-1979.

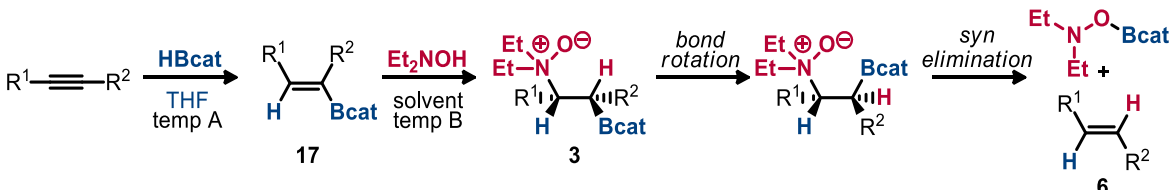
[192] For a review of catalytic semi-hydrogenation, see: (a) Decker, D.; Drexler, H.-J.; Heller, D.; Beweries, T. *Catal. Sci. Technol.* **2020**, *10*, 6449– 6463. For recent examples of (*E*)-selective semi-hydrogenation, see: (b) Srimani, D.; Diskin-Posner, Y.; Ben-David, Y.; Milstein, D. *Angew. Chem. Int. Ed.* **2013**, *52*, 14131-14134. (c) Karunananda, M. K.; Mankad, N. P. *J. Am. Chem. Soc.* **2015**, *137*, 14598–14601. (d) Thiel, N. O.; Kaewmee, B.; Ngoc, T. T.; Teichert, J. F. *Chem. Eur. J.* **2019**, *26*, 1597-1603. (e) Wang, Y.; Huang, Z.; Huang, Z. *Nat. Catal.* **2019**, *2*, 529-536. (f) Chen, K.; Zhu, H.; Li, Y.; Peng, Q.; Guo, Y.; Wang, X. *ACS Catal.* **2021**, *11*, 13696–13705. (g) Hale, D. J.; Ferguson, M. J.; Turculet, L. *ACS Catal.* **2022**, *12*, 146– 155. (h) Farrar-Tobar, R. A.; Weber, S.; Csendes, Z.; Ammaturo, A.; Fleissner, S.; Hoffmann, H.; Veiros, L. F.; Kirchner, K. *ACS Catal.* **2022**, *12*, 2253–2260. For a recent report of new Birch reduction conditions, see: (i) Burrows, J.; Kamo, S.; Koide, K. *Science* **2021**, *374*, 741-746.

Scheme 4. 25 (*Z*)-Alkene synthesis via hydroboration/protodeboration of alkynes



Early optimization of this reaction sequence used a catecholborane (HBcat) solution for the initial hydroboration step (Table 4. 10). This boronic ester solution in THF is commercially available and highly Lewis acidic. *N*,*N*-Diethylhydroxylamine was used due to the low cost and low molecular weight. Using phenylacetylene as the alkyne reagent, alkene product **6** (styrene) was formed in 35% yield after a combined 17 h reaction time (entry 1). Not including TFE as a solvent for the hydroamination/elimination step led to a higher yield of 47% (entry 2). In both cases, no alkyne starting material remained, so milder reaction conditions were attempted in case the vinyl catecholborane **17** was degrading before hydroamination could occur. The temperature was lowered to 50 °C or rt for the hydroboration and the hydroamination/elimination steps. While both rt and 50 °C were adequate temperatures for improved yields of styrene (entries 3-5), lower temperature significantly affected the hydroamination/elimination step (entries 6-7). Reducing the equivalents of HBcat to 1.0 equiv had no significant effect on the reaction (entry 8). Using equimolar HBcat, reactions at rt/50 °C and 50 °C/50 °C both led to observed product (entries 9-10), though higher temperature led to a higher yield of styrene (70%). Reducing the initial hydroboration reaction time to 4h led to a reduced observed yield (entry 11).

Table 4. 10 Early optimization of *(E)*-alkene synthesis via alkyne hydroboration/Cope-type hydroamination/bora-Cope elimination cascade[a]



Entry	R^1/R^2	Equiv HBcat	Equiv Et_2NOH	Solvent (M)	Temp A/B (°C)	Yield 6 (%)[b]
1	Ph/H	1.5	2.0	TFE (0.5)	70/50	35
2	Ph/H	1.5	2.0	-	70/50	47
3	Ph/H	1.5	2.0	-	50/50	56
4	Ph/H	1.5	3.0	-	50/50	53
5	Ph/H	1.5	3.0	-	rt/50	56
6	Ph/H	1.5	3.0	-	50/rt	19
7	Ph/H	1.5	3.0	-	rt/rt	17
8	Ph/H	1.0	3.0	-	rt/rt	14
9	Ph/H	1.0	2.0	-	rt/50	49
10	Ph/H	1.0	2.0	-	50/50	70
11[c]	Ph/H	1.0	2.0	-	50/50	47

(a) Phenylacetylene (1.0 equiv) added, then 1 M HBcat in THF, stirred at temp A for 16h under Ar, then hydroxylamine and solvent (0.5 M) if applicable added, stirred at temp B for 1h; (b) ^{1}H NMR yield of alkene using 1,3,5-trimethoxybenzene as an internal standard shown in parentheses; (c) Hydroboration reaction time was 4h instead of 16h. HBcat = catecholborane. TFE = 2,2,2-trifluoroethanol.

The best reaction conditions tested (Table 4. 10, entry 10) are simple, mild, inexpensive, and effective for the semi-hydrogenation of alkynes. The next stage of this reaction development is to further optimize these conditions and evaluate the scope and functional group tolerance. The predicted *(E)*-selectivity for this process also needs to be verified after the optimization of the hydroboration for internal alkynes. Catalytic dialkylboranes (9-BBN or $HBCy_2$) could be used to improve the efficiency of the initial hydroboration step.[193]

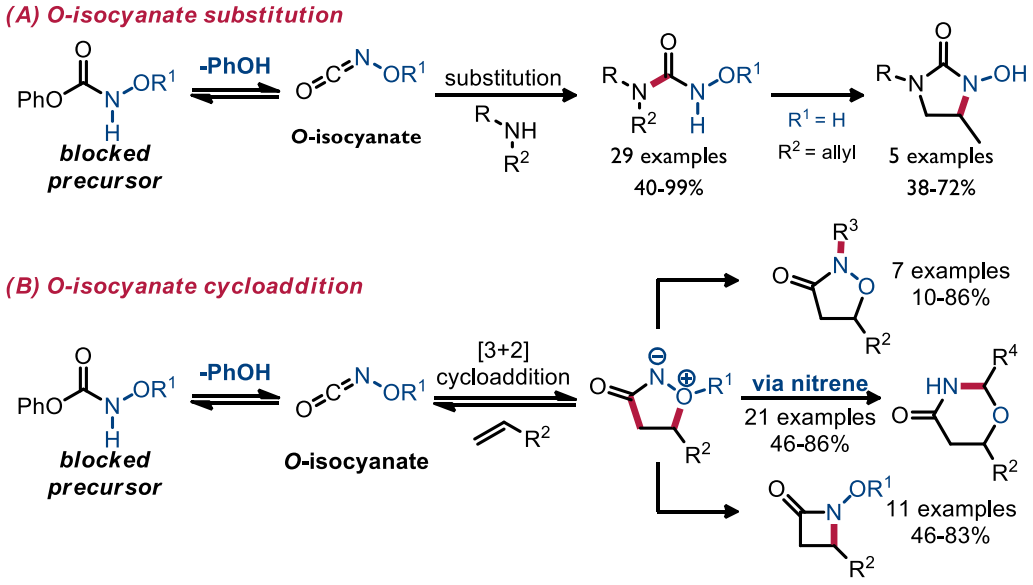
[193] (a) Nieto-Sepulveda, E.; Bage, A. D.; Evans, L. A.; Hunt, T. A.; Leach, A. G.; Thomas, S. P.; Lloyd-Jones, G. C. *J. Am. Chem. Soc.* **2019**, *141*, 18600−18611. (b) Nicholson, K.; Dunne, J.; DaBell, P.; Garcia, A. B.; Bage, A. D.; Docherty, J. H.; Hunt, T. A.; Langer, T.; Thomas, S. P. *ACS Catal.* **2021**, *11*, 2034–2040.

4.5 Conclusion

The hydroamination of vinylboronate species has proven a productive area of research for simple novel reactivity. The activating and stabilizing effects of boronic esters for Cope-type hydroamination allow for the synthesis of novel zwitterionic heterocycles, which as amphoteric species, can be derivatized into a variety of β-aminoboronic acid derivatives among other boron- or nitrogen-containing small molecules. Computational results help to elucidate that the lower LUMO of the alkene and the stabilizing effect of the B-O π* orbital are likely causing most of these beneficial effects. While the scope of alkene substitution of this reactivity has been limited thus far, the bora-Cope elimination reactivity encountered can potentially serve as part of a new metal-free *(E)*-selective semi-hydrogenation reaction sequence. Bora-amination reactivity using *O*-borylhydroxylamines has not yet been observed, though other synthetic methods to form the NOB intermediate may lead to the desired reactivity. Importantly. DFT results also fully support the feasibility of alkene bora-amination reactions. The in-situ monitoring suggested within this chapter could also help reveal the fate of these unstable NOB-containing species.

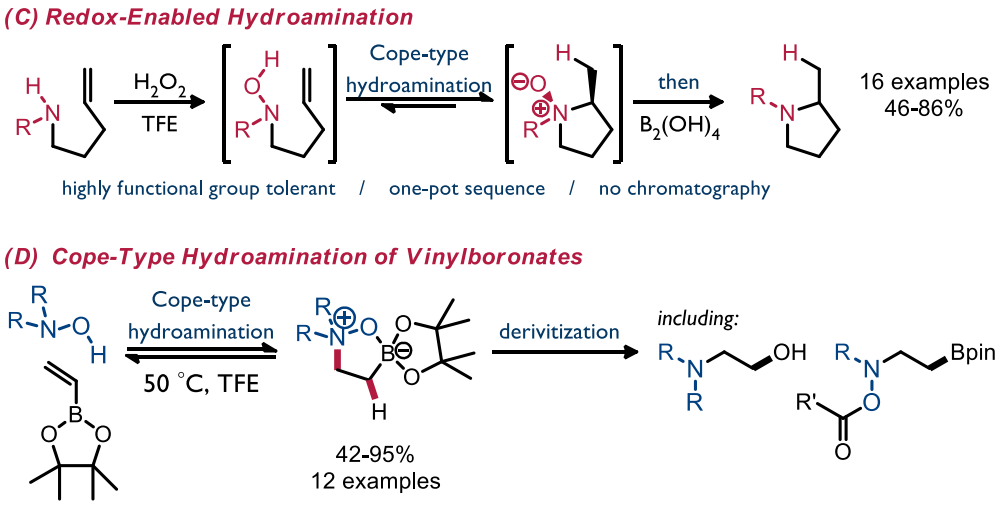
Chapter 5 Conclusions and Outlook

Diverse reactivity of hydroxylamines has been presented by the substitution and cycloaddition of electrophilic isocyanates and by the oxidation and hydroamination of nucleophilic hydroxylamines. First, the substitution reactions of rare and unstable oxygen-substituted isocyanates (*O*-isocyanates) with amines were optimized and a novel cascade reaction of substitution then Cope-type hydroamination was realized under forcing conditions (A). *O*-Isocyanates were used effectively using a blocking group approach, forming low concentrations of the active isocyanate via chemical equilibrium. This methodology provides improved access to *N*-oxyureas using primary or secondary amines as substrates and was applied the first examples of Cope-type hydroamination of acyl-substituted hydroxylamines. Then, blocked *O*-isocyanates were used for novel cycloaddition reactions, acting as uncharged 1,3-dipole equivalents (B). Divergently reactive aza-oxonium ylides are formed upon intra- or intermolecular cycloaddition with alkenes, which were exploited to form a variety of heterocycles. This novel reactivity was also studied computationally using DFT calculations.



Intramolecular Cope-type hydroamination of alkenes to form pyrrolidines is well established, however, its use is stymied from difficult synthetic and isolation procedures. An oxygen-transfer approach was imagined as a streamlined strategy and was enabled using newly developed practical oxidation (urea hydrogen peroxide (UHP)/$HOCH_2CF_3$ (TFE)) and reduction ($B_2(OH)_4$) conditions (C). Excellent functional group tolerance, demonstrated using a robustness screen, and an orthogonal substrate scope to metal-catalyzed variants were observed. Optimized isolation conditions are chromatography-free. Significant

solvent effects (TFE) and the stabilizing effects of a beta Lewis acidic substituents have been exploited for improved results for several intermolecular Cope-type hydroamination reactions as well. The reactivity with boronic ester substituents was studied experimentally in detail and computationally in collaboration with the Schwan research group (D). The effects of boron substitution appear to be both thermodynamically and kinetically beneficial.



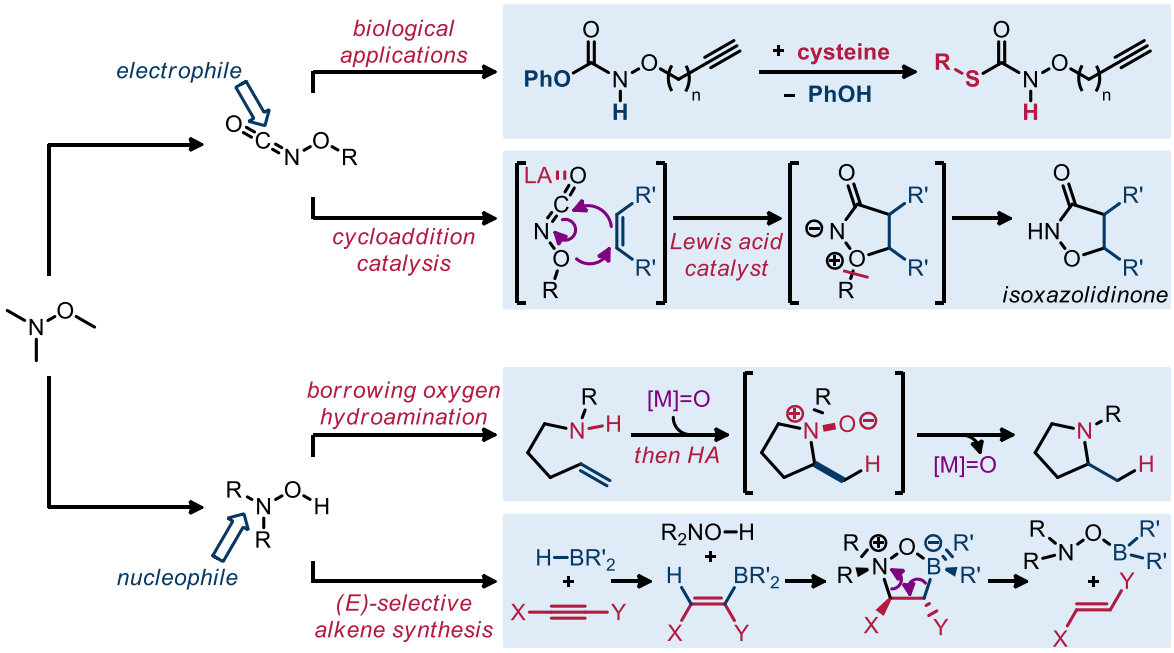
The substitution of *O*-isocyanates has been well explored under organic conditions in simple one-step or cascade reactions (section 2.1). Further work can explore the use of blocked *O*-isocyanates in bioorthogonal reactions for the identification and characterization of protein modifications.[194] Previous work using blocked imino-isocyanates demonstrated low selectivity in comparison to analogous carbamates. However, highly reactive, yet less easily deblocked, *O*-isocyanates could be more selective probes for serine or cysteine protein modifications.[195] Alkynes could easily be tethered to the *O*-isocyanate and would allow for click chemistry linkages to fluorescent reporters and blocking groups could be modified to influence selectivity.[196]

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[194] Bachovchin, D. A.; Ji, T.; Li, W.; Simon, G. M.; Blankman, J. L.; Adibekian, A.; Hoover, H.; Niessen, S.; Cravatt, B. F. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20941–20946.

[195] Shaw, T. A.; Powdrill, M. H.; Sherratt, A. R.; Garland, K.; Li, B.-J.; Beauchemin, A. M.; Pezacki, J. P. *RSC Med. Chem.* **2021**, *12*, 797-803.

[196] Cognetta, A. B.; Niphakis, M. J.; Lee, H. -C.; Martini, M. L.; Hulce, J. J.; Cravatt, B. F. *Chem. Biol.* **2015**, *22*, 928–937.



The novel *O*-isocyanate cycloaddition and aza-oxonium ylide chemistry presented in section 2.2 demonstrates controlled divergent reactivity of these highly reactive intermediates. While no effective Lewis acid catalysts have yet been identified to expand the substrate scope (section 2.3.2), further studies with organometallic Lewis acids or nitrene traps could allow for the synthesis of isoxazolidinones or oxazinones respectively via *syn*-oxycarbonylation.

A robust redox-enabled approach to intramolecular hydroamination was presented in section 3.2. The extension of work related to this currently involves an intermolecular hydroamination variant with electron-poor alkenes and an intermolecular catalytic borrowing oxygen approach. A catalytic oxo-transfer catalyst could also potentially allow for an enantioselective reaction via dynamic kinetic resolution. These works serve as a new class of oxygen-transfer enable process and could potentially be developed for other challenging amine reactivity, like imine condensation. Fundamental contributions to the solvent effects (section 3.3.1) and intramolecular Lewis acid stabilization (section 3.3.3/4.2) of *N*-oxides formed via Cope-type hydroamination are also included.

The first Cope-type hydroamination of vinyl boronates, forming oxazaborolidine zwitterions, was reported in section 4.2. Ongoing efforts to expand the substrate scope of the Cope-type hydroamination of vinyl boronates focus on modification of the boron ligands. Preliminary work on the “semi-hydrogenation” of alkynes via a hydroboration/hydroamination/elimination sequence (section 4.4.2) demonstrates promising results as a metal-free variant to hydrogenation.

Claims to original research and publications from this work

Claims to Original Research

1. Synthesis and study of a library of stable blocked *O*-isocyanates with various blocking groups.
2. Development of the first *O*-isocyanate cycloadditions and experimental/computational study of the various reaction pathways of a novel reaction intermediate - an aza-oxonium ylide.
3. Discovery and development of the direct oxidation of secondary amines to hydroxylamines and the isolation procedure.
4. Discovery, development, and scope of the first redox-enabled Cope-type hydroamination process and the novel isolation procedure.
5. Study of the beneficial solvent effects of 2,2,2-trifluoroethanol on a variety of inter- and intramolecular Cope-type hydroamination reactions.
6. Discovery and study of the effects of silicon-substitution for intermolecular Cope-type hydroamination reactions.
7. Discovery, development, and scope of the first Cope-type hydroamination reaction of vinylboronates with primary and secondary hydroxylamines.
8. Discovery and optimization of an (*E*)-selective reduction of alkynes using a hydroboration, hydroamination, and a bora-Cope elimination sequence.

Publications from this work

(**C** = communication, **A** = article, † equal contributions)

[5-C] Barriault, D.; **Allen, M. A.**; Volosheniuk, M.; Beauchemin, A. M. Oxidative Synthesis of Secondary Hydroxylamines. *Manuscript in preparation*.

[4-C] Allen, M. A.;† Volosheniuk, M.;† Nicol, E. A.; Schwan, A. L.; Beauchemin, A. M. Cope-Type Hydroamination of Vinylboronates. *Manuscript in preparation.*

[3-C] Allen, M. A.; Ly, H. M.; O'Keefe, G. F.; Beauchemin, A. M. A Redox-Enabled Strategy for Intramolecular Hydroamination. *Chem. Sci.* **2022**, *13*, 7264-7268.

[2-A] Allen, M. A.;† Ivanovich, R. A.;† Beauchemin, A. M. *O*-Isocyanates as Uncharged 1,3-Dipole Equivalents in [3+2] Cycloadditions. *Angew. Chem. Int. Ed.* **2020**, *59*, 23188–23197.

[1-C] Allen, M. A.†; Ivanovich, R. A.†; Polat, D. E.; Beauchemin, A. M. Synthesis of N-Oxyureas by Substitution and Cope-Type Hydroamination Reactions Using *O*-Isocyanate Precursors. *Org. Lett.* **2017**, *19*, 6574-6577.

Presentations from this work

(**O** = oral, **P** = poster, * indicates presenter, † virtual due to the COVID-19 pandemic)

[20-O] A Redox-Enabled Strategy for Intramolecular Hydroamination. **Allen, M. A.***; Ly, H. M.; O'Keefe, G.; Beauchemin, A. M. 105th Canadian Chemistry Conference and Exhibition, June 13-17, 2022.

[19-O] The Impact of Boron Substitution on Cope-Type Hydroamination. Volosheniuk, M.*; **Allen, M. A.**; Nicol, E. A.; Schwan, A. L.; Beauchemin, A. M. 105th Canadian Chemistry Conference and Exhibition, June 13-17, 2022.

[18-O] Cope-Type Hydroamination via Oxygen-Transfer Strategies. Ly, H. M.*; **Allen, M. A.**; Beauchemin, A. M Ottawa-Carleton Chemistry Institute Day, June 8, 2022.

[17-O] The Impact of Boron Substitution on Cope-Type Hydroamination. Volosheniuk, M.*; **Allen, M. A.**; Nicol, E. A.; Schwan, A. L.; Beauchemin, A. M. Ottawa-Carleton Chemistry Institute Day, June 8, 2022.

[16-O] Exploring the Concerted Transformations of Hydroxylamine-Containing Species. **Allen, M. A.***; Ivanovich, R. A; Volosheniuk, M.; Ly, H. M.; O'Keefe, G.; Beauchemin, A. M. Pacifichem†, December 15-20, 2021.

[15-P] A Redox-Enabled Strategy for Intramolecular Hydroamination. **Allen, M. A.***; Ly, H. L.; O'Keefe, G. F.; Beauchemin, A. M. 31st Québec-Ontario Mini-Symposium for Synthetic and Bioorganic Chemistry†, December 3-4, 2021.

[14-P] Cope-Type Hydroamination of Vinylboronates. Volosheniuk, M.*; **Allen, M. A.**; Beauchemin, A. M. 31st Québec-Ontario Mini-Symposium for Synthetic and Bioorganic Chemistry†, December 3-4, 2021.

[13-O] Oxygen-transfer enabled intramolecular Cope-type hydroamination. **Allen, M. A.***; O'Keefe, G.; Volosheniuk, M.; Barriault, D.; Ly, H. M.; Beauchemin, A. M. ACS Fall National Meeting & Exposition†, August 22-26, 2021.

[12-O] Cope-Type Hydroamination: Strategies to Resolve the *N*-Oxide Problem. **Allen, M. A.***; Volosheniuk, M.; O'Keefe, G.; Chen, M. X.; Beauchemin, A. M. 104th Canadian Chemistry Conference and Exhibition†, August 13-20, 2021.

[11-P] Saturated Heterocycle Formation via Cope-Type Hydroamination Redox Cascade. O'Keefe, G.*; **Allen, M. A.**; Beauchemin, A. M. 104th Canadian Chemistry Conference and Exhibition†, August 13-20, 2021.

[10-P] Expanding the scope of intermolecular Cope-type hydroamination with underdeveloped reagents. Volosheniuk, M.*; **Allen, M. A**.; Beauchemin, A. M. 104th Canadian Chemistry Conference and Exhibition†, August 13-20, 2021.

[9-O] Cope-Type Hydroamination: Strategies to Resolve the *N*-Oxide Problem. **Allen, M. A.***; Volosheniuk, M.; O'Keefe, G.; Chen, M. X.; Beauchemin, A. M. Ottawa-Carleton Chemistry Institute Day†, July 27, 2021.

[8-O] Expanding the scope of intermolecular Cope-type hydroamination with underdeveloped reagents. Volosheniuk, M.*; **Allen, M. A.**; Beauchemin, A. M. Ottawa-Carleton Chemistry Institute Day†, July 27, 2021.

[7-P] [3+2] Cycloaddition of *O*-isocyanates: Novel hydroxylamine-based 1,3-dipole equivalents. **Allen, M. A.***; Ivanovich, R. A; Beauchemin, A. M. Empowering Women in Organic Chemistry Conference†, August 13-14, 2020.

[6-P] Synthesis of azatides using *N*-isocyanate precursors. **Allen, M. A.***; Hussein, R.; Beauchemin, A. M. 30th Québec-Ontario Mini-Symposium for Synthetic and Bioorganic Chemistry, Ottawa, ON: Nov 8-10, 2019.

[5-O] [3+2] Cycloadditions of *O*-isocyanates as 1,3-dipole equivalents and nitrene precursors. **Allen, M. A.***; Ivanovich, R. A; Beauchemin, A. M. 102nd Canadian Chemistry Conference and Exhibition, Quebec, QC: June 3-7, 2019.

[4-P] [3+2] Cycloadditions of *O*-isocyanates: A novel 1,3-dipole equivalent and nitrene precursor. **Allen, M. A.***; Ivanovich, R. A; Beauchemin, A. M. 29th Québec-Ontario Mini-Symposium for Synthetic and Bioorganic Chemistry, Toronto, ON: Nov 16-18, 2018.

[3-O] Oxygen-Substituted Isocyanates: Key intermediates for heterocyclic synthesis. Polat, D. E.*; Ivanovich, R. A.; **Allen, M. A.**; Brzezinski, D. D.; Beauchemin, A. M. Ottawa-Carleton Chemistry Institute Day, Ottawa, ON: May 12, 2018.

[2-P] Synthesis of N-oxyureas via substitution and Cope-type hydroamination reactions with *O*-isocyanate precursors. **Allen, M. A.***; Ivanovich, R. A.; Polat, D. E.; Beauchemin, A. M. 28th Québec-Ontario Mini-Symposium for Synthetic and Bioorganic Chemistry, Montréal, QC: Nov 17-19, 2017.

[1-P] [3+2] Cycloadditions of *O*-isocyanates: A novel 1,3-dipole equivalent and nitrene precursor. Ivanovich, R. A*; **Allen, M. A**.; Beauchemin, A. M. 28th Québec-Ontario Mini-Symposium for Synthetic and Bioorganic Chemistry, Montréal, QC: Nov 17-19, 2017.

Chapter 6 Supporting Information

6.1 General information

Purification of reaction products was carried out by flash column chromatography using silica gel (40 – 63 µm), unless otherwise noted. Analytical thin layer chromatography (TLC) was performed on aluminum or glass, cut to size. Visualization was accomplished with UV light followed by staining with a potassium permanganate or ninhydrin solution and heating. ^{1}H NMR, ^{13}C NMR, ^{11}B NMR, and ^{19}F NMR spectra were recorded on Bruker AVANCE 300 MHz, 400 MHz, and 500 MHz spectrometers at ambient temperature, unless otherwise indicated. Spectral data was reported in ppm using solvent as the reference ($CDCl_3$ at 7.26 ppm, DMSO-d_6 at 2.50 ppm, CD_3OD at 3.31 ppm, or benzene-d_6 at 7.16 ppm for ^{1}H NMR and $CDCl_3$ at 77.0 ppm DMSO-d_6 at 39.52 ppm, or CD_3OD at 49.0 ppm for ^{13}C NMR). ^{1}H NMR data was reported as: multiplicity (ap = apparent, br = broad, s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextuplet, sept = septuplet, m = multiplet), integration and coupling constant(s) in Hz. ^{13}C NMR is reported indicating information from distortionless enhancement by polarization Transfer (DEPT) experiments. Infrared (IR) spectra were obtained on an Attenuated Total Reflectance Fourier Transform Infrared spectrometer (ATR-FTIR). High-resolution mass spectroscopy (HRMS) was performed on a mass spectrometer with an electron beam of 70 eV (EI) or Micromass Q-TOF I - Time of flight Electrospray Ionisation mass spectrometer (ESI).

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

6.2 Supporting Information for Chapter 2

6.2.1 General Procedures

General Procedure A: Synthesis of *N*-Acyloxycarbamates

To a flask charged with a stir bar was added *N*-hydroxycarbamate (1.00 equiv) then DCM (0.3 M) and allowed to stir at 0 °C. *Hydroxycarbamates are insoluble and will not always dissolve completely before the next step of the reaction. * Upon observing most of the hydroxycarbamate dissolve, Et_3N was added (1.00 equiv) and finally the acyl chloride was added dropwise (1.00 equiv). The reaction was allowed to warm gradually to room temperature. Upon completion, H_2O was added, and the reaction mixture was extracted with DCM. The organic layer was recollected and washed with sat. $NaHCO_3$, and then the organic

phase was recollected and washed with brine. The organic phase was dried over Na_2SO_4 (stirring for 15 minutes). Solids were filtered and the filtrate was collected and concentrated under reduced pressure to give the corresponding pure acyloxycarbamates.

General Procedure B: Substitution of *N*-Hydroxycarbamates

To a 5 mL microwave vial charged with a stir bar was added the phenyl *N*-hydroxycarbamate 1a (1.10 equiv), then THF (0.3 M), to which was added Et_3N (0.20 equiv) and the corresponding amine (1.00 equiv). The vial was sealed with a microwave cap and heated for 16 h at 70 °C via conventional (oil bath) heating. Solvent was removed under reduced pressure and the products were then purified by silica gel chromatography to give the corresponding pure hydroxyureas.

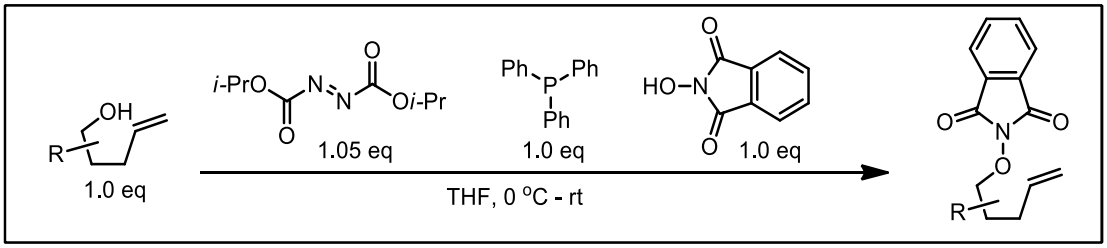
General Procedure C: Substitution of *N*-Alkoxycarbamates

To a 5 mL microwave vial charged with a stir bar was added the phenyl *N*-alkoxycarbamate (1.05 equiv), then MeCN (0.3 M), to which was added the corresponding amine (1.00 equiv). The vial was sealed with a microwave cap and heated for 30 min at 120 ^oC via microwave irradiation. The reaction mixture was diluted with EtOAc and transferred to a separatory funnel, then washed twice with 1 M NaOH and once with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the corresponding pure *N*-ethoxyureas.

General Procedure D: Substitution of *N*-Acyloxycarbamates

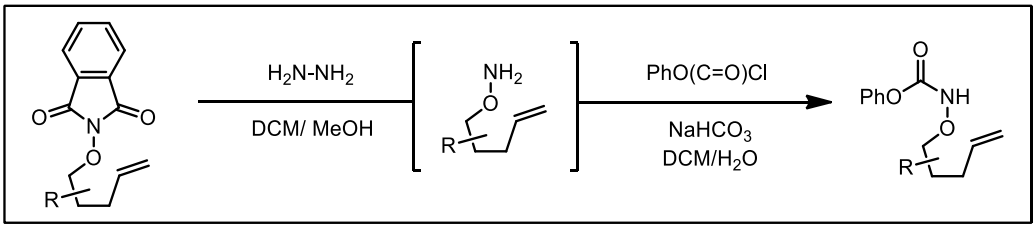
To a 5 mL microwave vial charged with a stir bar was added the phenyl *N*-acyloxycarbamate (1.00 equiv), then THF (0.2 M), to which was added the corresponding amine (1.05 equiv) and then imidazole (0.10 equiv). The vial was sealed with a microwave cap and heated for 1-3 hours at 100 ^oC via microwave irradiation. The reaction mixture was diluted with EtOAc and transferred to a separatory funnel, then washed twice with 1 M NaOH and once with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the corresponding pure acyloxyureas. In some cases, a higher degree of purity was needed after the extraction and the products could easily be recrystallized or purified by silica gel chromatography.

General procedure E: Synthesis of *N*-alkoxyphthalimides



N-Alkoxyphthalimide synthesis was completed using a modified literature procedure.[197] To a round bottom flask charged with a stir bar was added the corresponding alcohol (1.00 eq) followed by dilution in THF (0.3 M). To this solution was added *N*-hydroxyphthalimide (1.00 eq) and triphenylphosphine (1.00 eq) and cooled to 0 °C. To this stirred solution was added a diisopropyl azodicarboxylate dropwise over 10 minutes (1.05 eq). The reaction progress was monitored by TLC, or ^{1}H NMR aliquots when necessary, and stopped upon completion, as gauged by consumption of the alcohol. Upon completion, the reaction was concentrated via rotary evaporation and the triphenylphosphine oxide ($Ph_3P=O$) and reduced diisopropyl azodicarboxylate (DIAD-H_2) were removed via precipitation with ether/hexanes. The filtrate was concentrated via rotary evaporation and the resulting crude *N*-alkoxyphthalimides were either used without purification for the following hydrazine deprotection (General Procedure G) or isolated using silica-gel flash column chromatography or by recrystallization in EtOH (–20 °C) prior to hydrazine deprotection (General Procedure F).

General procedure F: Synthesis of *N*-alkoxycarbamates

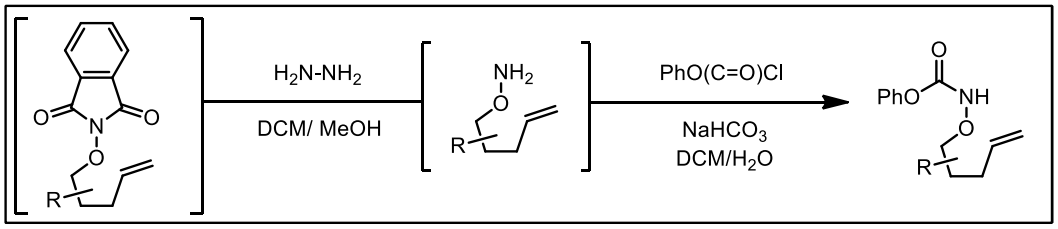


Phthalimide deprotection was completed using a modified literature procedure.[197] To a round bottom flask charged with a stir bar was added the corresponding *N*-alkoxyphthalimide (1.00 eq) followed by

[197] Ishikawa, T.; Kamiyama, K.; Matsunaga, N.; Tawada, H.; Iizawa, Y.; Okonogi K.; Miyake, A. *J. Antibiotics* **2000**, *53*, 1071.

dilution in DCM:MeOH (10:1) (0.3 M) and cooled to 0 °C. To this vigorously stirred solution was added a solution of 50% hydrazine hydrate (2.00 eq). The reaction progress was monitored by TLC and stopped upon completion, as gauged by consumption of the *N*-alkoxyphthalimide. Upon completion, the solution was filtered over a fritted funnel and the filtrate was collected (the white precipitate was discarded). The filtrate was extracted with sat. $NaHCO_3$ (x 2) and then brine (x1). The organic phase was dried with Na_2SO_4 and filtered over a fritted funnel. The filtrate was concentrated via rotary evaporation and used in the subsequent step without further purification. To a round bottom flask charged with a stir bar was added the corresponding crude *N*-alkyl hydroxylamine from the previous step (1.00 eq) followed by dilution with DCM:H_2O (2:1) (0.3 M) and cooled to 0 °C. To this vigorously stirred solution was added $NaHCO_3$ (2.20 eq). After addition of $NaHCO_3$, the solution was allowed to stir at 0 °C for 0.5 h. After 0.5 h passed, phenylchloroformate was added dropwise (1.00 eq). The solution was allowed to stir at rt. The reaction progress was monitored by TLC and stopped upon completion, as gauged by consumption of the phenylchloroformate. Upon completion, the reaction was extracted using sat. $NaHCO_3$ (x 2) and then brine (x1). The organic phase was dried with Na_2SO_4 and filtered over a fritted funnel. The filtrate was concentrated via rotary evaporation and isolated using silica-gel flash column chromatography or recrystallization.

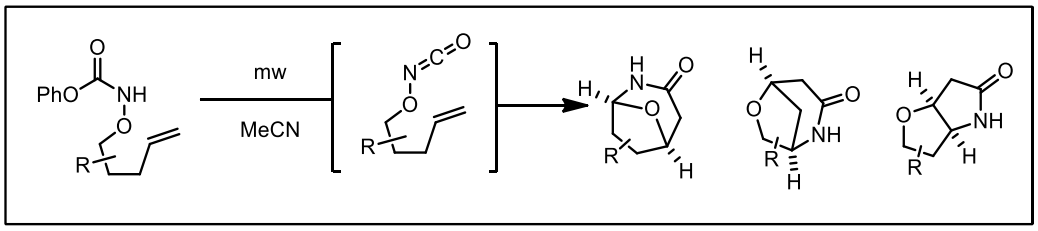
General procedure G: Express Synthesis of *N*-alkoxycarbamates



Phthalimide synthesis as seen in general procedure E. Upon completion (by TLC), Et_2O and hexanes were added to the solution, which induced a white precipitate to form upon cooling (Ph_3P=O and DIAD, usually co-crystallize). The precipitate was filtered and discarded and the filtrate, which contained the *N*-alkoxyphthalimide along with minor impurities, was used in the subsequent step without further purification. Phthalimide deprotection was completed using a modified literature procedure.[197] To a round bottom flask charged with a stir bar was added the corresponding crude *N*-alkoxyphthalimide (1.00 eq) followed by dilution in DCM:MeOH (10:1) (0.3 M) and cooled to 0 °C. To this vigorously stirred solution was added a solution of 50% hydrazine hydrate (2.00 eq). The reaction progress was monitored by TLC and stopped upon completion, as gauged by consumption of the *N*-alkoxyphthalimide. Upon completion,

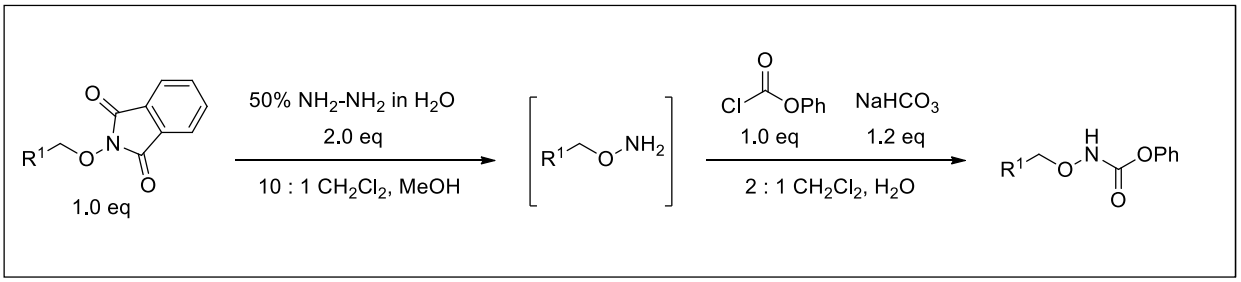
the solution was filtered over a fritted funnel and the filtrate was collected (the white precipitate was discarded). The filtrate was extracted with sat. $NaHCO_3$ (x 2) and then brine (x1). The organic phase was dried with Na_2SO_4 and filtered over a fritted funnel. The filtrate was concentrated via rotary evaporation and used in the subsequent step without further purification. To a round bottom flask charged with a stir bar was added the crude corresponding *N*-alkyl hydroxylamine (1.00 eq) followed by dilution with DCM:H_2O (2:1) (0.3 M) and cooled to 0 °C. To this vigorously stirred solution was added $NaHCO_3$ (2.20 eq). After addition of $NaHCO_3$, the solution was allowed to stir at 0 °C for 0.5 h. After 0.5 h passed, phenylchloroformate was added dropwise (1.00 eq). The solution was allowed to stir at rt. The reaction progress was monitored by TLC and stopped upon completion, as gauged by consumption of the phenylchloroformate. Upon completion, the reaction was extracted using sat. $NaHCO_3$ (x 2) and then brine (x1). The organic phase was dried with Na_2SO_4 and filtered over a fritted funnel. The filtrate was concentrated via rotary evaporation and isolated using silica-gel flash column chromatography or recrystallization.

General procedure H: Synthesis of oxo-azabicyclooctanones



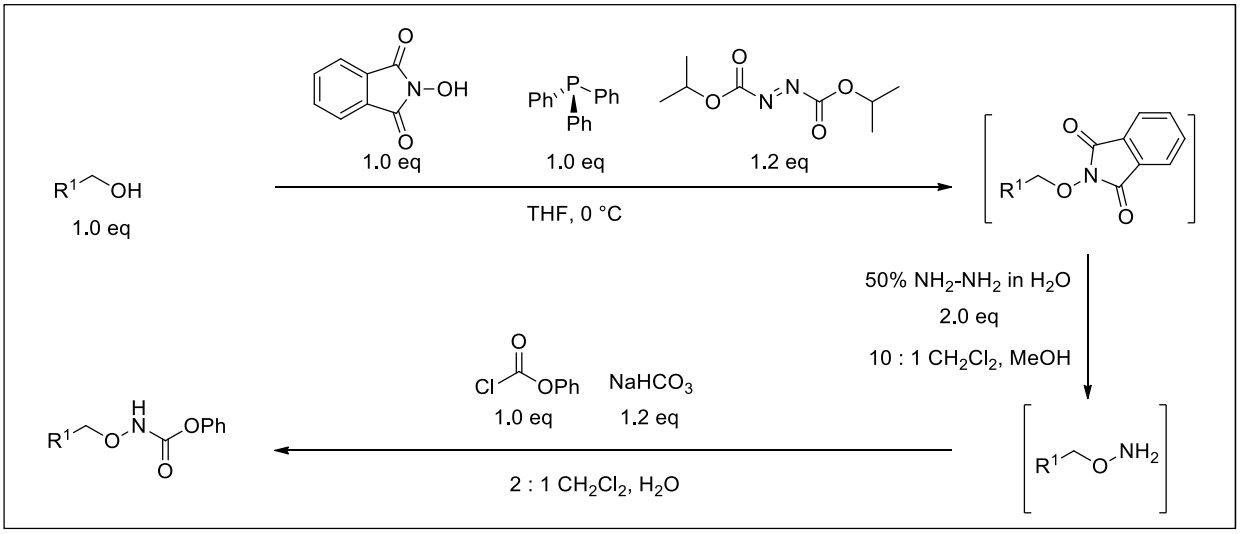
To a clean dry microwave vial charged with a stir bar was added the corresponding *N*-alkoxycarbamate followed by dilution with MeCN (0.05 M). The vial was sealed and Argon was bubbled through the solution for 10 min. The reaction vessel was heated at 180-200 °C via microwave irradiation for 3 – 10 h. Upon completion, the reaction was concentrated via rotary evaporation and isolated using silica-gel flash column chromatography.

General procedure I: Synthesis of *N*-alkoxycarbamates



To a round bottom flask charged with a stir bar was added the corresponding *N*-alkoxyphthalimide (1.00 equiv) followed by dilution in DCM:MeOH (10:1) (0.3 M) and cooled to 0 °C. To this vigorously stirred solution was added a solution of 50% hydrazine hydrate (2.00 equiv). The reaction progress was monitored by TLC and stopped upon completion, as gauged by consumption of the *N*-alkoxyphthalimide. Upon completion, the solution was filtered over a fritted funnel and the filtrate was collected (the white precipitate was discarded). The filtrate was washed with sat. $NaHCO_3$ (x 2) and then brine (x 1). The organic phase was dried with Na_2SO_4 and filtered over a fritted funnel. The filtrate was concentrated via rotary evaporation and used in the subsequent step without further purification. To a round bottom flask charged with a stir bar was added the corresponding crude *N*-alkyl hydroxylamine from the previous step (1.00 equiv) followed by dilution with DCM:H_2O (2:1) (0.3 M) and cooled to 0 °C. To this vigorously stirred solution was added $NaHCO_3$ (1.20 equiv). After addition of $NaHCO_3$, the solution was allowed to stir at 0 °C for 0.5 h. After 0.5 h passed, phenylchloroformate was added dropwise (1.00 equiv). The reaction progress was monitored by TLC and stopped upon completion, as gauged by consumption of the phenylchloroformate. Upon completion, the reaction was extracted using sat. $NaHCO_3$ (x 2) and then brine (x 1). The organic phase was dried with Na_2SO_4 and filtered over a fritted funnel. The filtrate was concentrated via rotary evaporation and isolated using silica-gel flash column chromatography or recrystallization.

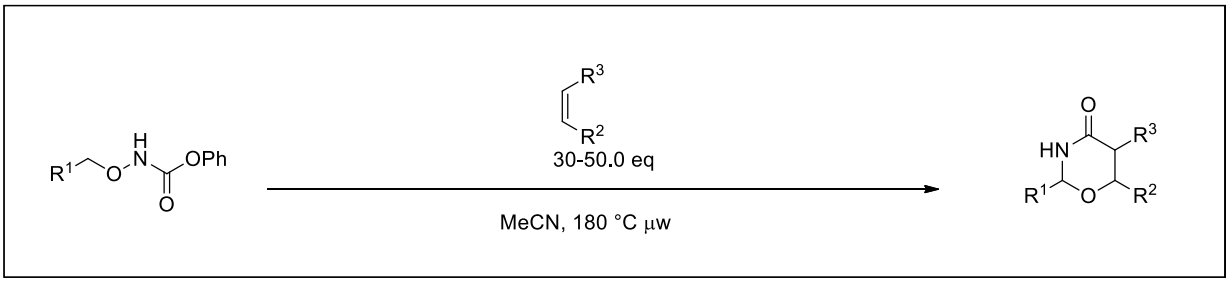
General procedure J: Express synthesis of *N*-alkoxycarbamates



To a round bottom flask charged with a stir bar was added *N*-hydroxyphthalimide (1.00 equiv) followed by dilution in dry THF (0.3 M). PPh_3 (1.00 equiv) and alcohol (1.00 equiv) were added sequentially and the resulting solution was allowed to stir at 0 °C for 0.3 h. DIAD (1.20 equiv) was added dropwise over 1 h, and the mixture was stirred at 0 °C until TLC monitoring indicated completion. Upon completion (by TLC), Et_2O and hexanes were added to the solution, which induced a white precipitate to form upon cooling (Ph_3P=O and DIAD, usually co-crystallize). The precipitate was filtered and discarded and the filtrate, which contained the *N*-alkoxyphthalimide along with minor impurities, was used in the subsequent step without further purification. To a round bottom flask charged with a stir bar was added the corresponding crude *N*-alkoxyphthalimide (1.00 eq) followed by dilution in DCM:MeOH (10:1) (0.3 M) and cooled to 0 °C. To this vigorously stirred solution was added a solution of 50% hydrazine hydrate (2.00 eq). The reaction progress was monitored by TLC and stopped upon completion, as gauged by consumption of the *N*-alkoxyphthalimide. Upon completion, the solution was filtered over a fritted funnel and the filtrate was collected (the white precipitate was discarded). The filtrate was washed with sat. $NaHCO_3$ (x 2) and then brine (x 1). The organic phase was dried with Na_2SO_4 and filtered over a fritted funnel. The filtrate was concentrated via rotary evaporation and used in the subsequent step without further purification. To a round bottom flask charged with a stir bar was added the crude corresponding *N*-alkyl hydroxylamine (1.00 eq) followed by dilution with DCM:H_2O (2:1) (0.3 M) and cooled to 0 °C. To this vigorously stirred solution was added $NaHCO_3$ (2.20 eq). After addition of $NaHCO_3$, the solution was allowed to stir at 0 °C for 0.5 h. After 0.5 h passed, phenylchloroformate was added dropwise (1.00 eq). The reaction progress was monitored by TLC and stopped upon completion, as gauged by consumption of the

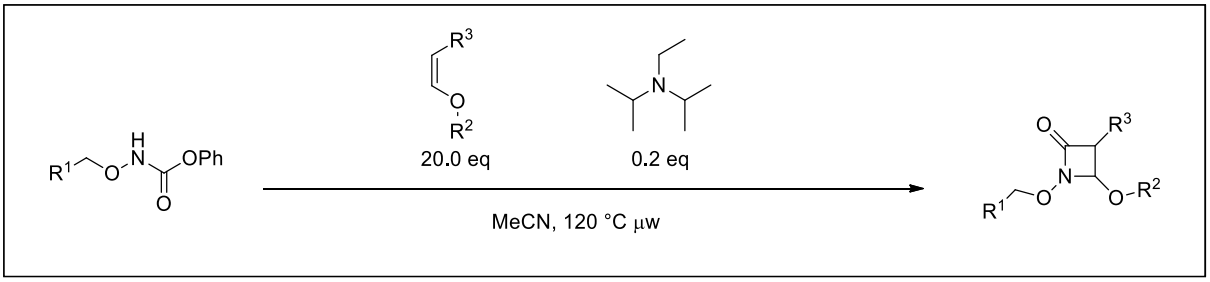
phenylchloroformate. Upon completion, the reaction was extracted using sat. $NaHCO_3$ (x 2) and then brine (x 1). The organic phase was dried with Na_2SO_4 and filtered over a fritted funnel. The filtrate was concentrated via rotary evaporation and isolated using silica-gel flash column chromatography or recrystallization.

General procedure K: Synthesis of oxo-azabicyclooctanones



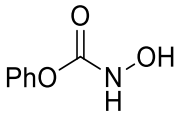
To a clean dry microwave vial charged with a stir bar was added the corresponding *N*-alkoxycarbamate (1.00 equiv) followed by alkene (50.0 equiv) and then MeCN (0.1 M). The vial was sealed and Argon was bubbled through the solution for 10 min. The reaction vessel was heated at 180 °C via microwave irradiation for 0.5–8 h. Upon completion, the reaction was concentrated via rotary evaporation and the product was isolated using silica-gel flash column chromatography.

General procedure L: Synthesis of β-lactams



To a clean dry microwave vial charged with a stir bar was added the corresponding *N*-alkoxycarbamate (1.00 equiv) followed by vinyl ether (20.0 equiv) and *i*-Pr_2NEt (0.20 equiv) then MeCN (0.1 M). The vial was sealed and Argon was bubbled through the solution for 10 min. The reaction vessel was heated at 120 °C via microwave irradiation for 2.5 h. Upon completion, the reaction was concentrated via rotary evaporation and the product was isolated using silica-gel flash column chromatography.

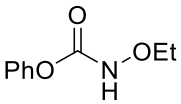
6.2.2 Characterization



Phenyl *N*-hydroxycarbamate (1a)

The title compound was synthesized according to a literature procedure.[198]

^{1}H NMR (300 MHz, $CDCl_3$): δ 10.31 (br s, 1H), 9.08 (br s, 1H), 7.40 (m, 2H), 7.22 (m, 1H), 7.10 (m, 2H).



Phenyl *N*-ethoxycarbamate (1b)

The title compound was synthesized according to a literature procedure[198] using phenyl chloroformate (12.6 mL, 0.100 mol), *O*-ethoxylamine hydrochloride (11.7 g, 0.120 mol), and sodium bicarbonate (18.5 g, 0.220 mol) in H_2O/DCM (1:1) (0.4 M). The title compound was obtained as a crystalline white solid (14.9 g, 82%).

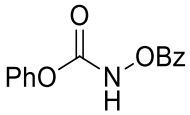
TLC R*f* : 0.73 in 2% MeOH/DCM. M. p. 60.5-61.6 ^oC.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64-7.57 (br s, 1H), 7.43-7.34 (m, 2H), 7.27-7.20 (m, 1H), 7.19-7.13 (m, 2H), 4.05 (q, *J* = 7.1 Hz, 2H), 1.32 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 155.3 (C), 150.4 (C), 129.4 (C), 125.8 (CH), 121.3 (CH), 72.7 (CH_2), 13.4 (CH_3).

IR (FTIR): 3204, 2983, 1719, 1588, 1475, 1376, 1251 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_9H_{11}NO_3Na$ [M+Na]+: 204.0637. Found: 204.0647.



Phenyl *N*-benzoyloxycarbamate (1c)

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[198] Stewart, A. O.; Brooks, D. W. *J. Org. Chem.* **1992**, *57*, 5020.

The title compound was synthesized according to general procedure **A** using phenyl *N*-hydroxycarbamate **1a** (38.3 g, 0.250 mol), Et_3N (34.9 g, 0.250 mol) and benzoyl chloride (29.0 mL, 0.250 mol) in DCM (0.83 L, 0.30 M). The reaction was allowed to stir at room temperature overnight. Upon completion, H_2O was added and the reaction mixture was extracted with DCM. The organic layer was recollected and washed with $NaHCO_3$, and then the organic phase was recollected again and washed with brine. The organic phase was dried over Na_2SO_4 (stirring for 15 minutes). Solids were filtered and the filtrate was collected and concentrated under reduced pressure to yield an amorphous white solid (61.2 g, 95%).

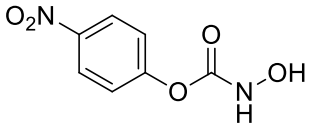
TLC R*f* : 0.35 in 20% EtOAc/Hexane.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.66 (s, 1H), 8.11 (d, *J* = 7.9 Hz, 2H), 7.66-7.61 (m, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 7.39-7.34 (m, 2H), 7.25-7.16 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 165.7 (C), 154.7 (C), 150.1 (C), 134.3 (CH), 129.9 (CH), 129.4 (CH), 128.7 (CH), 126.4 (C), 126.1 (CH), 121.2 (CH).

IR (FTIR): 3271, 1770, 1739, 1450, 1229, 1030 cm^{-1}.

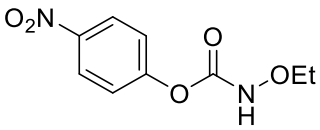
HRMS (ESI): Exact mass calcd for $C_{14}H_{11}NO_4Na$ $[M+Na]^+$: 280.0587. Found 280.0586.



4-Nitrophenyl hydroxycarbamate (1aa)

The title compound was synthesized according to a literature procedure.[199]

^{1}H NMR (300 MHz, DMSO-d_6): δ 10.71 (s, 1H), 9.31 (s, 1H), 8.30-8.25 (m, 2H), 7.44-7.38 (m, 2H).



1-(4-Nitrophenol)-N-(O-ethylhydroxy) carbamate (1ba)

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[199] Higgin, J. J.; Yakovlev, G. I.; Mitkevich, V. A.; Makarov, A. A.; Raines, R. T. *Bioorg. Med. Chem. Lett.*, **2003**, *13*, 409.

The title compound was synthesized according to a modified literature procedure[198] using *O*-ethyl hydroxylamine hydrochloride (0.610 g, 6.20 mmol), sodium bicarbonate (0.949 g, 11.3 mmol) and 4-nitrophenyl chloroformate (0.629 g, 3.10 mmol) in DCM (10 mL, 0.30 M) were stirred at room temperature overnight. The reaction mixture was diluted with DCM and transferred to a separatory funnel, then washed with brine, dried over $MgSO_4$ and filtered. The reaction mixture was concentrated under reduced pressure and recrystallized in diethyl ether. The title compound was obtained as a crystalline white solid (0.356 g, 51%).

TLC R*f* : 0.73 in 2% MeOH/DCM.

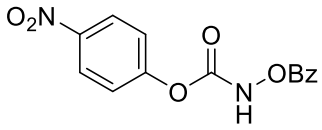
M.p. 128.9-129.9 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.31-8.25 (m, 2H), 7.75-7.67 (br s, 1H), 7.40-7.34 (m, 4H), 4.07 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): 155.1 (C), 153.9 (C), 145.1 (C), 125.2 (CH), 121.9 (CH), 72.9 (CH_2), 13.3 (CH_3).

IR (FTIR): 3164, 2930, 1755, 1737, 1615, 1519, 1487, 1344 cm^{-1}.

HRMS (EI): Exact mass could not be obtained for the molecular ion. Exact mass calcd for fragment $[C_6H_5NO_3]^+$ (*p*-nitrophenol): 139.0264. Found: 139.0276. Exact mass calcd for fragment $[C_3H_5NO_2]^+$ (ethoxy-isocyanate): 87.0315. Found: 87.0321.



1-(4-Nitrophenol)-N-(O-benzoylhydroxy) carbamate (1ca)

The title compound was synthesized according to general procedure **A** using 1-(4-nitrophenol)-*N*-hydroxycarbamate (0.198 g, 1.00 mmol), triethylamine (0.14 mL, 1.0 mmol) and benzoyl chloride (0.12 mL, 1.0 mmol) in DCM (3.3 mL, 0.30 M) were stirred at room temperature overnight. The reaction mixture was diluted with DCM and transferred to a separatory funnel, then washed with brine, dried over $MgSO_4$ and filtered. The reaction mixture was concentrated under reduced pressure and recrystallized in diethyl ether. The title compound as obtained as a crystalline white solid (0.109 g, 36%).

TLC R*f* : 0.77 in 2% MeOH/DCM.

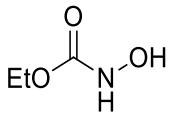
M. p. 152.3-153.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.69-8.63 (br s, 1H), 8.33-8.27 (m, 2H), 8.17-8.12 (m, 2H), 7.72-7.66 (m, 1H), 7.57-7.50 (m, 2H), 7.45-7.39 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 165.5 (C), 154.7 (C), 153.2 (C), 145.5 (C), 134.7 (CH), 130.1 (CH), 128.9 (CH), 126.0 (C), 125.3 (CH), 122.0 (CH).

IR (FTIR): 3167, 1773, 1755, 1520, 1487, 1344 cm^{-1}.

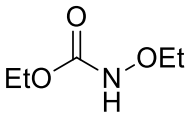
HRMS (ESI): Accurate mass could not be obtained due to the instability of this compound. Exact mass calcd for $C_{24}H_{15}N_3O_9Na$ $[M+Na]^+$ (*O*-benzoyl isocyanurate trimer): 512.0706. Found: 512.0724.



Ethyl hydroxycarbamate (1ab)

The title compound was synthesized according to a literature procedure using ethyl chloroformate (2.9 mL, 0.030 mol), hydroxylamine hydrochloride (10.4 g, 0.150 mol), and sodium hydroxide (7.20 g, 0.180 mol).[200] The title compound was obtained as a clear and colourless liquid (2.40 g, 76 %) and was used without further purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (br s, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 3H).



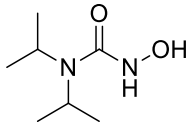
Ethyl ethoxycarbamate (1bb)

The title compound was synthesized according to a literature procedure[198] using ethyl chloroformate (1.44 mL, 15.0 mmol), *O*-ethoxylamine hydrochloride (1.83 g, 18.9 mmol), and sodium bicarbonate (2.77 g, 33.0 mmol) in DCM/ H_2O (1:1) (0.5 M). The crude reaction mixture was isolated using flash chromatography (25% EtOAc/Hexane). The title compound was obtained as a clear and colourless liquid (1.83 g, 91%).

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[200] Ng, K. -H.; Chan, A. S. C.; Yu, W. -Y. *J. Am. Chem. Soc.* **2010**, *132*, 12862.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.21 (q, *J* = 7.2 Hz, 2H), 3.93 (q, *J* = 7.0 Hz, 2H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.25 (t, *J* = 7.0 Hz, 3H).



3-Hydroxy-1,1-diisopropylurea (1ac)

The title compound was synthesized according to a procedure for the synthesis of *N*,*N*-diethyl hydroxyurea using diisopropylcarbamic chloride (1.64 g, 10 mmol), hydroxylamine hydrochloride (0.879 g, 11.5 mmol), and potassium carbonate (1.45 g, 10.5 mmol) in EtOAc/H_2O (60:1) (1.45 M).[201] The crude reaction mixture was isolated using flash chromatography (30% EtOAc/Hexane then 40% EtOAc/Hexane). The title compound was obtained as an amorphous white solid (0.544 g, 34%).

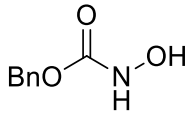
TLC R*f*: 0.34 in 40% EtOAc/Hexane.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.77 (br s, 1H), 6.48 (br s, 1H), 3.77 (sept, *J*= 6.8 Hz, 2H), 1.28 (d, *J* = 6.8 Hz, 12H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 160.6 (C), 45.9 (CH), 20.8 (CH_3).

IR (FTIR): 3292, 2964, 2927, 1632, 1493, 1446, 1376, 1367, 1047 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_7H_{16}N_2O_2$ $[M]^+$: 160.1212. Found: 160.1208.



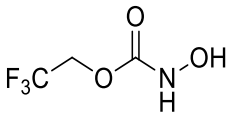
Benzyl hydroxycarbamate (1ad)

The title compound was synthesized according to a literature procedure[198] using benzyl chloroformate (1.43 mL, 10.0 mmol), hydroxylamine hydrochloride (0.777 g, 11.3 mmol), and sodium bicarbonate (1.85 g, 22.0 mmol) in 1.4:1 DCM/H_2O (0.5 M). The crude reaction mixture was isolated using flash

[201] Huang, J.; Zou, Z.; Kim-Shapiro, D. B.; Ballas, S. K.; King, S. B. *J. Med. Chem.* **2003**, *46*, 3748.

chromatography (2% MeOH/DCM, then 5% MeOH/DCM). The title compound was obtained as an amorphous white solid (0.998 g, 60%).

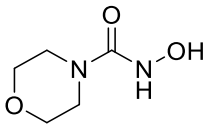
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 (s, 5H), 7.28 (s, 1H), 6.81 (br s), 5.18 (s, 2H).



2,2,2-Trifluoroethyl hydroxycarbamate (1ae)

The title compound was synthesized according to a literature procedure.[202]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (br s, 1H), 6.18 (br s, 1H), 4.56 (q, *J* = 8.3 Hz, 2H).



1-Morpholin-3-hydroxy-urea (3a)

The title compound was synthesized using a modified general procedure **B** using phenyl *N*-hydroxycarbamate **1a** (0.754 g, 4.93 mmol), DIPEA (0.013 mL, 0.20 mmol) and morpholine (0.43 mL, 5.0 mmol) in THF (17 mL, 0.30 M). The vial was sealed with a microwave cap and heated for 16 h at 70 °C via an oil bath. The reaction mixture was concentrated under reduced pressure and recrystallized in Et_2O/Hexane. The title compound was obtained as a crystalline white solid (0.511 g, 72%).

TLC R*f*: 0.73 in 2% MeOH/DCM.

M.p. 172.0-172.7 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ 9.09-9.06 (br s, 1H), 8.07-8.04 (br s, 1H), 3.54-3.49 (m, 4H), 3.24-3.19 (m, 4H).

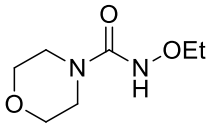
^{13}C NMR (75 MHz, DMSO-d_6): δ 159.7(C), 65.8 (CH_2), 43.6 (CH_2).

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[202] Lu, D.-F.; Zhu, C.-L.; Jia, Z.-X.; Xu, H. *J. Am. Chem. Soc.* **2014**, *136*, 13186.

IR (FTIR): 3303, 3163, 1773, 1519, 1487 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_5H_{10}N_2O_3$ $[M]^+$: 146.0691. Found: 146.0688.



1-Morpholin-3-ethoxy-urea (3b)

The title compound was synthesized according to general procedure **C** using phenyl *N*-ethoxycarbamate **1b** (0.901 g, 1.05 mmol) and morpholine (0.087 g, 1.0 mmol) in MeCN (5.0 mL, 0.20 M). The vial was sealed with a microwave cap and heated for 30 min at 120 °C via microwave irradiation. The reaction mixture was diluted with EtOAc and transferred to a separatory funnel, then washed twice with 1 M NaOH, with brine, dried over $MgSO_4$, filtered. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (3% MeOH/DCM then 10% MeOH/DCM). The title compound was obtained as an amorphous yellowish solid (0.174 g, 94%).

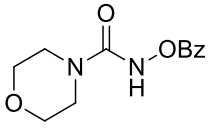
TLC R*f*: 0.35 in 5% MeOH/DCM.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15-6.82 (br s, 1H), 3.92 (q, *J* = 7.1 Hz, 2H), 3.73-3.64 (m, 4H), 3.45-3.37 (m, 4H), 1.26 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 159.2 (C), 71.8 (CH_2), 66.4 (CH_2), 44.0 (CH_2), 13.5 (CH_3).

IR (FTIR): 3165, 1773, 1518, 1487, 1451, 1253 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_7H_{14}N_2O_3Na$ $[M+Na]^+$: 197.0902. Found: 197.0902.



***N*-(Benzoyloxy)morpholine-4-carboxamide (3c)**

The title compound was synthesized according to general procedure **D** using phenyl *N*-benzoyloxycarbamate **1c** (0.257 g, 1.00 mmol), and diisobutylamine (0.18 mL, 1.05 mmol) and imidazole (0.007 g, 0.1 mmol) in THF (5.0 mL, 0.20 M). The reaction was heated under microwave irradiation for 3 h at 120 °C. Upon completion, a small amount of Hexane was added to the crude reaction resulting in a

precipitate that was filtered and subsequently washed with a small amount of ether. The title compound was obtained as an off-white amorphous solid (0.156 g, 57 %).

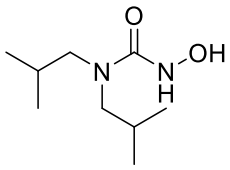
TLC R*f*: 0.18 in 50% EtOAc/Hexane.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.67-8.29 (br s, 1H), 8.16-8.08 (m, 2H), 7.69-7.60 (m, 1H), 7.55-7.46 (m, 2H), 3.80-3.69 (m, 4H), 3.59-3.50 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 166.7 (C), 157.2 (C), 134.2 (CH), 129.9 (CH), 128.7 (CH), 126.9 (C), 66.3 (CH_2), 44.2 (CH_2).

IR (FTIR): 3162, 3075, 2980, 2960, 2916, 2841, 1752, 1663, 1507, 1424, 1239 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{12}H_{14}N_2O_4Na$ $[M+Na]^+$: 273.0851. Found: 273.0866.



1,1-Diisobutyl-3-hydroxy-urea (3d)

The title compound was synthesized according to general procedure **B** using phenyl *N*-hydroxycarbamate **1a** (0.842 g, 5.50 mmol), triethylamine (0.14 mL, 1.0 mmol) and diisobutylamine (0.87 mL, 5.0 mmol) in THF (17 mL, 0.30 M). The vial was sealed with a microwave cap and heated for 16 h at 70 °C via oil bath heating. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (2% MeOH/DCM). The title compound was obtained as an amorphous white solid (0.785 g, 84%).

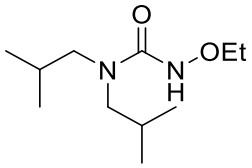
TLC R*f*: 0.54 in 2% MeOH/DCM.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.65-6.61 (br s, 1H), 6.60-6.52 (br s, 1H), 3.07 (d, *J* = 7.6 Hz, 4H), 1.99 (sept, *J* = 7.5 Hz, 2H), 0.92 (d, *J* = 6.7 Hz, 12H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 162.0 (C), 54.4 (CH_2), 27.1 (CH), 20.1 (CH_3).

IR (FTIR): 3365, 3295, 1699, 1496, 1276 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_9H_{20}N_2O_2$: 188.1525. Found: 188.1515.



1,1-Diisobutyl-3-ethoxy-urea (3e)

The title compound was synthesized according to general procedure **C** using phenyl *N*-ethoxycarbamate **1b** (0.901 g, 1.05 mmol) and diisobutylamine (0.129 g, 1.00 mmol) in MeCN (5.0 mL, 0.20 M). The vial was sealed with a microwave cap and heated for 30 min at 120 °C via microwave irradiation. The reaction mixture was diluted with EtOAc and transferred to a separatory funnel, then washed twice with 1 M NaOH, with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The title compound was obtained as an amorphous white solid (0.211 g, 98%).

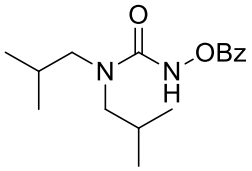
TLC R*f*: 0.65 in 5% MeOH/DCM.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08-7.05 (br s, 1H), 3.92 (q, *J* = 7.1 Hz, 2H), 3.03 (d, *J* = 7.6 Hz, 4H), 2.04-1.92 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H), 0.90 (d, *J* = 6.7 Hz, 12H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 159.7 (C), 71.8 (CH_2), 55.1 (CH_2), 27.3 (CH), 20.2 (CH), 13.6 (CH).

IR (FTIR): 3197, 2957, 1636, 1520, 1410, 1383 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{11}H_{24}N_2O_2Na$ $[M+Na]^+$: 239.1736. Found: 239.1729.



3-(Benzoyloxy)-1,1-diisobutylurea (3f)

The title compound was synthesized according to general procedure **D** using phenyl *N*-benzoyloxycarbamate **1c** (0.257 g, 1.00 mmol), and diisobutylamine (0.18 mL, 1.05 mmol) and imidazole (0.007 g, 0.10 mmol) in THF (5.0 mL, 0.20 M). The reaction was heated under microwave irradiation for 3 h. The reaction mixture was diluted with EtOAc (5.0 mL) and washed three times using 1 M NaOH (2.0 mL), followed by a single brine wash (2.0 mL). The organic phase was collected and dried over Na_2SO_4 (stirring for 15 min). The solids were filtered and rinsed with DCM (5.0 mL). The filtrate was collected and

concentrated under reduced pressure to yield the title compound as an amorphous white solid (0.260 g, 89%).

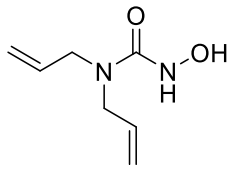
TLC R*f*: 0.35 in 40% EtOAc/Hexane.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56 (br s, 1H), 8.11 (dd, *J* = 8.4, 1.1 Hz, 2H), 7.62-7.58 (m, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 3.14 (d, *J* = 7.6 Hz, 4H), 2.16-1.97 (m, 2H), 0.95 (d, *J* = 6.7 Hz, 12H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.3 (C), 158.1 (C), 134.1 (C), 130.0 (CH), 128.7 (CH), 127.3 (CH), 55.1 (CH_2), 27.3 (CH), 20.3 (CH_3).

IR (FTIR): 3125, 2958, 2872, 1760, 1655, 1482, 1417, 1236 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{16}H_{24}N_2O_3Na$ $[M+Na]^+$: 315.1685. Found: 315.1700.



1,1-Diallyl-3-hydroxy-urea (3g)

The title compound was synthesized according to general procedure **B** using phenyl *N*-hydroxycarbamate **1a** (0.168 g, 1.00 mmol), triethylamine (0.03 mL, 0.2 mmol) and diallylamine (0.097 mg, 1.0 mmol) in THF (3.3 mL, 0.30 M). The vial was sealed with a microwave cap and heated for 16 h at 70 °C via an oil bath heating. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (2% MeOH/DCM). The title compound was obtained as an amorphous white solid (0.098 g, 63%).

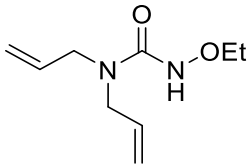
TLC R*f*: 0.53 in 5% MeOH/DCM.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.86-6.80 (br s, 1H), 6.69 (d, *J* = 3.1 Hz, 1H), 5.86-5.72 (m, 2H), 5.27-5.18 (m, 4H), 3.89 (dt, *J* = 5.5, 1.5 Hz, 4H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 161.5 (C), 132.8 (CH), 117.5 (CH_2), 49.0 (CH_2).

IR (FTIR): 3246, 2915, 1640, 1471, 1414, 1281 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{12}H_{14}N_2O_2$ $[M]^+$: 156.0899. Found: 156.0914.



1,1-Diallyl-3-ethoxy-urea (3h)

The title compound was synthesized according to general procedure **C** using phenyl *N*-ethoxycarbamate **1b** (0.901 g, 1.05 mmol) and diallylamine (0.097 g, 1.0 mmol) in MeCN (5.0 mL, 0.20 M). The vial was sealed with a microwave cap and heated for 30 min at 120 °C via microwave irradiation. The reaction mixture was diluted with EtOAc and transferred to a separatory funnel, then washed twice with 1 M NaOH, with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The title compound was obtained as a yellow oil (0.158 g, 86%).

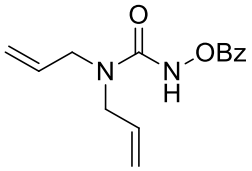
TLC R*f*: 0.26 in 2% MeOH/DCM.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14-7.11 (br s, 1H), 5.85-5.74 (m, 2H), 5.52-5.18 (m, 4H), 3.91 (q, *J* = 7.1Hz, 2H), 3.86 (dt, *J* = 5.6, 1.4 Hz, 4H), 1.24 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 159.3 (C), 133.4 (CH), 117.3 (CH_2), 71.8 (CH_2), 49.1 (CH_2), 13.5 (CH_3).

IR (FTIR): 3228, 2979, 1643, 1471, 1283 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_9H_{16}N_2O_2$ $[M]^+$: 184.1212. Found 184.1240.



1,1-Diallyl-3-(benzoyloxy)urea (3i)

The title compound was synthesized according to general procedure **D** using phenyl *N*-benzoyloxycarbamate **1c** (0.257 g, 1.00 mmol), and diallylamine (0.13 mL, 1.05 mmol) and imidazole (0.007 g, 0.10 mmol) in THF (5.0 mL, 0.20 M). The reaction was heated via microwave irradiation for 3 h. The reaction mixture was diluted with EtOAc (5.0 mL) and washed three times using 1 M NaOH (2.0 mL), followed by a single brine wash (2.0 mL). The organic phase was collected and dried over Na_2SO_4 (stirring for 15 min). The solids were filtered and rinsed with DCM (5.0 mL). The filtrate was collected and

concentrated under reduced pressure to yield the title compound as an amorphous white solid (0.232 g, 89%).

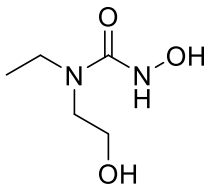
TLC R*f*: 0.35 in 30% EtOAc/Hexane.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.54 (br s, 1H), 8.11 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.61 (tt, *J* = 7.4, 1.6 Hz, 1H), 7.46 (tt, *J* = 7.6, 1.4 Hz, 2H), 5.86 (ddt, *J* = 17.2, 10.4, 5.3 Hz, 2H), 5.35-5.27 (m, 4H), 3.97 (dt, *J* = 5.4, 1.4 Hz, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9 (C), 157.8 (C), 134.1 (C), 132.7 (CH), 130.0 (CH), 128.6 (CH), 127.2 (CH), 117.8 (CH_2), 49.3 (CH_2).

IR (FTIR): 3226, 3078, 2959, 1759, 1662, 1600, 1484, 1235 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{14}H_{16}N_2O_3H$ $[M+H]^+$: 261.1239. Found: 261.1214.



1-Ethyl-3-hydroxy-1-(2-hydroxyethyl)urea (3j)

The title compound was synthesized according to general procedure **B** using phenyl *N*-hydroxycarbamate **1a** (0.842 g, 5.50 mmol), triethylamine (0.14 mL, 1.0 mmol) and 2-(ethylamino)ethanol (0.446 g, 5.00 mmol) in THF (17 mL, 0.30 M). The vial was sealed with a microwave cap and heated for 16 h at 70 °C via oil bath heating. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (2% MeOH/DCM then 5% MeOH/DCM). The title compound was obtained as an amorphous yellowish solid (0.671 g, 91%).

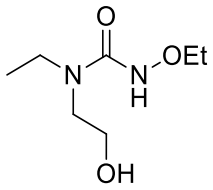
TLC R*f*: 0.10 in 2% MeOH/DCM.

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.69 (d, *J* = 1.8 Hz, 1H), 7.88 (d, *J* = 2.2 Hz, 1H), 4.87 (t, *J* = 5.1 Hz, 1H), 3.47 (q, *J* = 5.7 Hz, 2H), 3.24-3.16 (m, 4H), 1.00 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, DMSO-d_6): δ 160.1 (C), 59.9 (CH_2), 48.0 (CH_2), 41.4 (CH_2), 13.3 (CH_3).

IR (FTIR): 3164, 2931, 1773, 1615, 1519, 1344 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_5H_{12}N_2O_3$ $[M]^+$: 148.0848. Found: 148.0845.



3-Ethoxy-1-ethyl-1-(2-hydroxyethyl)urea (3k)

The title compound was synthesized according to general procedure **C** using phenyl *N*-ethoxycarbamate **1b** (0.901 g, 1.05 mmol) and 2-(ethylamino)ethanol (0.089 g, 1.0 mmol) in MeCN (5.0 mL, 0.20 M). The vial was sealed with a microwave cap and heated for 30 min at 120 °C via microwave irradiation. The reaction mixture was diluted with EtOAc and transferred to a separatory funnel, then washed twice with 1 M NaOH, with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The title compound was obtained as a yellowish solid (0.155 g, 88%).

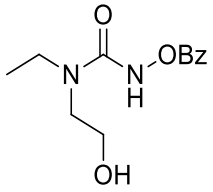
TLC R*f*: 0.26 in 5% MeOH/DCM.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.36-8.28 (br s, 1H), 3.87 (q, *J* = 7.0 Hz, 2H), 3.80-3.74 (m, 2H), 3.37-3.26 (m, 4H), 1.23 (t, *J* = 7.0 Hz, 3H), 1.15 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 161.4 (C), 71.4 (CH_2), 61.4 (CH_2), 48.5 (CH_2), 41.8 (CH_2), 13.5 (CH_3), 13.0 (CH_3).

IR (FTIR): 3383, 3275, 2976, 1625, 1518, 1487, 1382 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_7H_{16}N_2O_3Na$ $[M+Na]^+$: 199.1059. Found: 199.1064.



3-(Benzoyloxy)-1-ethyl-1-(2-hydroxyethyl)urea (3l)

The title compound was synthesized according to general procedure **D** using phenyl *N*-benzoyloxycarbamate **1c** (0.257 g, 1.00 mmol), and *N*-ethylethanolamine (0.10 mL, 1.05 mmol) and imidazole (0.007 g, 0.1 mmol) in THF (5.0 mL, 0.20 M). The reaction was heated under microwave irradiation for 6 h at 120 °C. The reaction mixture was diluted with EtOAc (5.0 mL) and washed three times

using 1 M NaOH (2.0 mL), followed by a single brine wash (2.0 mL). The organic phase was collected and dried over Na_2SO_4 (stirring for 15 min). The solids were filtered and rinsed with DCM (5.0 mL). The filtrate was collected and concentrated under reduced pressure to yield the title compound as an amorphous white solid (0.159 g, 63%).

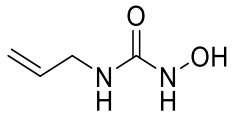
TLC R*f*: 0.28 in 50% EtOAc/Hexane.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.66-9.65 (br s, 1H), 8.12-8.08 (m, 2H), 7.62-7.56 (m, 1H), 7.48-7.43 (m, 2H), 3.84 (t, *J* = 4.8 Hz, 2H), 3.47 (t, *J* = 4.8 Hz, 2H), 3.39 (q, *J* = 7.1 Hz, 2H), 3.20 (br s, 1H), 1.18 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0 (C), 159.1 (C), 134.0 (C), 130.0 (CH), 128.7 (CH), 127.6 (CH), 62.2 (CH_2) 48.7 (CH_2) 42.7 (CH_2) 13.2 (CH_3).

IR (FTIR): 3355, 3156, 2987, 2916, 1726, 1655, 1464, 1448, 1268, 1236 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{12}H_{16}N_2O_4H$ $[M+H]^+$: 253.1188. Found: 253.1161.



1-Allyl-3-hydroxy-urea (3m)

The title compound was synthesized according to a modified general procedure **B** using phenyl *N*-hydroxycarbamate **1a** (0.306 g, 2.00 mmol), triethylamine (0.006 g, 0.2 mmol) and allylamine (0.75 mL, 10 mmol) in THF (6.7 mL, 0.30 M). The vial was sealed with a microwave cap and heated for 16 h at 70 °C via oil bath heating. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (3% MeOH/DCM then 10% MeOH/DCM). The title compound was obtained as an amorphous white solid (0.156 g, 67%).

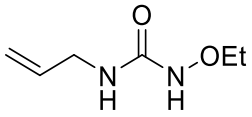
TLC R*f*: 0.10 in 2% MeOH/DCM.

^{1}H NMR (300 MHz, DMSO-d_6): δ 8.57 (d, *J* = 1.2 Hz, 1H), 8.33-8.31 (br s, 1H), 6.82-6.74 (br s, 1H), 5.88-5.74 (m, 1H), 5.13-4.98 (m, 2H), 3.70-3.63 (m, 2H).

^{13}C NMR (75 MHz, DMSO-d_6): δ 161.3 (C), 136.5 (CH), 114.4 (CH_2), 41.0 (CH_2).

IR (FTIR): 3310, 3161, 2853, 1592, 1519, 1488, 1345 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_4H_8N_2O_2$ $[M]^+$: 116.0586. Found 116.0607.



1-Allyl-3-ethoxy-urea (3n)

The title compound was synthesized according to a modified general procedure **C** using phenyl *N*-ethoxycarbamate **1b** (0.901 g, 1.05 mmol) and allylamine (0.37 mL, 5.0 mmol) in MeCN (5.0 mL, 0.20 M). The vial was sealed with a microwave cap and heated for 30 min at 120 °C via microwave irradiation. The reaction mixture was diluted with EtOAc and transferred to a separatory funnel, then washed twice with 1 M NaOH, with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The title compound was obtained as a white solid (0.113 g, 79%).

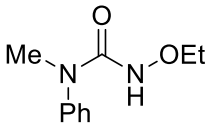
TLC R*f*: 0.47 in 5% MeOH/DCM.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.07-6.96 (br s, 1H), 5.98-5.74 (m, 2H), 5.33-5.12 (m, 2H), 3.98-3.85 (m, 4H), 1.20 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 160.0 (C), 134.5 (CH), 115.9 (CH_2), 71.9 (CH_2), 41.9 (CH_2), 13.7 (CH_3).

IR (FTIR): 3164, 2971, 1669, 1650, 1529, 1441, 1364 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_6H_{12}N_2O_2$ $[M]^+$: 144.0899. Found: 144.0900.



3-Ethoxy-1-methyl-1-phenylurea (3q)

The title compound was synthesized according to a modified general procedure **C** using phenyl *N*-ethoxycarbamate **1b** (0.901 g, 1.05 mmol), *N*-methylaniline (0.107 g, 1.00 mmol) and imidazole (0.006 g, 0.2 mmol) in MeCN (5.0 mL, 0.20 M). The vial was sealed with a microwave cap and heated for 2 h at 120 °C via microwave irradiation. The reaction mixture was diluted with EtOAc and transferred to a separatory funnel, then washed twice with 1 M NaOH, with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The reaction mixture was concentrated under reduced pressure and isolated using flash

chromatography (3% MeOH/DCM then 10% MeOH/DCM). The title compound was obtained as an amorphous yellowish solid (0.078 g, 40%).

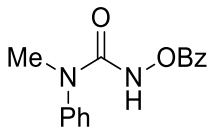
TLC R*f*: 0.84 in DCM.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43-7.37 (m, 2H), 7.33-7.27 (m, 1H), 7.24-7.19 (m, 2H), 7.00-6.97 (br s, 1H), 3.83 (q, *J* = 6.9 Hz, 2H), 3.24 (s, 3H), 1.14 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 158.2 (C), 141.9 (C), 129.9 (CH), 127.7 (CH), 126.9 (CH), 71.8 (CH_2), 37.4 (CH_3), 13.3 (CH_3).

IR (FTIR): 3409, 2980, 1747, 1669, 1603, 1507, 1202 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{10}H_{14}N_2O_2Na$ $[M+Na]^+$: 217.0953. Found: 217.0943.



3-(Benzoyloxy)-1-methyl-1-phenylurea (3r)

The title compound was synthesized according to general procedure **D** using phenyl *N*-benzoyloxycarbamate **1c** (0.257 g, 1.00 mmol), and *N*-methylaniline (0.13 mL, 1.05 mmol) and imidazole (0.007 g, 0.1 mmol) in THF (5.0 mL, 0.20 M). The reaction was heated under microwave irradiation for 6 h at 120 °C. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (10% EtOAc/Hexane then 40% EtOAc/Hexane). The title compound was obtained as an amorphous white solid (0.232 g, 91%).

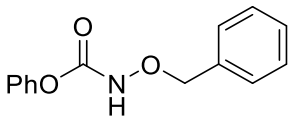
TLC R*f*: 0.40 in 50% EtOAc/Hexane.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (br s, 1H), 8.07-8.04 (m, 2H), 7.62-7.57 (m, 1H), 7.51-7.35 (m, 7H), 3.33 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8 (C), 157.1 (C), 141.4 (C), 134.0 (C), 130.4 (CH), 130.0 (CH), 128.7 (CH), 128.6 (CH), 127.2 (CH), 127.1 (CH), 38.0 (CH_3).

IR (FTIR): 3125, 2958, 2873, 1760, 1655, 1483, 1452, 1237 cm^{-1}.

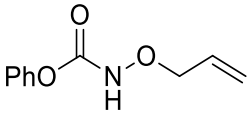
HRMS (ESI): Exact mass calcd for $C_{15}H_{14}N_2O_3Na$ $[M+Na]^+$: 293.0902. Found: 293.0900.



Phenyl benzyloxycarbamate (1d)

The title compound was synthesized according to a literature procedure.[203]

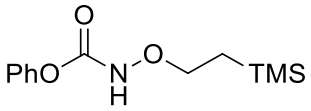
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (br s, 1H), 7.48-7.37 (m, 7H), 7.28-7.23 (m, 1H), 7.18-7.15 (m, 2H), 4.99 (s, 2H).



Phenyl allyloxycarbamate (1e)

The title compound was synthesized according to a literature procedure.[204]

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 (br s, 1H), 7.42-7.35 (m, 2H), 7.26-7.20 (m, 1H), 7.18-7.13 (m, 2H), 6.02 (ddt, *J*= 17.3, 10.3, 6.4 Hz, 1H), 5.44-5.34 (m, 2H), 4.46 (dt, *J*= 6.4, 1.2 Hz, 2H).



Phenyl 2-(trimethylsilyl)ethoxycarbamate (1f)

The title compound was synthesized according to a literature procedure[198] using *O*-(2-(trimethylsilyl)ethyl)hydroxylamine (5.00 g, 37.5 mmol), and phenyl chloroformate (3.93 mL, 31.3 mmol) in 1 : 1 DCM/H_2O (78 mL, 0.40 M). The reaction was allowed to stir at room temperature overnight. Upon completion, the reaction mixture was diluted with DCM (78 mL) and extracted from the H_2O. The organic phase was recollected and washed three times using saturated $NaHCO_3$ (25 mL), followed by a single brine wash (25 mL). The organic phase was collected and dried over Na_2SO_4 (stirring for 15 min). The solids

[203] Hirai, N.; Kagayama, T.; Tatsukawa, Y.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **2004**, *45*, 8277.
[204] Wang, Q.; An, J.; Alper, H.; Xiao, W.-J.; Beauchemin, A. M. *Chem. Commun.* **2017**, *53*, 13055-13058.

were filtered and rinsed with DCM (50 mL). The filtrate was collected and concentrated under reduced pressure to yield the title compound as a clear oil (7.51 g, 95%).

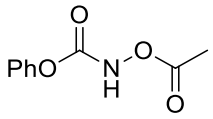
TLC R*f*: 0.75 in 20% EtOAc/Hexane.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (br s, 1H), 7.40-7.35 (m, 2H), 7.25-7.20 (m, 1H), 7.18-7.15 (m, 2H), 4.06-4.01 (m, 2H), 1.09-1.03 (m, 2H), 0.05 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6 (C), 150.6 (C), 129.5 (CH), 125.9 (CH), 121.5 (CH), 75.0 (CH_2), 16.8 (CH_2), -1.3 (CH_3).

IR (FTIR): 3273, 2952, 1733, 1593, 1474, 1370, 1248, 1201 cm^{-1}.

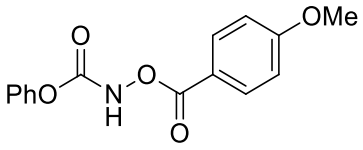
HRMS (ESI): Exact mass calcd for $C_{12}H_{19}NO_3Si$ $[M+Na]^+$: 276.1032. Found: 276.1034.



Phenyl acyloxycarbamate (1g)

The title compound was synthesized according to a literature procedure.[205]

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.44-8.39 (br s, 1H), 7.41-7.33 (m, 2H), 7.27-7.21 (m, 1H), 7.18-7.10 (m, 2H), 2.23 (s, 3H).



Phenyl (4-methoxybenzoyl)oxycarbamate (1i)

The title compound was synthesized according to general procedure **D** using phenyl *N*-hydroxycarbamate **1a** (17.8 g, 0.117 mol), triethylamine (16.4 mL, 0.117 mol) and 4-methoxybenzoyl chloride (20.0 g, 0.117 mol) in DCM (390 mL, 0.30 M). The reaction was allowed to stir at room temperature overnight. Upon completion the organic phase was washed three times using saturated $NaHCO_3$ (100 mL), followed by a

[205] Dias, L. C.; Farina, L. S.; Ferreira, M. A. B. *J. Braz. Chem. Soc.* **2013**, *24*, 184.

single brine wash (100 mL). The organic phase was collected and dried over Na_2SO_4 (stirring for 15 min). The solids were filtered and rinsed with DCM (100 mL). The filtrate was collected and concentrated under reduced pressure to yield the title compound as a white solid (30.92 g, 92%).

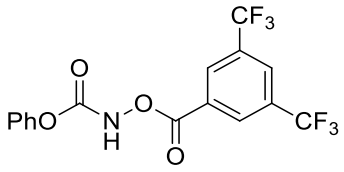
TLC R*f*: 0.35 in 20% EtOAc/Hexane.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.82 (br s, 1H), 8.10 (d, *J* = 8.9 Hz, 2H), 7.40 (t, *J* = 7.8 Hz, 2H), 7.28-7.20 (m, 3H), 6.98 (d, *J* = 8.9 Hz, 2H), 3.89 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 165.5 (C), 164.6 (C), 154.9 (C), 150.3 (C), 132.3 (CH), 129.6 (CH), 126.2 (CH), 121.3 (CH), 118.6 (C), 114.2 (CH), 55.6 (CH_3).

IR (FTIR): 3207, 3020, 2938, 1725, 1605, 1471, 1234 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{15}H_{13}NO_5Na$ $[M+Na]^+$: 310.0692. Found: 310.0698.



Phenyl (3,5-trifluoromethylbenzoyl)oxycarbamate (1j)

The title compound was synthesized according to general procedure **A** using phenyl *N*-hydroxycarbamate **1a** (1.02 g, 6.70 mmol), triethylamine (0.93 mL, 6.7 mmol) and 3,5-trifluoromethylbenzoyl chloride (1.21 mL, 6.70 mmol) in DCM (22 mL, 0.30 M). The reaction was allowed to stir at room temperature overnight. Upon completion, the reaction mixture was diluted with H_2O (5.0 mL) and extracted three times using DCM (5.0 mL), followed by a single brine wash (5.0 mL). The organic phase was collected and dried over Na_2SO_4 (stirring for 15 min). The solids were filtered and rinsed with DCM (10.0 mL). The filtrate was collected and concentrated under reduced pressure to yield the title compound as a white solid (2.63 g, 99%).

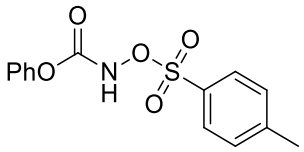
TLC R*f*: 0.75 in 20% EtOAc/Hexane.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.94 (s, 1H), 8.57 (s, 2H), 8.17 (s, 1H), 7.43-7.38 (m, 2H), 7.29-7.18 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 163.4 (C), 154.7 (C), 150.1 (C), 132.8 (q, *J* = 34.5 Hz) (C), 130.2 (m) (CH), 129.7 (CH), 128.9 (C), 127.8 (m) (CH), 126.5 (CH), 122.7 (q, *J* = 273.1 Hz) (CH), 121.2 (CH).

IR (FTIR): 3214, 3092, 1780, 1734, 1614, 1591, 1475, 1378, 1279 cm^{-1}.

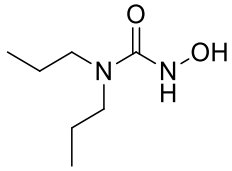
HRMS (EI): Exact mass calcd for $C_{16}H_9F_6NO_4$ $[M]^+$: 393.0436. Found: 393.0450.



Phenyl tosyloxycarbamate (1k)

The title compound was synthesized according to a literature procedure.[206]

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07 (s, 1H), 8.00-7.91 (m, 2H), 7.46-7.11 (m, 5H), 6.95-6.84 (m, 2H), 2.48 (s, 3H).



3-Hydroxy-1,1-dipropylurea (3s)

The title compound was synthesized according to general procedure **B** using phenyl *N*-hydroxycarbamate **1a** (0.101 g, 0.660 mmol), triethylamine (0.0121 g, 0.120 mmol) and dipropylamine (0.0607 g, 0.060 mmol) in THF (0.30 M). The vial was sealed with a microwave cap and heated for 16 h at 70 °C via oil bath heating. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (3% MeOH/DCM then 12% MeOH/DCM). The title compound was obtained as an amorphous white solid (0.081 g, 85%).

TLC R*f*: 0.18 in 50% EtOAc/Hexane.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.64 (br s, 1H), 6.58 (br s, 1H), 3.19-3.15 (m, 4H), 1.63-1.54 (m, 4H), 0.91 (t, *J* = 7.4 Hz, 6H).

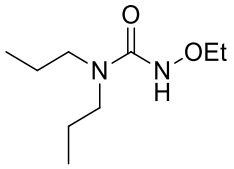
^{13}C NMR (100 MHz, $CDCl_3$): δ 161.4 (C), 48.4 (CH_2), 21.3 (CH_2), 11.2 (CH_3).

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[206] Steinberg, G. M.; Bolger, J. *J. Org. Chem.* **1956**, *21*, 660.

IR (FTIR): 3274, 2959, 2931, 2875, 1613, 1498, 1376, 1250, 1094 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_7H_{16}N_2O_2$ $[M]^+$: 160.1212. Found: 160.1209.



3-Ethoxy-1,1-dipropylurea (3t)

The title compound was synthesized according to general procedure **C** using phenyl *N*-ethoxycarbamate **1b** (0.181 g, 1.00 mmol), and dipropylamine (0.14 mL, 1.1 mmol) in MeCN (5.0 mL, 0.20 M). The reaction was heated via microwave irradiation for 20 min at 120 °C. Upon completion, the reaction mixture was diluted with EtOAc (5.0 mL) and washed three times using 1 M NaOH (2.0 mL), followed by a single brine wash (2.0 mL). The organic phase was collected and dried over Na_2SO_4 (stirring for 15 min). The solids were filtered and rinsed with DCM (5.0 mL). The filtrate was collected and concentrated under reduced pressure to yield the title compound as a clear oil (0.171 g, 91%).

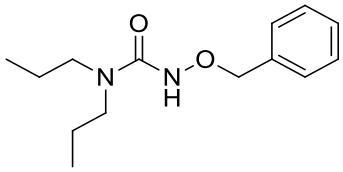
TLC R*f*: 0.44 in 20% EtOAc/Hexane.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.03 (br s, 1H), 3.91 (q, *J* = 7.0 Hz, 2H), 3.13 (t, *J* = 7.7 Hz, 4H), 1.57 (ap sext, *J* = 7.6 Hz, 4H), 1.24 (t, *J* = 7.0 Hz, 3H), 0.90 (t, *J* = 7.4 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.4 (C), 71.9 (CH_2), 49.1 (CH_2), 21.7 (CH_2), 13.7 (CH_3), 11.4 (CH_3).

IR (FTIR): 3216, 2964, 2933, 2875, 1725, 1644, 1478, 1243 cm^{-1}.

HRMS (EI): Exact mass could not be obtained for the molecular ion. Exact mass calcd for fragment $[C_2H_6NO]^+$ (*O*-ethylhydroxylamine): 60.0449. Found: 60.0440, Exact mass calcd for fragment $[C_7H_{14}NO]^+$ (*N,N*-dipropyl carbamoyl): 128.1075. Found: 128.1056.



3-(Benzyloxy)-1,1-dipropylurea (3u)

The title compound was synthesized according to general procedure **C** using phenyl benzyloxycarbamate **1d** (0.243 g, 1.00 mmol), and dipropylamine (0.14 mL, 1.05 mmol) in MeCN (5.0 mL, 0.20 M). The reaction was heated under microwave irradiation for 20 min. Upon completion, the reaction mixture was diluted with EtOAc (5.0 mL) and washed three times using 1 M NaOH (2.0 mL), followed by a single brine wash (2.0 mL). The organic phase was collected and dried over Na_2SO_4 (stirring for 15 min). The solids were filtered and rinsed with DCM (5.0 mL). The filtrate was collected and concentrated under reduced pressure to yield the title compound as an amorphous white solid (0.240 g, 96%).

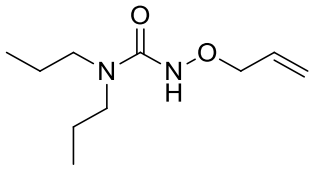
TLC R*f*: 0.39 in 20% EtOAc/Hexane.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41-7.30 (m, 5H), 6.96 (br s, 1H), 4.87 (s, 2H), 3.08 (t, *J* = 7.7 Hz, 4H), 1.51 (ap sext, *J* = 7.6 Hz, 4H), 0.84 (t, *J* = 7.4 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.0 (C), 136.3 (C), 129.3 (CH), 128.6 (CH), 128.5 (C), 78.1 (CH_2), 49.0 (CH_2), 21.6 (CH_2), 11.4 (CH_3).

IR (FTIR): 3203, 3064, 3033, 2958, 2928, 2872, 1648, 1505, 1473, 1455, 1413, 1239 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{14}H_{22}N_2O_2$ $[M]^+$: 250.1681. Found: 250.1664.



3-(Allyloxy)-1,1-dipropylurea (3v)

The title compound was synthesized according to general procedure **C** using phenyl allyloxycarbamate **1e** (0.193 g, 1.00 mmol), and dipropylamine (0.14 mL, 1.1 mmol) in MeCN (5.0 mL, 0.20 M). The reaction was heated via microwave irradiation for 20 min. Upon completion, the reaction mixture was diluted with EtOAc (5.0 mL) and washed three times using 1 M NaOH (2.0 mL), followed by a single brine wash (2.0 mL). The organic phase was collected and dried over Na_2SO_4 (stirring for 15 min). The solids were filtered and rinsed with DCM (5.0 mL). The filtrate was collected and concentrated under reduced pressure to yield the title compound as an amorphous white solid (0.188 g, 94%).

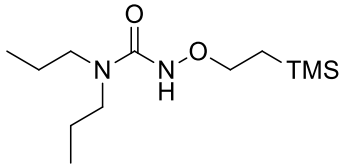
TLC R*f*: 0.43 in 20% EtOAc/Hexane.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13 (br s, 1H), 5.97 (ddt, *J* = 17.1, 10.5, 6.4 Hz, 1H), 5.33-5.24 (m, 2H), 4.34 (dt, *J* = 6.3, 1.1 Hz, 2H), 3.11 (t, *J* = 7.7 Hz, 4H), 1.55 (ap sext, *J* = 7.6 Hz, 4H), 0.87 (t, *J* = 7.4 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.1 (C), 133.1 (CH), 119.7 (CH_2), 77.2 (CH_2), 48.9 (CH_2), 21.6 (CH_2), 11.4 (CH_3).

IR (FTIR): 3219, 2962, 2927, 2873, 1644, 1481, 1405, 1379, 1244 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{10}H_{20}N_2O_2Na$ $[M+Na]^+$: 223.1423. Found: 223.1394.



1,1-Dipropyl-3-(2-(trimethylsilyl)ethoxy)urea (3w)

The title compound was synthesized according to general procedure **C** using phenyl 2-(trimethylsilyl)ethoxycarbamate **1f** (0.253 g, 1.00 mmol), and dipropylamine (0.14 mL, 1.05 mmol) in MeCN (5.0 mL, 0.20 M). The reaction was heated under microwave irradiation for 20 min. Upon completion, the reaction mixture was diluted with EtOAc (5.0 mL) and washed three times using 1 M NaOH (2.0 mL), followed by a single brine wash (2.0 mL). The organic phase was collected and dried over Na_2SO_4 (stirring for 15 min). The solids were filtered and rinsed with DCM (5.0 mL). The filtrate was collected and concentrated under reduced pressure to yield the title compound as an amorphous white solid (0.242 g, 93%).

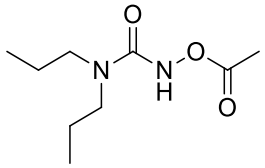
TLC R*f*: 0.38 in 20% EtOAc/Hexane.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.98 (br s, 1H), 3.91-3.87 (m, 2H), 3.11 (dd, *J* = 8.4, 7.0 Hz, 4H), 1.55 (ap sext, *J* = 7.6 Hz, 4H), 1.01-0.97 (m, 2H), 0.87 (t, *J* = 7.4 Hz, 6H), -0.05 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.4 (C), 74.1 (CH_2), 49.1(CH_2), 21.7 (CH_2), 16.9 (CH_2), 11.5 (CH_3), 1.28 (CH_3).

IR (FTIR): 3192, 2959, 2929, 2875, 1636, 1518, 1490, 1405, 1426 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{12}H_{28}N_2O_2SiNa$ $[M+Na]^+$: 283.1818. Found: 283.1821.



3-Acetoxy-1,1-dipropylurea (3x)

The title compound was synthesized according to general procedure **D** using phenyl acetoxycarbamate **1g** (0.195 g, 1.00 mmol), and dipropylamine (0.14 mL, 1.05 mmol) and imidazole (0.007 g, 0.1 mmol) in THF (5.0 mL, 0.20 M). The reaction was heated under microwave irradiation for 3 h. Upon completion, the reaction mixture was diluted with EtOAc (5.0 mL) and washed three times using 1 M NaOH (2.0 mL), followed by a single brine wash (2.0 mL). The organic phase was collected and dried over Na_2SO_4 (stirring for 15 min). The solids were filtered and rinsed with DCM (5.0 mL). The filtrate was collected and concentrated under reduced pressure to yield the title compound as an amorphous white solid (0.125 g, 62%).

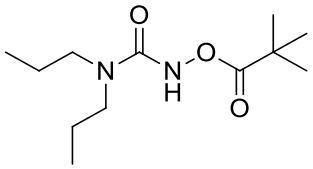
TLC R*f*: 0.42 in 20% EtOAc/Hexane.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.32 (br s, 1H), 3.17 (t, *J* = 7.6 Hz, 4H), 2.19 (s, 3H), 1.57 (ap sext, *J* = 7.5, 4H), 0.89 (t, *J* = 7.4 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1 (C), 157.5 (C), 48.9 (CH_2), 21.4 (CH_2), 18.6 (CH_3), 11.3 (CH_3).

IR (FTIR): 3162, 2964, 2936, 2877, 1782, 1655, 1478, 1376 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_9H_{18}N_2O_3$ $[M]^+$: 202.1317. Found: 202.1324.



3-(Pivaloyloxy)-1,1-dipropylurea (3y)

The title compound was synthesized according to general procedure **D** with slight modification, phenyl pivaloyloxycarbamate (0.237 g, 1.00 mmol) was formed *in situ* following general procedure **1** and used without purification, to which was added dipropylamine (0.14 mL, 1.1 mmol) and imidazole (0.007 g, 0.1 mmol) in THF (5.0 mL, 0.20 M). The reaction was heated under microwave irradiation for 3 h at 120 °C.

Upon completion, the reaction mixture was diluted with EtOAc (5.0 mL) and washed three times using 1 M NaOH (2.0 mL), followed by a single brine wash (2.0 mL). The organic phase was collected and dried over Na_2SO_4 (stirring for 15 min). The solids were filtered and rinsed with DCM (5.0 mL). The filtrate was collected and concentrated under reduced pressure to yield the title compound as an amorphous white solid (0.215 g, 88%) over two steps.

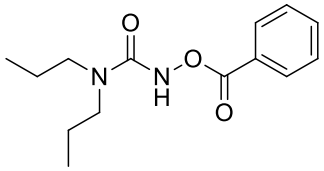
TLC R*f*: 0.66 in 20% EtOAc/Hexane.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.17 (s, 1H), 3.19 (t, *J* = 7.7 Hz, 4H), 1.61 (ap sext, *J* = 7.5 Hz, 4H), 1.31 (s, 9H), 0.91 (t, *J* = 7.4, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 179.0 (C), 157.6 (C), 48.9 (CH_2), 38.4 (C), 27.1 (CH_3), 21.4 (CH_2), 11.3 (CH_3).

IR (FTIR): 3231, 2964, 2936, 2874, 1773, 1659, 1478, 1241 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{12}H_{24}N_2O_3$ $[M]^+$: 244.1787. Found: 244.1791.



3-(Benzoyloxy)-1,1-dipropylurea (3z)

The title compound was synthesized according to general procedure **D** using phenyl *N*-benzoyloxycarbamate **1c** (0.257 g, 1.00 mmol), and dipropylamine (0.14 mL, 1.1 mmol) and imidazole (0.007 g, 0.1 mmol) in THF (5.0 mL, 0.20 M). The reaction was heated under microwave irradiation for 3 h at 120 °C. Upon completion, the reaction mixture was diluted with EtOAc (5.0 mL) and washed three times using 1 M NaOH (2.0 mL), followed by a single brine wash (2.0 mL). The organic phase was collected and dried over Na_2SO_4 (stirring for 15 min). The solids were filtered and rinsed with DCM (5.0 mL). The filtrate was collected and concentrated under reduced pressure to yield the title compound as an amorphous white solid (0.230 g, 87%).

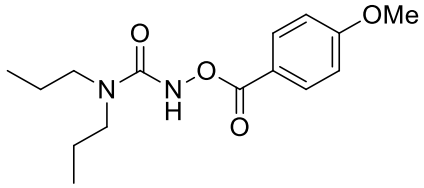
TLC R*f*: 0.40 in 20% EtOAc/Hexane.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.57 (br s, 1H), 8.12-8.08 (m, 2H), 7.62-7.56 (m, 1H), 7.44 (tt, *J* = 7.5, 1.3 Hz, 2H), 3.24 (t, *J* = 7.6 Hz, 4H), 1.64 (ap sext, *J* = 7.5 Hz, 4H), 0.92 (t, *J* = 7.4 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2 (C), 157.6 (C), 134.0 (C), 129.9 (CH), 128.6 (CH), 127.3 (C), 49.0 (CH_2), 21.4 (CH_2), 11.3 (CH_3).

IR (FTIR): 3213, 2963, 2931, 2874, 1781, 1762, 1647, 1510, 1483, 1378 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{14}H_{20}N_2O_3$ $[M]^+$: 264.1474. Found: 264.1453.



3-((4-Methoxybenzoyl)oxy)-1,1-dipropylurea (3aa)

The title compound was synthesized according to general procedure **D** using phenyl (4-methoxybenzoyl)oxycarbamate **1i** (0.287 g, 1.00 mmol), and dipropylamine (0.14 mL, 1.1 mmol) and imidazole (0.007 g, 0.1 mmol) in THF (5.0 mL, 0.20 M). The reaction was heated under microwave irradiation for 1 h at 120 °C. Upon completion, the reaction mixture was diluted with EtOAc (5.0 mL) and washed three times using 1 M NaOH (2.0 mL), followed by a single brine wash (2.0 mL). The organic phase was collected and dried over Na_2SO_4 (stirring for 15 min). The solids were filtered and rinsed with DCM (5.0 mL). The filtrate was collected and concentrated under reduced pressure to yield the title compound as an amorphous white solid (0.280 g, 95%).

TLC R*f* : 0.33 in 20% EtOAc/Hexane.

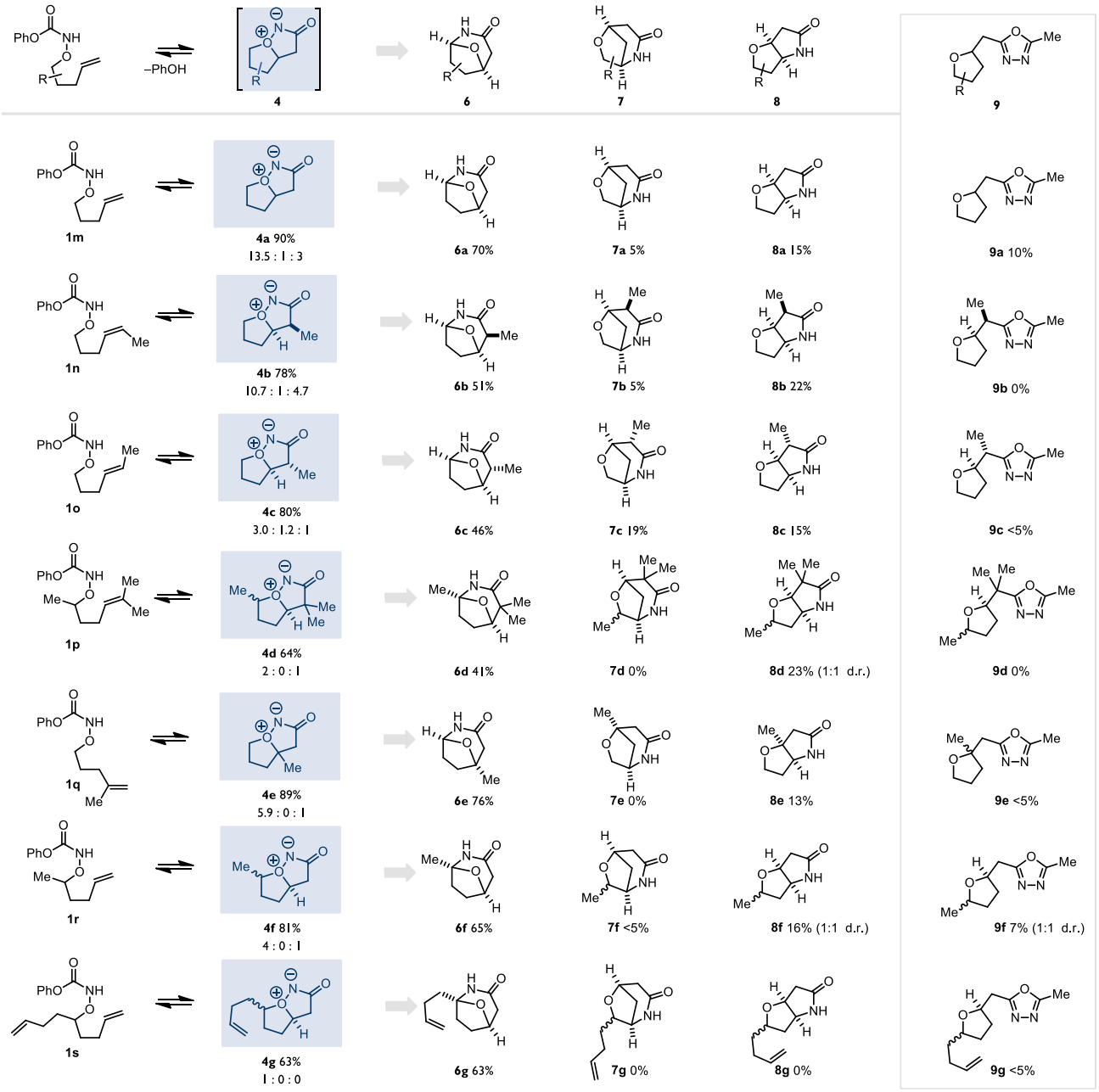
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.49 (s, 1H), 8.07-8.04 (m, 2H), 6.93-6.91 (m, 2H), 3.23 (t, *J* = 7.6 Hz, 4H), 1.64 (ap sext, 7.5 Hz, 4H), 0.92 (t, *J* = 7.4 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0 (C), 164.3 (C), 157.8 (C), 132.2 (CH), 119.5 (C), 114.1 (CH), 55.6 (CH_3), 49.1 (CH_2), 21.6 (CH_2), 11.4 (CH_3).

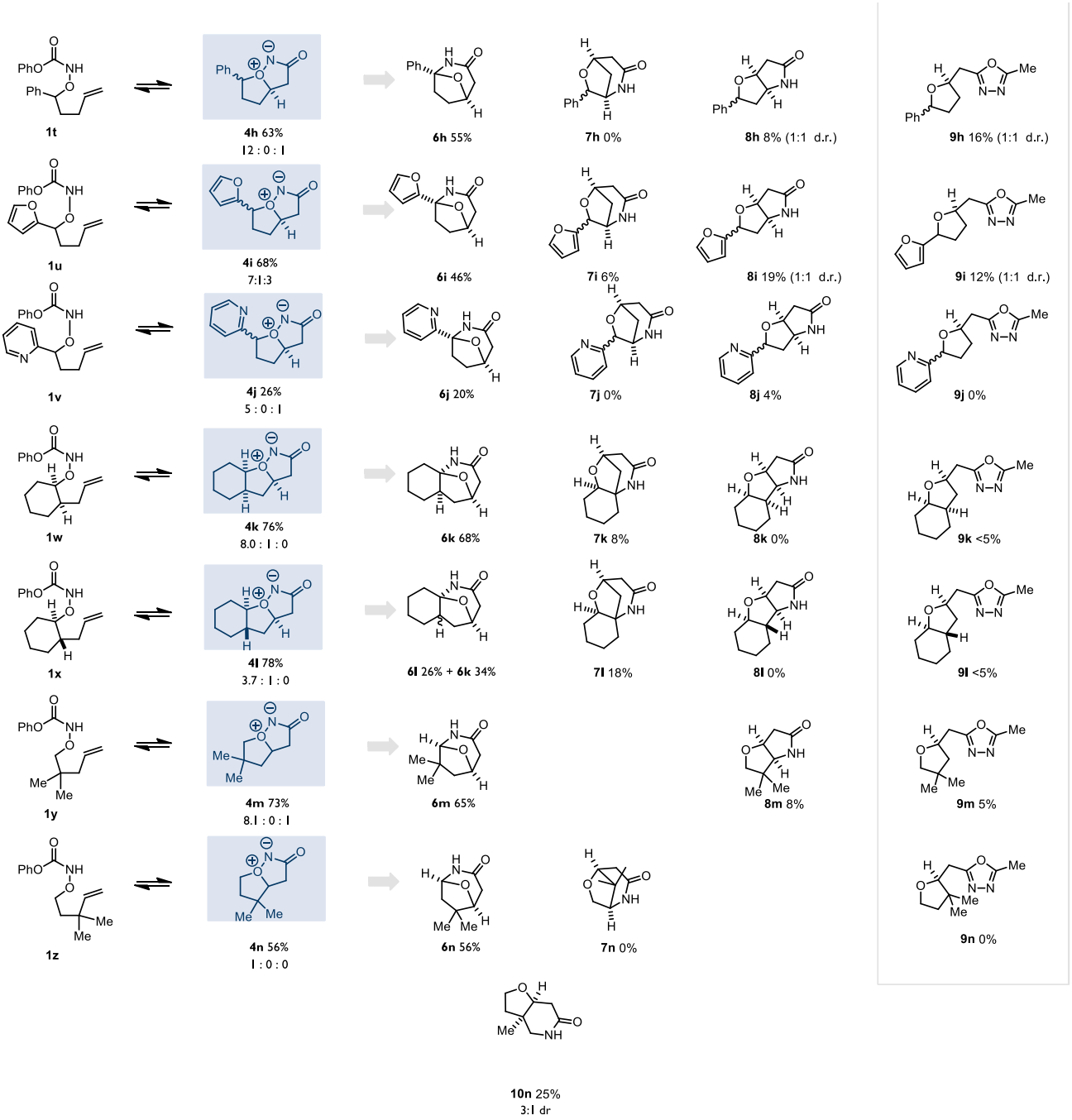
IR (FTIR): 3218, 2963, 2933, 2874, 1748, 1666, 1604, 1509, 1463, 1238, 1165 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{15}H_{22}N_2O_4$ $[M]^+$: 294.1580. Found: 294.1595.

Scheme S1: ^{1}H NMR yields and structures for intramolecular oxycarbonylations

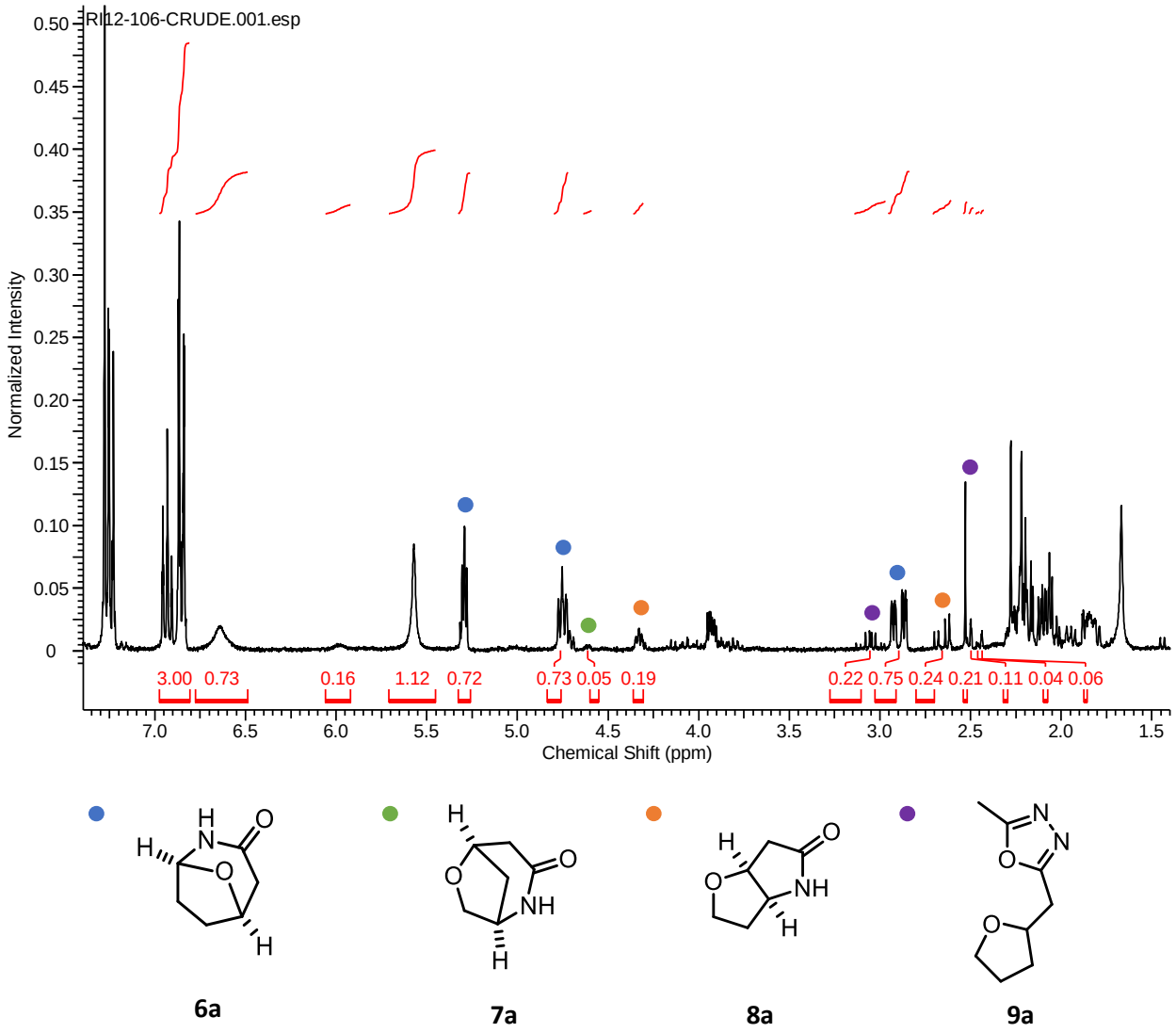


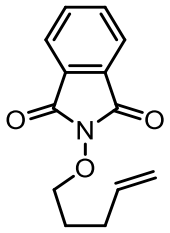
Scheme S2: ^{1}H NMR yields and structures for intramolecular oxycarbonylations cont.



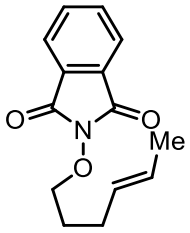
The structural determination of the products was secured by X-ray crystallography and NMR analyses. Fortunately, for a single experiment the three types of structural isomers could be crystallized, and structural determination was obtained by X-ray crystallography. The combination of this data with the distinct, characteristic ^{1}H NMR spectrum for each adduct made it possible to assign the structure of all products obtained with other substrates by analogy.

Figure S1: NMR with diagnostic peaks shown for all isolated compounds

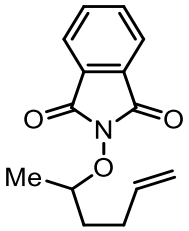




2-(Pent-4-en-1-yloxy)isoindoline-1,3-dione (SI1): The title compound was synthesized following a known procedure.[207]

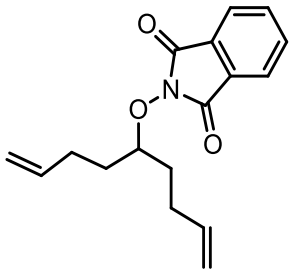


(E)-2-(Hex-4-en-1-yloxy)isoindoline-1,3-dione (SI2): The title compound was synthesized following a known procedure.[208]



2-(Hex-5-en-2-yloxy)isoindoline-1,3-dione (SI3): The title compound was synthesized following a known procedure.[209]

[207] M. L. Becker and J. Zheng, Ca. Pat., 2 878 059, **2014**.
[208] A. V. Malkov, D. S. Lee, M. Barłóg, M. R. J. Elsegood and P. Kočovský, *Chem. Eur. J.* **2014**, *20*, 4901.
[209] J. Cornil, A. Guérinot, S. Reymond and J. Cossy, *J. Org. Chem.* **2013**, *78*, 10273.



2-(Nona-1,8-dien-5-yloxy)isoindoline-1,3-dione (SI4)

The title compound was synthesized according to general procedure **E** using nona-1,8-dien-5-ol (2.28 g, 20.00 mmol), *N*-hydroxyphthalimide (0.470 g, 2.88 mmol), triphenylphosphine (0.755 g, 2.88 mmol), diisopropyl azodicarboxylate (0.60 mL, 3.0 mmol) in THF (0.3 M). After 4 d of stirring at rt, TLC analysis revealed starting material present. An NMR aliquot displayed ~ 80% yield of the desired Mitsunobu product, but complete $Ph_3P=O$ and DIAD-H_2. The product was purified by recrystallization in ether/hexanes, then using silica-gel flash column chromatography (5% EtOAc/Toluene), then recrystallization again in hexanes to yield the title compound as a white solid (2.323 g, 33%).

M.p.: 47.6-47.9 °C.

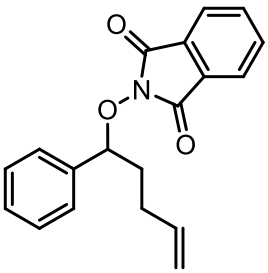
TLC R_f: 0.30 in 10% EtOAc/Hexanes

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.86-7.81 (m, 2H), 7.77-7.72 (m, 2H), 5.84 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 2H), 5.08 (ap dq, *J* = 17.1, 1.7 Hz, 2H), 4.98 (ddt, *J* = 10.2, 2.0, 1.2 Hz, 2H), 4.27 (ap quint, *J* = 5.9 Hz, 1H), 2.40-2.20 (m, 4H), 1.87-1.71 (m, 4H).

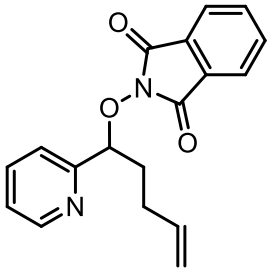
^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3 (C), 137.9 (C), 134.4 (CH), 129.0 (CH), 123.4 (CH), 115.1 (CH), 87.1 (CH), 31.7 (CH2), 29.1 (CH2).

IR (FTIR): 3072, 2944, 2848, 1850, 1786, 1723, 1637, 1463, 1368, 1185 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{17}H_{19}NO_3$ $[M+Na]^+$ 308.1263. Found: 308.1273.



2-((1-Phenylpent-4-en-1-yl)oxy)isoindoline-1,3-dione (SI5): The title compound was synthesized following a known procedure.[210]



2-((1-(Pyridin-2-yl)pent-4-en-1-yl)oxy)isoindoline-1,3-dione (SI6): The title compound was synthesized according to general procedure **E** using 1-(pyridin-2-yl)pent-4-en-1-ol (0.998 g, 6.12 mmol), *N*-hydroxyphthalimide (1.05 g, 6.42 mmol), triphenylphosphine (1.68 g, 6.42 mmol), diisopropyl azodicarboxylate (1.30 mL, 6.42 mmol) in THF (0.3 M). The product was purified using silica-gel flash column chromatography (10% EtOAc/Toluene) to yield the title compound as a white solid (1.00 g, 53%).

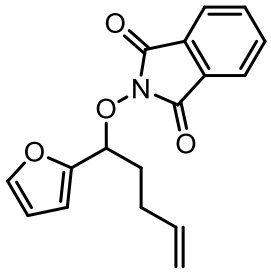
TLC R_f: 0.48 in 10% EtOAc/Toluene.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.49 (dt, *J* = 4.8, 1.4 Hz, 1H), 7.74-7.65 (m, 6H), 7.23-7.18 (m, 1H), 5.91-5.81 (m, 1H), 5.36-5.33 (m, 1H), 5.09-4.97 (m, 2H), 2.34-2.23 (m, 3H), 2.12-2.02 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 163.6 (C), 158.3 (C), 148.9 (CH), 137.4 (CH), 136.7 (CH), 134.3 (CH), 128.9 (C), 123.6 (CH), 123.4 (CH), 122.4 (CH), 115.4 (CH_2), 89.9 (CH), 33.5 (CH_2), 29.5 (CH_2).

IR (FTIR): 3065, 2950, 1782, 1724, 1587, 1467, 1353, 1115 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{18}H_{16}N_2O_3$ $[M+Na]^+$ 331.1057. Found: 331.1059.



[210] M. Zlotorzynska and G. M. Sammis, *Org. Lett.* **2011**, *18*, 6264.

2-((1-(Furan-2-yl)pent-4-en-1-yl)oxy)isoindoline-1,3-dione (SI7): The title compound was synthesized according to general procedure **E** using 1-(furan-2-yl)pent-4-en-1-ol (1.52 g, 10.00 mmol), *N*-hydroxyphthalimide (1.72 g, 10.50 mmol), triphenylphosphine (2.75 g, 10.50 mmol), diisopropyl azodicarboxylate (2.06 mL, 10.50 mmol) in THF (0.3 M). The product was purified by recrystallization in EtOH (–20 °C) to afford a crystalline white solid (1.60 g, 53%).

M.p.: 103.5-104.0 °C.

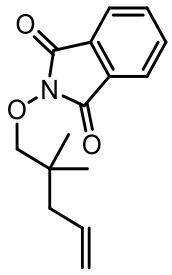
TLC R_f: 0.48 in 10% EtOAc/Toluene.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80-7.71 (m, 4H), 7.47 (s, 1H), 6.36 (d, *J* = 3.1 Hz, 1H), 6.31-6.30 (m, 1H), 5.95-5.82 (m, 1H), 5.23 (t, *J* = 6.8 Hz, 1H), 5.14-5.03 (m, 2H), 2.46-2.35 (m, 1H), 2.30-2.18 (m, 3H).

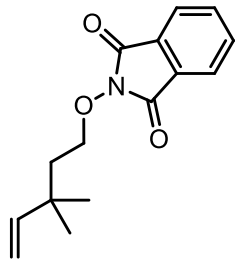
^{13}C NMR (100 MHz, $CDCl_3$): δ 163.6 (C), 150.8 (C), 143.95 (CH), 137.2 (CH), 134.5 (CH), 128.9 (C), 123.6 (CH), 115.8 (CH_2), 111.7 (CH), 110.6 (CH), 80.9 (CH), 30.5 (CH_2), 29.8 (CH_2).

IR (FTIR): 3139, 3069, 2951, 1783, 1724, 1640, 1491, 1464, 1363, 1185, 1150 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{17}H_{15}NO_4$ $[M+Na]^+$ 320.0916. Found: 320.0899.

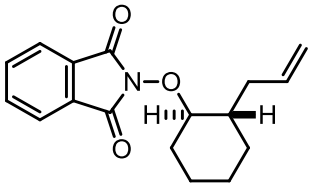


2-((2,2-Dimethylpent-4-en-1-yl)oxy)isoindoline-1,3-dione (SI8): The title compound was synthesized following a known procedure.[211]



[211] J. Escudero, V. Bellosta and J. Cossy, *Angew. Chem. Int. Ed.* **2018**, *57*, 574**.**

2-((3,3-Dimethylpent-4-en-1-yl)oxy)isoindoline-1,3-dione (SI9): The title compound was synthesized according to known procedure.[211]



***trans*-2-Allylcyclohexyl)oxy)isoindoline-1,3-dione (SI10)**

The title compound was synthesized according to general procedure **E** using *cis*-2-allylcyclohexanol (1.08 g, 7.67 mmol), *N*-hydroxyphthalimide (1.25 g, 7.67 mmol), triphenylphosphine (2.01 g, 7.67 mmol), diisopropyl azodicarboxylate (1.60 mL, 8.06 mmol) in THF (0.3 M). After 67 h of stirring at rt, TLC analysis revealed starting material present. An NMR aliquot displayed ~ 20% yield of the desired Mitsunobu product, but complete Ph_3P=O and DIAD-H_2. To remedy this, excess *N*-hydroxyphthalimide (0.310 g, 1.92 mmol), triphenylphosphine (0.498 g, 1.92 mmol) and diisopropyl azodicarboxylate (0.37 mL, 2.01 mmol) were added in quick succession and the reaction was allowed to stir overnight at rt. After an additional 24 h of stirring at rt, TLC analysis revealed starting material present. An NMR aliquot displayed ~ 20% yield of the desired Mitsunobu product, but complete Ph_3P=O and DIAD-H_2. To remedy this, excess *N*-hydroxyphthalimide (0.620 g, 3.84 mmol), triphenylphosphine (0.996 g, 3.84 mmol) and diisopropyl azodicarboxylate (0.74 mL, 4.02 mmol) were added in quick succession and the reaction was allowed to stir overnight at rt. After a total of 5 days of stirring at rt, TLC analysis revealed starting material present, though the reaction was worked up nonetheless. The product was purified using silica-gel flash column chromatography (10% EtOAc/Hexanes) to yield the title compound as a white solid (0.930 g, 43%).

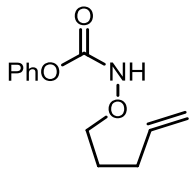
TLC R_f: 0.74 in 50% EtOAc/Hexanes.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.83-7.78 (m, 2H), 7.74-7.69, (m, 2H), 5.90 (dddd, *J* = 16.9, 10.1, 7.8, 6.6 Hz, 1H), 5.10- 5.01 (m, 2H), 3.95 (td, *J* = 10.1, 4.2 Hz, 1H), 2.78-2.71 (m, 1H), 2.16 (dt, *J* = 14.8, 8.1 Hz, 1H), 2.02-1.96 (m, 1H), 1.93-1.87 (m, 1H), 1.79-1.68 (m, 2H), 1.64-1.48 (m, 2H), 1.27-1.09 (m, 2H), 1.08-0.97 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.4 (C), 136.6 (CH), 134.4 (CH), 129.0 (C), 123.4 (CH), 116.4 (CH_2), 89.9 (CH), 40.9 (CH), 36.4 (CH_2), 30.5 (CH_2), 29.9 (CH_2), 24.7 (CH_2), 24.1 (CH_2).

IR (FTIR): 3162, 3002, 2943, 1734, 1669, 1440, 1375, 1034 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{17}H_{19}NO_3$ [M+Na]$^+$ 308.1263. Found: 308.1261



Phenyl pent-4-en-1-yloxycarbamate (1m): The title compound was synthesized according to general procedure **F** using a two-step deprotection then acylation sequence. First, 2-(pent-4-en-1-yloxy)isoindoline-1,3-dione (1.62 g, 7.00 mmol) and 50% hydrazine hydrate (0.90 mL, 14 mmol) in DCM:MeOH (10:1) (0.3 M) were stirred overnight at 0 °C to rt. The crude *O*-(pent-4-en-1-yl)hydroxylamine obtained from this phthalimide deprotection was used in the subsequent step without further purification. The crude *O*-(pent-4-en-1-yl)hydroxylamine was diluted in DCM:H_2O (2:1) (0.3 M) and $NaHCO_3$ (1.29 g, 15.4 mmol) and phenylchloroformate (0.88 mL, 7.0 mmol) were added at 0 °C and allowed to stir overnight at rt. The product was purified using silica-gel flash column chromatography (10% EtOAc/Hexanes 20% EtOAc/Hexanes) to yield the title compound as a colourless oil (1.41 g, 91%) over two steps.

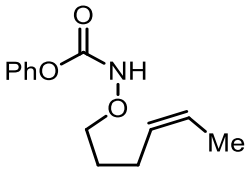
TLC R_f: 0.41 in 20% EtOAc/Hexanes.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (s, 1H), 7.41-7.34 (m, 2H), 7.26-7.20 (m, 1H), 7.18-7.13 (m, 2H), 5.83 (ddt, *J* = 17.0, 10.3, 6.7 Hz, 1H), 5.09-4.97 (m, 2H), 3.99 (t, *J* = 6.6 Hz, 2H), 2.22-2.15 (m, 2H), 1.84-1.74 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6 (C), 150.4 (C), 137.7 (CH), 129.5 (CH), 125.8 (CH), 121.4 (CH), 115.3 (CH_2), 76.6 (CH_2), 29.9 (CH_2), 27.1 (CH_2).

IR (FTIR): 3282, 3075, 2924, 1730, 1639, 1591, 1471, 1333, 1215, 1200, 1162, 1089 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{12}H_{15}NO_3$ [M+Na]$^+$ 244.0939. Found: 244.0950.



(Z)-Phenyl hex-4-en-1-yloxycarbamate (1n)

The title compound was synthesized according to general procedure **E** and **G** using a three-step Mitsunobu, deprotection then acylation sequence. First, (Z)-hex-4-en-1-ol (1.50 g, 15.0 mmol), *N*-hydroxyphthalimide (2.45 g, 15.0 mmol), triphenylphosphine (3.93 g, 15.0 mmol), and diisopropyl azodicarboxylate (3.10 mL, 15.8 mmol) in THF (0.3 M) were stirred at 0 °C. Upon completion, hexanes and Et_2O were added to the solution leading to precipitation of $Ph_3P{=}O$ and DIAD-H_2 which was removed by filtration. The filtrate containing the(Z)-2-(hex-4-en-1-yloxy)isoindoline-1,3-dione and minor impurities was used in the subsequent step without further purification. The crude (Z)-2-(hex-4-en-1-yloxy)isoindoline-1,3-dione was diluted in DCM:MeOH (10:1) (0.3 M) and 50% hydrazine hydrate (1.9 mL, 30 mmol) was added at 0 °C and allowed to stir overnight at rt. The (Z)-O-(hex-4-en-1-yl)hydroxylamine obtained from this phthalimide deprotection was used in the subsequent step without further purification. The (Z)-O-(hex-4-en-1-yl)hydroxylamine was diluted in DCM:H_2O (2:1) (0.3 M) and $NaHCO_3$ (2.77 g, 33.0 mmol) and phenylchloroformate (2.06 mL, 16.5 mmol) were added at 0 °C and allowed to stir overnight at rt. The product was purified using silica-gel flash column chromatography (10% EtOAc/Hexanes) to yield the title compound as a colourless oil (1.542 g, 44%) over three steps.

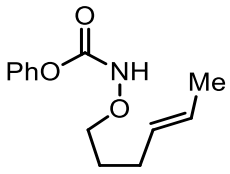
TLC R_f: 0.78 in 50% EtOAc/Hexanes.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 (br s, 1H), 7.40-7.35 (m, 2H), 7.25-7.21 (m, 1H), 7.18-7.14 (m, 2H), 5.54-5.46 (m, 1H), 5.43-5.35 (m, 1H), 3.98 (t, *J* = 6.6Hz, 2H), 2.17 (ap q, *J* = 7.3 Hz, 2H), 1.76 (ap quin, *J* = 6.7 Hz, 2H), 1.62 (ddt, *J* = 6.7, 1.6, 0.9 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.5 (C), 150.4 (C), 129.4 (CH), 129.3 (CH), 125.8 (CH), 124.9 (CH), 121.3 (CH), 76.7 (CH_2), 27.7 (CH_2), 23.08 (CH_2), 12.7 (CH_3).

IR (FTIR): 3265, 3012, 2937, 1731, 1592, 1475, 1456, 1198, 1091 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{13}H_{17}NO_3$ $[M+Na]^+$ 258.1106. Found: 258.1111.



(E)-Phenyl hex-4-en-1-yloxycarbamate (1o): The title compound was synthesized according to general procedure **F** using a two-step deprotection then acylation sequence. First, (E)-2-(hex-4-en-1-yloxy)isoindoline-1,3-dione (0.936 g, 3.80 mmol) and 50% hydrazine hydrate (0.48 mL, 7.6 mmol) in

DCM:MeOH (10:1) (0.3 M) were stirred overnight at 0 °C to rt. The crude(E)-O-(hex-4-en-1-yl)hydroxylamine obtained from this phthalimide deprotection was used in the subsequent step without further purification. The crude(E)-O-(hex-4-en-1-yl)hydroxylamine was diluted in DCM:H_2O (2:1) (0.3 M) and $NaHCO_3$ (0.702 g, 8.36 mmol) and phenylchloroformate (0.52 mL, 4.18 mmol) were added at 0 °C and allowed to stir overnight at rt. The product was purified using silica-gel flash column chromatography (10% EtOAc/Hexanes) to yield the title compound as a colourless oil (0.614 g, 68%) over two steps.

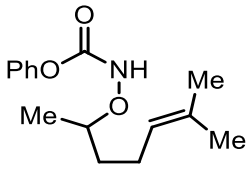
TLC R_f: 0.78 in 50% EtOAc/Hexanes.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 (br s, 1H), 7.41-7.34 (m, 2H), 7.26-7.20 (m, 1H), 7.17-7.13 (m, 2H), 5.53-5.37 (m, 2H), 3.97 (t, *J* = 6.6 Hz, 2H), 2.14-2.05 (m, 2H), 1.74 (quint, *J* = 6.7 Hz, 2H), 1.65 (d, *J* = 5.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.3 (C), 150.5 (C), 130.1 (CH), 129.4 (CH), 125.81 (CH), 125.79 (CH), 121.3 (CH), 76.7 (CH_2), 28.7 (CH_2), 27.8 (CH_2), 17.9 (CH_3).

IR (FTIR): 3266, 3019, 2935, 1729, 1592, 1475, 1454, 1198, 1091 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{13}H_{17}NO_3$ $[M+Na]^+$ 258.1106. Found: 258.1093.



Phenyl (6-methylhept-5-en-2-yl)oxycarbamate (1p)

The title compound was synthesized according to general procedure **E** and **G** using a three-step Mitsunobu, deprotection then acylation sequence. First, 6-methylhept-5-en-2-ol (3.00 mL, 19.7 mmol), *N*-hydroxyphthalimide (3.21 g, 19.7 mmol), triphenylphosphine (5.17 g, 19.7 mmol), and diisopropyl azodicarboxylate (4.08 mL, 20.7 mmol) in THF (0.3 M) were stirred at 0 °C. Upon completion, hexanes and Et_2O were added to the solution leading to precipitation of Ph_3P=O and DIAD-H_2 which was removed by filtration. The filtrate containing the 2-((6-methylhept-5-en-2-yl)oxy)isoindoline-1,3-dione and minor impurities was used in the subsequent step without further purification. The crude 2-((6-methylhept-5-en-2-yl)oxy)isoindoline-1,3-dione was diluted in DCM:MeOH (10:1) (0.3 M) and 50% hydrazine hydrate (2.53 mL, 39.4 mmol) was added at 0 °C and allowed to stir overnight at rt. The crude *O*-(hex-5-en-2-yl)hydroxylamine obtained from this phthalimide deprotection was used in the subsequent step without further purification. The crude *O*-(6-methylhept-5-en-2-yl)hydroxylamine was diluted in DCM:H_2O (2:1)

(0.3 M) and $NaHCO_3$ (3.64 g, 43.3 mmol) and phenylchloroformate (2.47 mL, 19.7 mmol) were added at 0 °C and allowed to stir overnight at rt. The product was purified using silica-gel flash column chromatography (5% EtOAc/Hexanes 15% EtOAc/Hexanes) to yield the title compound as a colourless oil (2.58 g, 50%) over three steps.

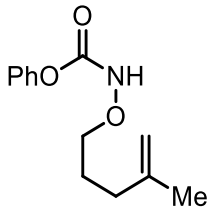
TLC R_f: 0.46 in 20% EtOAc/Hexanes.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46 (s, 1H), 7.40-7.35 (m, 2H), 7.25-7.20 (m, 1H), 7.18-7.14 (m, 2H), 5.15-5.09 (m, 1H), 4.01 (sextet, *J* = 6.2 Hz, 1H), 2.15-2.08 (m, 2H), 1.80 (s, 1H), 1.69 (d, *J* = 1.1 Hz, 3H), 1.61 (d, *J* = 0.2 Hz, 3H), 1.55-1.47 (m, 1H), 1.29 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.9 (C), 150.6 (C), 132.2 (C), 129.5 (CH), 125.9 (CH), 123.9 (CH), 121.5 (CH), 82.2 (CH), 34.8 (CH_2), 25.8 (CH_3), 24.1 (CH_2), 18.6 (CH_3), 17.8 (CH_3).

IR (FTIR): 3268, 2927, 2856, 1735, 1592, 1475, 1454, 1375, 1199, 1069 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{15}H_{21}NO_3$ $[M+Na]^+$ 286.1394. Found: 286.1419.



Phenyl (4-methylpent-4-en-1-yl)oxycarbamate (1q)

The title compound was synthesized according to general procedure **E** and **G** using a three-step Mitsunobu, deprotection then acylation sequence. First, 4-methylpent-4-en-1-ol (0.542 g, 5.41 mmol), *N*-hydroxyphthalimide (0.883 g, 5.41 mmol), triphenylphosphine (1.42 g, 5.41 mmol), and diisopropyl azodicarboxylate (1.12 mL, 5.68 mmol) in THF (0.3 M) were stirred at 0 °C. Upon completion, hexanes and Et_2O were added to the solution leading to precipitation of Ph_3P=O and DIAD-H_2 which was removed by filtration. The filtrate containing the 2-((4-methylpent-4-en-1-yl)oxy)isoindoline-1,3-dione and minor impurities was used in the subsequent step without further purification. The crude 2-((4-methylpent-4-en-1-yl)oxy)isoindoline-1,3-dione was diluted in DCM:MeOH (10:1) (0.3 M) and 50% hydrazine hydrate (0.67 mL, 11 mmol) was added at 0 °C and allowed to stir overnight at rt. The crude *O*-(4-methylpent-4-en-1-yl)hydroxylamine obtained from this phthalimide deprotection was used in the subsequent step without further purification. The crude *O*-(4-methylpent-4-en-1-yl)hydroxylamine was diluted in DCM:H_2O

(2:1) (0.3 M) and $NaHCO_3$ (1.00 g, 11.9 mmol) and phenylchloroformate (0.75 mL, 6.0 mmol) were added at 0 °C and allowed to stir overnight at rt. The product was purified using silica-gel flash column chromatography (10% EtOAc/Hexanes) to yield the title compound as a colourless oil (0.892 g, 70%) over three steps.

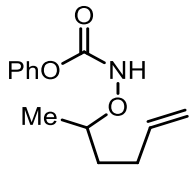
TLC R_f: 0.75 in 50% EtOAc/Hexanes.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 (br s, 1H), 7.41-7.34 (m, 2H), 7.26-7.20 (m, 1H), 7.18-7.13 (m, 2H), 4.76-4.73 (m, 1H), 4.73-4.70 (m, 1H), 3.98 (t, *J* = 6.6 Hz, 2H), 2.14 (dd, *J* = 8.5, 7.0 Hz, 2H), 1.88-1.79 (m, 2H), 1,74 (td, *J* = 1.3, 0.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6 (C), 150.4 (C), 144.8 (C), 129.4 (CH), 125.8 (CH), 121.3 (CH), 110.4 (CH2), 76.8 (CH2), 33.8 (CH2), 25.9 (CH2), 22.4 (CH3)

IR (FTIR): 3265, 3073, 2938, 1731, 1649, 1592, 1476, 1456, 1198, 1023 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{13}H_{17}NO_3$ $[M+Na]^+$ 258.1106. Found: 258.1090.



Phenyl hex-5-en-2-yloxycarbamate (1r)

The title compound was synthesized according to general procedure **F** using a two-step deprotection then acylation sequence. First, 2-(hex-5-en-2-yloxy)isoindoline-1,3-dione (4.26 g, 17.36 mmol) and 50% hydrazine hydrate (2.22 mL, 34.72 mmol) in DCM:MeOH (10:1) (0.3 M) were stirred overnight at 0 °C to rt. The crude *O*-(hex-5-en-2-yl)hydroxylamine obtained from this phthalimide deprotection was used in the subsequent step without further purification. The crude *O*-(hex-5-en-2-yl)hydroxylamine was diluted in DCM:H_2O (2:1) (0.3 M) and $NaHCO_3$ (3.21 g, 38.2 mmol) and phenylchloroformate (2.17 mL, 17.36 mmol) were added at 0 °C and allowed to stir overnight at rt. The product was purified using silica-gel flash column chromatography (10% EtOAc/Hexanes) to yield the title compound as a colourless oil (3.81 g, 93%) over two steps.

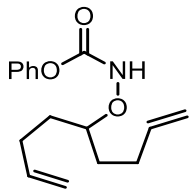
TLC R_f: 0.15 in 10% EtOAc/Hexanes.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53 (s, 1H), 7.38-7.33 (m, 2H), 7.23-7.18 (m, 1H), 7.18-7.12 (m, 2H), 5.82 (ddt, *J* = 17.0, 10.3, 6.7 Hz, 1H), 5.07-4.93 (m, 2H), 4.01 (sextet, *J* = 6.2 Hz, 1H), 2.19 (q, *J* = 7.2 Hz, 2H), 1.84-1.72 (m, 1H), 1.62-1.50 (m, 1H), 1.27 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 156.0 (C), 150.6 (C), 138.2 (CH), 129.5 (CH), 125.9 (CH), 121.5 (CH), 115.0 (CH_2), 82.0 (CH), 33.9 (CH_2), 29.7 (CH_2), 18.6 (CH_3).

IR (FTIR): 3273, 2974, 2936, 1725, 1640, 1592, 1490, 1464, 1374, 1188, 1081 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{13}H_{17}NO_3$ $[M+Na]^+$ 258.1116. Found: 258.1106.



Phenyl nona-1,8-dien-5-yloxycarbamate (1s)

The title compound was synthesized according to general procedure **F** using a two-step deprotection then acylation sequence. First, 2-(nona-1,8-dien-5-yloxy)isoindoline-1,3-dione (2.29 g, 8.04 mmol) and 50% hydrazine hydrate (1.05 mL, 16.9 mmol) in DCM:MeOH (10:1) (0.3 M) were stirred overnight at 0 °C to rt. The crude *O*-(nona-1,8-dien-5-yl)hydroxylamine obtained from this phthalimide deprotection was used in the subsequent step without further purification. The crude *O*-(nona-1,8-dien-5-yl)hydroxylamine was diluted in DCM:H_2O (2:1) (0.3 M) and $NaHCO_3$ (1.48 g, 17.6 mmol) and phenylchloroformate (1.1 mL, 8.8 mmol) were added at 0 °C and allowed to stir overnight at rt. The product was purified using silica-gel flash column chromatography (10% EtOAc/Hexanes 18% EtOAc/Hexanes) to yield the title compound as a colourless oil (1.65 g, 87%).

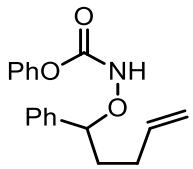
TLC R_f: 0.83 in 50% EtOAc/Hexanes.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45 (br s, 1H), 7.41-7.34 (m, 2H), 7.25-7.20 (m, 1H), 7.18-7.13 (m, 2H), 5.84 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 2H), 5.05 (ap dq, *J* = 17.1, 3.5, 2H), 4.98 (ddt, *J* = 10.2, 2.0, 1.2 Hz, 2H), 3.92 (tt, *J* = 6.6, 5.3 Hz, 1H), 2.21 (dtt, *J* = 8.1, 6.8, 1.4 Hz, 4H), 1.84-1.61 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6 (C), 150.4 (C), 138.2 (CH), 129.4 (CH), 125.8 (CH), 121.4 (CH), 114.9 (CH_2), 85.2 (CH), 31.5 (CH_2), 29.4 (CH_2).

IR (FTIR): 3272, 2074, 2937, 1734, 1639, 1592, 1487, 1451, 1359, 1198, 1085 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{16}H_{21}NO_3$ $[M+Na]^+$ 298.1419. Found: 298.1406.



Phenyl (1-phenylpent-4-en-1-yl)oxycarbamate (1t)

The title compound was synthesized according to general procedure **F** using a two-step deprotection then acylation sequence. First, 2-((1-phenylpent-4-en-1-yl)oxy)isoindoline-1,3-dione (0.715 g, 2.34 mmol) and 50% hydrazine hydrate (0.30 mL, 4.68 mmol) in DCM:MeOH (10:1) (0.3 M) were stirred overnight at 0 °C to rt. The crude *O*-(1-phenylpent-4-en-1-yl)hydroxylamine obtained from this phthalimide deprotection was used in the subsequent step without further purification. The crude *O*-(1-phenylpent-4-en-1-yl)hydroxylamine was diluted in DCM:H_2O (2:1) (0.3 M) and $NaHCO_3$ (0.432 g, 5.15 mmol) and phenylchloroformate (0.29 mL, 2.34 mmol) were added at 0 °C and allowed to stir overnight at rt. The product was purified by recrystallization (Et_2O/ Hexanes) to yield the title compound as a crystalline solid (0.694 g, 99%) over two steps.

M.p.: 69.9-70.2 °C.

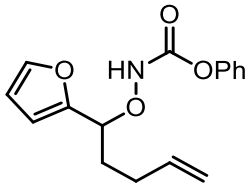
TLC R_f: 0.43 in 20% EtOAc/Hexanes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.34 (m, 8H), 7.22 (tt, *J* = 7.4, 1.3 Hz, 1H), 7.12-7.10 (m, 2H), 5.84 (ddt, *J* = 17.0, 10.4, 6.5 Hz, 1H), 5.07-4.97 (m, 2H), 4.87 (dd, *J* = 7.2, 6.2 Hz, 1H), 2.30-2.07 (m, 3H), 1.87-1.77 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.3 (C), 150.5 (C), 140.0 (C), 137.8 (CH), 129.5 (CH), 128.9 (CH), 128.7 (CH), 127.3 (CH), 125.9 (CH), 121.5 (CH), 115.4 (CH_2), 88.0 (CH), 34.6 (CH_2), 29.9 (CH_2).

IR (FTIR): 3249, 3062, 2944, 1720, 1482, 1258, 1204, 1162, 1097 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{18}H_{19}NO_3$ $[M+Na]^+$ 320.1241. Found: 320.1263.



Phenyl (1-(furan-2-yl)pent-4-en-1-yl)oxycarbamate (1u)

The title compound was synthesized according to general procedure **F** using a two-step deprotection then acylation sequence. First, 2-((1-(furan-2-yl)pent-4-en-1-yl)oxy)isoindoline-1,3-dione (1.97 g, 6.63 mmol) and 50% hydrazine hydrate (0.85 mL, 13 mmol) in DCM:MeOH (10:1) (0.3 M) were stirred overnight at 0 °C to rt. The crude *O*-(1-(furan-2-yl)pent-4-en-1-yl)hydroxylamine obtained from this phthalimide deprotection was used in the subsequent step without further purification. The crude *O*-(1-(furan-2-yl)pent-4-en-1-yl)hydroxylamine was diluted in DCM:H_2O (2:1) (0.3 M) and $NaHCO_3$ (1.23 g, 14.6 mmol) and phenylchloroformate (0.83 mL, 6.6 mmol) were added at 0 °C and allowed to stir overnight at rt. The product was purified using silica-gel flash column chromatography (10% EtOAc/Hexanes) to yield the title compound as a pale yellow solid (1.65 g, 87%).

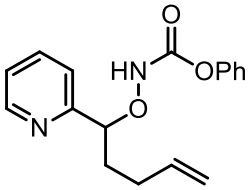
TLC R_f: 0.29 in 20% EtOAc/Hexanes.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46-7.45 (m, 1H), 7.45-7.43 (m, 1H), 7.37-7.32 (m, 2H), 7.22-7.18 (m, 1H), 7.12-7.08 (m, 2H), 6.41 (dt, *J* = 3.2, 0.4 Hz, 1H), 6.38 (dd, *J* = 3.2, 1.8 Hz, 1H), 5.81 (ddt, *J* = 17.0, 10.4, 6.5 Hz, 1H), 5.05-4.96 (m, 2H), 4.87 (dd, *J* = 8.6, 5.0 Hz, 1H), 2.22-2.12 (m, 3H), 2.03-1.94 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.1 (C), 152.2 (C), 150.4 (C), 143.1 (CH), 137.4 (CH), 129.4 (CH), 125.8 (CH), 121.3 (CH), 115.4 (CH_2), 110.3 (CH), 109.9 (CH), 80.2 (CH), 30.7 (CH_2), 29.6 (CH_2).

IR (FTIR): 3283, 3119, 2924, 1730, 1639, 1591, 1469, 1332, 1246, 1204, 1151, 1015 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{16}H_{17}NO_4$ $[M+Na]^+$ 310.1050. Found: 310.1055.



Phenyl (1-(pyridin-2-yl)pent-4-en-1-yl)oxycarbamate (1v)

The title compound was synthesized according to general procedure **F** using a two-step deprotection then acylation sequence. First, 2-((1-(pyridin-2-yl)pent-4-en-1-yl)oxy)isoindoline-1,3-dione (0.840 g, 2.72 mmol) and 50% hydrazine hydrate (0.35 mL, 5.44 mmol) in DCM:MeOH (10:1) (0.3 M) were stirred overnight at 0 °C to rt. The crude *O*-(1-(pyridin-2-yl)pent-4-en-1-yl)hydroxylamine obtained from this phthalimide deprotection was used in the subsequent step without further purification. The crude *O*-(1-(pyridin-2-yl)pent-4-en-1-yl)hydroxylamine was diluted in DCM:H_2O (2:1) (0.3 M) and $NaHCO_3$ (0.502 g, 5.98 mmol) and phenylchloroformate (0.34 mL, 2.7 mmol) were added at 0 °C and allowed to stir for 12 h. After stirring for 12 h, the reaction vessel was cooled in the fridge overnight. A white precipitate formed and was filtered over a fritted funnel to yield the title compound as an amorphous white solid (0.781 g, 96% over two steps).

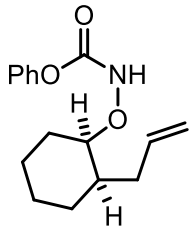
TLC R_f: 0.37 in 20% EtOAc/Hexanes.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.60 (d, *J* = 4.6 Hz, 1H), 7.99 (s, 1H), 7.74 (td, *J* = 7.7, 1.6 Hz, 1H), 7.42 (d, *J* = 7.8 Hz, 1H), 7.36-7.31 (m, 2H), 7.28-7.25 (m, 1H), 7.22-7.16 (m, 1H), 7.11-7.07 (m, 2H), 5.83 (ddt, *J* = 17.0, 10.3, 6.6 Hz, 1H), 5.07-4.93 (m, 3H), 2.34-1.85 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8 (C), 155.3 (C), 150.5 (C), 149.3 (CH), 137.7 (CH), 137.2 (CH), 129.5 (CH), 125.9 (CH), 123.3 (CH), 121.9 (CH), 121.5 (CH), 115.5 (CH_2), 87.9 (CH), 33.9 (CH_2), 29.7 (CH_2).

IR (FTIR): 3091, 2914, 1756, 1594, 1516, 1491, 1435, 1343, 1244, 1203, 1166, 1084 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{17}H_{18}N_2O_3$ $[M+Na]^+$ 321.1212. Found: 321.1215



***syn*-Phenyl (2-allylcyclohexyl)oxycarbamate (1w)**

The title compound was synthesized according to general procedure **E** and **G** using a three-step Mitsunobu, deprotection then acylation sequence. First, *trans*-2-allylcyclohexanol (1.08 g, 7.67 mmol), *N*-hydroxyphthalimide (1.25 g, 7.67 mmol), triphenylphosphine (2.01 g, 7.67 mmol), and diisopropyl azodicarboxylate (1.6 mL, 8.06 mmol) in THF (0.3 M) were stirred at 0 °C. Upon completion, hexanes and Et_2O were added to the solution leading to precipitation of Ph_3P=O and DIAD-H_2 which was removed by

filtration. The filtrate containing the *cis*-2-Allylcyclohexyl)oxy)isoindoline-1,3-dione and minor impurities was used in the subsequent step without further purification. The crude *cis*-2-Allylcyclohexyl)oxy)isoindoline-1,3-dione was diluted in DCM:MeOH (10:1) (0.3 M) and 50% hydrazine hydrate (0.40 mL, 6.2 mmol) was added at 0 °C and allowed to stir overnight at rt. The crude *cis*-*O*-2-allylcyclohexyl)hydroxylamine obtained from this phthalimide deprotection was used in the subsequent step without further purification. The crude *cis*-*O*-2-allylcyclohexyl)hydroxylamine was diluted in DCM:H_2O (2:1) (0.3 M) and $NaHCO_3$ (0.575 g, 6.84 mmol) and phenylchloroformate (0.43 mL, 3.4 mmol) were added at 0 °C and allowed to stir overnight at rt. The product was purified using silica-gel flash column chromatography (4% EtOAc/Toluene) to yield the title compound as a pale yellow oil (0.332 g, 16%) over three steps.

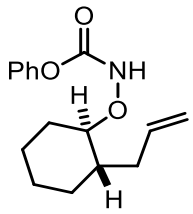
TLC R_f: 0.77 in 100% EtOAc.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42 (br s, 1H), 7.41-7.34 (m, 2H), 7.25-7.19 (m, 1H), 7.18-7.13 (m, 2H), 5.86 (ddt, *J* = 17.1, 10.1, 7.2 Hz, 1H), 5.09-4.97 (m, 2H), 4.06 (dt, *J* = 5.4, 2.7 Hz, 1H), 2.37 (dtt, *J* = 13.9, 6.7, 1.2 Hz, 1H), 2.15-2.05 (m, 2H), 1.74-1.61 (m, 3H), 1.53-1.30 (m, 5H),

^{13}C NMR (150 MHz, $CDCl_3$): 155.6 (C), 150.4 (C), 137.5 (CH), 129.4 (CH), 125.8 (CH), 121.4 (CH), 115.9 (CH_2), 83.6 (CH), 40.1 (CH), 35.9 (CH_2), 28.0 (CH_2), 26.9 (CH_2), 24.7 (CH_2), 21.0 (CH_2).

IR (FTIR): 3249, 3070, 2919, 1855, 1755, 1729, 1637, 1590, 1478, 1252, 1209, 1090 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{16}H_{21}NO_3$ $[M+Na]^+$ 298.1419. Found: 298.1404.



***anti*-Phenyl (2-allylcyclohexyl)oxycarbamate (1x)**

The title compound was synthesized according to general procedure **F** using a two-step deprotection then acylation sequence. First, *trans*-2-((2-allylcyclohexyl)oxy)isoindoline-1,3-dione (0.175 g, 0.613 mmol) and 50% hydrazine hydrate (0.08 mL, 1.2 mmol) in DCM:MeOH (10:1) (0.3 M) were stirred overnight at 0 °C to rt. The crude *trans*-*O*-(2-allylcyclohexyl)hydroxylamine obtained from this phthalimide deprotection was used in the subsequent step without further purification. The crude *trans*-*O*-(2-

allylcyclohexyl)hydroxylamine was diluted in DCM:H_2O (2:1) (0.3 M) and $NaHCO_3$ (0.113 g, 1.35 mmol) and phenylchloroformate (0.09 mL, 0.67 mmol) were added at 0 °C and allowed to stir overnight at rt. The product was purified by recrystallization in ether/hexanes to yield the title compound as a off-white crystals (0.110 g, 65%).

M.p.: 84.0-84.3 °C.

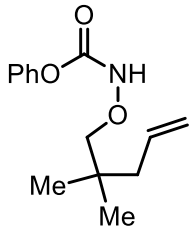
TLC R_f: 0.88 in 50% EtOAc/Hexanes

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46 (br s, 1H), 7.40-7.35 (m, 2H), 7.24-7.20 (m, 1H), 7.17-7.14 (m, 2H), 5.84 (dddd, *J* = 16.9, 10.1, 7.9, 6.6 Hz, 1H), 5.06-4.99 (m, 2H), 3.57 (td, *J* = 14.0, 5.5 Hz, 1H), 2.60 (dt, *J* = 14.0, 5.5 Hz, 1H), 2.27-2.21 (m, 1H), 2.03 (dt, *J* = 14.9, 8.0 Hz, 1H), 1.88-1.77 (m, 2H), 1.66-1.51 (m, 2H), 1.38 (tdd, *J* = 12.4, 10.4, 3.5 Hz, 1H), 1.30-1.13 (m, 2H), 1.07-0.96 (m, 1H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 155.8 (C), 150.4 (C), 136.9 (CH), 129.4 (CH), 125.8 (CH), 121.4 (CH), 116.1 (CH_2), 87.8 (CH), 40.7 (CH), 36.7 (CH_2), 30.2 (CH_2), 30.2 (CH_2), 25.0 (CH_2), 24.3 (CH_2).

IR (FTIR): 3262, 3071, 2931, 2857, 1720, 1642, 1594, 1482, 1255, 1207, 1160, 1097 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{16}H_{21}NO_3$ $[M+Na]^+$ 298.1419. Found: 298.1412.



Phenyl (2,2-dimethylpent-4-en-1-yl)oxycarbamate (1y)

The title compound was synthesized according to general procedure **F** using a two-step deprotection then acylation sequence. First, 2-((2,2-dimethylpent-4-en-1-yl)oxy)isoindoline-1,3-dione (1.63 g, 6.30 mmol) and 50% hydrazine hydrate (0.80 mL, 13 mmol) in DCM:MeOH (10:1) (0.3 M) were stirred overnight at 0 °C to rt. The crude *O*-(2,2-dimethylpent-4-en-1-yl)hydroxylamine obtained from this phthalimide deprotection was used in the subsequent step without further purification. The crude *O*-(2,2-dimethylpent-4-en-1-yl)hydroxylamine was diluted in DCM:H_2O (2:1) (0.3 M) and $NaHCO_3$ (1.16 g, 13.9 mmol) and phenylchloroformate (0.87 mL, 6.9 mmol) were added at 0 °C and allowed to stir overnight at

rt. The product was purified using silica-gel flash column chromatography (1.5% *i*-PrOH/Toluene) to yield the title compound as a pale yellow oil (1.04 g, 66%).

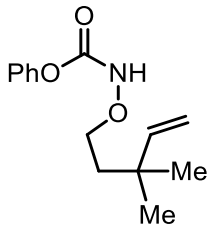
TLC R_f: 0.57 in 25% EtOAc/Hexanes

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (br s, 1H), 7.40-7.35 (m, 2H), 7.25-7.21 (m, 1H), 7.18-7.14 (m, 2H), 5.91-5.77 (m, 1H), 5.07-5.02 (m, 2H), 3.72 (s, 2H), 2.08 (dt, *J* = 7.5, 1.1 Hz, 2H), 0.97 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.4 (C), 150.4 (C), 134.7 (CH), 129.4 (CH), 125.8 (CH), 121.4 (CH), 117.6 (CH_2), 85.43 (CH_2), 43.5 (CH_2), 34.5 (C), 24.3 (CH_3).

IR (FTIR): 3279, 3073, 2959, 1732, 1638, 1593, 1472, 1364, 1199, 1094 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{14}H_{19}NO_3$ $[M+Na]^+$ 272.1263. Found: 272.1266.



Phenyl (3,3-dimethylpent-4-en-1-yl)oxycarbamate (1z)

The title compound was synthesized according to general procedure **F** using a two-step deprotection then acylation sequence. First, 2-((3,3-dimethylpent-4-en-1-yl)oxy)isoindoline-1,3-dione (2.07 g, 8.00 mmol) and 50% hydrazine hydrate (1.03 mL, 16.00 mmol) in DCM:MeOH (10:1) (0.3 M) were stirred overnight at 0 °C to rt. The crude *O*-(3,3-dimethylpent-4-en-1-yl)hydroxylamine obtained from this phthalimide deprotection was used in the subsequent step without further purification. The crude *O*-(3,3-dimethylpent-4-en-1-yl)hydroxylamine was diluted in DCM:H_2O (2:1) (0.3 M) and $NaHCO_3$ (1.48 g, 17.6 mmol) and phenylchloroformate (1.00 mL, 8.00 mmol) were added at 0 °C and allowed to stir overnight at rt. The product was purified using silica-gel flash column chromatography (5% EtOAc/Hexanes 20% EtOAc/Hexanes) to yield the title compound as a colourless oil (1.93 g, 97%) over two steps.

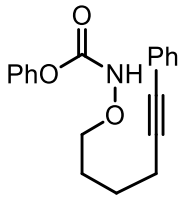
TLC R_f: 0.35 in 20% EtOAc/Hexanes.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (br s, 1H), 7.40-7.35 (m, 2H), 7.25-7.20 (m, 1H), 7.18-7.13 (m, 2H), 5.80 (dd, *J* = 17.8, 10.4 Hz, 1H), 4.98-4.92 (m, 2H), 3.97 (t, *J* = 7.3 Hz, 2H), 1.71 (t, *J* = 7.3 Hz, 2H), 1.05 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6 (C), 150.5 (C), 147.6 (CH), 129.6 (CH), 125.9 (CH), 121.5 (CH), 111.1 (CH_2), 74.8 (CH), 39.8 (CH_2), 35.7 (C), 27.2 (CH_3).

IR (FTIR): 3253, 3065, 2951, 2862, 1725, 1639, 1588, 1465, 1437, 1353, 1185 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{14}H_{19}NO_3$ $[M+Na]^+$ 272.1245. Found: 272.1263.



Phenyl (6-phenylhex-5-yn-1-yl)oxycarbamate (1aa):

The title compound was synthesized according to general procedure **F** using a two-step deprotection then acylation sequence. First,2-(6-phenylhex-5-yn-1-yloxy)isoindoline-1,3-dione (3.00 g, 9.39 mmol) and 50% hydrazine hydrate (1.20 mL, 18.8 mmol) in DCM:MeOH (10:1) (0.3 M) were stirred overnight at 0 °C to rt. The crude O-(hex-5-yn-1-yl)hydroxylamine obtained from this phthalimide deprotection was used in the subsequent step without further purification. The crude O-(6-phenylhex-5-yn-1-yl)hydroxylamine was diluted in DCM:H2O (2:1) (0.3 M) and NaHCO3 (0.946 g, 11.3 mmol) and phenylchloroformate (1.17 mL, 9.39 mmol) were added at 0 °C and allowed to stir overnight at rt. The product was purified using silica-gel flash column chromatography (10% EtOAc/Hexanes → 20% EtOAc/Hexanes) to yield the title compound as a colourless oil (2.90 g, 80%) over two steps.

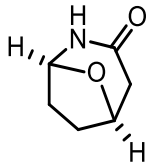
TLC R_f: 0.18 in 10% EtOAc/Hexanes.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69 (s, 1H), 7.39-7.33 (m, 4H), 7.27-7.21 (m, 5H), 7.15-7.13 (m, 2H), 4.02 (t, 2H), 2.47 (t, 2H), 1.88-1.83 (m, 2H), 1.77-1.71 (m, 2H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6 (C), 150.4 (C), 131.6 (CH), 129.5 (CH), 128.2 (CH), 127.6 (CH), 125.8 (CH), 123.9 (C), 121.4 (CH), 89.6 (C), 81.2 (C), 76.7 (CH), 27.1 (CH_2), 25.1 (CH_2), 19.1 (CH_2).

IR (FTIR): 3259, 3054, 2948, 2799, 1724, 1640, 1599, 1461, 1430, 1352, 1189 cm^{-1}.

HRMS (ESI): Exact mass calcd for C19H19NO3Na $[M+Na]^+$ 332.1263. Found: 332.1260.



8-Oxa-2-azabicyclo[3.2.1]octan-3-one (6a)

The title compound was synthesized following general procedure **H** using phenyl pent-4-en-1-yloxycarbamate **1m** (0.221, 1.00 mmol) in MeCN (0.05 M) at 180 °C for 3 h. The product was purified using silica-gel flash column chromatography (100% EtOAc) to yield the title compound as a white solid (0.089 g, 70%).

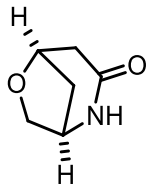
TLC R_f: 0.10 in 100% EtOAc.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.70 (br s, 1H), 5.25 (t, *J* = 3.9 Hz, 1H), 4.71 (ddd, *J* = 7.4, 5.7, 1.5 Hz, 1H), 2.84 (ddd, *J* = 17.5, 5.6, 2.0 Hz, 1H), 2.22-2.12 (m, 3H), 2.09-1.97 (m, 1H), 1.85-1.75 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.0 (C), 82.7 (CH), 73.7 (CH), 40.8 (CH_2), 36.2 (CH_2), 27.8 (CH_2).

IR (FTIR): 3227, 2920, 2850, 1627, 1467, 1441, 1397, 1359, 1290, 1151, 1073 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_6H_9NO_2$ $[M]^+$ 127.0633. Found: 127.0634.



6-Oxa-2-azabicyclo[3.2.1]octan-3-one (7a)

The title compound was synthesized following general procedure **H** using phenyl pent-4-en-1-yloxycarbamate **1m** (0.221, 1.00 mmol) in MeCN (0.05 M) at 180 °C for 3 h. The product was purified using silica-gel flash column chromatography (100% EtOAc to 5% MeOH/DCM to 10% MeOH/DCM) to yield the title compound as a white solid (0.006 g, 5%).

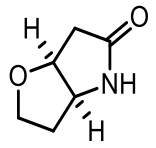
TLC R_f: 0.15 in 5% MeOH/DCM.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.86 (br s, 1H), 4.56 (dt, *J* = 5.4, 2.7 Hz, 1H), 4.03 (dd, *J* = 8.3, 1.1 Hz, 1H), 3.92-3.86 (m, 1H), 3.81 (dd, *J* = 8.3, 2.7 Hz, 1H), 2.58 (dt, *J* = 18.0, 1.7 Hz, 1H), 2.43 (dd, *J* = 18.1, 2.5 Hz, 1H), 2.09-1.97 (m, 2H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 171.0 (C), 76.9 (CH_2), 72.8 (CH), 52.4 (CH), 41.8 (CH_2), 35.3 (CH_2).

IR (FTIR): 3447, 2953, 2919, 2851, 2156, 1653, 1458, 1375, 1299 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_6H_9NO_2$ $[M]^+$ 127.0633. Found: 127.0612.



Tetrahydro-2H-furo[3,2-b]pyrrol-5(3H)-one (8a)

The title compound was synthesized following general procedure **H** using phenyl pent-4-en-1-yloxycarbamate **1m** (0.221, 1.00 mmol) in MeCN (0.05 M) at 180 °C for 3 h. The product was purified using silica-gel flash column chromatography (100% EtOAc to 5% MeOH/DCM) to yield the title compound as a white solid (0.020 g, 15%).

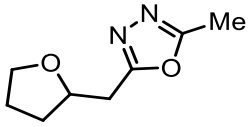
TLC R_f: 0.21 in 5% MeOH/DCM.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.65 (br s, 1H), 4.67-4.63 (m, 1H), 4.28 (td, *J* = 5.7, 1.5 Hz, 1H), 3.88 (td, *J* = 5.5, 2.9 Hz, 2H), 2.60 (dd, *J* = 18.2, 6.8 Hz, 1H), 2.40 (ddd, *J* = 18.2, 1.3, 0.6 Hz, 1H), 2.07-1.89 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 176.7 (C), 77.9 (CH), 66.5 (CH), 58.7 (CH_2), 38.0 (CH_2), 34.0 (CH_2).

IR (FTIR): 3166, 3075, 2943, 2875, 1673, 1439, 1386, 1308, 1236, 1187, 1061 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_6H_9NO_2$ $[M]^+$ 127.0633. Found: 127.0633.



2-Methyl-5-((tetrahydrofuran-2-yl)methyl)-1,3,4-oxadiazole (9a)

The title compound was synthesized following general procedure **H** using phenyl pent-4-en-1-yloxycarbamate **1m** (0.221, 1.00 mmol) in MeCN (0.05 M) at 180 °C for 3 h. The product was purified using

silica-gel flash column chromatography (100% EtOAc to yield the title compound as a clear oil (0.016 g, 10%).

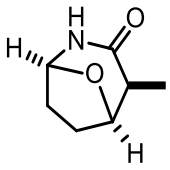
TLC R_f: 0.55 in 100% EtOAc

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.27 (quintet, *J* = 6.5 Hz, 1H), 3.88 (dt, *J* = 8.3, 6.8 Hz, 1H), 3.78-3.72 (m, 1H), 3.00 (qd, *J* = 16.3, 6.4 Hz, 2H), 2.49-2.47 (m, 3H), 2.13-2.05 (m, 1H), 1.94-1.87 (m, 2H), 1.70-1.63 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.8 (C), 164.0 (C), 76.0 (CH), 68.4 (CH_2), 31.8 (CH_2), 31.3 (CH_2), 25.7 (CH_2), 11.1 (CH_3).

IR (FTIR): 1678, 1531, 1444, 1372, 1223, 1022, 929 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_8H_{12}N_2O_2$ $[M]^+$ 168.0899. Found: 168.0900.



4-Methyl-8-oxa-2-azabicyclo[3.2.1]octan-3-one (6b)

The title compound was synthesized following general procedure **H** using (Z)-phenyl hex-4-en-1-yloxycarbamate **1n** (0.235g, 1.00 mmol) in MeCN (0.05 M) at 180 °C for 4 h. The product was purified using silica-gel flash column chromatography (100% EtOAc 1% MeOH/DCM) to yield the title compound as a white solid (0.072g, 51%).

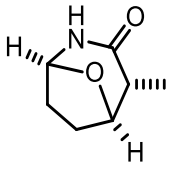
TLC R_f: 0.24 in 100% EtOAc.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.36 (br s, 1H), 5.25 (q, *J* = 2.5 Hz, 1H), 4.54 (ddd, *J* = 6.3, 4.8, 2.7 Hz, 1H), 2.89 (*J* = 7.7, 6.9, 5.2 Hz, 1H), 2.13-1.92 (m, 4H), 1.13 (d, *J* = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.4 (C), 83.5 (CH), 78.5 (CH), 42.5 (CH), 35.9 (CH_2), 21.8 (CH_2), 10.7 (CH_3).

IR (FTIR): 3294, 3178, 2954, 1651, 1471, 1409, 1353, 1279, 1249, 1073 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_7H_{11}NO_2$ $[M]^+$ 141.0790. Found: 141.0765



4-Methyl-8-oxa-2-azabicyclo[3.2.1]octan-3-one (6c)

The title compound was synthesized following general procedure **H** using (E)-phenyl hex-4-en-1-yloxycarbamate **1o** (0.235 g, 1.00 mmol) in MeCN (0.05 M) at 180 °C for 4 h. The product was purified using silica-gel flash column chromatography (100% EtOAc) to yield the title compound as a white solid (0.069 g, 49%).

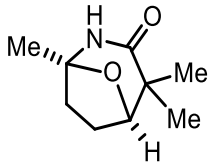
TLC R_f: 0.16 in 100% EtOAc.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.42 (br s, 1H), 5.23 (dd, *J* = 4.2, 3.4 Hz, 1H), 4.38 (dd, *J* = 8.1, 1.4 Hz, 1H), 2.30-1.94 (m, 4H), 1.83-1.73 (m, 1H), 1.38 (d, *J* = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.6 (C), 82.8 (CH), 79.3 (CH), 46.2 (CH), 35.7 (CH_2), 27.4 (CH_2), 17.9 (CH_3).

IR (FTIR): 3223, 2977, 2875, 1732, 1656, 1621, 1471, 1441, 1372, 1295, 1253, 1060 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_7H_{11}NO_2$ $[M]^+$ 141.0790. Found: 141.0800.



1,4,4-Trimethyl-8-oxa-2-azabicyclo[3.2.1]octan-3-one (6d)

The title compound was synthesized following general procedure **H** using phenyl (6-methylhept-5-en-2-yl)oxycarbamate **1p** (0.235, 1.00 mmol) in MeCN (0.05 M) at 180 °C for 4 h. The product was purified using silica-gel flash column chromatography (50% EtOAc/Hexanes to 100% EtOAc) to yield the title compound as a white solid (0.079 g, 47%).

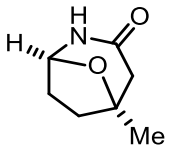
TLC R_f: 0.29 in 100% EtOAc.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.03 (br. s, 1H), 4.10 (dd, *J* = 7.4, 2.0 Hz, 1H), 2.12-1.97 (m, 3H), 1.85-1.79 (m, 1H), 1.53 (s, 3H), 1.34 (s, 3H), 1.09 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 176.2 (C), 90.5 (C), 83.7 (CH), 44.0 (CH), 40.7 (CH_2), 27.3 (CH_3), 24.4 (CH_2), 23.4 (CH_3), 20.2 (CH_3).

IR (FTIR): 3171, 3053, 2981, 2919, 1655, 1476, 1437, 1397, 1316, 1203, 1138 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_9H_{15}NO_2$ $[M]^+$ 169.1103. Found: 169.1106.



5-Methyl-8-oxa-2-azabicyclo[3.2.1]octan-3-one (6e)

The title compound was synthesized following general procedure **H** using phenyl (4-methylpent-4-en-1-yl)oxycarbamate **1q** (0.235 g, 1.00 mmol) in MeCN (0.05 M) at 180 °C for 6 h. The product was purified using silica-gel flash column chromatography (100% EtOAc 1% MeOH/DCM) to yield the title compound as a pale yellow solid (0.110 g, 78%).

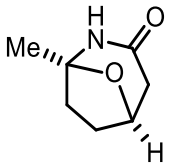
TLC R_f: 0.13 in 100% EtOAc.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.89 (br s, 1H), 5.26 (td, *J* = 3.5, 1.1 Hz, 1H), 2.59 (ddd, *J* = 17.3, 2.6, 0.8 Hz, 1H), 2.32 (d, *J* = 17.3 Hz, 1H), 2.22-2.10 (m, 2H), 2.00-1.93 (m, 1H), 1.83 (tdd, *J* = 12.8, 4.7, 2.5 Hz, 1H), 1.47 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3 (C), 82.3 (CH), 80.5 (C), 46.7 (CH_2), 37.1 (CH_2), 34.0 (CH_2), 20.6 (CH_3).

IR (FTIR): 3166, 2974, 2873, 1651, 1471, 1442, 1320, 1303, 1197, 1061 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_7H_{11}NO_2$ $[M]^+$ 141.0790. Found: 141.0777.



1-Methyl-8-oxa-2-azabicyclo[3.2.1]octan-3-one (6f)

The title compound was synthesized following general procedure **H** using phenyl hex-5-en-2-yloxycarbamate **1r** (0.235, 1.00 mmol) in MeCN (0.05 M) at 180 °C for 4 h. The product was purified using

silica-gel flash column chromatography (100% EtOAc) to yield the title compound as a white solid (0.092 g, 65%).

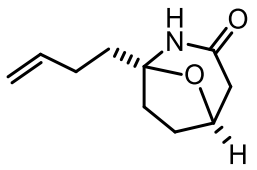
TLC R_f: 0.13 in 100% EtOAc.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.15 (br s, 1H), 4.69 (dd, *J* = 7.3, 5.8 Hz, 1H), 2.78 (ddd, *J* = 17.4, 5.4, 1.6 Hz, 1H), 2.33-2.16 (m, 3H), 1.90-1.77 (m, 2H), 1.57 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6 (C), 89.8 (C), 74.1 (CH), 41.4 (CH_2), 40.1 (CH_2), 29.6 (CH_2), 23.4 (CH_3).

IR (FTIR): 3458, 3175, 2920, 2850, 1637, 1435, 1393, 1359, 1305, 1160, 1015 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_7H_{11}NO_2$ $[M]^+$ 141.0790. Found: 141.0805.



1-(But-3-en-1-yl)-8-oxa-2-azabicyclo[3.2.1]octan-3-one (6g)

The title compound was synthesized following general procedure **H** using phenyl nona-1,8-dien-5-yloxycarbamate **1s** (0.275 g, 1.00 mmol) in MeCN (0.05 M) at 180 °C for 3 h. The product was purified using silica-gel flash column chromatography (50% EtOAc/Hexanes to 70% EtOAc/Hexanes 100% EtOAc) to yield the title compound as a white solid (0.101 g, 56%).

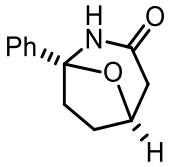
TLC R_f: 0.18 in 100% EtOAc.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.37 (br s, 1H), 5.85 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.08 (ap dd, *J* = 17.1, 1.6 Hz, 1H), 5.02 (ap dt, *J* = 10.2, 1.4 Hz, 1H), 4.71 (ddd, *J* = 7.6, 5.6, 1.1 Hz, 1H), 2.80 (ddd, *J* = 17.4, 5.5, 1.7 Hz, 1H), 2.33-2.14 (m, 5H), 1.95-1.78 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2 (C), 137.3 (CH), 115.6 (CH_2), 91.8 (C), 73.8 (CH), 40.2 (CH_2), 39.8 (CH_2), 35.8 (CH_2), 28.9 (CH_2), 27.9 (CH_2).

IR (FTIR): 3178, 3068, 2954, 2874, 1654, 1459, 1435, 1397, 1310, 1245, 1170, 1002 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{10}H_{15}NO_2$ $[M]^+$ 181.1103. Found: 181.1086.



1-Phenyl-8-oxa-2-azabicyclo[3.2.1]octan-3-one (6h)

The title compound was synthesized following general procedure **H** using phenyl pent-4-en-1-yloxycarbamate **1t** (0.235, 1.00 mmol) in MeCN (0.05 M) at 180 °C for 4 h. The product was purified using silica-gel flash column chromatography (50% EtOAc/Hexanes to 100% EtOAc) to yield the title compound as a white solid (0.111 g, 55%).

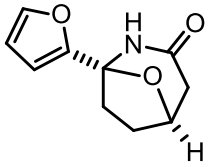
TLC R_f: 0.15 in 100% EtOAc.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53-7.50 (m, 2H), 7.43-7.37 (m, 3H), 6.28 (br s, 1H), 4.88 (ddd, *J* = 7.5, 5.6, 1.6 Hz, 1H), 2.91 (ddd, *J* = 17.4, 5.5, 1.6 Hz, 1H), 2.66 (ddd, *J* = 12.0, 9.2, 2.7 Hz, 1H), 2.45-2.36 (m, 1H), 2.33-2.22 (m, 2H), 1.98-1.90 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6 (C), 139.0 (C), 129.3 (CH), 129.0 (CH), 125.3 (CH), 92.2 (C), 74.3 (CH), 41.0 (CH_2), 40.4 (CH_2), 29.0 (CH_2).

IR (FTIR): 3450, 3175, 2960, 2919, 2850, 1637, 1435, 1393, 1332, 1325, 1160 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{12}H_{13}NO_2$ $[M]^+$ 203.0946. Found: 203.0921.



1-(Furan-2-yl)-8-oxa-2-azabicyclo[3.2.1]octan-3-one (6i)

The title compound was synthesized following general procedure **H** using phenyl pent-4-en-1-yloxycarbamate **1u** (0.144, 0.500 mmol) in MeCN (0.05 M) at 180 °C for 4 h. The product was purified using silica-gel flash column chromatography (100% EtOAc 5% MeOH/DCM) to yield the title compound as a white solid (0.045 g, 46%).

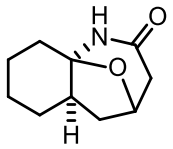
TLC R_f: 0.16 in 100% EtOAc.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45 (dd, *J* = 1.8, 0.8 Hz, 1H), 6.93 (br s, 1H), 6.57 (dd, *J* = 3.4, 0.8 Hz, 1H), 6.42 (dd, *J* = 3.4, 1.8 Hz, 1H), 4.86-4.83 (m, 1H), 2.90 (ddd, *J* = 17.4, 5.4, 1.5 Hz, 1H), 2.56-2.39 (m, 3H), 2.27 (dd, *J* = 17.4, 0.5 Hz, 1H), 1.97-1.90 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1 (C), 150.2 (C), 143.5 (CH), 110.9 (CH), 108.8 (CH), 88.1 (C), 74.7 (CH), 40.6 (CH_2), 39.9 (CH_2), 28.7 (CH_2).

IR (FTIR): 3167, 3066, 2913, 1657, 1501, 1465, 1392, 1311, 1219, 1159, 1072 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{10}H_{11}NO_3$ $[M]^+$ 193.0739. Found: 193.0743.



Octahydro-4,9a-epoxybenzo[b]azepin-2(1H)-one (6k)

The title compound was synthesized following general procedure **H** using *cis*-phenyl (2-allylcyclohexyl)oxycarbamate **1w** (0.275 g, 1.00 mmol) in MeCN (0.05 M) at 180 °C for 10 h. The product was purified using silica-gel flash column chromatography (90% EtOAc) to yield the title compound as a white solid (0.100 g, 55%).

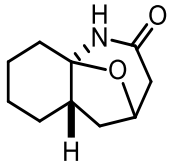
TLC R_f: 0.23 in 100% EtOAc.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.38 (br s, 1H), 4.69 (ddd, *J* = 7.6, 4.7, 2.4 Hz, 1H), 2.75 (dddd *J* = 17.1, 4.9, 1.5, 0.8 Hz, 1H), 2.26-2.14 (m, 3H), 1.95 (ddd, *J* = 12.4, 7.6, 2.4 Hz, 1H), 1.82 (ddt, *J* = 12.7, 7.9, 1.3 Hz, 1H), 1.75-1.62 (m, 3H), 1.54-1.40 (m, 2H), 1.20-1.03 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4 (C), 90.0 (C), 72.7 (CH), 47.5 (CH), 41.0 (CH_2), 36.6 (CH_2), 32.9 (CH_2), 32.5 (CH_2), 24.5 (CH_2), 21.6 (CH_2).

IR (FTIR): 3156, 3047, 2924, 2829, 1669, 1473, 1441, 1392, 1328, 1252, 1089 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{10}H_{15}NO_2$ $[M]^+$ 181.1103. Found: 181.1103.



Octahydro-4,9a-epoxybenzo[b]azepin-2(1H)-one (6l)

The title compound was synthesized following general procedure **H** using *trans*-Phenyl (2-allylcyclohexyl)oxycarbamate **1x** (0.106 g, 0.38 mmol) in MeCN (0.05 M) at 200 °C for 6 h. The product was purified using silica-gel flash column chromatography (100% EtOAc) to yield the title compound as a white solid (0.018 g, 26%).

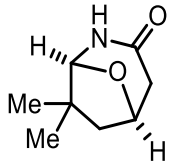
TLC R_f: 0.21 in 100% EtOAc.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (br s, 1H), 4.67 (ddd, *J* = 7.3, 4.8, 1.9 Hz, 1H), 2.74 (dd, *J* = 17.2, 4.8 Hz, 1H), 2.20 (t, *J* = 9.6 Hz, 2H), 2.16 (d, *J* = 17.1 Hz, 1H), 1.94 (ddd, *J* = 13.0, 7.6, 2.3 Hz, 1H), 1.81 (dd, *J* = 13.0, 8.0 Hz, 1H), 1.70 (ddd, *J* = 13.0, 5.7, 2.8 Hz, 1H), 1.64 (tt, *J* = 15.3, 2.5 Hz, 2H), 1.54-1.44 (m, 2H), 1.17 (dddt, *J* = 12.3, 10.7, 9.8, 2.7 Hz, 1H), qd (qd, *J* = 12.3, 2.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8 (C), 90.0 (C), 72.6 (CH), 47.4 (CH), 41.0 (CH_2), 36.6 (CH_2), 32.7 (CH_2), 32.5 (CH_2), 24.5 (CH_2), 21.6 (CH_2).

IR (FTIR): 3155, 3047, 2924, 2849, 1669, 1441, 1392, 1372, 1328, 1254, 1090 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{10}H_{15}NO_2$ $[M]^+$ 181.1103. Found: 181.1089.



7,7-Dimethyl-8-oxa-2-azabicyclo[3.2.1]octan-3-one (8m)

The title compound was synthesized following general procedure **H** using phenyl (2,2-dimethylpent-4-en-1-yl)oxycarbamate **1y** (0.249 g, 1.00 mmol) in MeCN (0.05 M) at 180 °C for 6 h. The product was purified using silica-gel flash column chromatography (90% EtOAc/Hexanes to 100% EtOAc to 1% MeOH/DCM to 5% MeOH/DCM) to yield the title compound as a white solid (0.090 g, 58%).

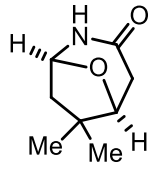
TLC R_f: 0.23 in 100% EtOAc.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.43 (br s, 1H), 4.67 (ddd, *J* = 7.7, 5.3, 1.9 Hz, 1H), 4.58 (d, *J* = 3.4 Hz, 1H), 2.84 (ddd, *J* = 17.3, 5.4, 1.8, 0.7 Hz, 1H), 2.17 (dd, *J* = 17.3, 0.7 Hz, 1H), 2.04 (ddd, *J* = 12.8, 7.9, 1.5 hz, 1H), 1.51 (dd, *J* = 12.9, 1.9 Hz, 1H), 1.18 (s, 3H), 1.12 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5 (C), 90.1 (CH), 74.2 (CH), 47.4 (C), 43.3 (CH_2), 41.2 (CH_2), 28.6 (CH_3), 23.5 (CH_3).

IR (FTIR): 3249, 2962, 2871, 1662, 1636, 1457, 1412, 1387, 1356, 1281, 1079 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_8H_{13}NO_2$ $[M]^+$ 155.0946. Found: 155.0944.



6,6-Dimethyl-8-oxa-2-azabicyclo[3.2.1]octan-3-one (6n)

The title compound was synthesized following general procedure **H** using phenyl pent-4-en-1-yloxycarbamate **1z** (0.125, 0.500 mmol) in MeCN (0.05 M) at 180 °C for 4 h. The product was purified using silica-gel flash column chromatography (100% EtOAc) to yield the title compound as a white solid (0.043g, 56%).

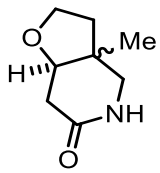
TLC R_f: 0.32 in 100% EtOAc.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57 (br s, 1H), 5.19 (t, *J* = 3.9 Hz, 1H), 4.12 (d, *J* = 6.0 Hz, 1H), 2.72 (dd, *J* = 17.9, 6.0 Hz, 1H), 2.44 (d, *J* = 17.9 Hz, 1H), 1.95 (dq, *J* = 12.8, 6.8 Hz, 2H), 1.18 (s, 3H), 1.17 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3 (C), 84.2 (CH), 83.6 (CH), 51.5 (CH_2), 40.4 (C), 35.7 (CH_2), 32.1 (CH_3), 25.4 (CH_3).

IR (FTIR): 3231, 2958, 2869, 1639, 1467, 1411, 1356, 1309, 1276, 1129, 1042 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_8H_{13}NO_2$ $[M+Na]^+$ 178.0851. Found: 178.0844.



3a-Methylhexahydrofuro[3,2-c]pyridin-6(2H)-one (10n)

The title compound was synthesized following general procedure **H** using phenyl pent-4-en-1-yloxycarbamate **1z** (0.125, 0.500 mmol) in MeCN (0.05 M) at 180 °C for 4 h. The product was purified using

silica-gel flash column chromatography (100% EtOAc 5% MeOH/ DCM 10% MeOH/ DCM) to yield the title compound as a white solid (0.019 g, 25%, 3:1 diastereomeric mixture).

TLC R_f: 0.08 in 100% EtOAc.

Major diastereomer

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.74 (s, 1H), 3.94 (ddd, *J* = 8.7, 7.8, 3.2 Hz, 1H), 3.79 (dd, *J* = 4.7, 3.3 Hz, 1H), 3.64 (td, *J* = 9.1, 6.4 Hz, 1H), 3.14 (dd, *J* = 13.1, 4.3 Hz, 1H), 3.02 (dd, *J* = 13.0, 2.9 Hz, 1H), 2.55 (dd, *J* = 16.1, 3.2 Hz, 1H), 2.46 (dd, *J* = 16.1, 4.9 Hz, 1H), 1.95 (ddd, *J* = 12.2, 9.3, 7.8 Hz, 1H), 1.74 (ddd, *J* = 12.2, 6.4, 3.2 Hz, 1H), 1.16 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 173.1 (C), 82.7 (CH), 66.4 (CH_2), 49.6 (CH_2), 42.0 (C), 38.7 (CH_2), 36.3 (CH_2), 23.8 (CH_3).

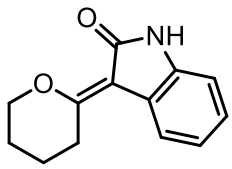
Minor diastereomer (1H is overlapped)

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.53 (s, 1H), 4.12-4.00 (m, 2H), 3.62 (dd, *J* = 12.4, 5.8 Hz, 1H), 3.28 (dd, *J* = 11.5, 3.9 Hz, 1H), 2.75 (dd, *J* = 17.0, 5.9 Hz, 1H), 2.40 (dd, *J* = 16.8, 12.5 Hz, 1H), 1.83-1.80 (m, 2H), 1.02 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 171.6 (C), 79.2 (CH), 67.6 (CH_2), 50.6 (CH_2), 39.2 (C), 36.8 (CH_2), 34.7 (CH_2), 16.1 (CH_3).

IR (FTIR): 3240, 2954, 2868, 1653, 1482, 1454, 1383, 1314, 1267, 1212, 1060 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_8H_{13}NO_2$ $[M]^+$ 155.0946. Found: 155.0937.

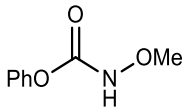


(Z)-3-(Tetrahydro-2H-pyran-2-ylidene)indolin-2-one (14a)

TLC R_f: 0.26 in 30% EtOAc/Hexanes.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85 (s), 7.73 (d, *J* = 7.5 Hz), 7.11 (td, *J* = 7.6, 1.3 Hz), 6.99 (td, *J* = 7.6, 1.1 Hz), 6.84 (d, *J* = 7.6 Hz), 4.43 (t, *J* = 5.8 Hz, 1H), 3.38 (t, *J* = 6.9 Hz, 1H), 1.98 (quintet, *J* = 6.4 Hz, 1H), 1.89 (quintet, *J* = 6.7 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.3 (C), 170.6 (C), 136.7 (C), 126.0 (CH), 123.8 (C), 123.1 (CH), 121.8 (CH), 108.8 (CH), 104.6 (C), 67.9 (CH_2), 24.0 (CH_2), 22.9 (CH_2), 17.3 (CH_2).

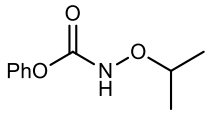


Phenyl methoxycarbamate (1ab)

The title compound was synthesized according to a literature procedure.[212] NMR spectra are consistent with previous literature reports.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (br s, 1H), 7.43–7.33 (m, 2H), 7.25–7.21 (m, 1H), 7.19–7.12 (m, 2H), 3.82 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.5 (C), 150.3 (C), 129.5 (CH), 125.9 (CH), 121.4 (CH), 64.8 (CH_3).



Phenyl isopropoxycarbamate (1ad)

The title compound was synthesized according to general procedure **I** using a two-step deprotection then acylation sequence. First, 2-isopropoxyisoindoline-1,3-dione[213] (2.05 g, 10.0 mmol) and 50% hydrazine hydrate (1.26 mL, 20.0 mmol) in DCM:MeOH (10:1) (0.3 M) were stirred overnight at 0 °C to rt. The crude hydroxylamine obtained from this phthalimide deprotection was used in the subsequent step without further purification. Second, the crude hydroxylamine was diluted in DCM:H_2O (2:1) (0.3 M) and $NaHCO_3$ (1.01 g, 12.0 mmol) and phenylchloroformate (1.25 mL, 10.0 mmol) were added at 0 °C and allowed to stir overnight at rt. Upon completion the reaction was extracted using saturated $NaHCO_3$ and then brine. The organic layer was separated and concentrated under reduced pressure. The product was purified by silica gel flash column chromatography (10% EtOAc/Hexanes) to yield the title compound as clear oil (1.82 g, 88%) over two steps.

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[212] Q. Wang, J. An, H. Alper, W.-J. Xiao, A. M. Beauchemin, *Chem. Commun.* **2017**, *53*, 13055–13058.
[213] Q.-A. Sun, Z.-H. Lu, X.-Q. Pu, H.-L. Hu, J. Zhang, X.-J. Yang, *European J. Org. Chem.* **2018**, *2018*, 3920–3927.

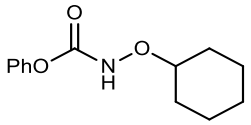
TLC R_f: 0.32 in 20% EtOAc/Hexanes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (s, 1H), 7.37–7.33 (m, 2H), 7.22–7.18 (m, 1H), 7.15–7.13 (m, 2H), 4.16 (sept, *J* = 6.2 Hz, 1H), 1.27 (d, *J* = 6.2 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.8 (C), 150.5 (C), 129.4 (CH), 125.8 (CH), 121.4 (CH), 78.5 (CH), 20.5 (CH_3)

IR (FTIR): 3180, 2978, 2909, 1732, 1593, 1482, 1374, 1264, 1202, 1147 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{10}H_{13}NO_3Na$ $[M+Na]^+$ 218.0793. Found: 218.0808.

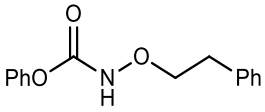


Phenyl cyclohexyloxycarbamate (1ae)

The title compound was synthesized according to a literature report.[212] NMR spectra are consistent with previous literature reports.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (s, 1H), 7.39–7.31 (m, 2H), 7.23–7.17 (m, 1H), 7.17–7.07 (m, 2H), 3.86 (tt, *J* = 9.3, 3.8 Hz, 1H), 2.06–1.94 (m, 2H), 1.84–1.70 (m, 2H), 1.58–1.53 (m, 1H), 1.50–1.38 (m, 2H), 1.36–1.19 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.7 (C), 150.5 (C), 129.4 (CH), 125.7 (CH), 121.4 (CH), 83.8 (CH), 30.5 (CH_2), 25.6 (CH_2), 23.7 (CH_2).



Phenyl phenethoxycarbamate (1af)

The title compound was synthesized according to general procedure **I** using a two-step deprotection then acylation sequence. First, 2-phenethoxyisoindoline-1,3-dione[214] (2.67 g, 10.0 mmol) and 50% hydrazine hydrate (1.26 mL, 20.0 mmol) in DCM:MeOH (10:1) (0.3 M) were stirred overnight at 0 °C to rt. The crude

[214] D.-K. Kim, J. Gam, Y.-W. Kim, J. Lim, H.-T. Kim, K. H. Kim, *J. Med. Chem.* **1997**, *40*, 2363–2373.

hydroxylamine obtained from this phthalimide deprotection was used in the subsequent step without further purification. Second, the crude hydroxylamine was diluted in DCM:H_2O (2:1) (0.3 M) and $NaHCO_3$ (1.01 g, 12.0 mmol) and phenylchloroformate (1.25 mL, 10.0 mmol) were added at 0 °C and allowed to stir overnight at rt. Upon completion the reaction was extracted using saturated $NaHCO_3$ and then brine. The organic layer was separated and concentrated under reduced pressure. The product was purified by silica gel flash column chomatography in (10% Et_2OAc/Hexanes) to yield the title compound as a white solid (2.31 g, 90%) over two steps.

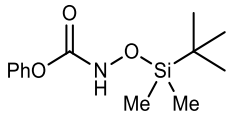
TLC R_f: 0.30 in 20% EtOAc/Hexanes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, *J* = 0.3 Hz, 1H), 7.40–7.33 (m, 2H), 7.31-7.19 (m, 6H), 7.16–7.11 (m, 2H), 4.20 (t, *J* = 7.1 Hz, 2H), 3.01 (t, *J* = 7.1 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6 (C), 150.4 (C), 137.8 (C), 129.5 (CH), 128.9 (CH), 128.6 (CH), 126.6 (CH), 125.9 (CH), 121.4 (CH), 77.6 (CH_2), 34.6 (CH_2).

IR (FTIR): 3177, 3034, 2958, 2917, 1782, 1601, 1477, 1434, 1265, 1177 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{15}H_{15}NO_3Na$ $[M+Na]^+$ 280.0950. Found: 280.0935.



Phenyl (*tert*-butyldimethylsilyl)oxycarbamate (1ag)

The title compound was synthesized according to a modified general procedure **I**. First, $NaHCO_3$ (0.680 g, 8.10 mmol) was diluted in 10 mL of DCM. Then a solution *O*-(*tert*-butyldimethylsilyl)hydroxylamine (0.597 g, 4.05 mmol) in the remaining DCM (0.25 M) was added dropwise at 0 °C and allowed to stir for 30 min. Phenylchloroformate (0.46 mL, 3.7 mmol) was then added dropwise at 0 °C and allowed to stir overnight at rt. Upon completion, the reaction was diluted with water, then extracted using DCM twice. The combined organic layers were washed using saturated $NaHCO_3$ and then brine. The organic phase was dried with Na_2SO_4 and filtered over a fritted funnel. The filtrate was concentrated via rotary evaporation and isolated using silica-gel flash column chromatography (10% EtOAc/Hexanes) to yield the title compound as a white solid (1.434 g, 88%).

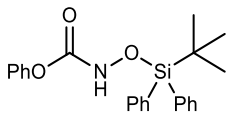
TLC R_f: 0.62 in 15% EtOAc/Hexanes

^{1}H NMR (400 MHz, $CDCl_3$): 7.41 – 7.34 (m, 2H), 7.24 – 7.20 (m, 1H), 7.18 – 7.13 (m, 3H), 0.99 (s, 9H), 0.24 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 156.7 (C), 150.5 (C), 129.4 (CH), 125.8 (CH), 121.3 (CH), 25.8 (CH_3), -5.7 (CH_3).

IR (FTIR): 3306, 3242, 2926, 2854, 1727, 1589, 1457, 1360, 1248, 1202 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{13}H_{21}NO_3SiNa$ $[M+Na]^+$ 290.1188. Found: 290.1211.



Phenyl (*tert*-butyldiphenylsilyl)oxycarbamate (1ah)

The title compound was synthesized according to a modified general procedure **I**. First, $NaHCO_3$ (0.840 g, 10.0 mmol) was diluted in 40 mL of DCM (0.25 M). Then a solution *O*-(*tert*-butyldiphenylsilyl)hydroxylamine (1.36 g, 5.00 mmol) in the remaining DCM (0.25 M) was added dropwise at 0 °C and allowed to stir for 30 min. Phenylchloroformate (0.57 mL, 4.6 mmol) was then added dropwise at 0 °C and allowed to stir overnight at rt. Upon completion, the reaction was diluted with water, then extracted using DCM twice. The combined organic layers were washed using saturated $NaHCO_3$ and then brine. The organic phase was dried with Na_2SO_4 and filtered over a fritted funnel. The filtrate was concentrated via rotary evaporation and isolated using silica-gel flash column chromatography (10% EtOAc/Hexanes) to yield the title compound as a white solid (1.54 g, 81%).

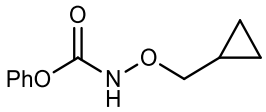
TLC R_f: 0.49 in 20% EtOAc/Hexanes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (dd, *J* = 8.0, 1.4 Hz, 4H), 7.50–7.45 (m, 2H), 7.43–7.39 (m, 4H), 7.33–7.29 (m, 2H), 7.19–7.17 (m, 1H), 7.16 (s, 1H), 6.96 (d, *J* = 7.7 Hz, 2H), 1.16 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.9 (C), 150.5 (C), 135.8 (CH), 131.5 (C), 130.4 (CH), 129.4 (CH), 128.0 (CH), 125.7 (CH), 121.3 (CH), 26.9 (CH_3), 19.2 (C).

IR (FTIR): 3204, 3120, 2954, 2868, 1705, 1425, 1370, 1224, 1198, 1112 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{23}H_{25}NO_3SiNa$ $[M]^+$ 414.1501. Found: 414.1497.



Phenyl cyclopropylmethoxycarbamate (1ai)

The title compound was synthesized according to general procedure **I** using a two-step deprotection then acylation sequence. First, 2-(cyclopropylmethoxy)isoindoline-1,3-dione[215] (2.17 g, 10.0 mmol) and 50% hydrazine hydrate (1.26 mL, 20.0 mmol) in DCM:MeOH (10:1) (0.3 M) were stirred overnight at 0 °C to rt. The crude hydroxylamine obtained from this phthalimide deprotection was used in the subsequent step without further purification. Second, the crude hydroxylamine was diluted in DCM:H_2O (2:1) (0.3 M) and $NaHCO_3$ (1.01 g, 12.0 mmol) and phenylchloroformate (1.25 mL, 10.0 mmol) were added at 0 °C and allowed to stir overnight at rt. Upon completion the reaction was extracted using saturated $NaHCO_3$ and then brine. The organic layer was separated and concentrated under reduced pressure. The product was purified by silica gel flash column chromatography (10% EtOAc/Hexanes) to yield the title compound as a white solid (1.82 g, 88%) over two steps.

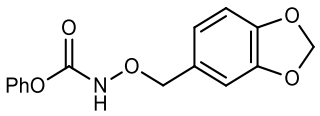
TLC R_f: 0.29 in 20% EtOAc/Hexanes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69–7.63 (m, 1H), 7.38–7.33 (m, 2H), 7.23–7.19 (m, 1H), 7.15–7.13 (m, 2H), 3.78 (d, *J* = 7.3 Hz, 2H), 1.21–1.11 (m, 1H), 0.62–0.58 (m, 2H), 0.33–0.30 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.4 (C), 150.4 (C), 129.5 (CH), 125.8 (CH), 121.4 (CH), 81.8 (CH_2), 9.1 (CH), 3.1 (CH_2).

IR (FTIR): 3248, 3064, 2996, 2932, 2876, 1725, 1591, 1472, 1255, 1196 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{11}H_{13}NO_3Na$ $[M+Na]^+$ 230.0793. Found: 230.0813.



[215] S. D. Barrett, A. J. Bridges, D. T. Dudley, A. R. Saltiel, J. H. Fergus, C. M. Flamme, A. M. Delaney, M. Kaufman, S. LePage, W. R. Leopold, et al., *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6501–6504.

Phenyl benzo[d][1,3]dioxol-5-ylmethoxycarbamate (1aj)

The title compound was synthesized according to general procedure **J**. To a round bottom flask charged with a stir bar was added *N*-hydroxyphthalimide (2.45 g, 15.0 mmol) followed by dilution in dry THF (0.3 M). PPh_3 (3.93 g, 15.0 mmol) and piperonyl alcohol (2.28 g, 15.0 mmol) were added sequentially and the resulting solution was allowed to stir at 0 °C for 0.3 h. DIAD (3.1 mL, 15.75 mmol) was added dropwise over 1 h, and the mixture was stirred at 0 °C until TLC monitoring indicated completion. Upon completion (by TLC), Et_2O and hexanes were added to the solution, which induced a white precipitate to form upon cooling (Ph_3P=O and DIAD co-crystallize). The precipitate was filtered and the collected solids were discarded. The filtrate, which contained the *N*-alkoxyphthalimide along with minor impurities, was used in the subsequent step without further purification. Crude NMR spectra are consistent with previous literature reports.[216]

To a round bottom flask charged with a stir bar was added the corresponding crude *N*-alkoxyphthalimide (1.00 eq) followed by dilution in DCM:MeOH (10:1) (0.17 M) and cooled to 0 °C. To this vigorously stirred solution was added a solution of 50% hydrazine hydrate (1.9 mL, 30 mmol). The reaction progress was monitored by TLC and stopped upon completion, as gauged by consumption of the *N*-alkoxyphthalimide. Upon completion, the solution is filtered over a fritted funnel and the filtrate is collected (the white precipitate is discarded). The filtrate is extracted with sat. $NaHCO_3$ (x 2) and then brine (x1). The organic phase was dried with Na_2SO_4 and filtered over a fritted funnel. The filtrate was concentrated via rotary evaporation and used in the subsequent step without further purification.

To a round bottom flask charged with a stir bar was added $NaHCO_3$ (2.77 g, 33.0 mmol) followed by dilution with DCM:H_2O (1:1) (0.25 M) and cooled to 0 °C. To this vigorously stirred solution was added the crude corresponding *N*-alkyl hydroxylamine (1.00 eq) and was allowed to stir at 0 °C for 0.5 h. After 0.5 h passed, phenylchloroformate (2.06 mL, 16.5 mmol) was added dropwise. The reaction progress was monitored by TLC and stopped upon completion, as gauged by consumption of the phenylchloroformate. Upon completion, the reaction was extracted using sat. $NaHCO_3$ (x 2) and then brine (x1). The organic phase was dried with Na_2SO_4 and filtered over a fritted funnel. The filtrate was concentrated via rotary

[216] M.-Z. Wang, H. Xu, T.-W. Liu, Q. Feng, S.-J. Yu, S.-H. Wang, Z.-M. Li, *Eur. J. Med. Chem.* **2011**, *46*, 1463–1472.

evaporation and isolated using recrystallization with ether and hexanes. The product was isolated as white crystals (1.28 g, 30% yield over 3 steps).

M.p.: 113.8-114.1 °C.

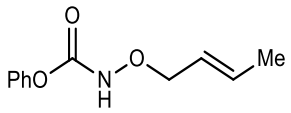
TLC R_f: 0.58 in 40% EtOAc/Hexanes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (br s, 1H), 7.43 – 7.33 (m, 2H), 7.25 – 7.20 (m, 1H), 7.19 – 7.12 (m, 2H), 6.94 (d, *J* = 1.6 Hz, 1H), 6.90 (dd, *J* = 7.9, 1.7 Hz, 1H), 6.82 (d, *J* = 7.9 Hz, 1H), 5.98 (s, 2H), 4.87 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.3 (C), 150.33 (C), 148.1 (C), 147.9 (C), 129.4 (CH), 128.8 (CH), 125.8 (CH), 123.3 (CH), 121.3 (CH), 109.7 (CH), 108.3 (CH), 101.2 (CH_2), 78.7 (CH_2).

IR (FTIR): 3293, 2919, 2851, 1720, 1593, 1473, 1441, 1362, 1251, 1203, 1036 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{15}H_{13}NO_5Na$ $[M+Na]^+$ 310.0691. Found: 310.0710.



(*E*)-Phenyl but-2-en-1-yloxycarbamate (1ak)

The title compound was synthesized according to general procedure **I** using a two-step deprotection then acylation sequence. First, (E)-2-(but-2-en-1-yloxy)isoindoline-1,3-dione[217] (1.24 g, 5.70 mmol) and 50% hydrazine hydrate (0.70 mL, 11 mmol) in DCM:MeOH (10:1) (0.17 M) were stirred overnight at 0 °C to rt. The crude hydroxylamine obtained from this phthalimide deprotection was used in the subsequent step without further purification. Second, the crude hydroxylamine was diluted in DCM:H_2O (1:1) (0.25 M) and $NaHCO_3$ (1.05 g, 12.54 mmol) and phenylchloroformate (0.80 mL, 6.3 mmol) were added at 0 °C and allowed to stir overnight at rt. Upon completion the reaction was extracted using saturated $NaHCO_3$ and then brine. The organic layer was separated and concentrated under reduced pressure. The product was purified by silica gel flash column chromatography (30% EtOAc/Hexanes) to yield the title compound as a white solid (0.639 g, 54%) over two steps.

[217] J. N. Kim, K. M. Kim, E. K. Ryu, *Synth. Commun.* **1992**, *22*, 1427–1432.

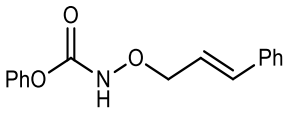
TLC R_f: 0.65 in 40% EtOAc/Hexanes.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53 (br s, 1H), 7.40 – 7.31 (m, 2H), 7.24 – 7.17 (m, 1H), 7.17 – 7.10 (m, 2H), 5.93 – 5.77 (m, 1H), 5.66 (dddd, *J* = 15.2, 6.8, 5.3, 1.6 Hz, 1H), 4.37 (dt, *J* = 6.8, 1.0 Hz, 2H), 1.75 (ddt, *J* = 6.4, 1.8, 1.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.2 (C), 150.4 (C), 133.9 (CH), 129.4 (CH), 125.8 (CH), 124.8 (CH), 121.3 (CH), 77.6 (CH_2), 17.9 (CH_3).

IR (FTIR): 2983, 2939, 1734, 1438, 1371, 1235, 1205, 1163, 1094, 1043 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{11}H_{13}NO_3Na$ $[M+Na]^+$ 230.0793. Found: 230.0768.



(*E*)-Phenyl cinnamyloxycarbamate (1al)

The title compound was synthesized according to general procedure **I** using a two-step deprotection then acylation sequence. First, 2-(cinnamyloxy)isoindoline-1,3-dione[218] (4.19 g, 15.0 mmol) and 50% hydrazine hydrate (1.90 mL, 30.0 mmol) in DCM:MeOH (10:1) (0.17 M) were stirred overnight at 0 °C to rt. The crude hydroxylamine obtained from this phthalimide deprotection was used in the subsequent step without further purification. Second, the crude hydroxylamine was diluted in DCM:H_2O (1:1) (0.25 M) and $NaHCO_3$ (2.772 g, 33.0 mmol) and phenylchloroformate (2.10 mL, 16.5 mmol) were added at 0 °C and allowed to stir overnight at rt. Upon completion the reaction was extracted using saturated $NaHCO_3$ and then brine. The organic layer was separated and concentrated under reduced pressure. The product was purified by silica gel flash column chromatography (20% EtOAc/Hexanes) to yield the title compound as a white solid (3.56 g, 88%) over two steps.

TLC R_f: 0.61 in 40% EtOAc/Hexanes.

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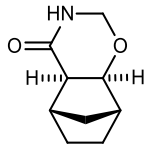
[218] C. Alamillo-Ferrer, J. M. Curle, S. C. Davidson, S. C. C. Lucas, S. J. Atkinson, M. Campbell, A. R. Kennedy, N. C. O. Tomkinson, *J. Org. Chem.* **2018**, *83*, 6728–6740.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (br s, 1H), 7.46 – 7.27 (m, 7H), 7.25 – 7.18 (m, 1H), 7.18 – 7.09 (m, 2H), 6.72 (d, *J* = 15.9 Hz, 1H), 6.38 (dt, *J* = 15.9, 6.8 Hz, 1H), 4.62 (dd, *J* = 6.8, 1.1 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.3 (C), 150.3 (C), 136.3 (CH), 136.0 (C), 129.4 (CH), 128.6 (CH), 128.3 (CH), 126.7 (CH), 125.8 (CH), 122.7 (CH), 121.3 (CH), 77.6 (CH_2).

IR (FTIR): 3027, 2928, 2853, 1730, 1593, 1490, 1472, 1453, 1238, 1202, 1163, 1086, 967 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{16}H_{15}NO_3Na$ $[M+Na]^+$ 292.0950. Found: 292.0966.



Hexahydro-2*H*-5,8-methanobenzo[*e*][1,3]oxazin-4(3*H*)-one (17a)

The title compound was synthesized according to general procedure **K** using phenyl methoxycarbamate **1ab** (0.167 g, 1.00 mmol), norbornene (4.71 g, 50.0 mmol) and MeCN (0.1 M) at 180 °C for 2 h. Upon completion the crude reaction mixture was concentrated under reduced pressure and the product was isolated using silica gel flash column chromatography (100% EtOAc). The product was isolated as a white solid (0.152 g, 91% yield).

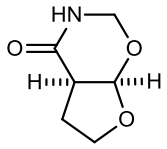
TLC R_f: 0.15 in 100% EtOAc

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 (s, 1H), 4.65 (qd, *J* = 9.5, 3.8 Hz, 2H), 3.95 (d, *J* = 6.9 Hz, 1H), 2.85 (t, *J* = 1.2 Hz, 1H), 2.38 (dd, *J* = 2.8, 1.0 Hz, 1H), 2.23 (dd, *J* = 6.9, 1.4 Hz, 1H), 1.64–1.51 (m, 3H), 1.27–1.08 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4 (C), 82.6 (CH), 72.4 (CH_2), 50.1 (CH), 42.4 (CH), 39.7 (CH), 34.2 (CH_2), 28.6 (CH_2), 24.3 (CH_2).

IR (FTIR): 3262, 2956, 2875, 1658, 1621, 1471, 1368, 1314, 1223, 1135 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_9H_{13}NO_2$ $[M]^+$ 167.0946. Found: 167.0926.



Tetrahydro-2*H*-furo[3,2-*e*][1,3]oxazin-4(3*H*)-one (17b)

The title compound was synthesized according to general procedure **K** using phenyl methoxycarbamate **1ab** (0.167 g, 1.00 mmol), 2,3,-dihydrofuran (2.10 g, 30 mmol) and MeCN (0.1 M) at 180 °C for 2 h. Upon completion the crude reaction mixture was concentrated under reduced pressure and the product was isolated using silica gel flash column chromatography (100% EtOAc 5% MeOH/DCM). The product was isolated as an off-white solid (0.041 g, 28% yield).

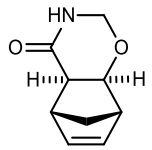
TLC R_f: 0.15 in 5% MeOH/DCM

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.40 (s, 1H), 5.45 (d, *J* = 5.4 Hz, 1H), 4.84 (dd, *J* = 9.4, 2.9 Hz, 1H), 4.70 (dd, *J* = 9.4, 2.7 Hz, 1H), 4.11 (td, *J* = 8.2, 4.9 Hz, 1H), 3.88 (q, *J* = 7.9 Hz, 1H), 2.96 (td, *J* = 9.1, 5.3 Hz, 1H), 2.40 (dddd, *J* = 12.5, 9.9, 7.4, 5.0 Hz, 1H), 2.16 (dq, *J* = 12.7, 8.1 Hz, 1H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 171.2 (C), 101.2 (CH), 68.6 (CH_2), 67.8 (CH_2), 45.4 (CH), 28.9 (CH_2).

IR (FTIR): 3198, 2973, 2875, 1656, 1453, 1374, 1263, 1209 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_6H_9NO_3$ $[M]^+$ 143.0582. Found: 143.0586.



4a,5,8,8a-Tetrahydro-2H-5,8-methanobenzo[e][1,3]oxazin-4(3H)-one (17c)

The title compound was synthesized according to general procedure **K** using phenyl methoxycarbamate **1ab** (0.167 g, 1.00 mmol), norbornadiene (2.76 g, 30.0 mmol) and MeCN (0.1 M) at 180 °C for 2 h. Upon completion the crude reaction mixture was concentrated under reduced pressure and the product was isolated using silica gel flash column chromatography (30% EtOAc/Hexanes 50% EtOAc/Hexanes 100% EtOAc). The product was isolated as a white solid (0.080 g, 54% yield).

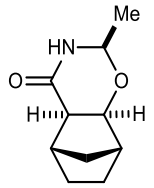
TLC R_f: 0.40 in 100% EtOAc

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.58 (s, 1H), 6.32 (dd, *J* = 5.7, 3.0 Hz, 1H), 6.06 (dd, *J* = 5.7, 3.2 Hz, 1H), 4.78 – 4.64 (m, 2H), 3.99 (dt, *J* = 6.9, 1.1 Hz, 1H), 3.41 (ddt, *J* = 3.2, 1.6, 0.8 Hz, 1H), 3.04 – 2.97 (m, 2H), 2.20 (dd, *J* = 6.9, 2.1 Hz, 1H), 1.72 (dt, *J* = 9.2, 1.6 Hz, 1H), 1.56 (dt, *J* = 9.1, 1.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8 (C), 140.0 (CH), 133.8 (CH), 79.0 (CH), 72.8 (CH_2), 48.0 (CH), 44.9 (CH_2), 44.6 (CH), 44.6 (CH).

IR (FTIR): 3231, 2916, 2854, 1665, 1624, 1469, 1367, 1321, 1270, 1080 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_9H_{11}NO_2$ $[M+Na]^+$ 188.0687. Found: 188.0680.



2-Methylhexahydro-2*H*-5,8-methanobenzo[*e*][1,3]oxazin-4(3*H*)-one (17d)

The title compound was synthesized according to general procedure **K** using phenyl ethoxycarbamate **1b** (0.181 g, 1.00 mmol), norbornene (4.71 g, 50.0 mmol) and MeCN (0.1 M) at 180 °C for 2 h. Upon completion the crude reaction mixture was concentrated under reduced pressure and the product was isolated using silica gel flash column chromatography (100% EtOAc). The product was isolated as an off-white solid in a 9:1 mixture of diastereoisomers (0.152 g, 84% yield).

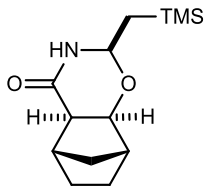
TLC R_f: 0.16 in 50% EtOAc/Hexanes

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (s, 1H), 4.73 (qd, *J* = 5.6, 2.0 Hz, 1H), 3.95 (d, *J* = 6.8 Hz, 1H), 2.84 (d, *J* = 1.6 Hz, 1H), 2.37 (d, *J* = 3.1 Hz, 1H), 2.16 (dd, *J* = 6.9, 1.2 Hz, 1H), 1.65–1.51 (m, 3H), 1.32 (d, *J* = 5.6 Hz, 3H), 1.20–1.09 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8 (C), 81.9 (CH), 78.2 (CH), 49.3 (CH), 42.4 (CH), 39.5 (CH), 34.2 (CH_2), 28.7 (CH_2), 24.3 (CH_2), 20.9 (CH_3).

IR (FTIR): 3166, 3070, 2958, 2873, 1660, 1485, 1450, 1403, 1298, 1147 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{10}H_{15}NO_2$ $[M]^+$ 181.1103. Found: 181.1073.



2-((Trimethylsilyl)methyl)hexahydro-2*H*-5,8-methanobenzo[*e*][1,3]oxazin-4(3*H*)-one (17e)

The title compound was synthesized according to general procedure **K** using phenyl 2-(trimethylsilyl)ethoxycarbamate **1f** (0.253 g, 1.00 mmol), norbornene (4.71 g, 50.0 mmol) and MeCN (0.1 M) at 180 °C for 2 h. Upon completion the crude reaction mixture was concentrated under reduced pressure and the product was isolated using silica gel flash column chromatography (100% EtOAc). The product was isolated as a white solid in a 9:1 mixture of diastereoisomers (0.223 g, 88% yield).

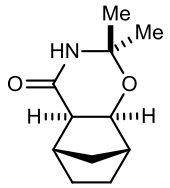
TLC R_f: 0.27 in 50% EtOAc/Hexanes

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.41 (s, 1H), 4.72 (ddd, *J* = 7.5, 5.3, 2.2 Hz, 1H), 3.92 (d, *J* = 6.9 Hz, 1H), 2.86 (d, *J* = 1.7 Hz, 1H), 2.36 (d, *J* = 2.4 Hz, 1H), 2.17 (dd, *J* = 6.9, 1.2 Hz, 1H), 1.62–1.56 (m, 3H), 1.26–1.10 (m, 4H), 1.03–0.89 (m, 2H), 0.07 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6 (C), 81.9 (CH), 80.4 (CH), 49.3 (CH), 42.5 (CH), 39.5 (CH), 34.3 (CH_2), 28.7 (CH_2), 24.3 (CH_2), 24.1 (CH_2), -0.8 (CH_3).

IR (FTIR): 3163, 2955, 2873, 1651, 1406, 1349, 1246, 1222, 1102 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{13}H_{23}NO_2SiNa$ $[M+Na]^+$ 276.1396. Found: 276.1371.



2,2-Dimethylhexahydro-2*H*-5,8-methanobenzo[*e*][1,3]oxazin-4(3*H*)-one (17g)

The title compound was synthesized according to general procedure **K** using phenyl isopropoxycarbamate **1ad** (0.195 g, 1.00 mmol), norbornene (4.71 g, 50.0 mmol) and MeCN (0.1 M) at 180 °C for 2 h. Upon completion the crude reaction mixture was concentrated under reduced pressure and the product was isolated using silica gel flash column chromatography (100% EtOAc). The product was isolated as a white solid (0.146 g, 75% yield).

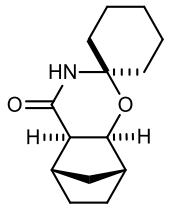
TLC R_f: 0.16 in 50% EtOAc/Hexanes

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (br. s, 1H), 4.09 (d, *J* = 6.5 Hz, 1H), 2.83 (d, *J* = 1.6 Hz, 1H), 2.30 (d, *J* = 2.5 Hz, 1H), 2.15 (dd, *J* = 6.5, 1.4 Hz, 1H), 1.67–1.56 (m, 3H), 1.49 (s, 3H), 1.41 (s, 3H), 1.30–1.09 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8 (C), 83.0 (C), 76.9 (C), 48.2 (CH), 42.6 (CH), 40.1 (CH), 33.9 (CH_2), 29.5 (CH_3), 28.9 (CH_2), 26.8 (CH_3), 24.3 (CH_2).

IR (FTIR): 3162, 2873, 1651, 1481, 1407, 1224, 1183, 1144 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{11}H_{17}NO_2Na$ $[M+Na]^+$ 218.1157. Found: 218.1144.



Hexahydrospiro[5,8-methanobenzo[*e*][1,3]oxazine-2,1'-cyclohexan]-4(3*H*)-one (17h)

The title compound was synthesized according to general procedure **K** using phenyl cyclohexyloxycarbamate **1ae** (0.235 g, 1.00 mmol), norbornene (4.71 g, 50.0 mmol) and MeCN (0.1 M) at 180 °C for 2 h. Upon completion the crude reaction mixture was concentrated under reduced pressure and the product was isolated using silica gel flash column chromatography (100% EtOAc). The product was isolated as a white solid (0.195 g, 83% yield).

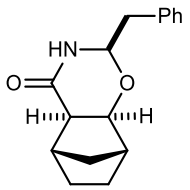
TLC R_f: 0.25 in 50% EtOAc/Hexanes

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.46–6.46 (m, 1H), 4.03 (d, *J* = 6.6 Hz, 1H), 2.83–2.83 (m, 1H), 2.31–2.30 (m, 1H), 2.17 (dd, *J* = 6.5, 1.3 Hz, 1H), 1.99–1.94 (m, 1H), 1.73–1.69 (m, 2H), 1.65–1.43 (m, 9H), 1.34–1.28 (m, 1H), 1.26–1.21 (m, 1H), 1.17–1.09 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8 (C), 83.7 (C), 76.0 (CH), 48.7 (CH), 42.6 (CH), 40.1 (CH), 38.0 (CH_2), 35.5 (CH_2), 34.0 (CH_2), 28.8 (CH_2), 24.9 (CH_2), 24.3 (CH_2), 22.4 (CH_2), 21.8 (CH_2).

IR (FTIR): 3159, 2913, 2872, 1658, 1477, 1404, 1228, 1143, 1117 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{14}H_{21}NO_2$ $[M]^+$ 235.1572. Found: 235.1551.



2-Benzylhexahydro-2*H*-5,8-methanobenzo[*e*][1,3]oxazin-4(3*H*)-one (17j)

The title compound was synthesized according to general procedure **K** using phenyl phenethoxycarbamate **1af** (0.257 g, 1.00 mmol), norbornene (4.71 g, 50.0 mmol) and MeCN (0.1 M) at 180 °C for 2 h. Upon completion the crude reaction mixture was concentrated under reduced pressure and the product was isolated using silica gel flash column chromatography (100% EtOAc). The product was isolated as an off-white solid in a 15:1 mixture of diastereoisomers (0.208 g, 81% yield).

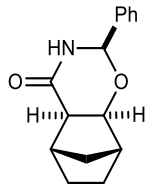
TLC R_f: 0.20 in 50% EtOAc/Hexanes

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33–7.25 (m, 3H), 7.22–7.18 (m, 2H), 6.24 (s, 1H), 4.84 (ddd, *J* = 7.1, 5.4, 1.7 Hz, 1H), 3.97 (d, *J* = 6.8 Hz, 1H), 3.07 (dd, *J* = 13.9, 5.4 Hz, 1H), 2.83 (dt, *J* = 0.8, 0.4 Hz, 1H), 2.71 (dd, *J* = 13.9, 7.1 Hz, 1H), 2.42–2.41 (m, 1H), 2.18–2.16 (m, 1H), 1.65–1.51 (m, 3H), 1.24–1.19 (m, 1H), 1.15–1.10 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3 (C), 134.3 (C), 129.5 (CH), 129.0 (CH), 127.4 (CH), 81.9 (CH), 81.8 (CH), 49.6 (CH), 42.5 (CH), 41.3 (CH_2), 39.7 (CH), 34.2 (CH_2), 28.8 (CH_2), 24.1 (CH_2).

IR (FTIR): 3178, 2954, 2875, 1664, 1399, 1309, 1221, 1173, 1148, 1113 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{16}H_{19}NO_2$ $[M]^+$ 257.1416. Found: 257.1449.



2-Phenylhexahydro-2*H*-5,8-methanobenzo[*e*][1,3]oxazin-4(3*H*)-one (17l)

The title compound was synthesized according to general procedure **K** using phenyl benzyloxycarbamate **1d** (0.243 g, 1.00 mmol), norbornene (4.71 g, 50.0 mmol) and MeCN (0.1 M) at 180 °C for 2 h. Upon completion the crude reaction mixture was concentrated under reduced pressure and the product was isolated using silica gel flash column chromatography (100% EtOAc). The product was isolated as an off-white solid in a 15:1 mixture of diastereoisomers (0.097 g, 40% yield).

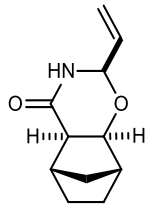
TLC R_f: 0.32 in 50% EtOAc/Hexanes

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41–7.37 (m, 5H), 6.51 (s, 1H), 5.55 (d, *J* = 1.8 Hz, 1H), 4.12 (d, *J* = 6.9 Hz, 1H), 2.89 (d, *J* = 1.4 Hz, 1H), 2.46 (d, *J* = 3.1 Hz, 1H), 2.29 (dd, *J* = 6.9, 1.0 Hz, 1H), 1.72 (dt, *J* = 10.3, 1.8 Hz, 1H), 1.65–1.54 (m, 2H), 1.29–1.23 (m, 1H), 1.19–1.14 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2 (C), 137.5 (C), 129.9 (CH), 129.0 (CH), 126.5 (CH), 83.0 (CH), 82.2 (CH), 49.5 (CH), 42.6 (CH), 39.8 (CH), 34.4 (CH_2), 28.8 (CH_2), 24.2 (CH_2).

IR (FTIR): 3156, 2954, 2870, 1648, 1476, 1398, 1353, 1297, 1222, 1172 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{15}H_{17}NO_2$ $[M]^+$ 243.1259. Found: 243.1286.



2-Vinylhexahydro-2*H*-5,8-methanobenzo[*e*][1,3]oxazin-4(3*H*)-one (17m)

The title compound was synthesized according to general procedure **K** using phenyl allyloxycarbamate **1e** (0.193 g, 1.00 mmol), norbornene (4.71 g, 50.0 mmol) and MeCN (0.1 M) at 180 °C for 2 h. Upon completion the crude reaction mixture was concentrated under reduced pressure and the product was isolated using silica gel flash column chromatography (100% EtOAc). The product was isolated as an off-white solid in a 10:1 mixture of diastereoisomers (0.044 g, 23% yield).

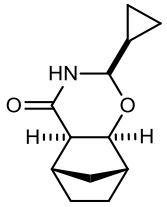
TLC R_f: 0.18 in 50% EtOAc/Hexanes

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.60 (s, 1H), 5.79 (ddd, *J* = 17.3, 10.4, 6.2 Hz, 1H), 5.47 (dt, *J* = 17.3, 0.9 Hz, 1H), 5.38 (dt, *J* = 10.4, 0.8 Hz, 1H), 5.04 (dt, *J* = 6.2, 1.0 Hz, 1H), 4.01 (d, *J* = 6.9 Hz, 1H), 2.85–2.83 (m, 1H), 2.41 (d, *J* = 3.5 Hz, 1H), 2.21 (dd, *J* = 6.9, 1.2 Hz, 1H), 1.63–1.53 (m, 3H), 1.25–1.20 (m, 1H), 1.16–1.10 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3 (C), 133.7 (CH), 120.6 (CH_2), 82.0 (CH), 81.9 (CH), 49.6 (CH), 42.5 (CH), 39.7 (CH), 34.2 (CH_2), 28.7 (CH_2), 24.2 (CH_2).

IR (FTIR): 3162, 2920, 2851, 1655, 1468, 1400, 1299, 1072 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{11}H_{15}NO_2$ $[M]^+$ 193.1103. Found: 193.1127.



2-Cyclopropylhexahydro-2*H*-5,8-methanobenzo[*e*][1,3]oxazin-4(3*H*)-one (17n)

The title compound was synthesized according to general procedure **K** using phenyl cyclopropylmethoxycarbamate **1ai** (0.207 g, 1.00 mmol), norbornene (4.71 g, 50.0 mmol) and MeCN (0.1 M) at 180 °C for 2 h. Upon completion the crude reaction mixture was concentrated under reduced pressure and the product was isolated using silica gel flash column chromatography (100% EtOAc). The product was isolated as a white solid in a 5:1 mixture of diastereoisomers (0.159 g, 77% yield).

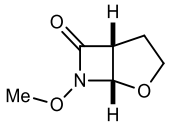
TLC R_f: 0.19 in 50% EtOAc/Hexanes

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.62 (s, 1H), 3.90–3.88 (m, 2H), 2.85–2.83 (s, 1H), 2.42 (d, *J* = 3.4 Hz, 1H), 2.15 (dd, *J* = 6.8, 1.1 Hz, 1H), 1.63–1.50 (m, 4H), 1.25–1.18 (m, 2H), 1.14–1.08 (m, 2H), 1.03 (tt, *J* = 7.8, 4.6 Hz, 1H), 0.65–0.56 (m, 2H), 0.48–0.43 (m, 1H), 0.35–0.31 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3 (C), 85.8 (CH), 82.0 (CH), 49.5 (CH), 42.5 (CH), 39.6 (CH), 34.2 (CH_2), 28.8 (CH_2), 24.2 (CH_2), 15.1 (CH), 2.4 (CH_2), 1.3 (CH_2).

IR (FTIR): 3171, 2950, 2873, 1652, 1471, 1392, 1368, 1296, 1099 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{12}H_{17}NO_2$ $[M]^+$ 207.1259. Found: 207.1238.



***cis*-7-Methoxy-2-oxa-7-azabicyclo[3.2.0]heptan-6-one (19a)**

The title compound was synthesized according to general procedure **L** using phenyl methoxycarbamate **1ab** (0.334 g, 2.00 mmol) followed by 2,3-dihydrofuran (3.0 mL, 40 mmol) and *i*-Pr_2NEt (0.052 g, 0.40 mmol) then MeCN (0.1 M). The reaction vessel was heated at 120 °C via microwave irradiation for 2.5 h. Upon completion the crude reaction mixture was concentrated under reduced pressure and the product

was isolated using silica gel flash column chromatography (60% EtOAc/Hexanes). The product was isolated as a pale yellow oil (0.183 g, 64% yield).

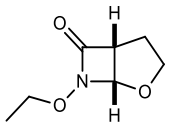
TLC R_f: 0.29 in 60% EtOAc/Hexanes

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.77 (d, *J* = 3.0 Hz, 1H), 4.26 (ddt, *J* = 9.5, 8.1, 0.7 Hz, 1H), 3.98 (ddd, *J* = 12.0, 9.5, 5.6 Hz, 1H), 3.85 (d, *J* = 0.7 Hz, 3H), 3.44 (ddt, *J* = 8.4, 3.0, 0.7 Hz, 1H), 2.21 (ddq, *J* = 13.1, 5.5, 0.7 Hz, 1H), 1.79 (dddd, *J* = 13.1, 12.0, 8.6, 7.9 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 163.6 (C), 90.9 (CH), 66.8 (CH_2), 64.3 (CH_3), 51.5 (CH), 24.9 (CH_2).

IR (FTIR): 2983, 2888, 1669, 1642, 1488, 1442, 1364, 1256, 1219, 1064 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_6H_9NO_3$ $[M]^+$ 143.0582. Found: 143.0573.



***cis*-7-Ethoxy-2-oxa-7-azabicyclo[3.2.0]heptan-6-one (19b)**

The title compound was synthesized according to general procedure **L** using phenyl ethoxycarbamate **1b** (0.362 g, 2.00 mmol) followed by 2,3-dihydrofuran (3.0 mL, 40 mmol) and *i*-Pr_2NEt (0.052 g, 0.40 mmol) then MeCN (0.1 M). The reaction vessel was heated at 120 °C via microwave irradiation for 2.5 h. Upon completion the crude reaction mixture was concentrated under reduced pressure and the product was isolated using silica gel flash column chromatography (45% EtOAc/Hexanes). The product was isolated as a pale yellow oil (0.248 g, 79% yield).

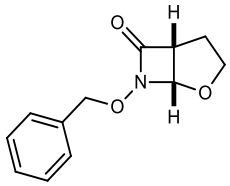
TLC R_f: 0.32 in 40% EtOAc/Hexanes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.74 (d, *J* = 3.0 Hz, 1H), 4.25 (ddq, *J* = 9.6, 8.2, 0.7 Hz, 1H), 4.05 (ddddd, *J* = 16.6, 9.5, 7.1, 2.5, 0.7 Hz, 2H), 3.96 (ddd, *J* = 12.0, 9.5, 5.5 Hz, 1H), 3.44 (dd, *J* = 8.6, 2.9 Hz, 1H), 2.21 (ddt, *J* = 13.2, 5.6, 0.8 Hz, 1H), 1.87 – 1.70 (m, 1H), 1.29 (td, *J* = 7.1, 0.7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3 (C), 91.2 (CH), 72.5 (CH_2), 66.8 (CH_2), 51.3 (CH), 24.9 (CH_2), 14.0 (CH_3).

IR (FTIR): 2978, 2892, 1656, 1614, 1510, 1383, 1280, 1120, 1046 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_7H_{11}NO_3$ $[M]^+$ 157.0739. Found: 157.0748.



***cis*-7-(Benzyloxy)-2-oxa-7-azabicyclo[3.2.0]heptan-6-one (19c)**

The title compound was synthesized according to general procedure **L** using *N*-benzyloxycarbamate **1d** (0.486 g, 2.00 mmol) followed by 2,3-dihydrofuran (3.0 mL, 40 mmol) and *i*-Pr_2NEt (0.052 g, 0.40 mmol) then MeCN (0.1 M). The reaction vessel was heated at 120 °C via microwave irradiation for 2.5 h. Upon completion the crude reaction mixture was concentrated under reduced pressure and the product was isolated using silica gel flash column chromatography (40% EtOAc/Hexanes). The product was isolated as an off-white solid (0.335 g, 76% yield).

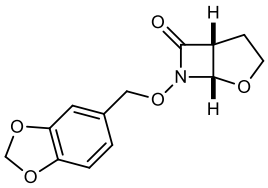
TLC R_f: 0.34 in 40% EtOAc/Hexanes

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 – 7.29 (m, 5H), 5.42 (d, *J* = 3.0 Hz, 1H), 4.98 (s, 2H), 4.14 (ddd, *J* = 9.5, 8.1, 0.7 Hz, 1H), 3.79 (ddd, *J* = 12.0, 9.5, 5.5 Hz, 1H), 3.36 (dd, *J* = 8.4, 3.0 Hz, 1H), 2.12 (dd, *J* = 13.1, 5.5 Hz, 1H), 1.70 (ddt, *J* = 13.1, 12.0, 8.3 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3 (C), 135.0 (C), 129.0 (CH), 128.6 (CH), 91.6 (CH), 78.4 (CH_2), 66.8 (CH_2), 51.4 (CH), 24.9 (CH_2). * One CH peak is overlapped.

IR (FTIR): 3030, 2985, 2881, 1766, 1686, 1498, 1442, 1362, 1234, 1214, 1067 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{12}H_{13}NO_3Na$ $[M+Na]^+$ 242.0793. Found: 242.0785.



***cis*-7-(benzo[d][1,3]dioxol-5-ylmethoxy)-2-oxa-7-azabicyclo[3.2.0]heptan-6-one (19d)**

The title compound was synthesized according to general procedure **L** using phenyl benzo[d][1,3]dioxol-5-ylmethoxycarbamate **1aj** (0.574 g, 2.00 mmol) followed by 2,3-dihydrofuran (3.0 mL, 40 mmol) and *i*-Pr_2NEt (0.052 g, 0.40 mmol) then MeCN (0.1 M). The reaction vessel was heated at 120 °C via microwave irradiation for 2.5 h. Upon completion the crude reaction mixture was concentrated under reduced

pressure and the product was isolated using silica gel flash column chromatography (50% EtOAc/Hexanes). Analysis of the mixture indicated 75% conversion to the product (by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard). Isolation using silica gel flash column chromatography was attempted under a variety of conditions, but this product proved prone to degradation. The product was isolated as a pale yellow oil (0.226 g, 43% yield).

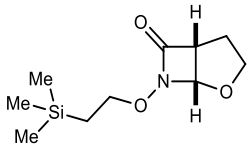
TLC R_f: 0.21 in 40% EtOAc/Hexanes

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.93 (d, *J* = 1.7 Hz, 1H), 6.87 (dd, *J* = 7.9, 1.7 Hz, 1H), 6.80 (d, *J* = 7.9 Hz, 1H), 5.98 (s, 2H), 5.48 (d, *J* = 3.1 Hz, 1H), 4.88 (s, 1H), 4.18 (dd, *J* = 9.5, 8.2 Hz, 1H), 3.85 (ddd, *J* = 12.2, 9.6, 5.6 Hz, 1H), 3.40 (dd, *J* = 8.2, 3.0 Hz, 1H), 2.16 (dd, *J* = 13.2, 5.4 Hz, 1H), 1.73 (ddt, *J* = 13.1, 12.0, 8.2 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.4 (C), 149.6 (C), 148.3 (C), 143.0 (C), 141.1 (CH), 123.2 (CH), 108.2 (CH), 101.3 (CH_2), 91.6 (CH), 78.4 (CH_2), 66.8 (CH_2), 51.5 (CH), 24.9 (CH_2).

IR (FTIR): 3115, 2998, 2883, 1766, 1662, 1605, 1500, 1441, 1379, 1361, 1250, 1214, 1038 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{13}H_{13}NO_5Na$ $[M+Na]^+$ 286.0691. Found: 286.0686.



***cis*-7-(2-(Trimethylsilyl)ethoxy)-2-oxa-7-azabicyclo[3.2.0]heptan-6-one (19e)**

The title compound was synthesized according to general procedure **L** using phenyl 2-(trimethylsilyl)ethoxycarbamate **1f** (0.507 g, 2.00 mmol) followed by 2,3-dihydrofuran (3.0 mL, 40 mmol) and *i*-Pr_2NEt (0.052 g, 0.40 mmol) then MeCN (0.1 M). The reaction vessel was heated at 120 °C via microwave irradiation for 2.5 h. Upon completion the crude reaction mixture was concentrated under reduced pressure and the product was isolated using silica gel flash column chromatography (30% EtOAc/Hexanes). The product was isolated as a pale yellow oil (0.348 g, 76% yield).

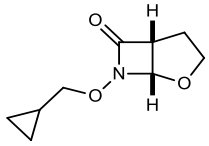
TLC R_f: 0.45 in 40% EtOAc/Hexanes

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.74 (d, *J* = 3.0 Hz, 1H), 4.25 (ddt, *J* = 9.5, 8.1, 0.7 Hz, 1H), 4.13 – 3.99 (m, 2H), 3.96 (ddd, *J* = 12.0, 9.8, 5.9 Hz, 1H), 3.44 (ddt, *J* = 8.4, 3.1, 0.6 Hz, 1H), 2.21 (ddt, *J* = 13.1, 5.6, 0.7 Hz, 1H), 1.78 (ddt, *J* = 13.1, 12.0, 8.3 Hz, 1H), 1.09 – 1.00 (m, 2H), 0.03 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3 (C), 91.2 (CH), 74.9 (CH_2), 66.8 (CH_2), 51.3 (CH), 24.8 (CH_2), 17.3 (CH_2), -1.2 (CH_3), -1.5 (CH_3).

IR (FTIR): 2951, 2882, 1766, 1500, 1442, 1362, 1250, 1214, 1069, 1039 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{10}H_{19}NO_3SiNa$ $[M+Na]^+$ 252.1032. Found: 252.1049.



***cis*-7-(Cyclopropylmethoxy)-2-oxa-7-azabicyclo[3.2.0]heptan-6-one (19f)**

The title compound was synthesized according to general procedure **L** using phenyl cyclopropylmethoxycarbamate **1ai** (0.207 g, 1.00 mmol) followed by 2,3-dihydrofuran (1.5 mL, 20 mmol) and *i*-Pr_2NEt (0.026 g, 0.20 mmol) then MeCN (0.1 M). The reaction vessel was heated at 120 °C via microwave irradiation for 2.5 h. Upon completion the crude reaction mixture was concentrated under reduced pressure and the product was isolated using silica gel flash column chromatography (45% EtOAc/Hexanes→100% EtOAc). The product was isolated as a pale yellow oil (0.146 g, 80% yield).

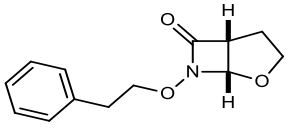
TLC R_f: 0.30 in 45% EtOAc/Hexanes

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.75 (d, *J* = 3.0 Hz, 1H), 4.24 (dd, *J* = 9.5, 8.1 Hz, 1H), 3.96 (ddd, *J* = 12.0, 9.5, 5.5 Hz, 1H), 3.81 (d, *J* = 7.3 Hz, 2H), 3.44 (dd, *J* = 8.3, 3.0 Hz, 1H), 2.21 (dd, *J* = 13.0, 5.6 Hz, 1H), 1.78 (ddt, *J* = 13.1, 12.0, 8.3 Hz, 1H), 1.15 (dddd, *J* = 15.3, 8.0, 4.0, 2.7 Hz, 1H), 0.70 – 0.56 (m, 2H), 0.38 – 0.26 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2 (C), 91.4 (CH), 81.6 (CH_2), 66.8 (CH_2), 51.4 (CH), 24.9 (CH_2), 9.5 (CH), 3.4 (CH_2), 3.1 (CH_2).

IR (FTIR): 3082, 2949, 2878, 1765, 1686, 1469, 1363, 1218, 1067 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_9H_{13}NO_3Na$ $[M+Na]^+$ 206.0793. Found: 206.0817.



***cis*-7-Phenethoxy-2-oxa-7-azabicyclo[3.2.0]heptan-6-one (19h)**

The title compound was synthesized according to general procedure **L** using phenyl phenethoxycarbamate **1af** (0.515 g, 2.00 mmol) followed by 2,3-dihydrofuran (3.0 mL, 40 mmol) and *i*-Pr_2NEt (0.052 g, 0.40 mmol) then MeCN (0.1 M). The reaction vessel was heated at 120 °C via microwave irradiation for 2.5 h. Upon completion the crude reaction mixture was concentrated under reduced pressure and the product was isolated using silica gel flash column chromatography (40% EtOAc/Hexanes). The product was isolated as an off-white solid (0.386 g, 83% yield).

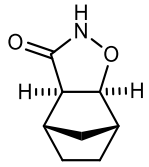
TLC R_f: 0.30 in 40% EtOAc/Hexanes

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 – 7.29 (m, 2H), 7.25 – 7.21 (m, 3H), 5.70 (d, *J* = 3.1 Hz, 1H), 4.33 – 4.11 (m, 3H), 3.97 (ddd, *J* = 12.0, 9.5, 5.6 Hz, 1H), 3.43 (dd, *J* = 8.4, 3.1 Hz, 1H), 3.00 (t, *J* = 7.3 Hz, 2H), 2.21 (dd, *J* = 13.2, 5.6 Hz, 1H), 1.78 (ddt, *J* = 13.1, 11.9, 8.3 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2 (C), 137.1 (C), 128.9 (CH), 128.6 (CH), 126.6 (CH), 91.3 (CH), 77.4 (CH_2), 66.8 (CH_2), 51.3 (CH), 35.0 (CH_2), 24.9 (CH_2).

IR (FTIR): 3026, 2946, 2880, 1768, 1495, 1453, 1362, 1066, 1046 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{13}H_{15}NO_3Na$ $[M+Na]^+$ 256.0950. Found: 256.0959.



Hexahydro-4,7-methanobenzo[*d*]isoxazol-3(2*H*)-one (20a)

The title compound was synthesized according to general procedure **K** using phenyl (*tert*-butyldiphenylsilyl)oxycarbamate **1ah** (0.391 g, 1.00 mmol), norbornene (4.71 g, 50.0 mmol) and MeCN (0.1 M) at 180 °C for 0.5 h. Upon completion the crude reaction mixture was concentrated under reduced pressure and the product was isolated using silica gel flash column chromatography (100% EtOAc). The product was isolated as a white solid (0.083 g, 54% yield).

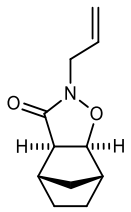
TLC R_f: 0.20 in 100% EtOAc

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.55 (d, *J* = 7.7 Hz, 1H), 2.74 (d, *J* = 7.6 Hz, 1H), 2.68 (d, *J* = 2.6 Hz, 1H), 2.54 (d, *J* = 4.3 Hz, 1H), 1.77–1.73 (m, 1H), 1.62–1.49 (m, 2H), 1.30–1.18 (m, 3H), 1.06–1.00 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.4 (C), 85.8 (CH), 52.3 (CH), 43.1 (CH), 39.2 (CH), 33.0 (CH), 27.6 (CH_2), 22.3 (CH_2)

IR (FTIR): 2966, 2869, 2741, 1673, 1633, 1359, 1297, 1034, 997, cm^{-1}.

HRMS (EI): Exact mass calcd for $C_8H_{11}NO_2$ $[M]^+$ 153.0790. Found: 153.0807.



2-Allylhexahydro-4,7-methanobenzo[*d*]isoxazol-3(2*H*)-one (20c)

The title compound was synthesized according to general procedure **K** using phenyl allyloxycarbamate **1e** (0.193 g, 1.00 mmol), norbornene (4.71 g, 50.0 mmol) and MeCN (0.1 M) at 180 °C for 2 h. Upon completion the crude reaction mixture was concentrated under reduced pressure and the product was isolated using silica gel flash column chromatography (100% EtOAc). The product was isolated as a clear oil (0.120 g, 62% yield).

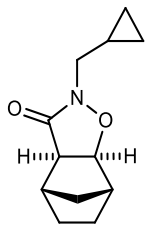
TLC R_f: 0.58 in 50% EtOAc/Hexanes

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.75 (ddt, *J* = 17.1, 10.2, 6.0 Hz, 1H), 5.26 (dq, *J* = 17.1, 1.4 Hz, 1H), 5.19 (dq, *J* = 10.2, 1.3 Hz, 1H), 4.39 (dt, *J* = 7.7, 1.2 Hz, 1H), 4.11–4.00 (m, 2H), 2.74 (d, *J* = 7.6 Hz, 1H), 2.67–2-65 (m, 1H), 2.49 (d, *J* = 3.4 Hz, 1H), 1.61–1.46 (m, 3H), 1.24–1.20 (m, 1H), 1.20–1.12 (m, 1H), 1.06–0.97 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8 (C), 131.2 (CH), 118.8 (CH_2), 82.6 (CH), 52.7 (CH), 46.9 (CH_2), 42.8 (CH), 39.5 (CH), 32.9 (CH_2), 27.5 (CH_2), 22.3 (CH_2).

IR (FTIR): 3415, 3083, 2965, 2877, 1667, 1447, 1411, 1331, 1252, 1047, 974 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{11}H_{15}NO_2$ $[M]^+$ 193.1103. Found: 193.1090.



2-(Cyclopropylmethyl)hexahydro-4,7-methanobenzo[*d*]isoxazol-3(2*H*)-one (20d)

The title compound was synthesized according to general procedure **K** using phenyl cyclopropylmethoxycarbamate **1ai** (0.207 g, 1.00 mmol), norbornene (4.71 g, 50.0 mmol) and MeCN (0.1 M) at 180 °C for 2 h. Upon completion the crude reaction mixture was concentrated under reduced pressure and the product was isolated using silica gel flash column chromatography (100% EtOAc). The product was isolated as a clear oil (0.020 g, 10% yield).

TLC R_f: 0.56 in 50% EtOAc/Hexanes

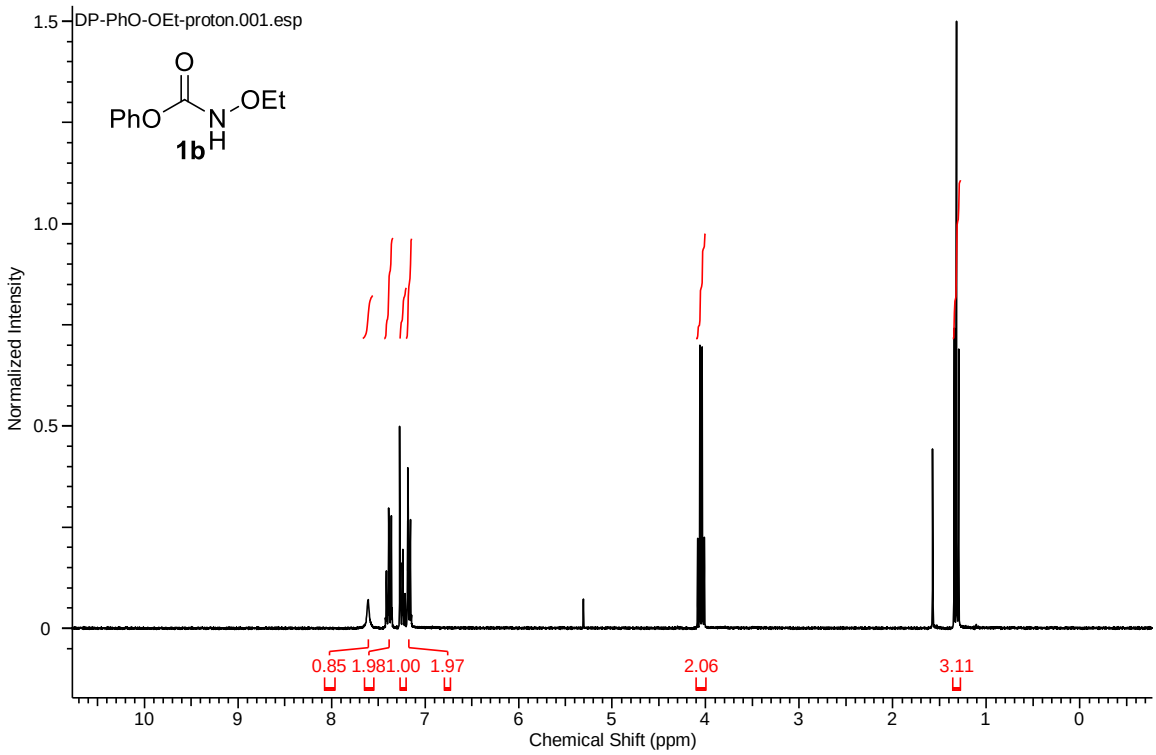
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.74–3.66 (m, 2H), 3.64 (d, *J* = 3.4 Hz, 1H), 2.66 (dt, *J* = 3.2, 1.5 Hz, 1H), 2.58 (dd, *J* = 3.2, 1.4 Hz, 1H), 2.48 (dd, *J* = 4.1, 1.3 Hz, 1H), 1.69–1.49 (m, 3H), 1.22–1.19 (m, 2H), 1.15–1.01 (m, 3H), 0.62–0.54 (m, 2H), 0.28–0.24 (m, 2H).

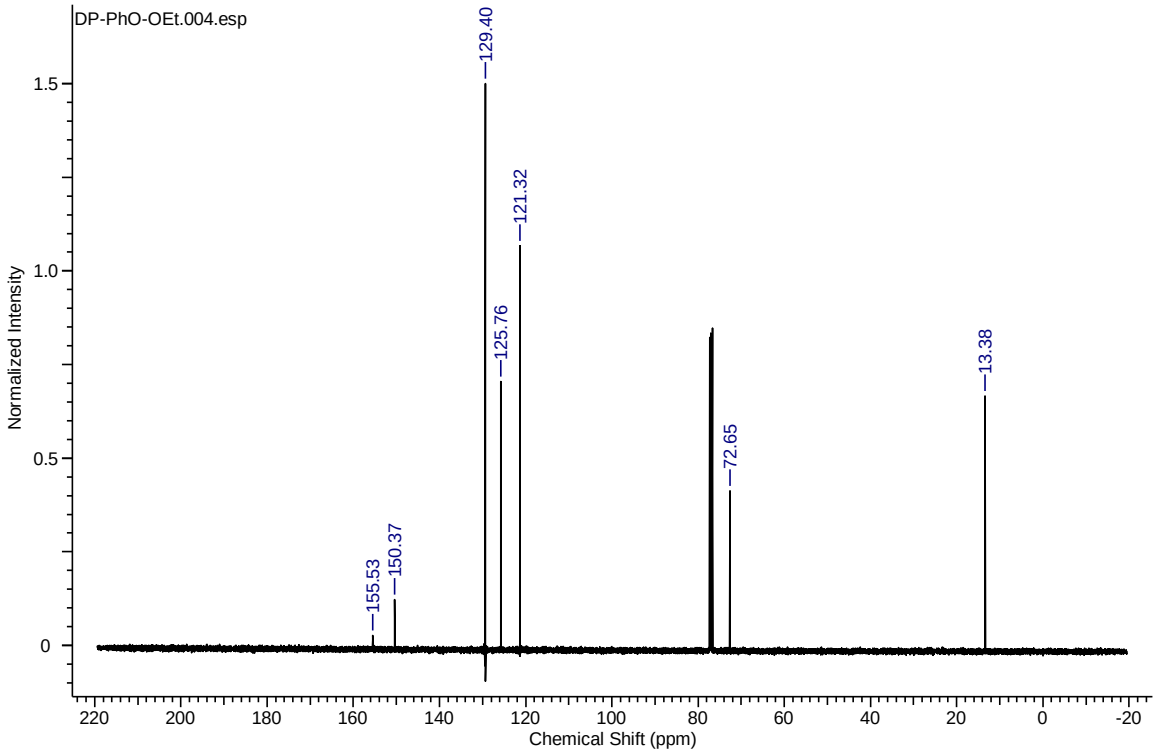
^{13}C NMR (100 MHz, $CDCl_3$): δ 165.8 (C), 80.6 (CH_2), 63.4 (CH), 52.1 (CH), 36.5 (CH), 35.5 (CH), 30.9 (CH_2), 27.3 (CH_2), 24.7 (CH_2), 9.7 (CH), 3.5 (CH_2), 3.0 (CH_2).

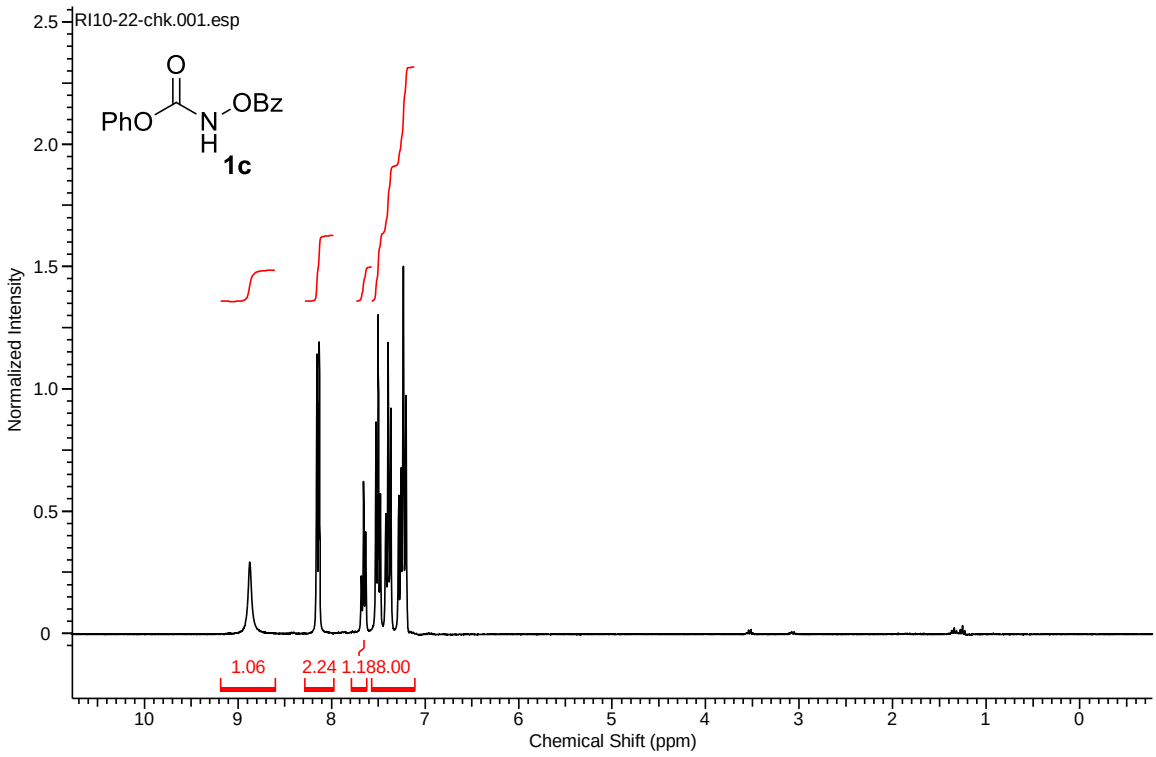
IR (FTIR): 2960, 2877, 2252, 1759, 1660, 1454, 1375, 1210, 1114 cm^{-1}.

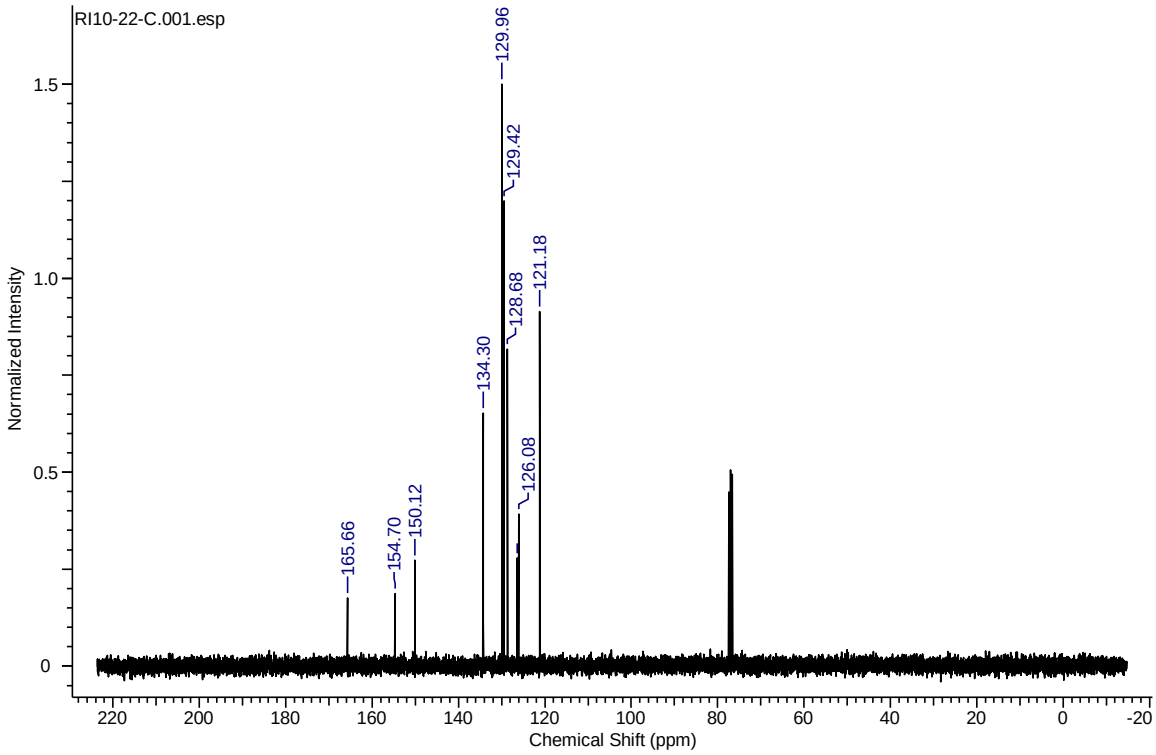
HRMS (EI): Exact mass calcd for $C_{12}H_{17}NO_2$ $[M]^+$ 207.1259. Found: N/A.

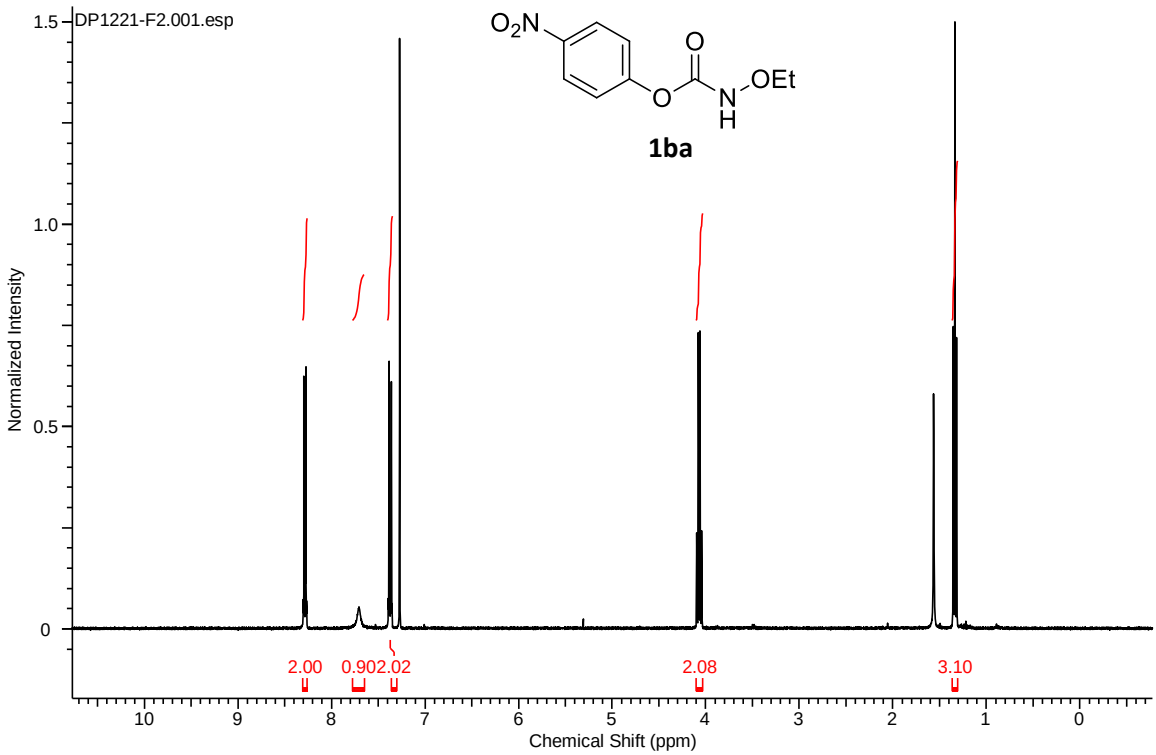
6.2.3 NMR spectra

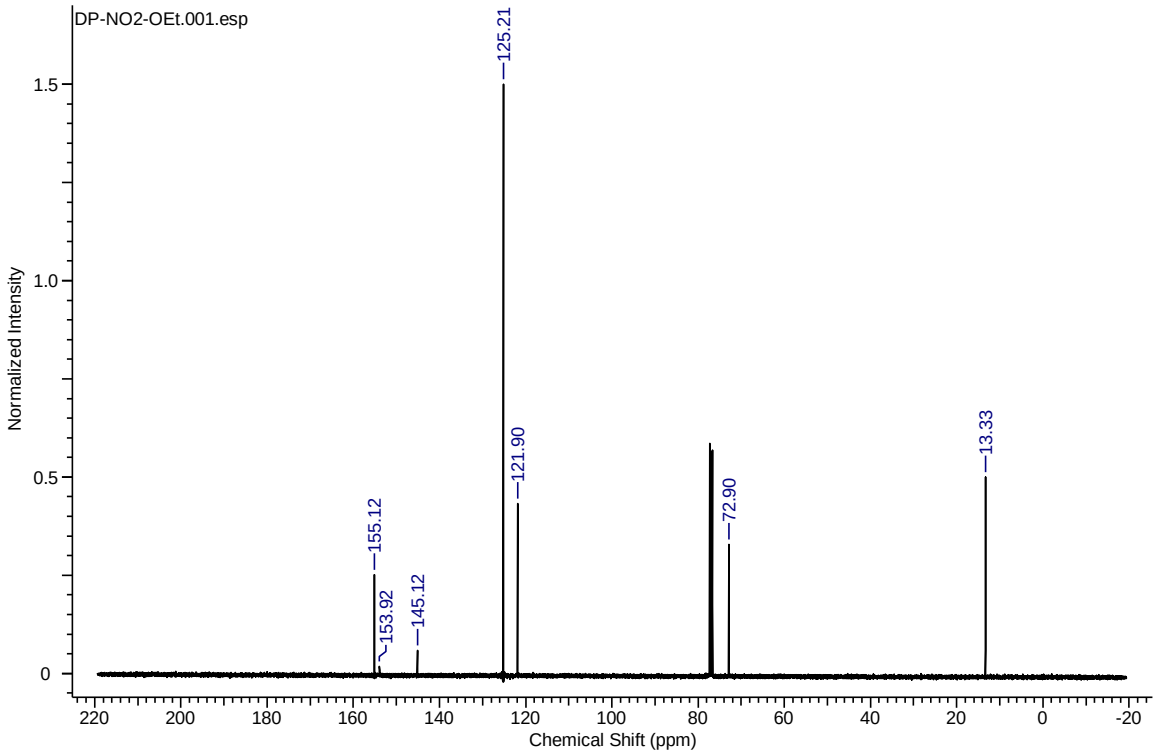


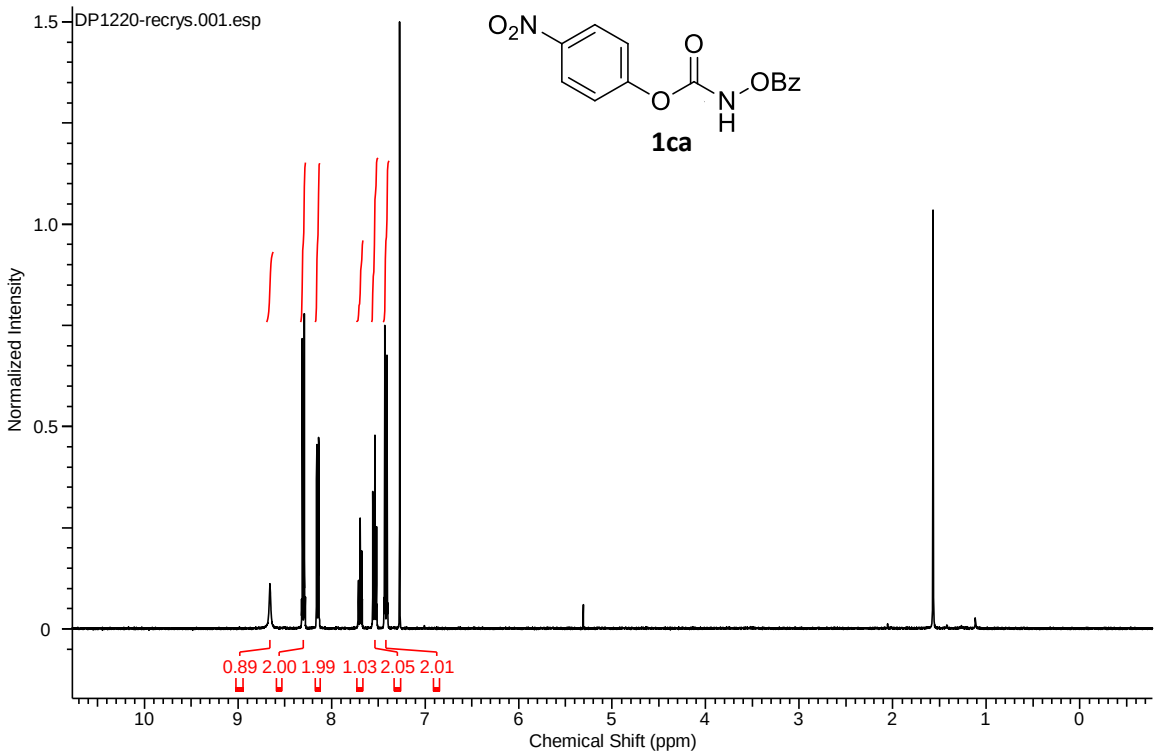


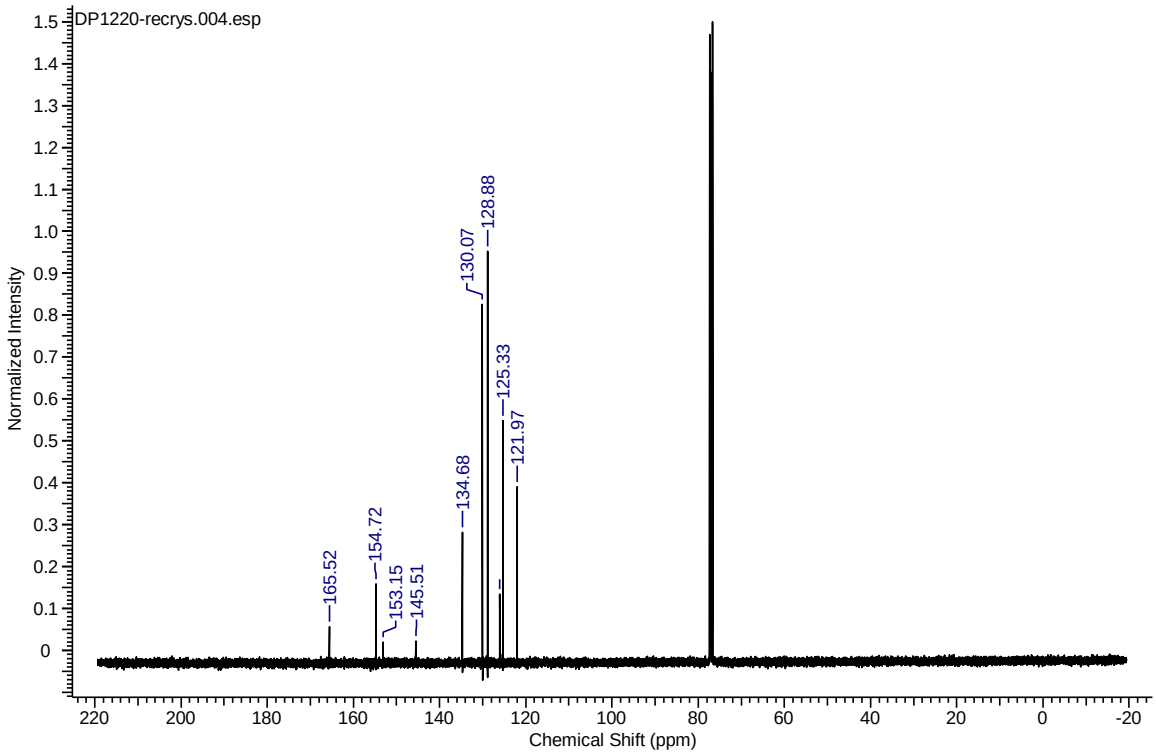

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H
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9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

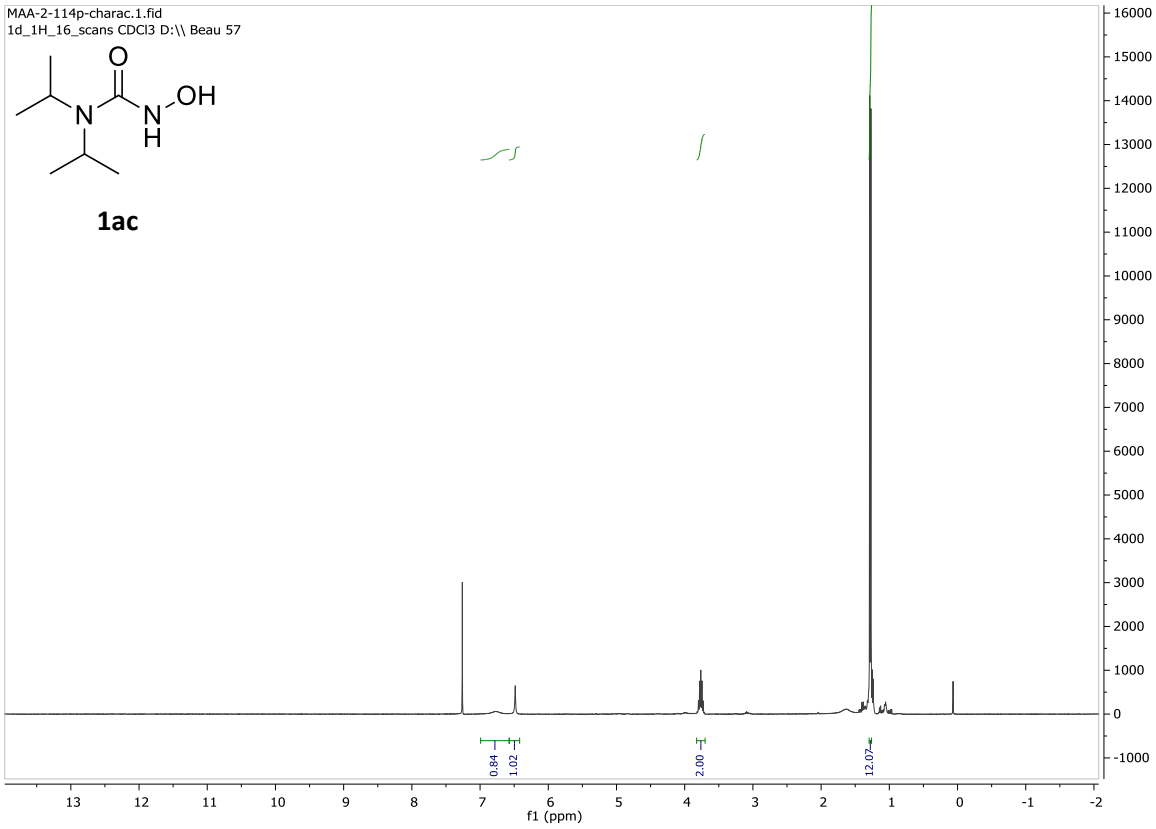

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140
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100
80
60
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20
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-20
Chemical Shift (ppm)

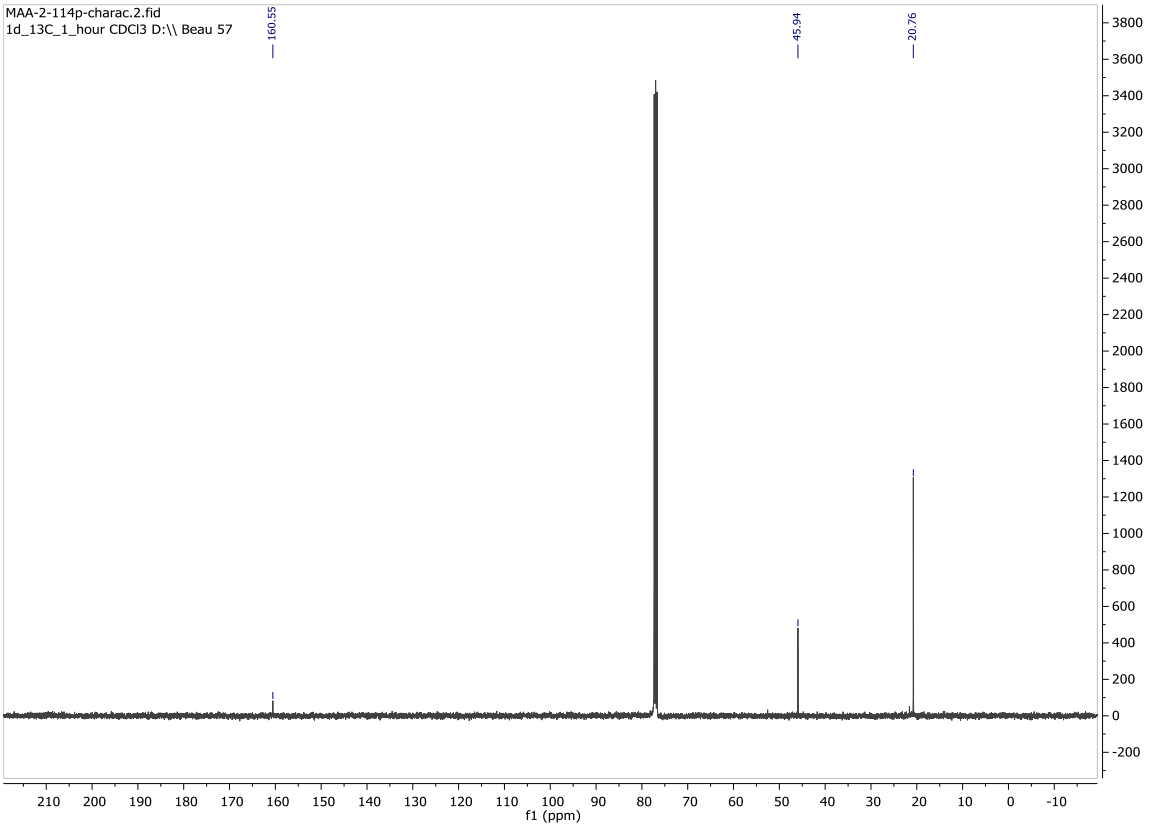

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9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

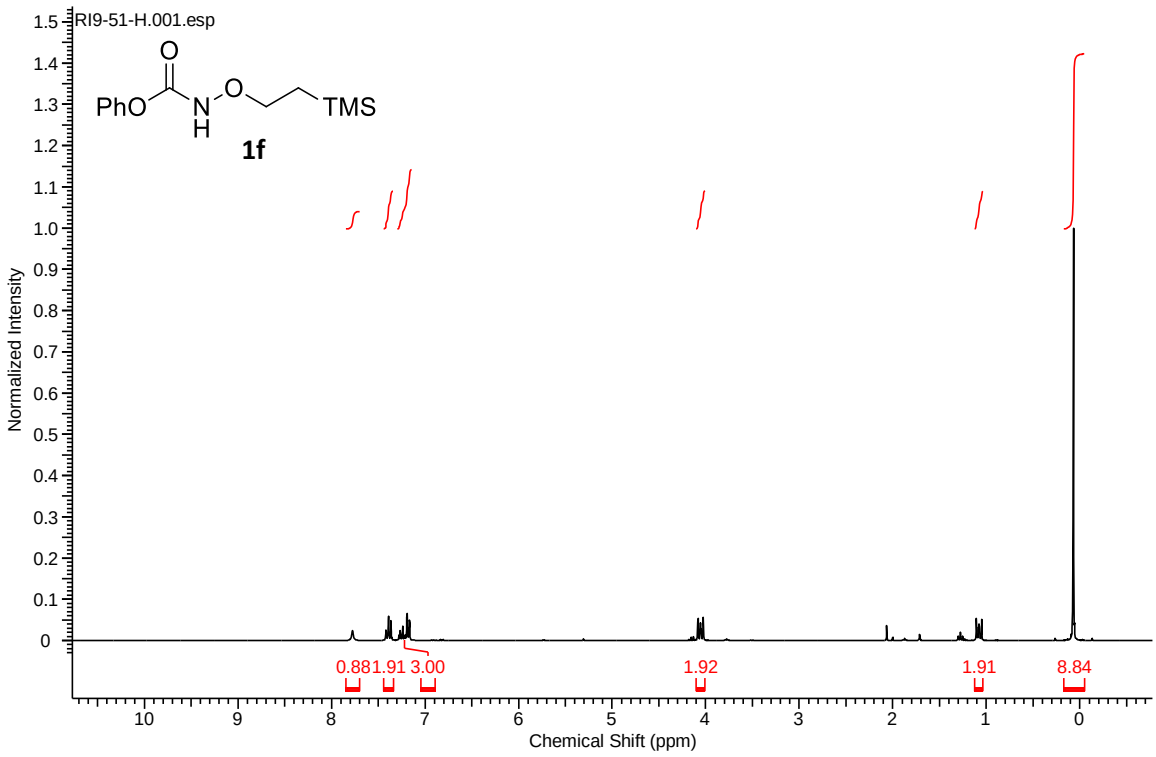

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145.12
72.90
13.33
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

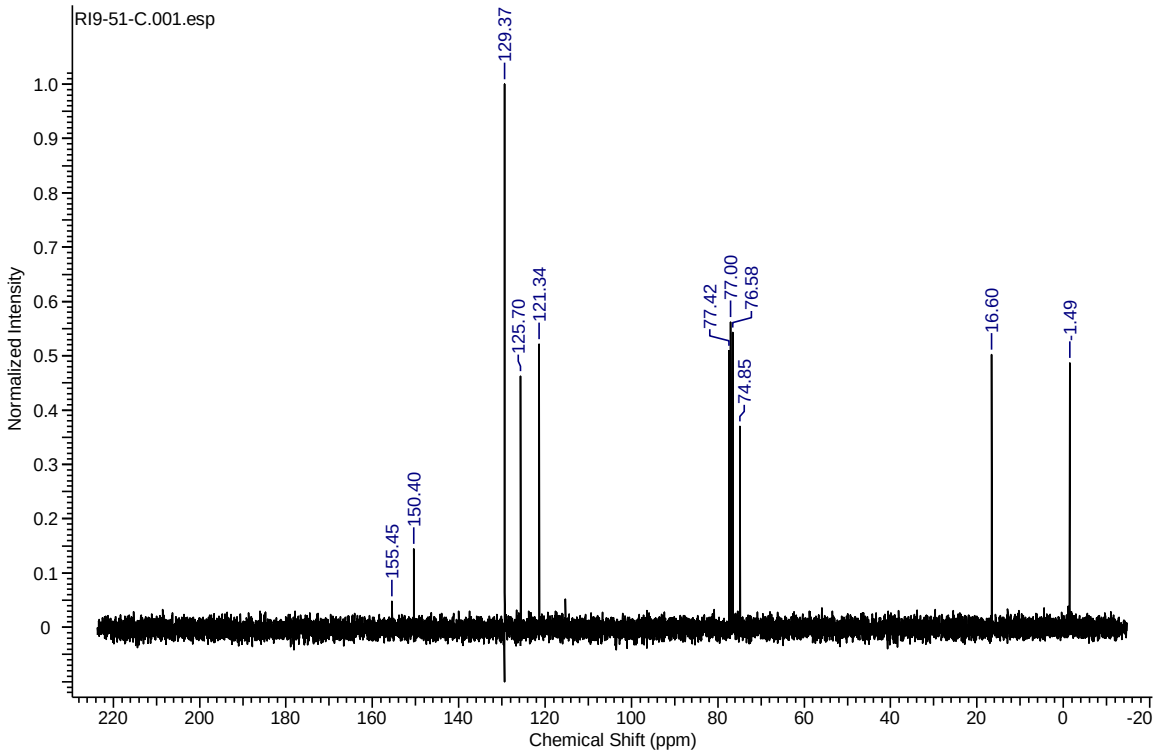

DP1220-recrys.001.esp
O_2N
O
O
N
H
OBz
1ca
Normalized Intensity
0.89 2.00 1.99 1.03 2.05 2.01
Chemical Shift (ppm)

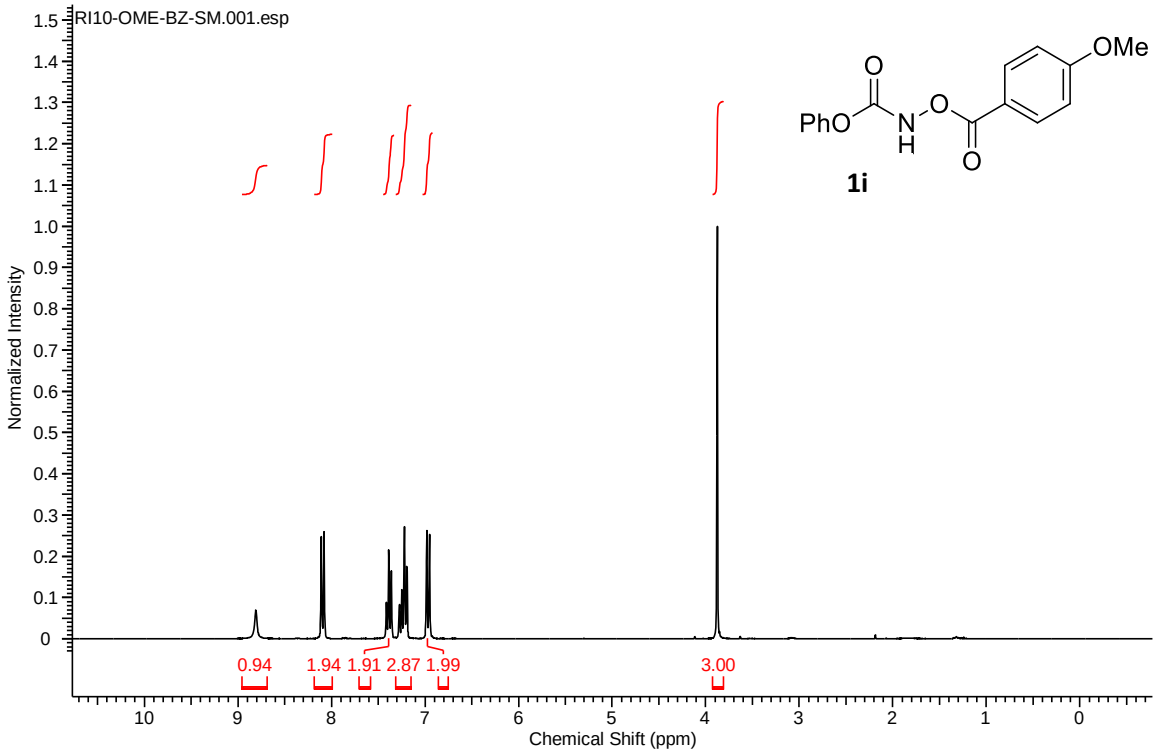

DP1220-recrys.004.esp
Normalized Intensity
165.52
154.72
153.15
145.51
134.68
130.07
128.88
125.33
121.97
Chemical Shift (ppm)

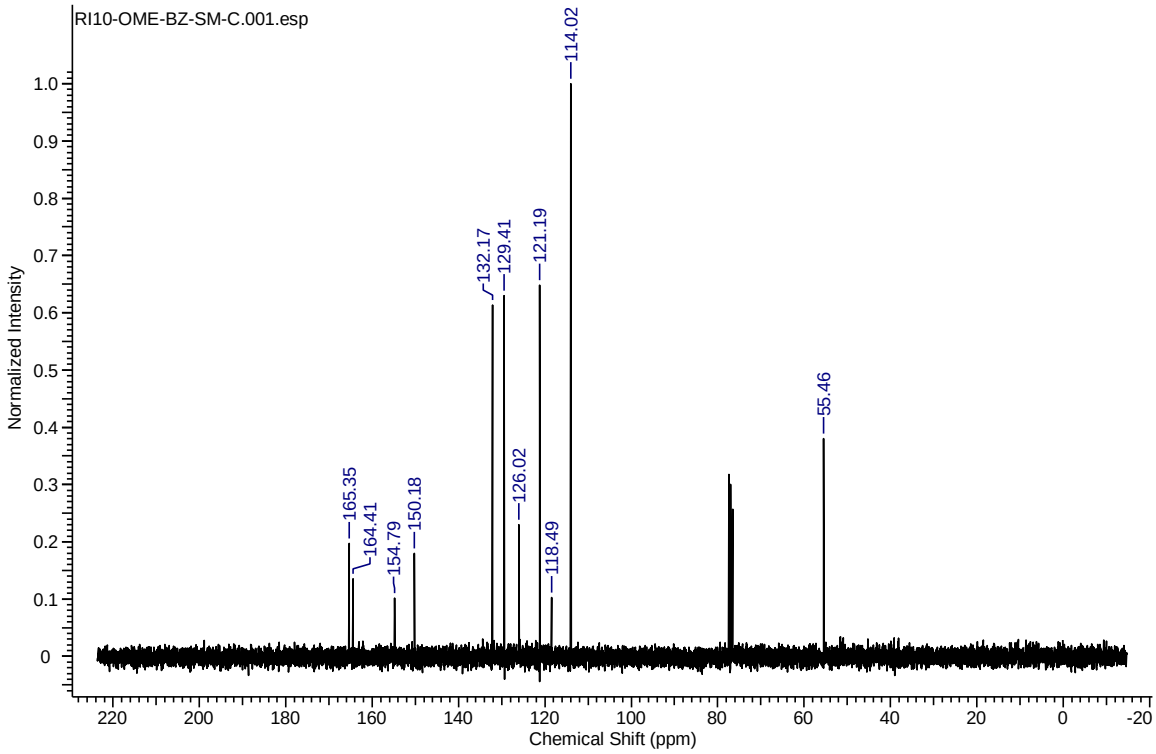

MAA-2-114p-charac.1.fid
1d_1H_16_scans CDCl3 D:\\ Beau 57
O
N
N
H
OH
1ac
0.84
1.02
2.00
12.07
f1 (ppm)

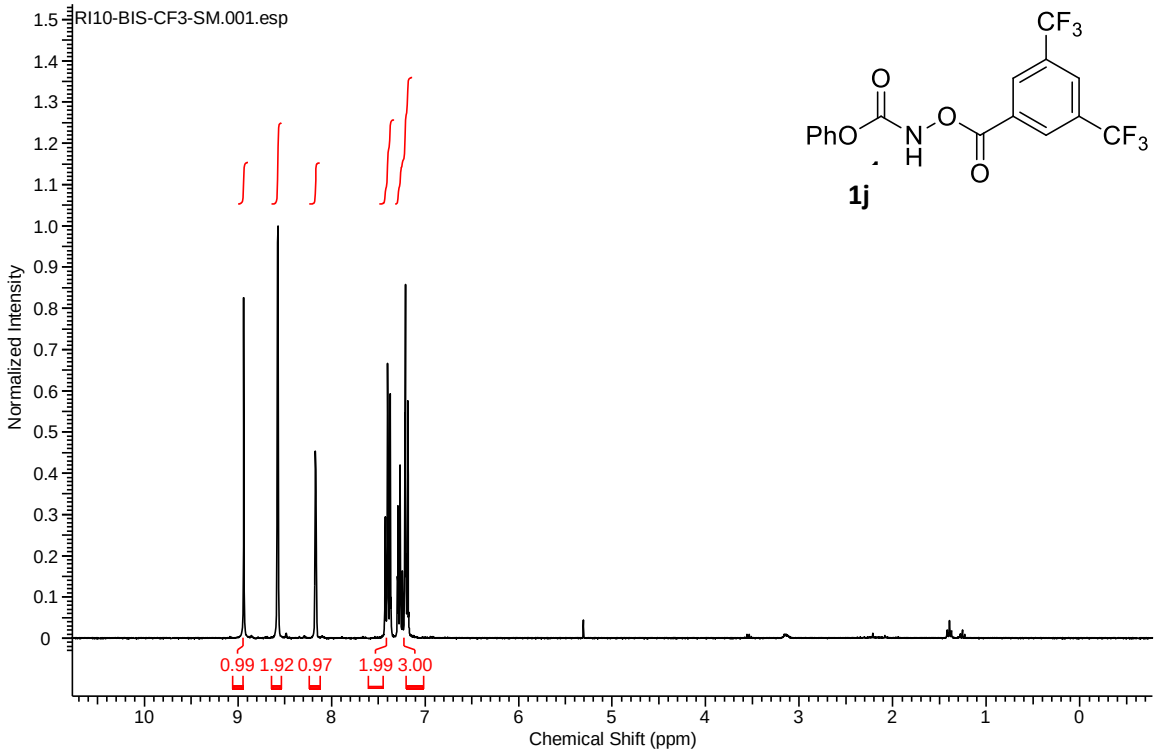

MAA-2-114p-charac.2.fid
1d_13C_1_hour CDCl3 D:\\ Beau 57
160.55
45.94
20.76
f1 (ppm)

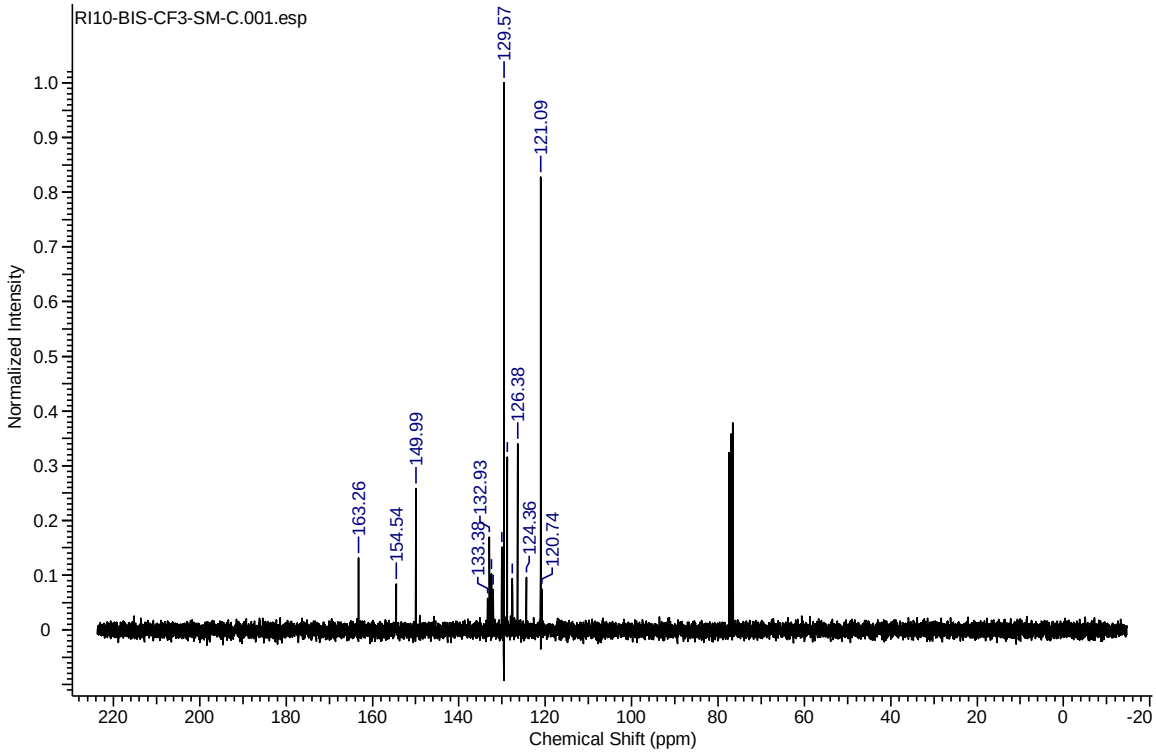

RI9-51-H.001.esp
PhO
O
N
H
O
TMS
1f
Normalized Intensity
0.88 1.91 3.00
1.92
1.91
8.84
Chemical Shift (ppm)

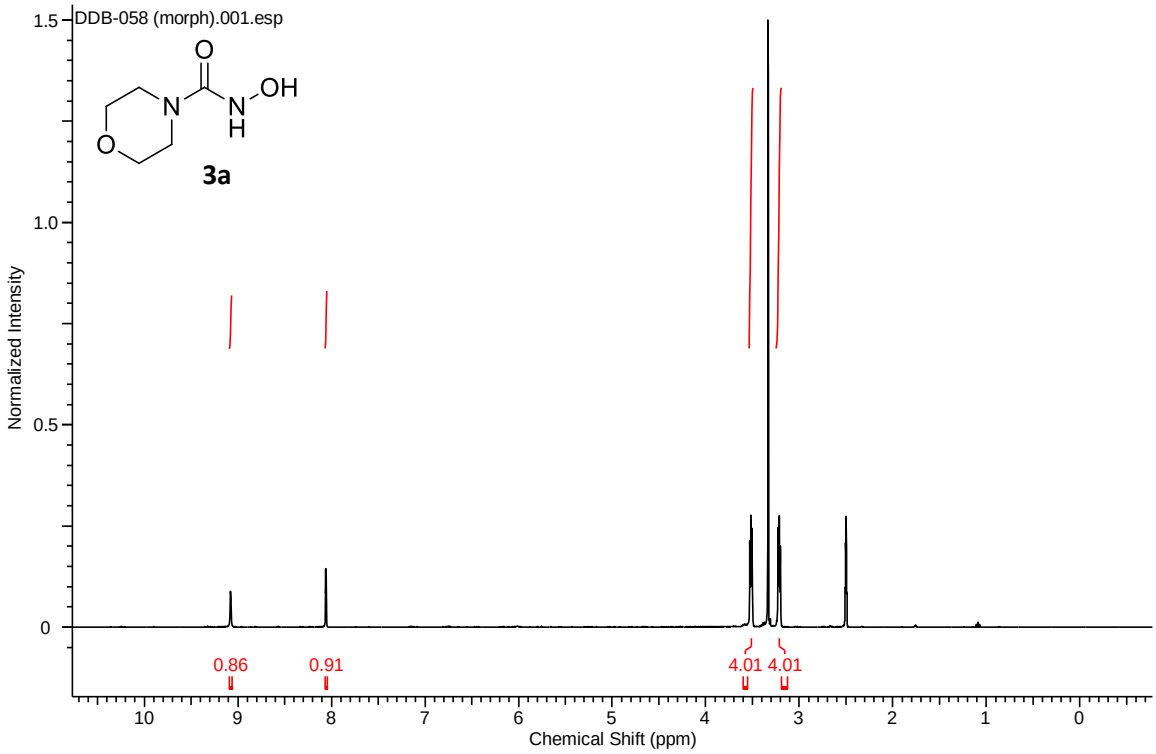

RI9-51-C.001.esp
129.37
125.70
121.34
77.42
77.00
76.58
74.85
155.45
150.40
16.60
1.49
Normalized Intensity
Chemical Shift (ppm)

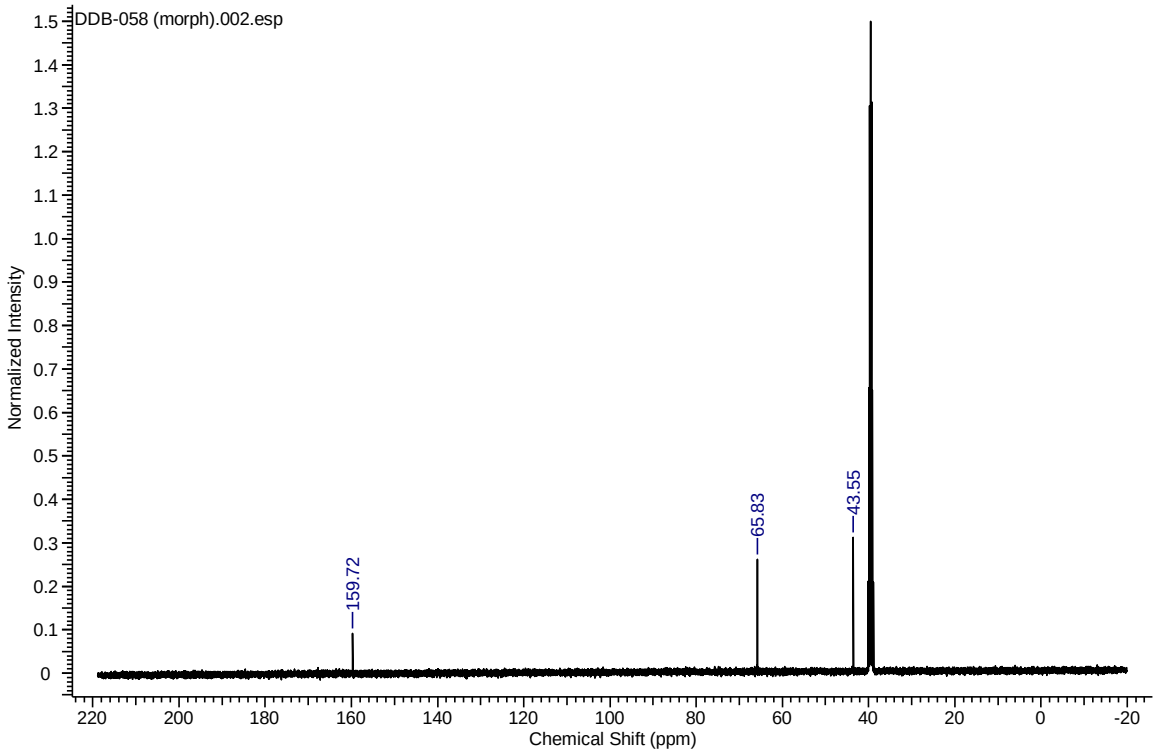

RI10-OME-BZ-SM.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.94
1.94
1.91
2.87
1.99
3.00
PhO
O
N
H
O
O
OMe
1i

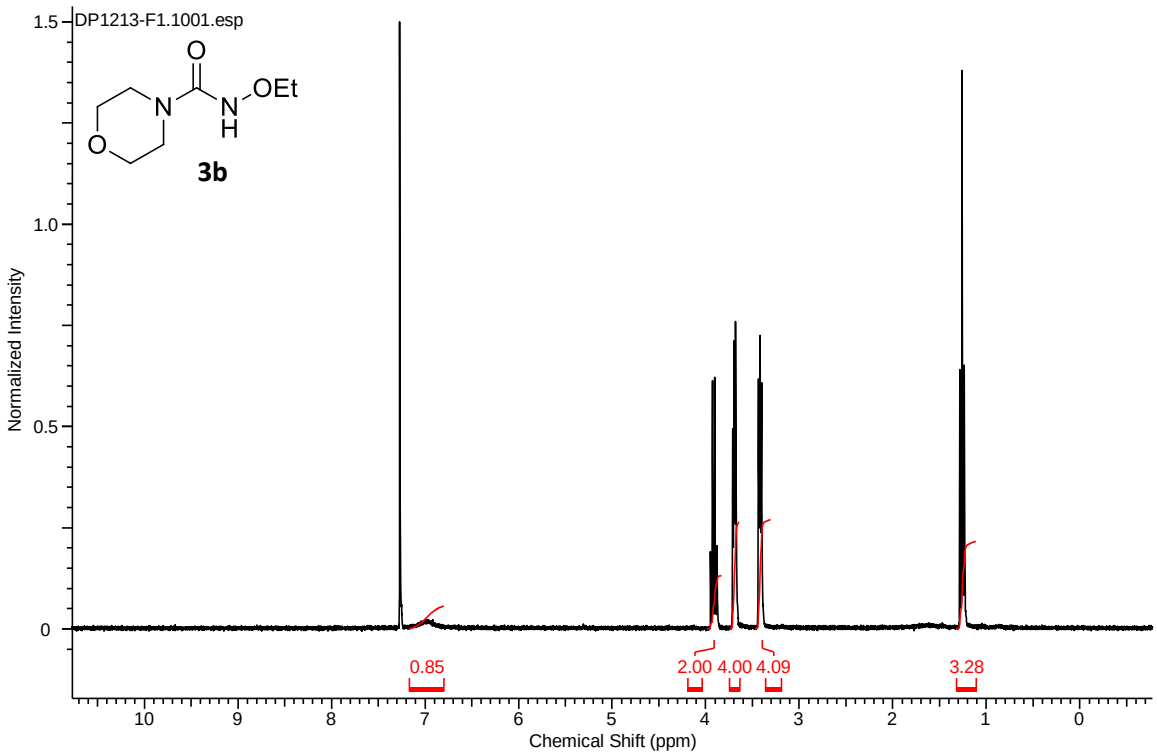

RI10-OME-BZ-SM-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
165.35
164.41
154.79
150.18
132.17
129.41
126.02
121.19
118.49
114.02
55.46

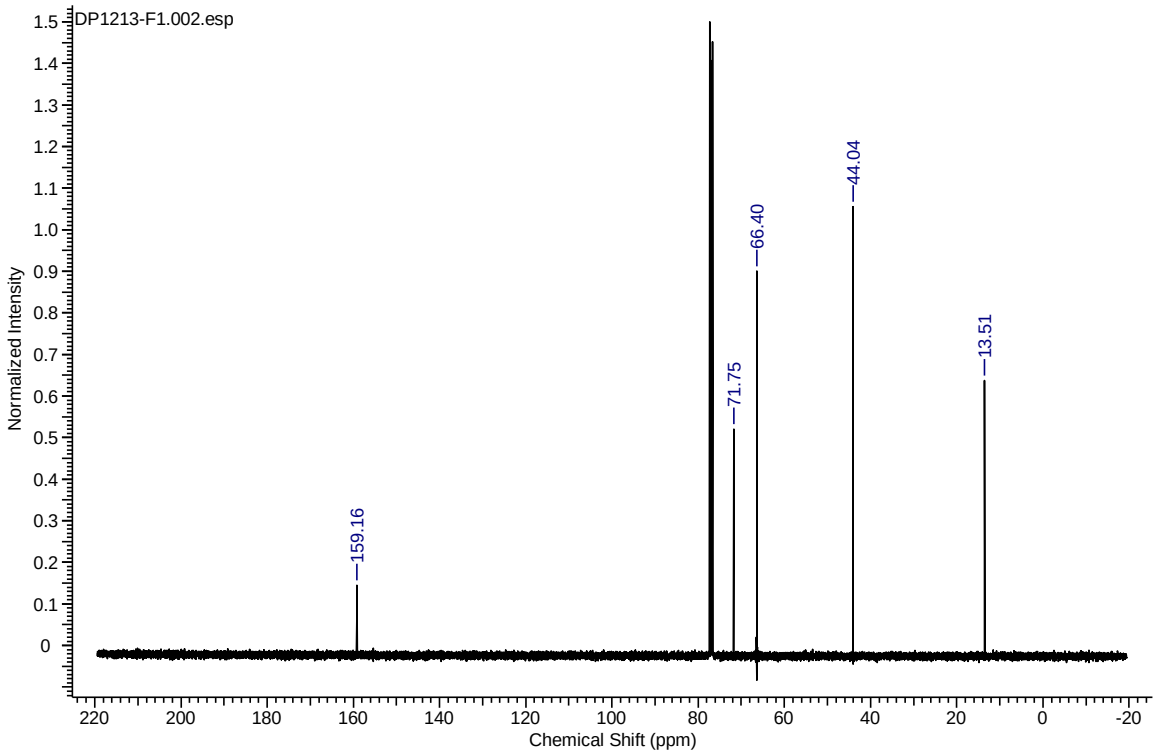

RI10-BIS-CF3-SM.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.99 1.92 0.97 1.99 3.00
PhO
O
N
H
O
O
CF3
CF3
1j

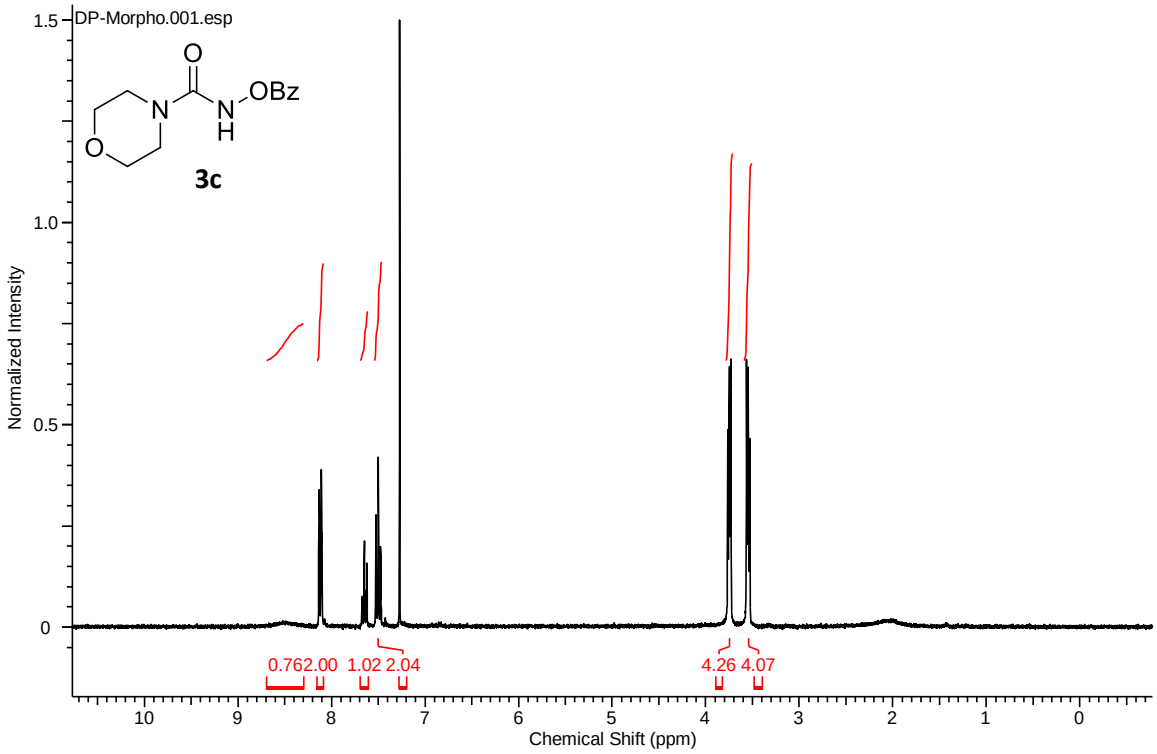

RI10-BIS-CF3-SM-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
129.57
121.09
126.38
149.99
163.26
154.54
133.38
132.93
124.36
120.74

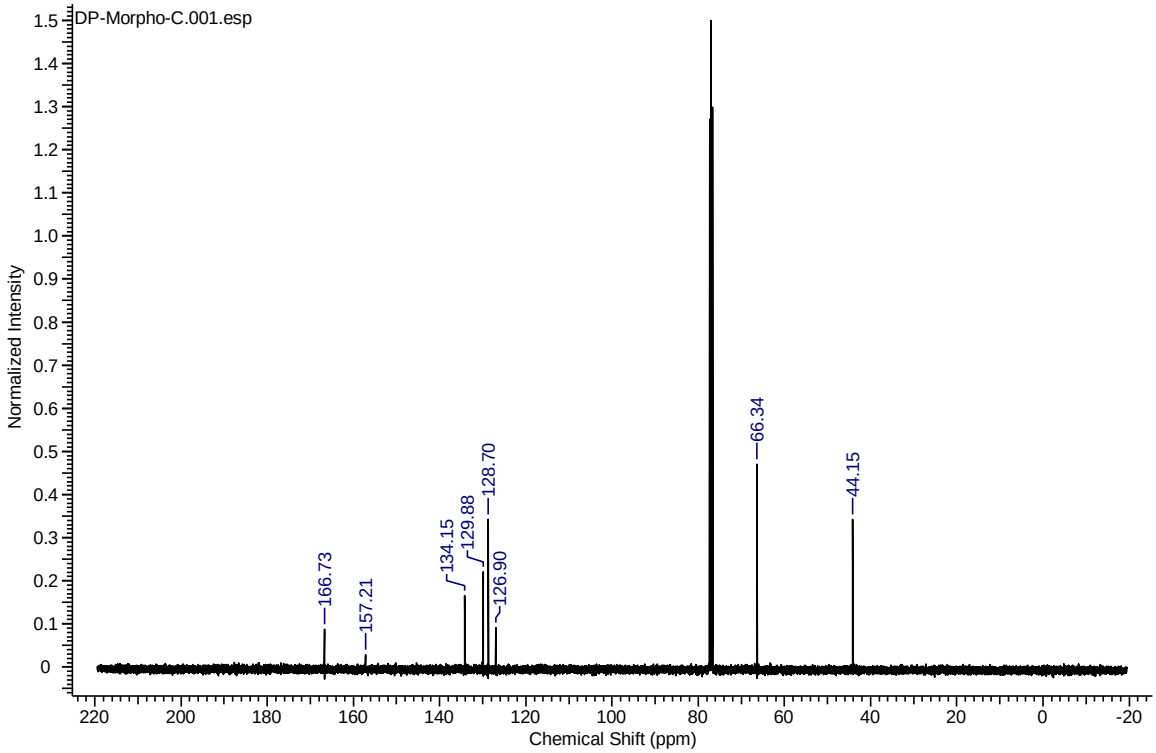

DDB-058 (morph).001.esp
O
N
N
OH
H
O
3a
Normalized Intensity
1.5
1.0
0.5
0
0.86
0.91
4.01
4.01
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

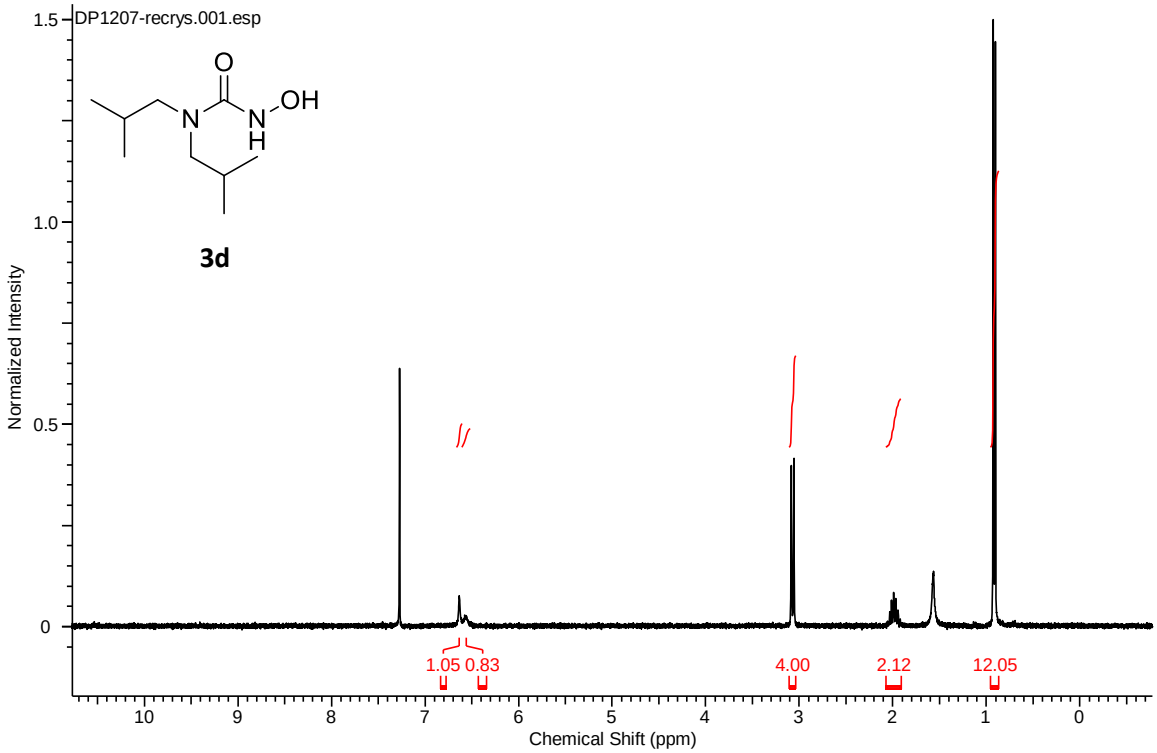

DDB-058 (morph).002.esp
Normalized Intensity
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
159.72
65.83
43.55
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

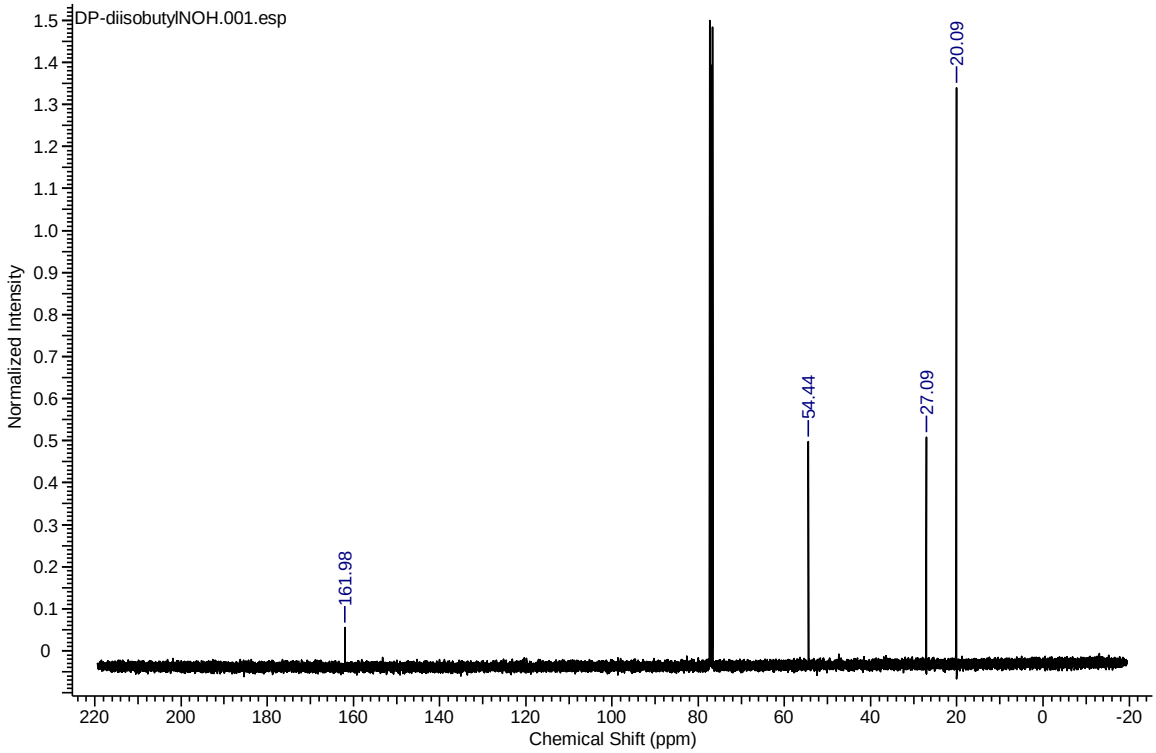

DP1213-F1.1001.esp
O
N
N
OEt
H
O
3b
Normalized Intensity
1.5
1.0
0.5
0
0.85
2.00
4.00
4.09
3.28
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

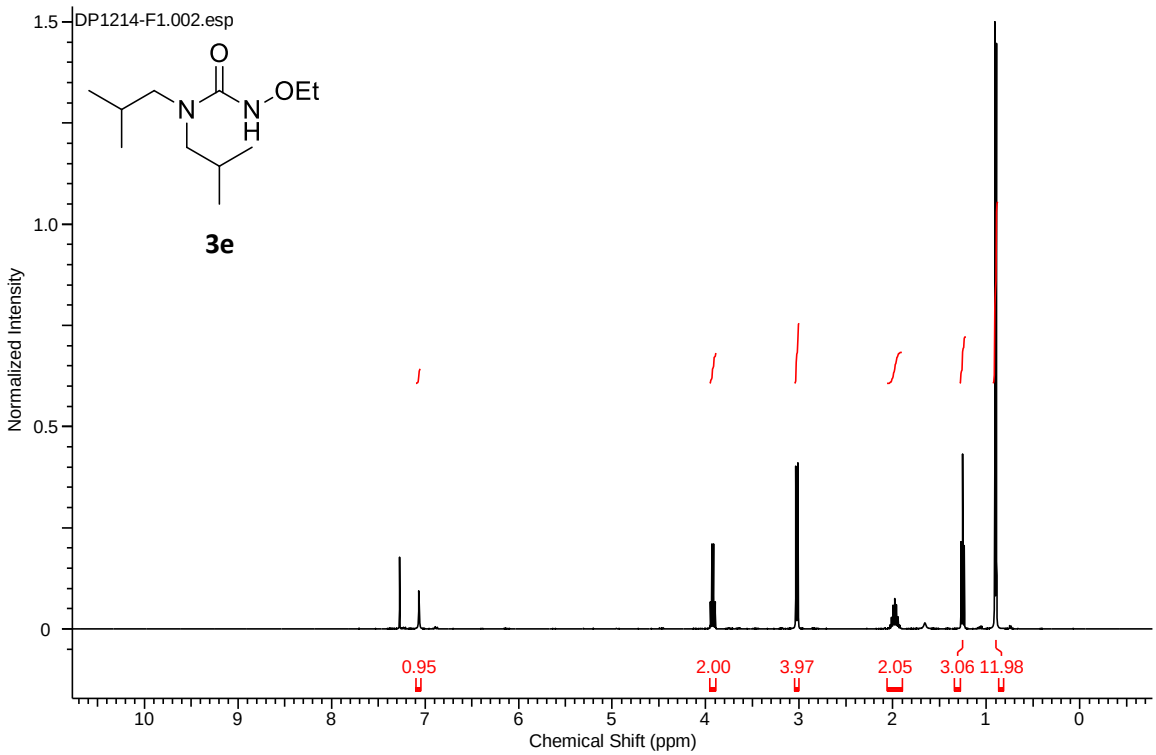

DP1213-F1.002.esp
Normalized Intensity
159.16
71.75
66.40
44.04
13.51
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

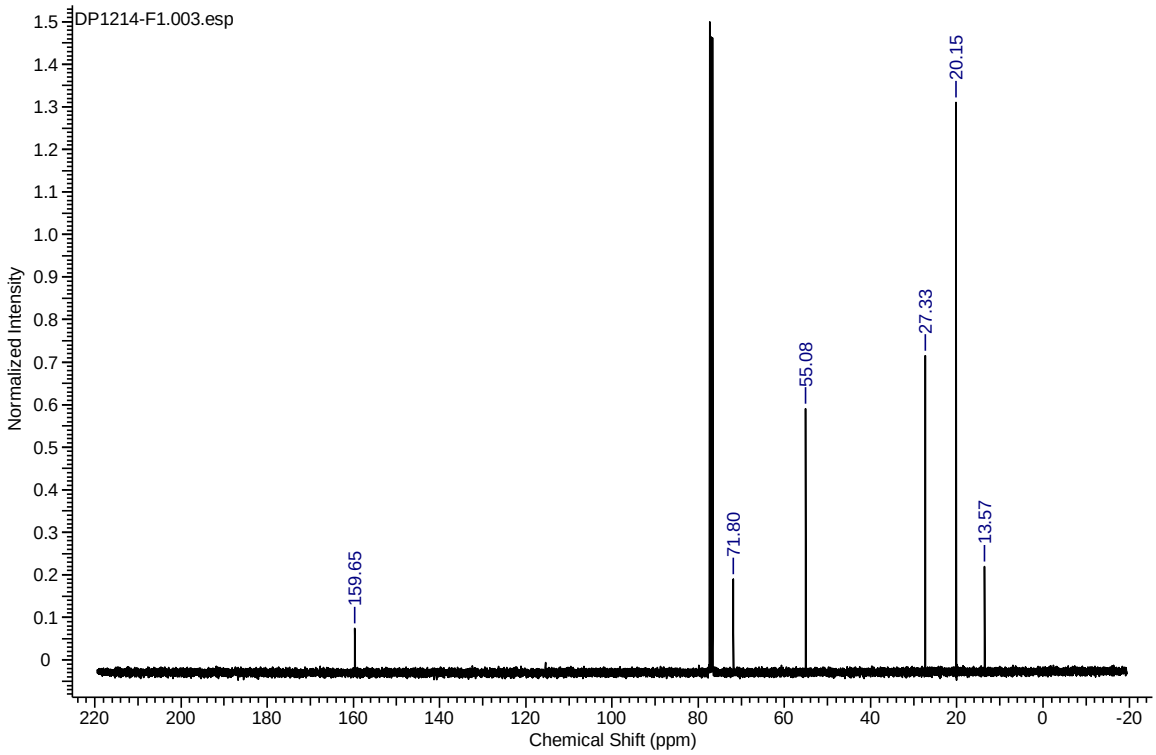

DP-Morpho.001.esp
O
N
N
H
OBz
O
3c
Normalized Intensity
1.5
1.0
0.5
0
0.76
2.00
1.02
2.04
4.26
4.07
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

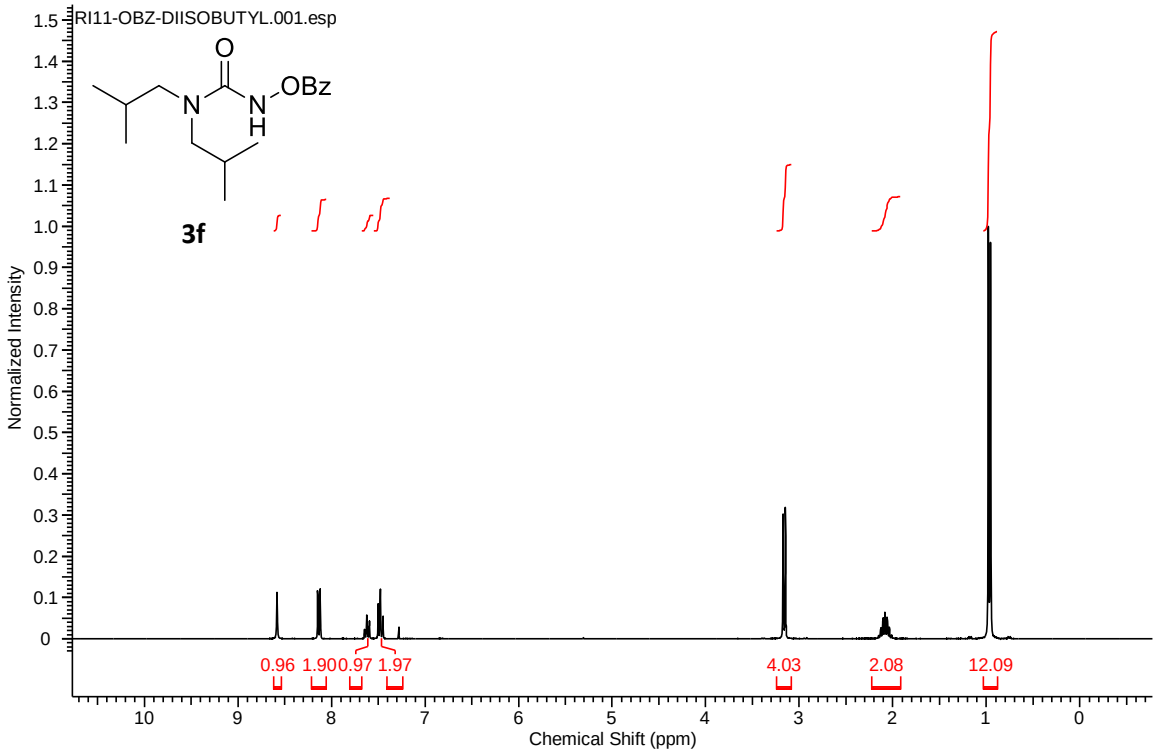

DP-Morpho-C.001.esp
Normalized Intensity
166.73
157.21
134.15
129.88
128.70
126.90
66.34
44.15
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

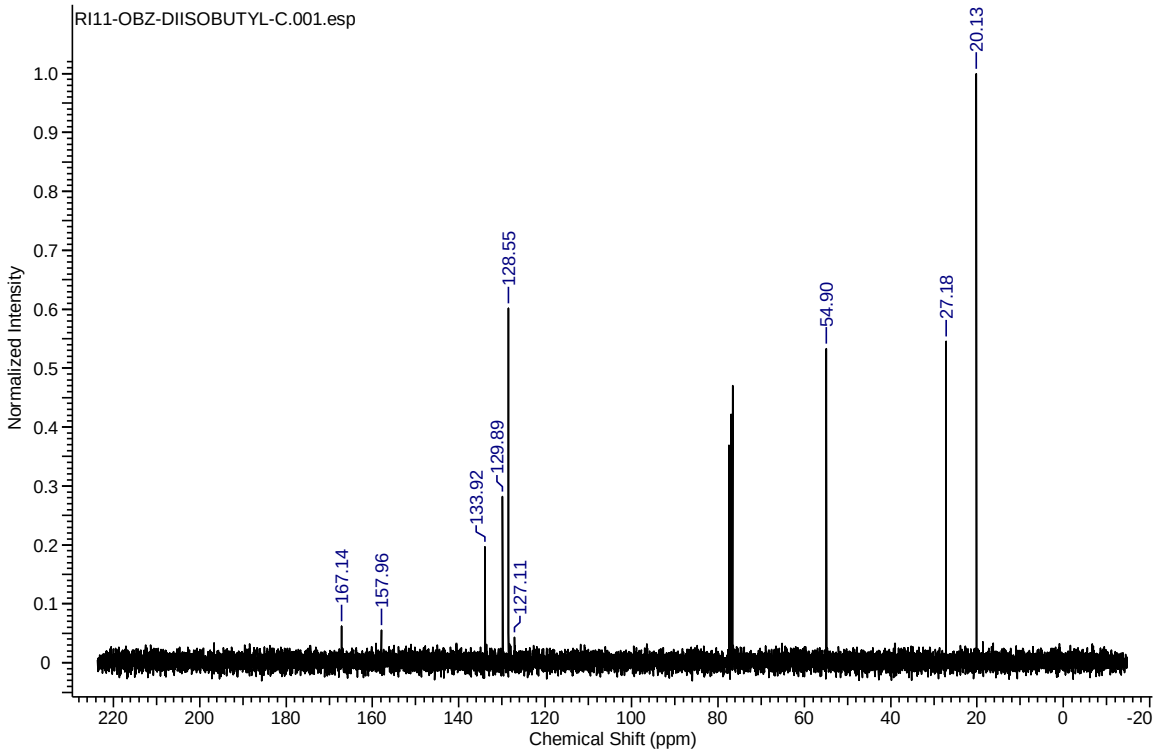

DP1207-recrys.001.esp
O
N
N
H
OH
3d
Normalized Intensity
1.05
0.83
4.00
2.12
12.05
Chemical Shift (ppm)

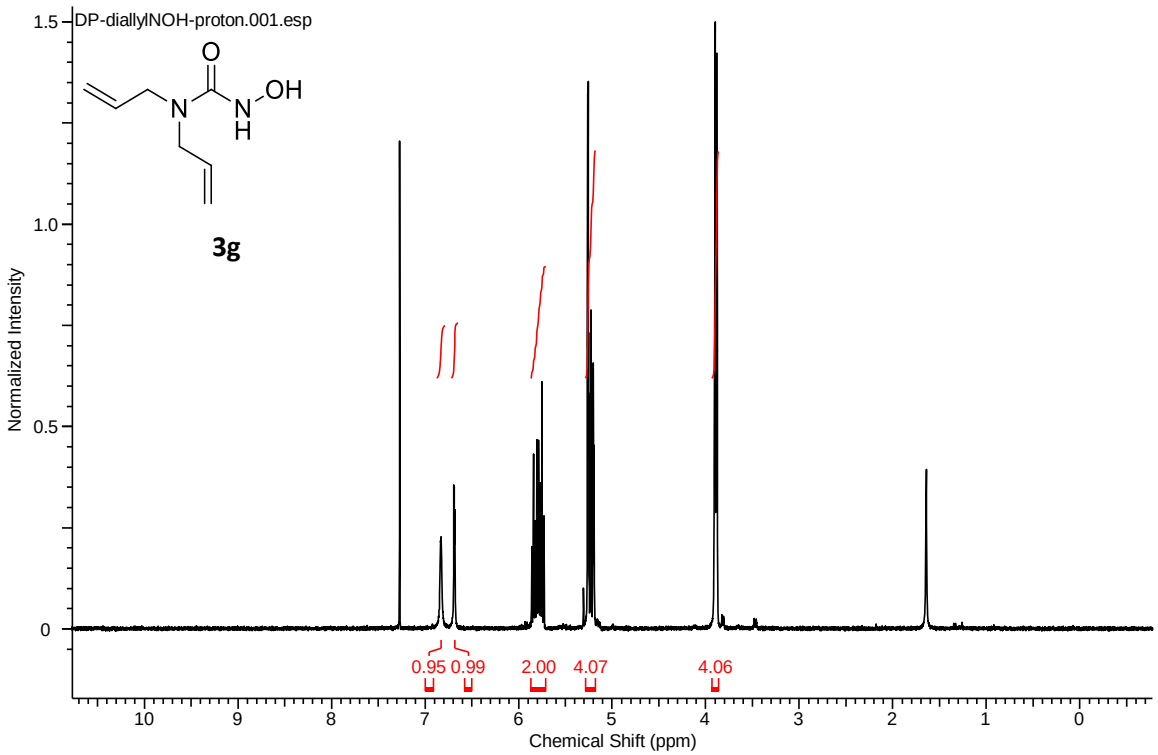

DP-diisobutylNOH.001.esp
161.98
54.44
27.09
20.09
Normalized Intensity
Chemical Shift (ppm)

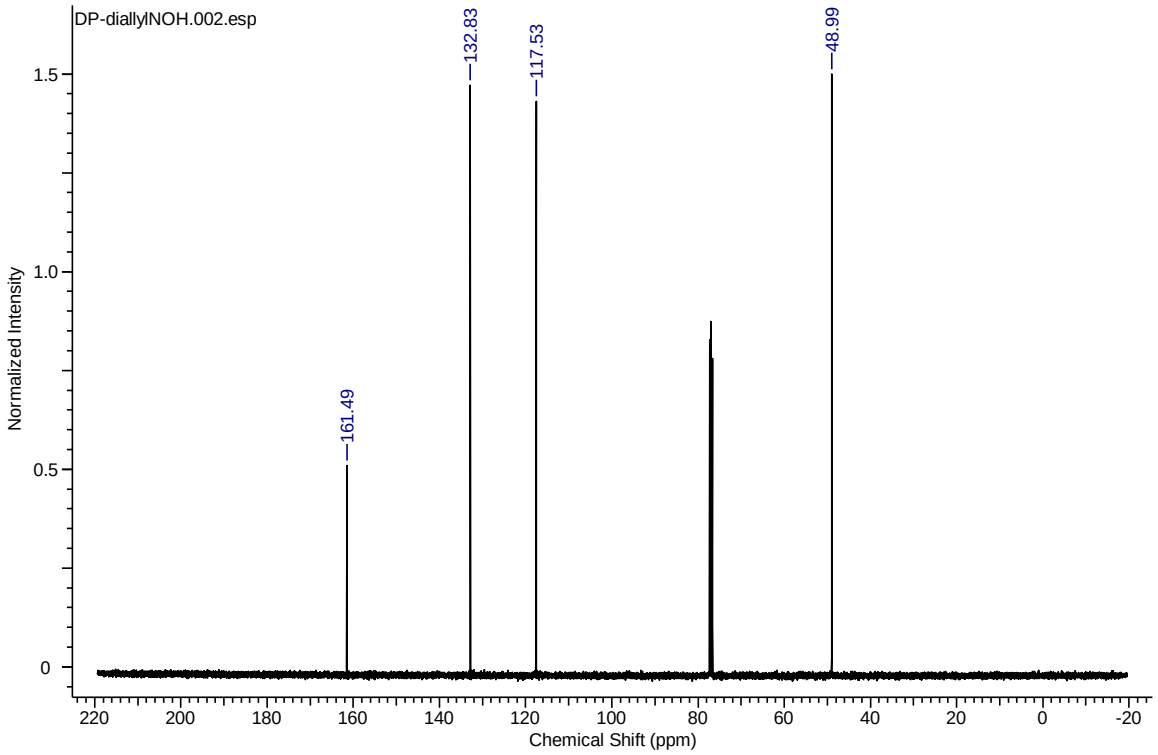

DP1214-F1.002.esp
O
N
N
H
OEt
3e
Normalized Intensity
1.5
1.0
0.5
0
0.95
2.00
3.97
2.05
3.06
11.98
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

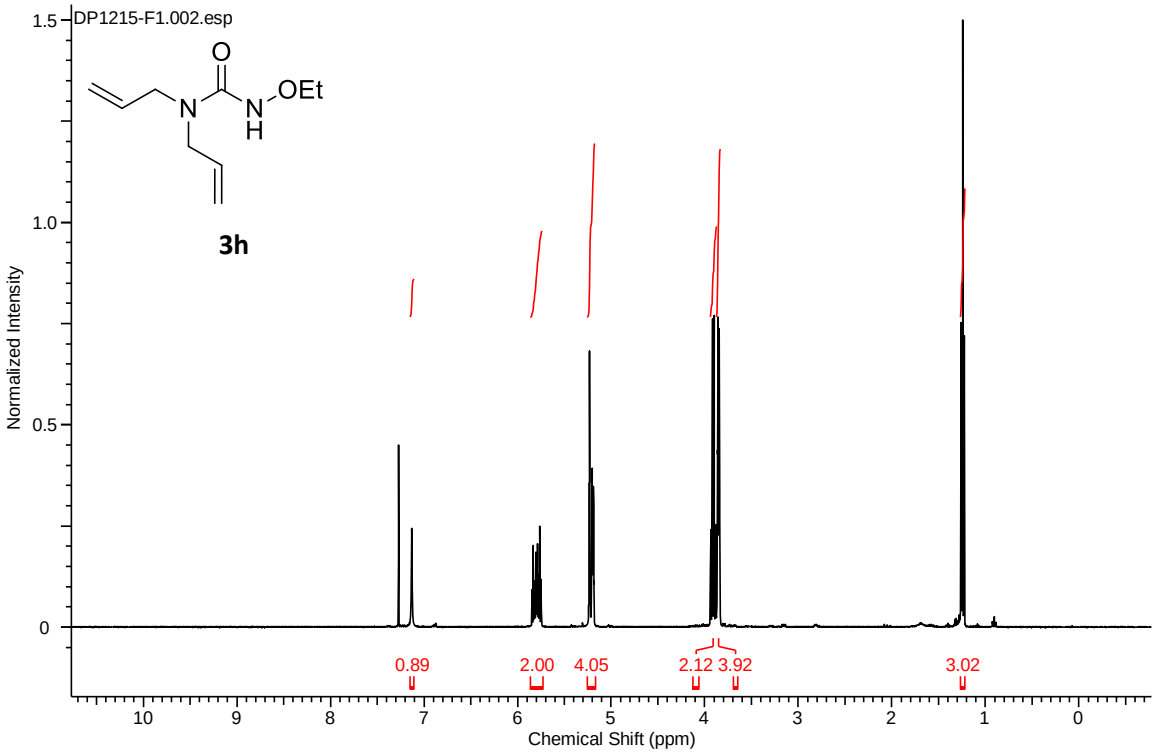

DP1214-F1.003.esp
Normalized Intensity
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
159.65
71.80
55.08
27.33
20.15
13.57
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

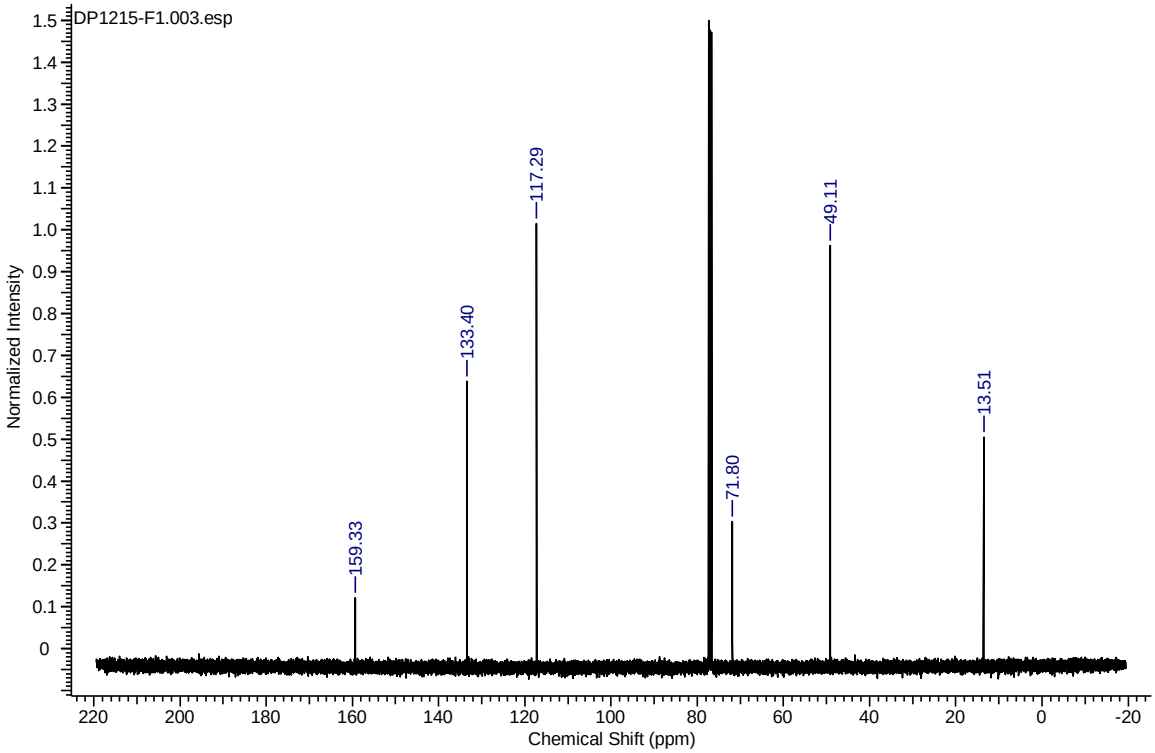

RI11-OBZ-DIISOBUTYL.001.esp
O
N
N
H
OBz
3f
Normalized Intensity
0.96
1.90
0.97
1.97
4.03
2.08
12.09
Chemical Shift (ppm)

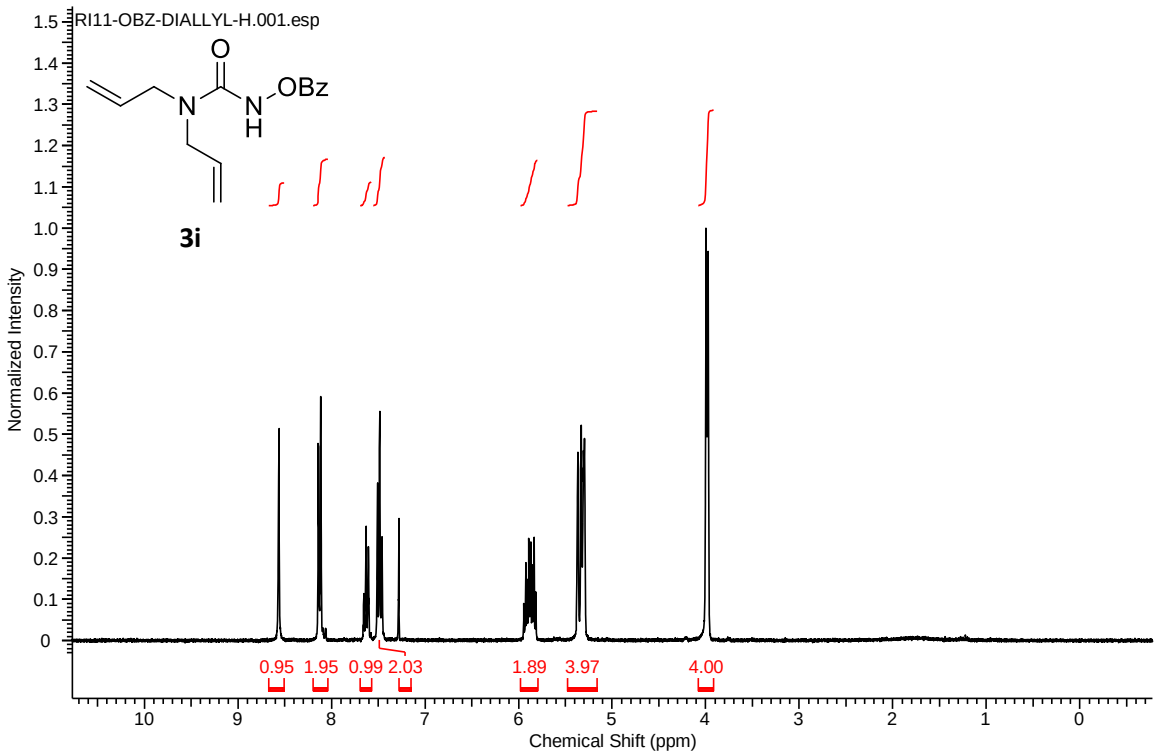

RI11-OBZ-DIISOBUTYL-C.001.esp
Normalized Intensity
167.14
157.96
133.92
129.89
128.55
127.11
54.90
27.18
20.13
Chemical Shift (ppm)

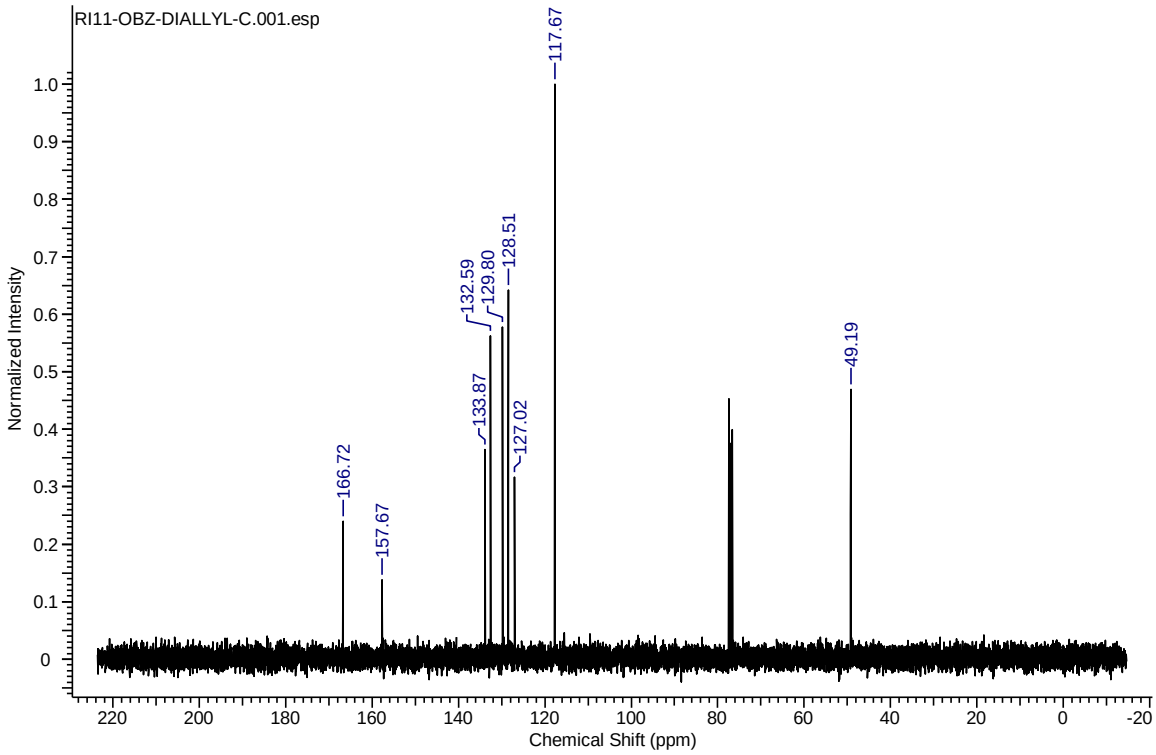

DP-diallylNOH-proton.001.esp
O
N
N
H
OH
3g
Normalized Intensity
1.5
1.0
0.5
0
0.95
0.99
2.00
4.07
4.06
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

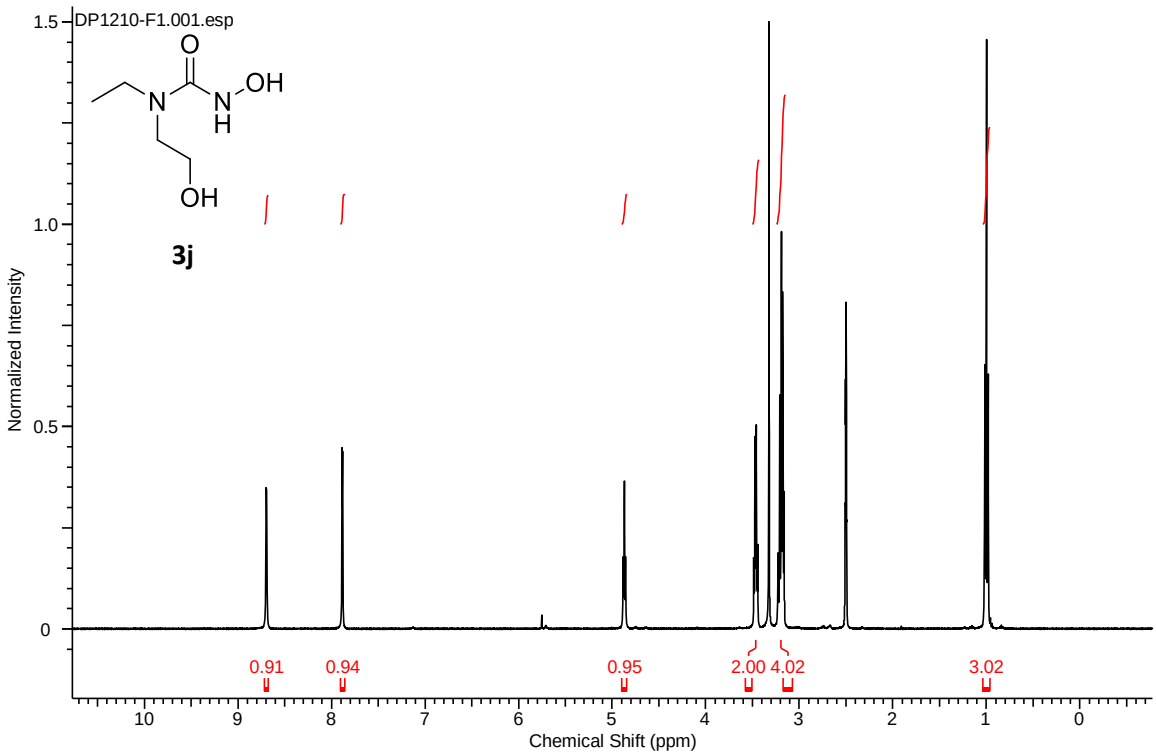

DP-diallylNOH.002.esp
132.83
117.53
48.99
161.49
Normalized Intensity
1.5
1.0
0.5
0
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

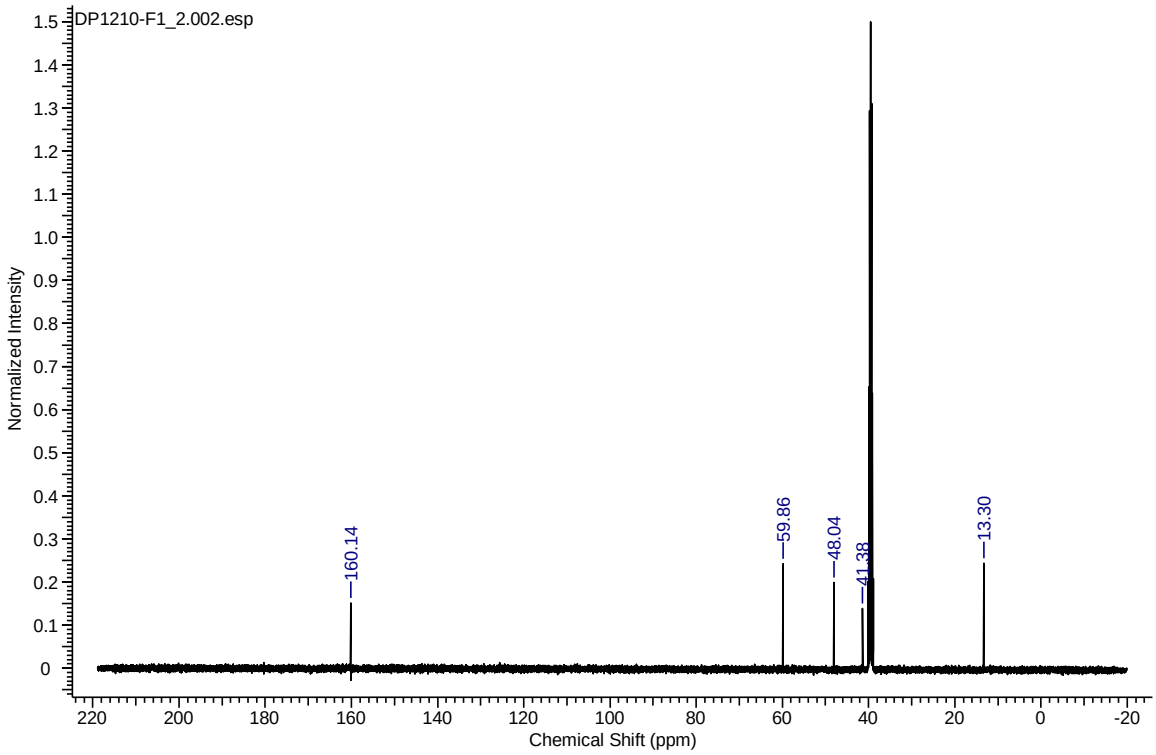

DP1215-F1.002.esp
O
N
N
H
OEt
3h
Normalized Intensity
0.89
2.00
4.05
2.12
3.92
3.02
Chemical Shift (ppm)

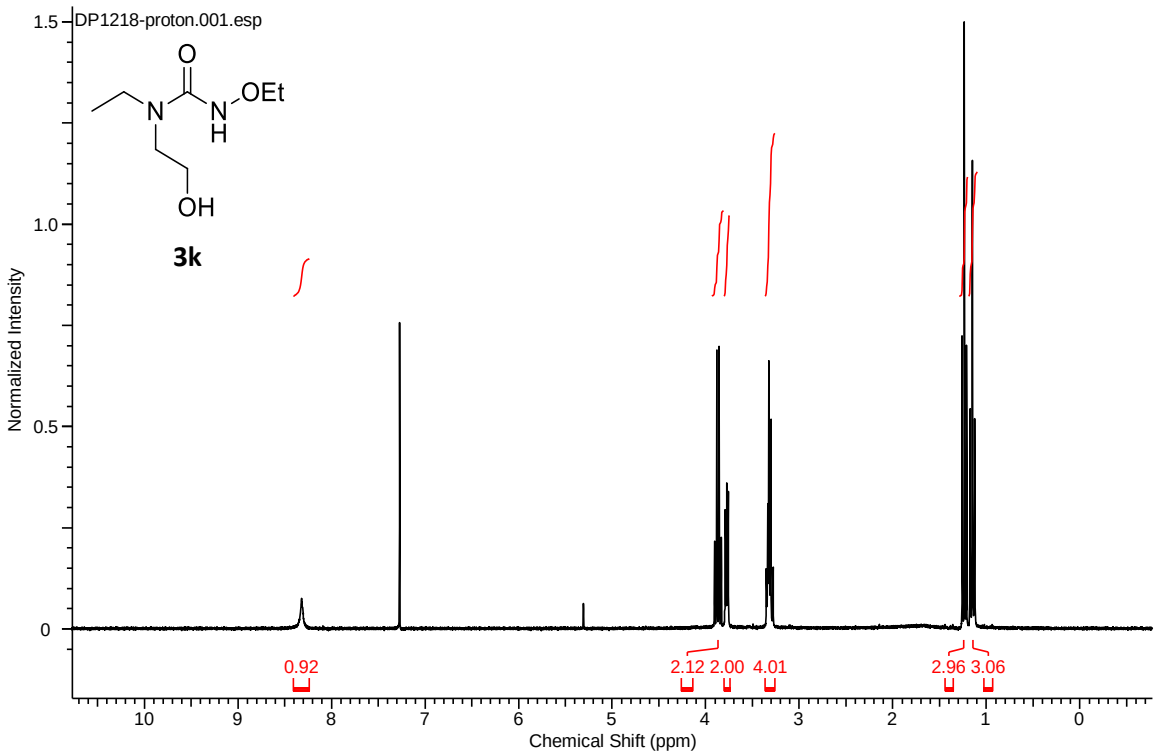

DP1215-F1.003.esp
159.33
133.40
117.29
71.80
49.11
13.51
Normalized Intensity
Chemical Shift (ppm)

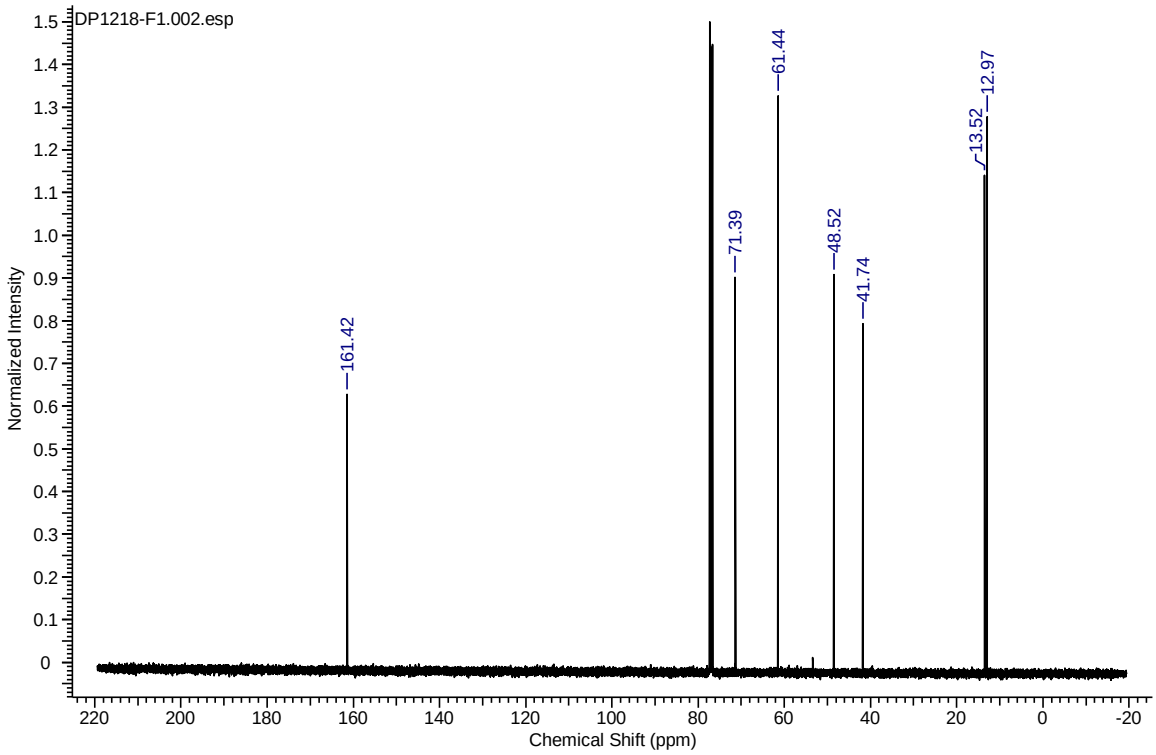

RI11-OBZ-DIALLYL-H.001.esp
O
N
N
H
OBz
3i
Normalized Intensity
0.95
1.95
0.99
2.03
1.89
3.97
4.00
Chemical Shift (ppm)

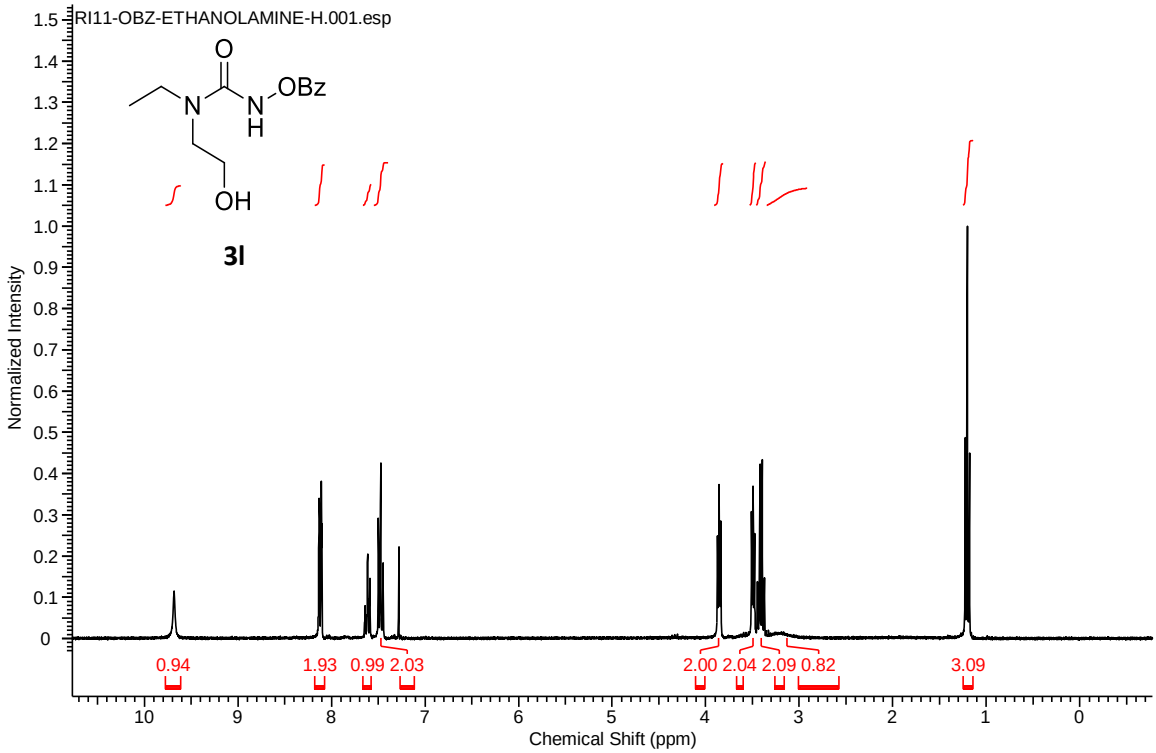

RI11-OBZ-DIALLYL-C.001.esp
117.67
132.59
129.80
128.51
133.87
127.02
49.19
166.72
157.67
Normalized Intensity
Chemical Shift (ppm)

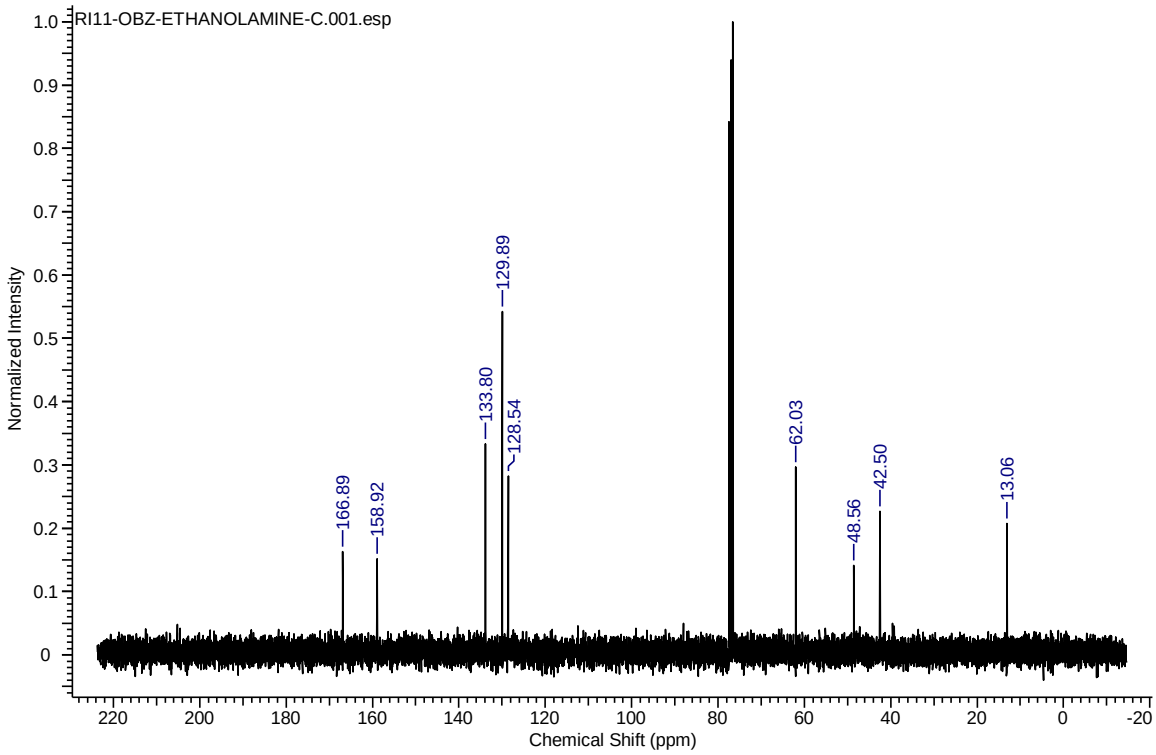

DP1210-F1.001.esp
O
N
N
H
OH
OH
3j
Normalized Intensity
1.5
1.0
0.5
0
0.91
0.94
0.95
2.00
4.02
3.02
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

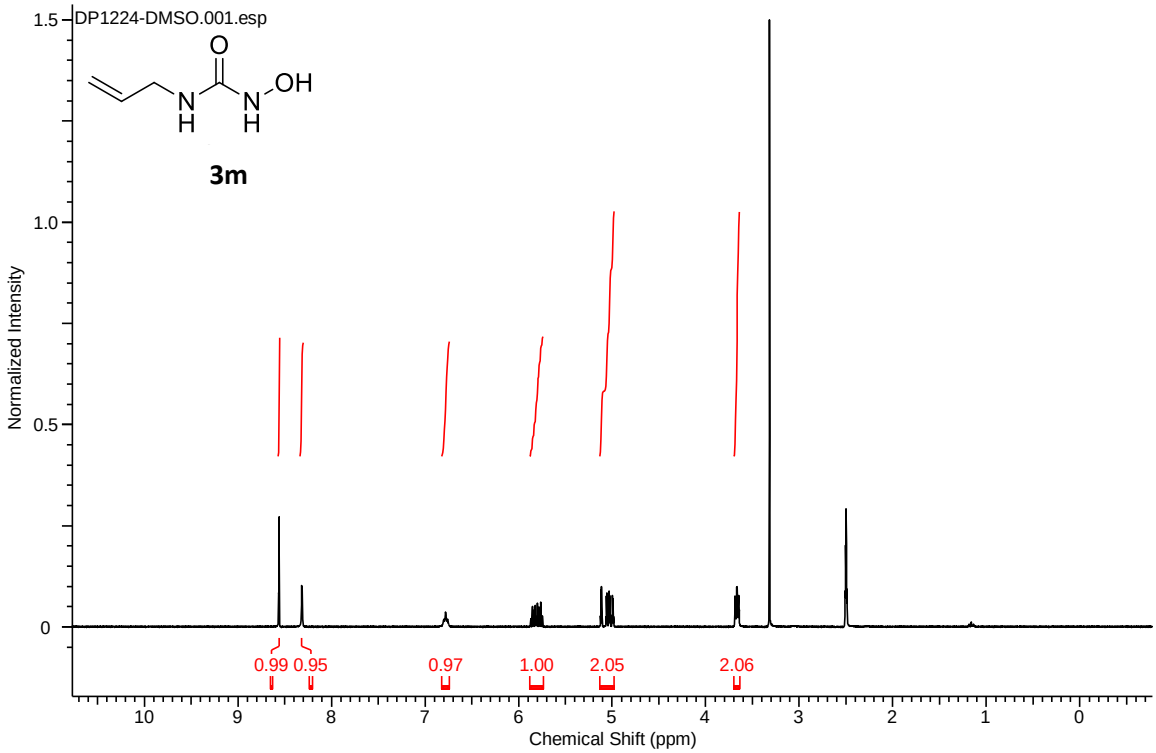

DP1210-F1_2.002.esp
Normalized Intensity
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
160.14
59.86
48.04
41.38
13.30
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

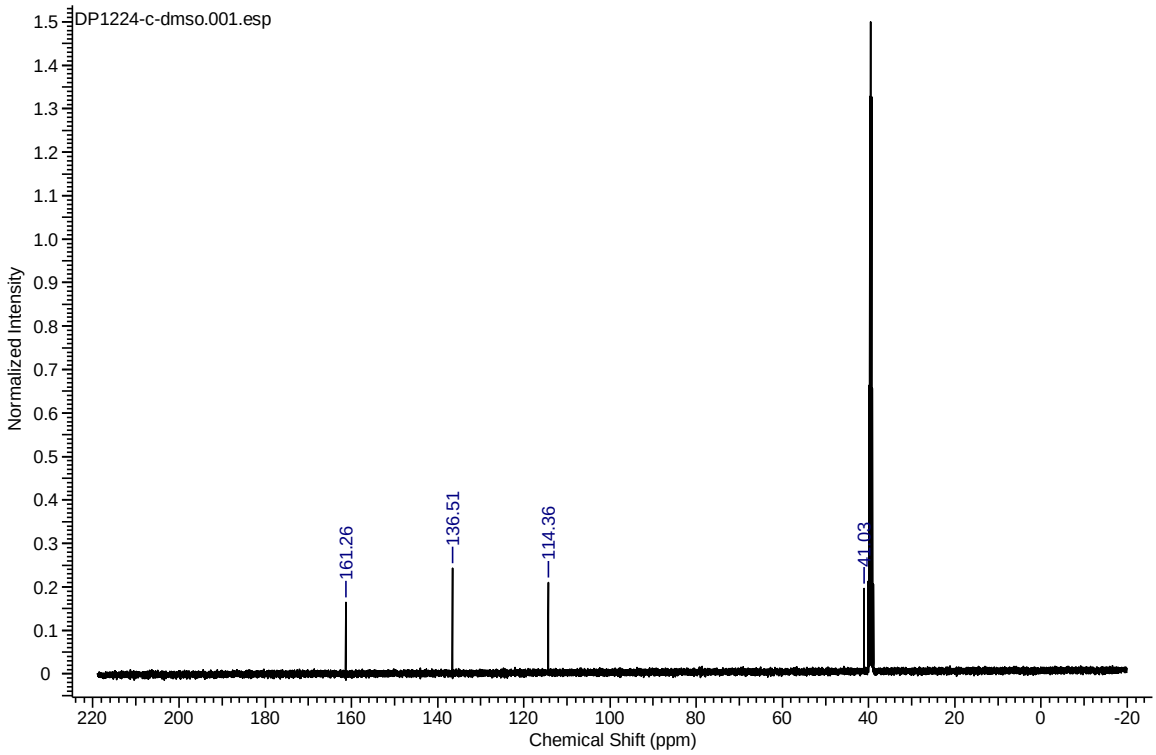

DP1218-proton.001.esp
O
N
N
H
OEt
OH
3k
Normalized Intensity
0.92
2.12
2.00
4.01
2.96
3.06
Chemical Shift (ppm)

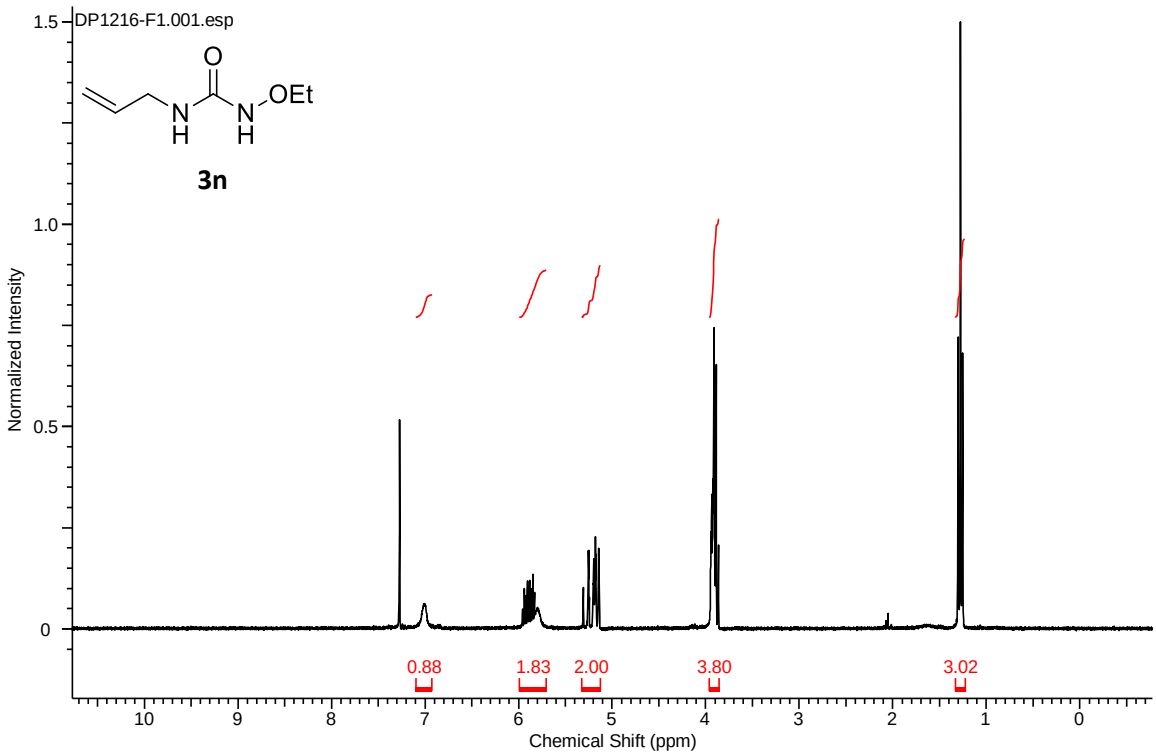

DP1218-F1.002.esp
Normalized Intensity
161.42
71.39
61.44
48.52
41.74
13.52
12.97
Chemical Shift (ppm)

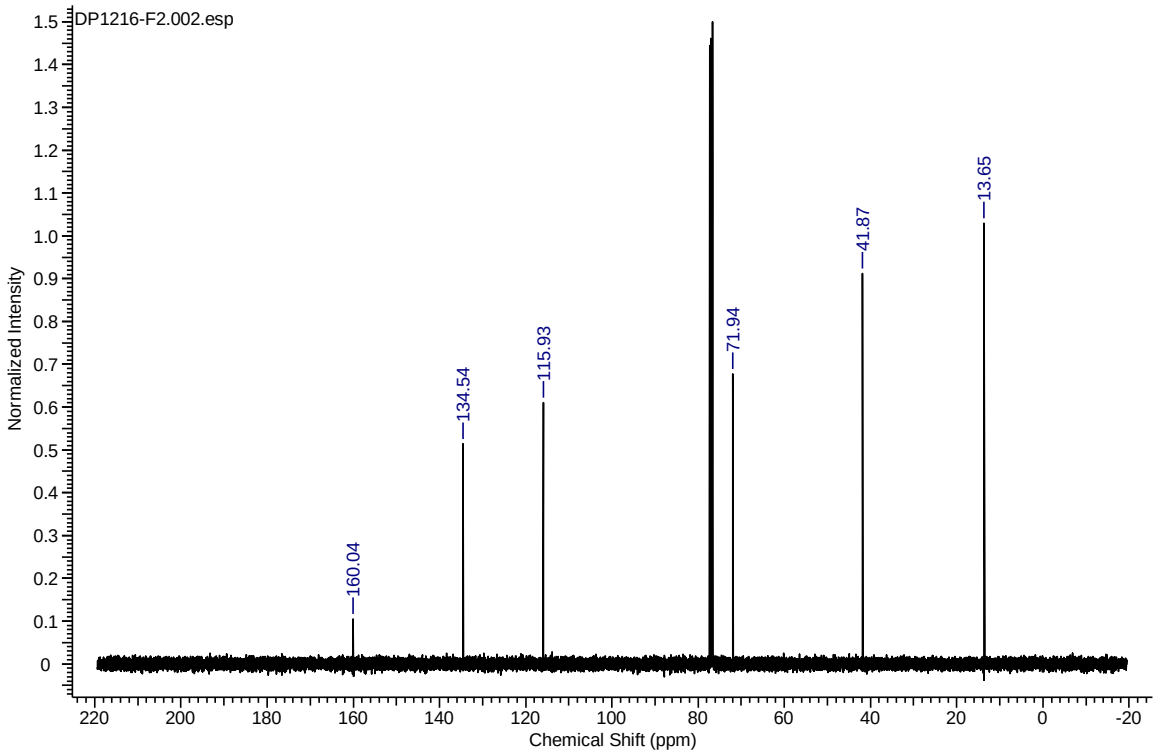

RI11-OBZ-ETHANOLAMINE-H.001.esp
O
N
N
H
OBz
OH
3l
Normalized Intensity
0.94
1.93
0.99
2.03
2.00
2.04
2.09
0.82
3.09
Chemical Shift (ppm)

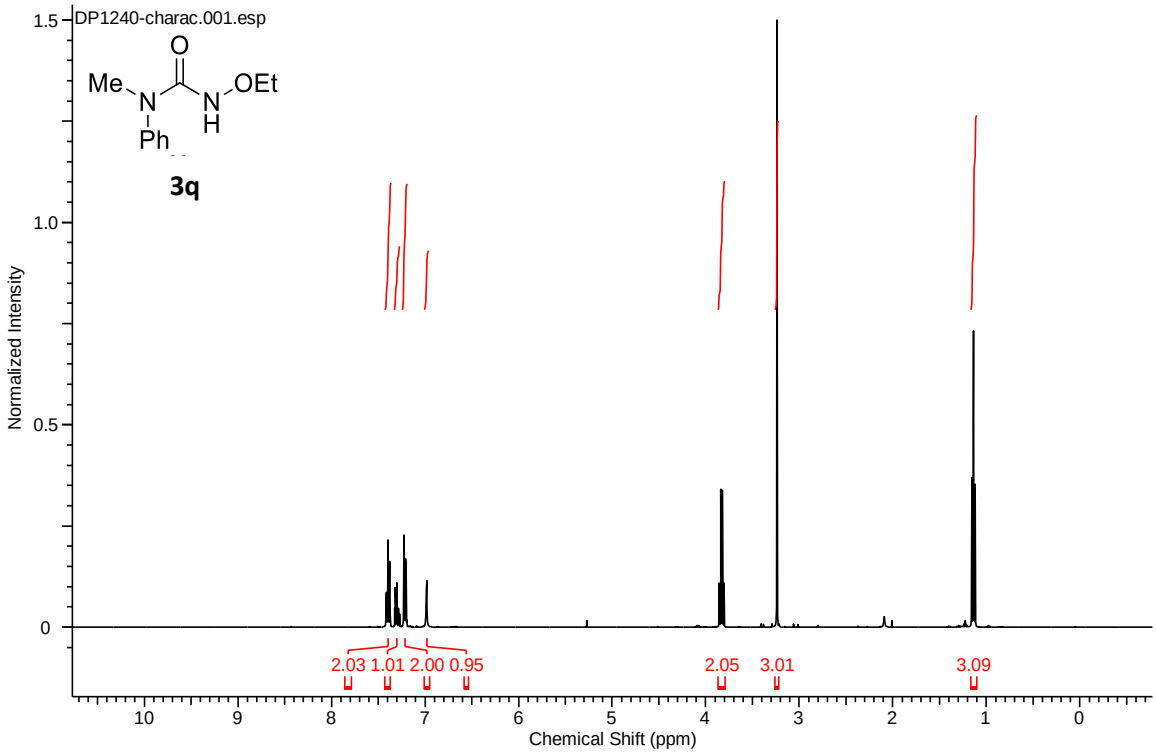

RI11-OBZ-ETHANOLAMINE-C.001.esp
Normalized Intensity
166.89
158.92
133.80
129.89
128.54
62.03
48.56
42.50
13.06
Chemical Shift (ppm)

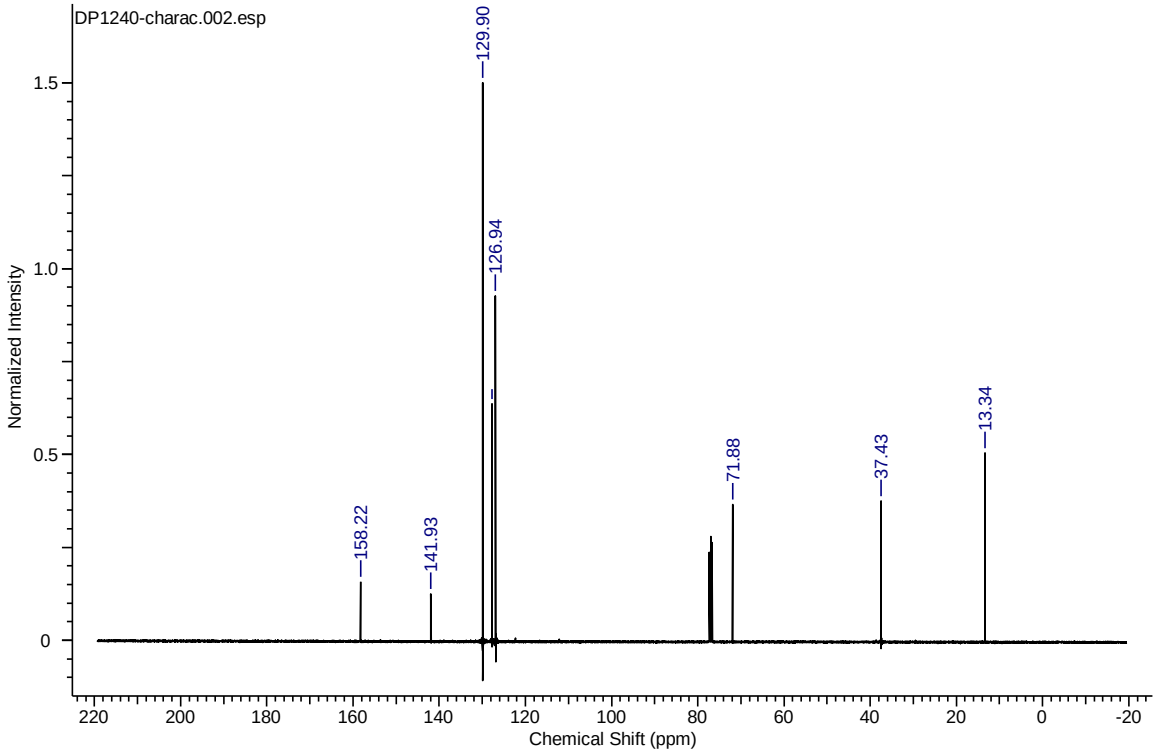

DP1224-DMSO.001.esp
O
N
H
N
H
OH
3m
Normalized Intensity
0.99
0.95
0.97
1.00
2.05
2.06
Chemical Shift (ppm)

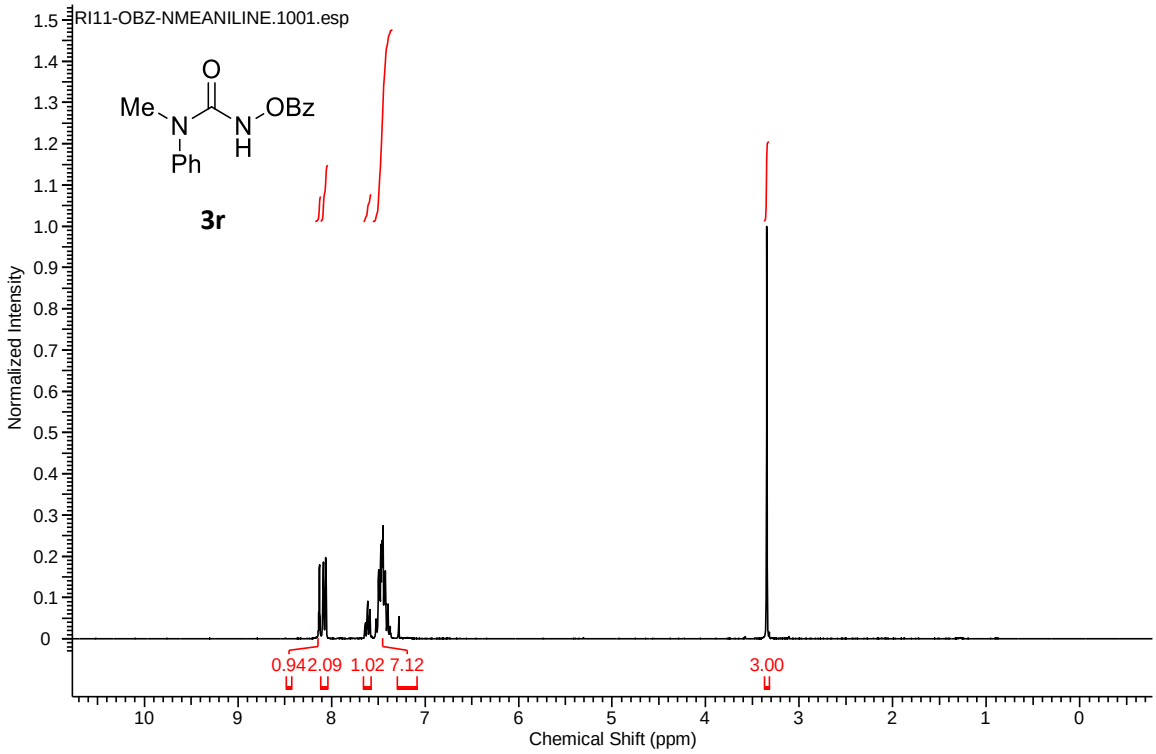

DP1224-c-dmso.001.esp
Normalized Intensity
161.26
136.51
114.36
41.03
Chemical Shift (ppm)

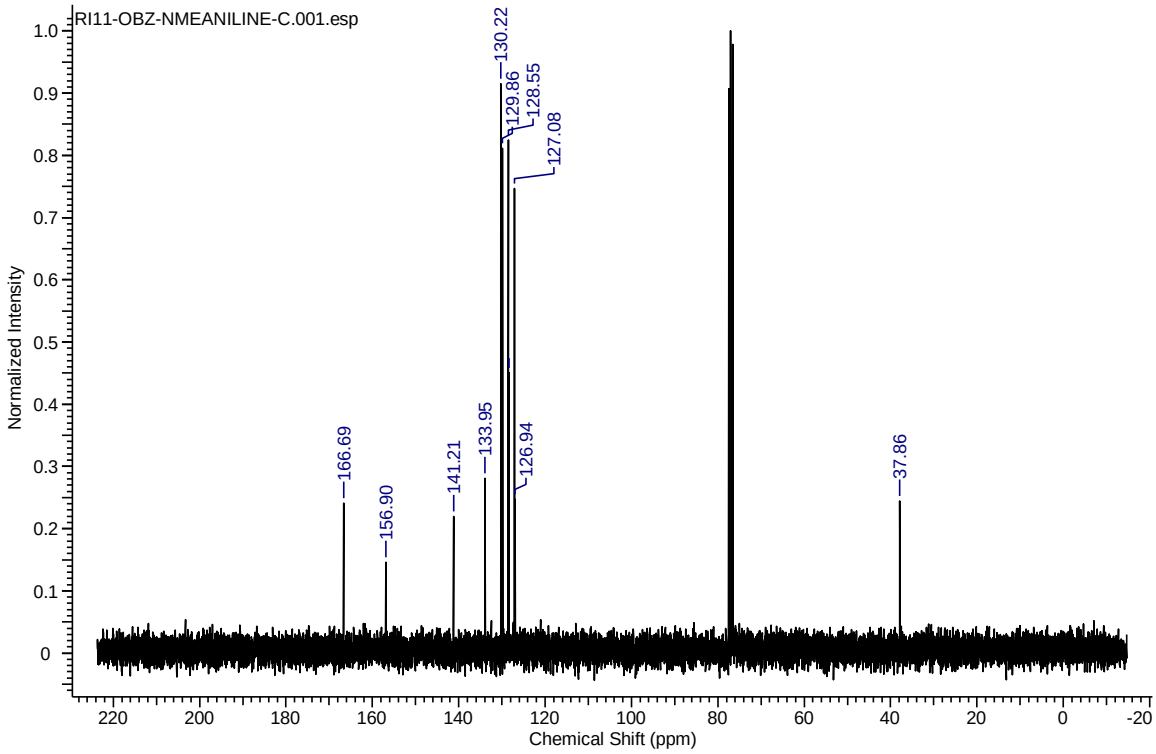

DP1216-F1.001.esp
O
N
H
N
H
OEt
3n
Normalized Intensity
1.5
1.0
0.5
0
0.88
1.83
2.00
3.80
3.02
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

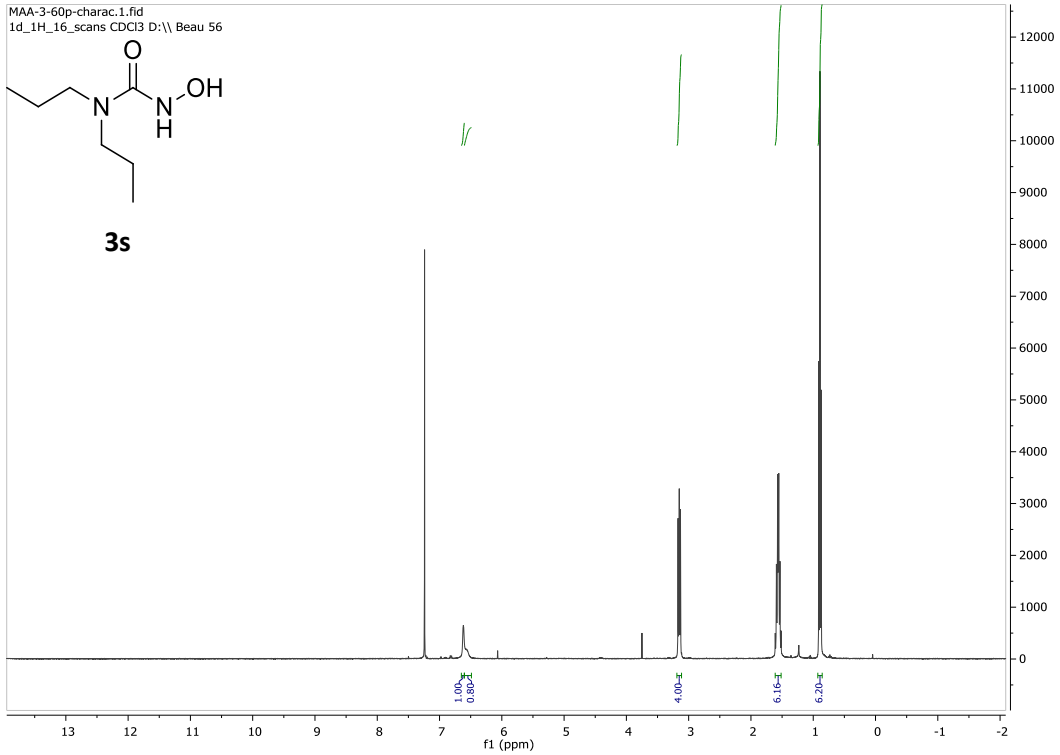

DP1216-F2.002.esp
Normalized Intensity
160.04
134.54
115.93
71.94
41.87
13.65
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

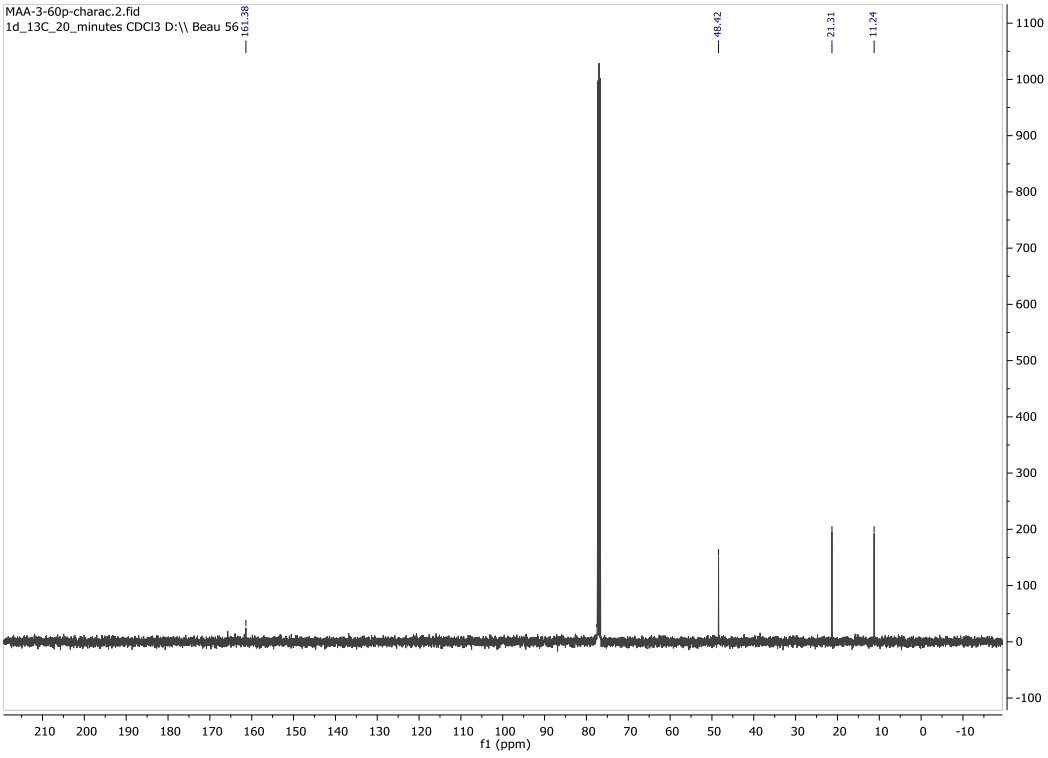

DP1240-charac.001.esp
Me
N
O
N
H
OEt
Ph
3q
Normalized Intensity
Chemical Shift (ppm)
2.03 1.01 2.00 0.95
2.05
3.01
3.09

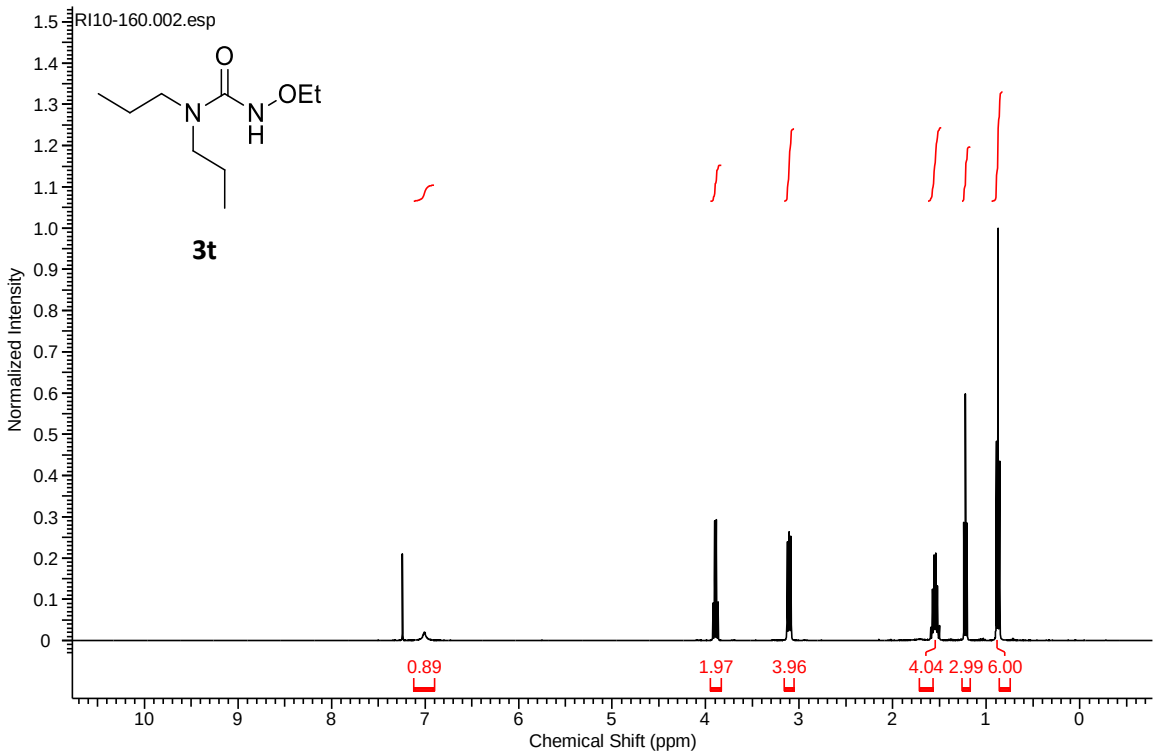

DP1240-charac.002.esp
129.90
126.94
158.22
141.93
71.88
37.43
13.34
Normalized Intensity
Chemical Shift (ppm)

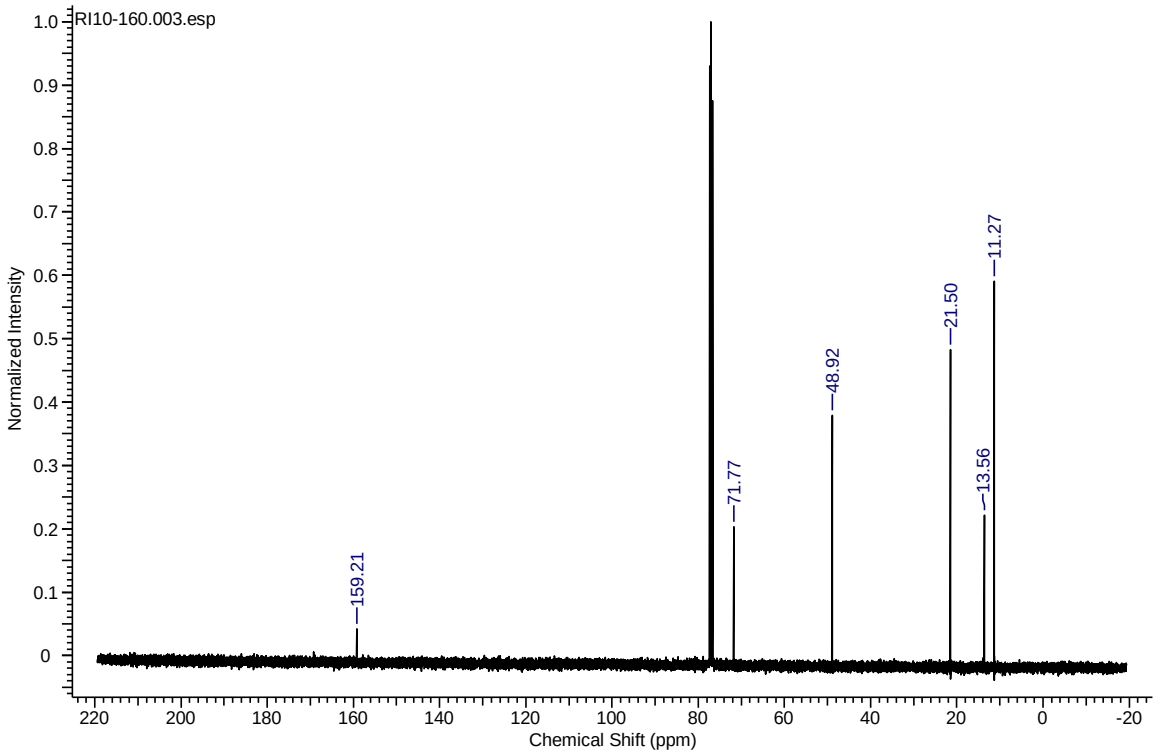

RI11-OBZ-NMEANILINE.1001.esp
Me
N
Ph
O
N
H
OBz
3r
Normalized Intensity
0.94 2.09 1.02 7.12
3.00
Chemical Shift (ppm)

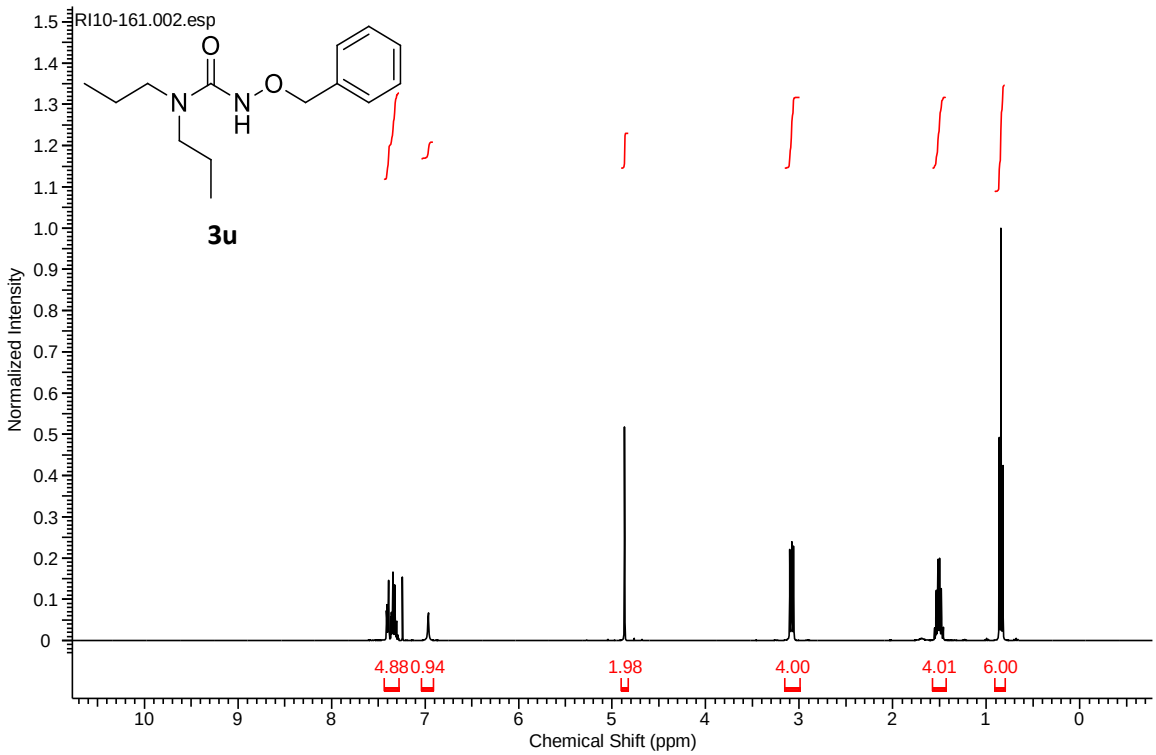

RI11-OBZ-NMEANILINE-C.001.esp
130.22
129.86
128.55
127.08
166.69
156.90
141.21
133.95
126.94
37.86
Normalized Intensity
Chemical Shift (ppm)

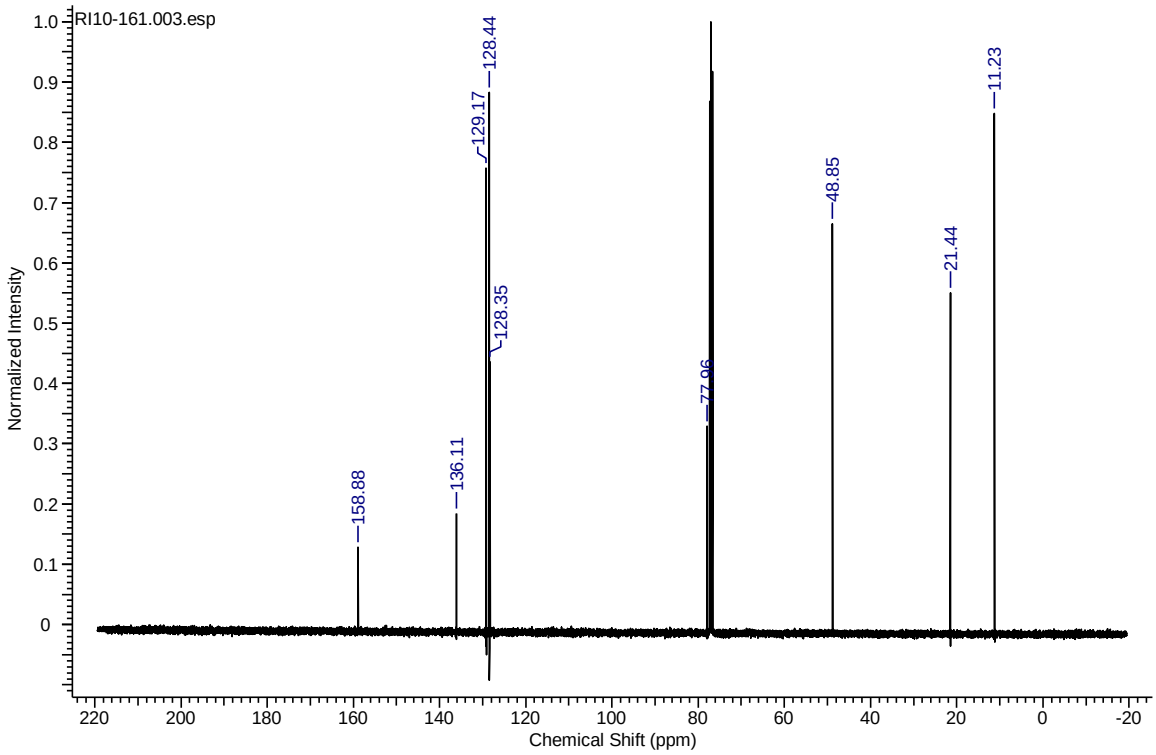

MAA-3-60p-charac.1.fid
1d_1H_16_scans CDCl3 D:\\ Beau 56
O
N
N
OH
H
3s
1.00
0.80
4.00
6.16
6.20
f1 (ppm)

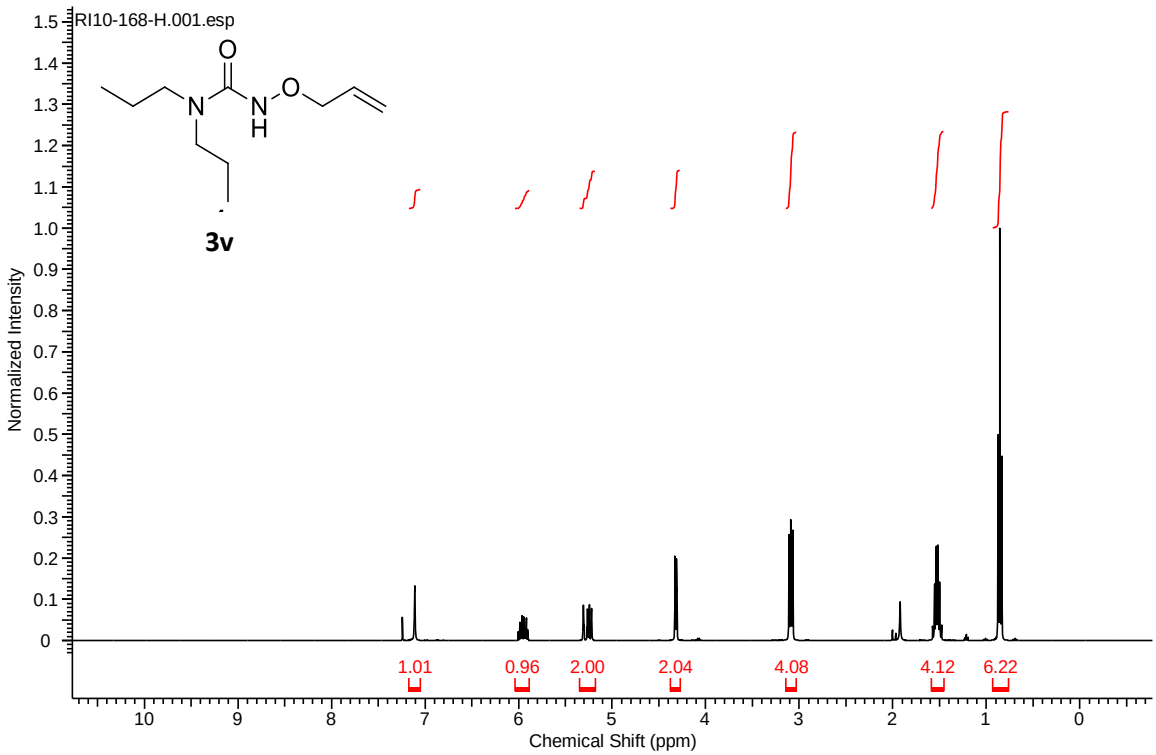

MAA-3-60p-charac.2.fid
1d_13C_20_minutes CDCl3 D:\\ Beau 56
161.38
48.42
21.31
11.24
f1 (ppm)

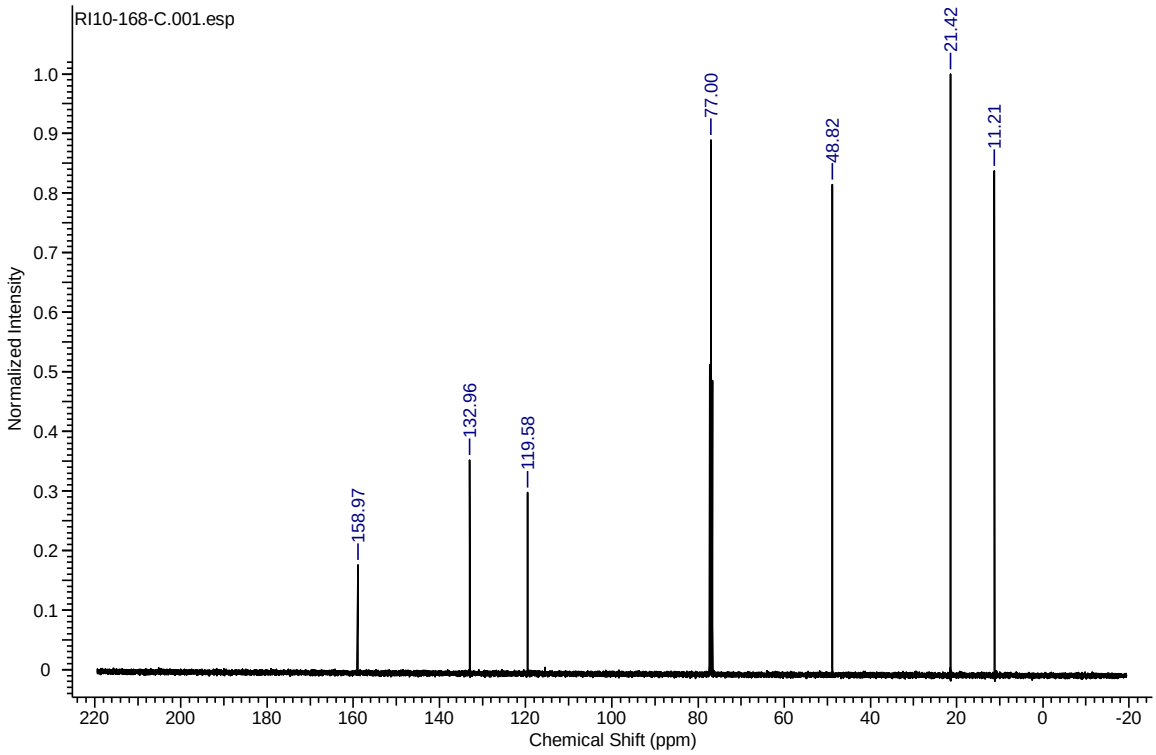

RI10-160.002.esp
O
N
N
H
OEt
3t
Normalized Intensity
0.89
1.97
3.96
4.04
2.99
6.00
Chemical Shift (ppm)

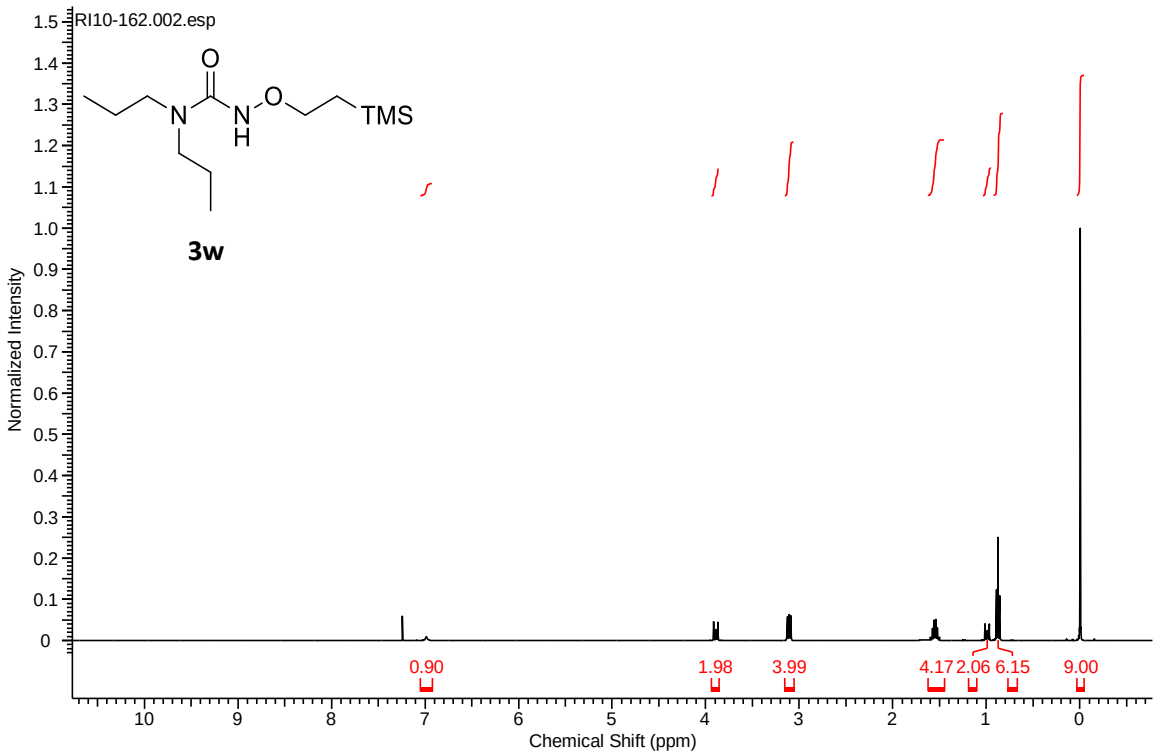

RI10-160.003.esp
Normalized Intensity
159.21
71.77
48.92
21.50
13.56
11.27
Chemical Shift (ppm)

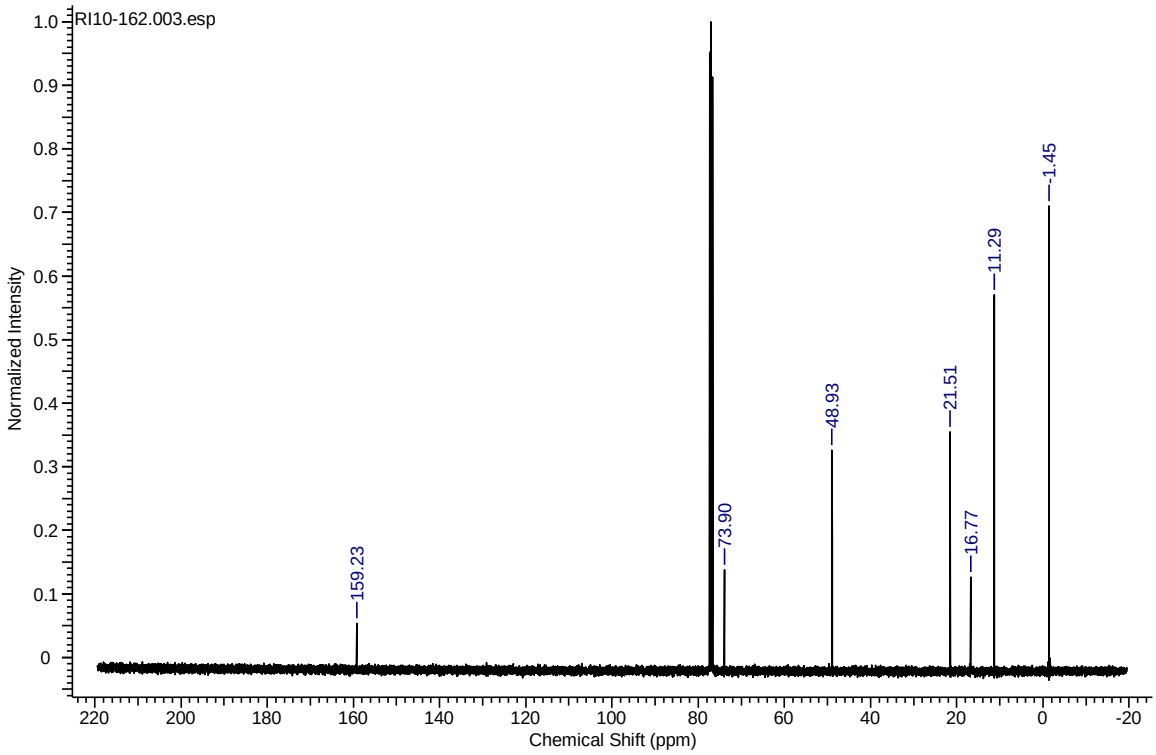

RI10-161.002.esp
3u
Normalized Intensity
4.88
0.94
1.98
4.00
4.01
6.00
Chemical Shift (ppm)

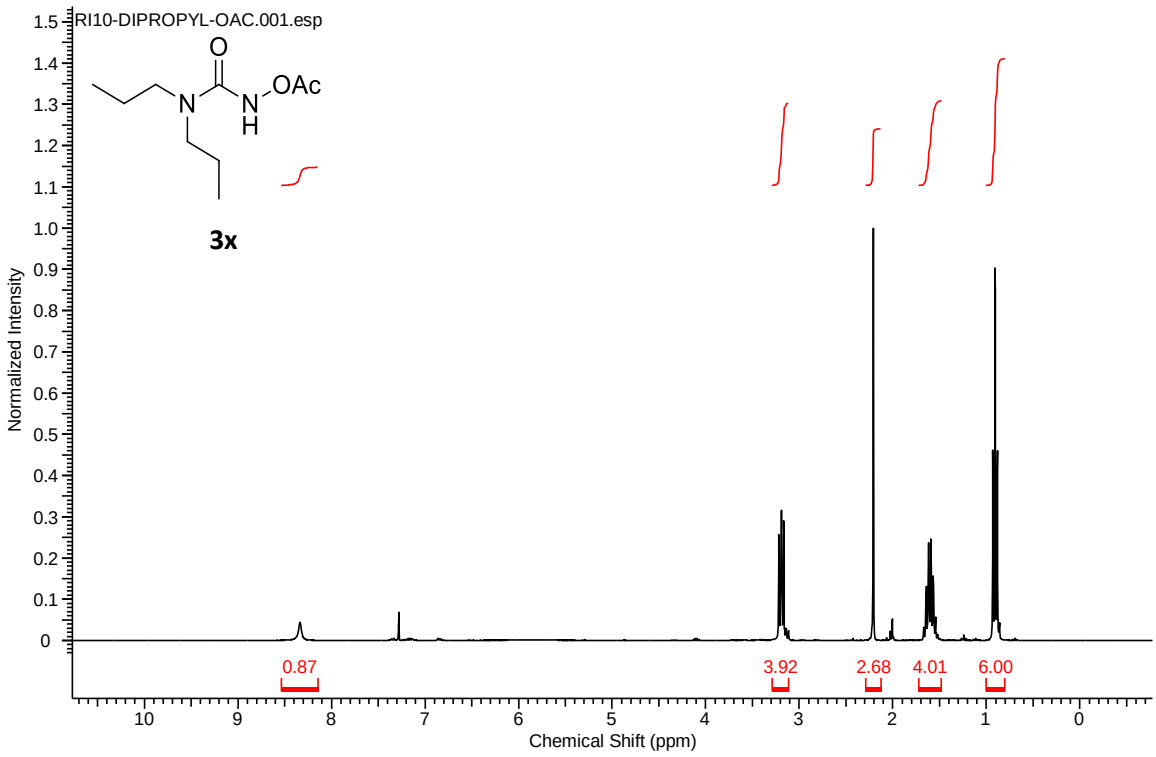

RI10-161.003.esp
Normalized Intensity
158.88
136.11
129.17
128.44
128.35
77.06
48.85
21.44
11.23
Chemical Shift (ppm)

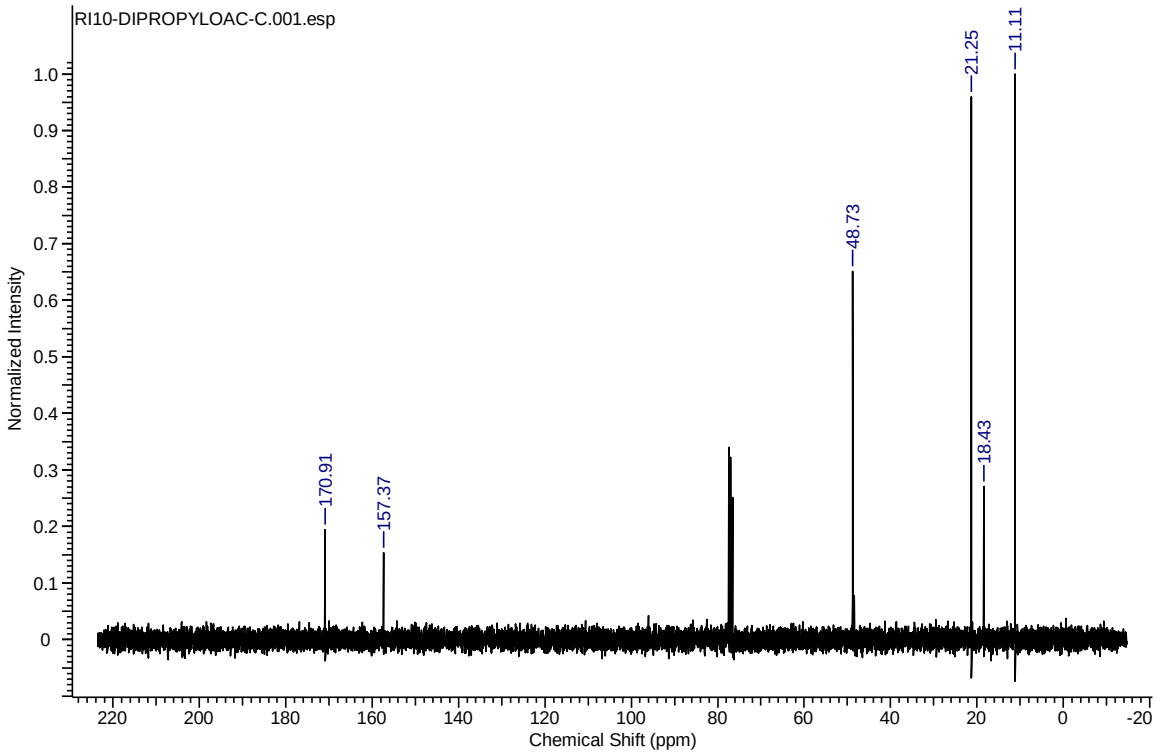

RI10-168-H.001.esp
O
N
N
H
O
3v
Normalized Intensity
1.01
0.96
2.00
2.04
4.08
4.12
6.22
Chemical Shift (ppm)

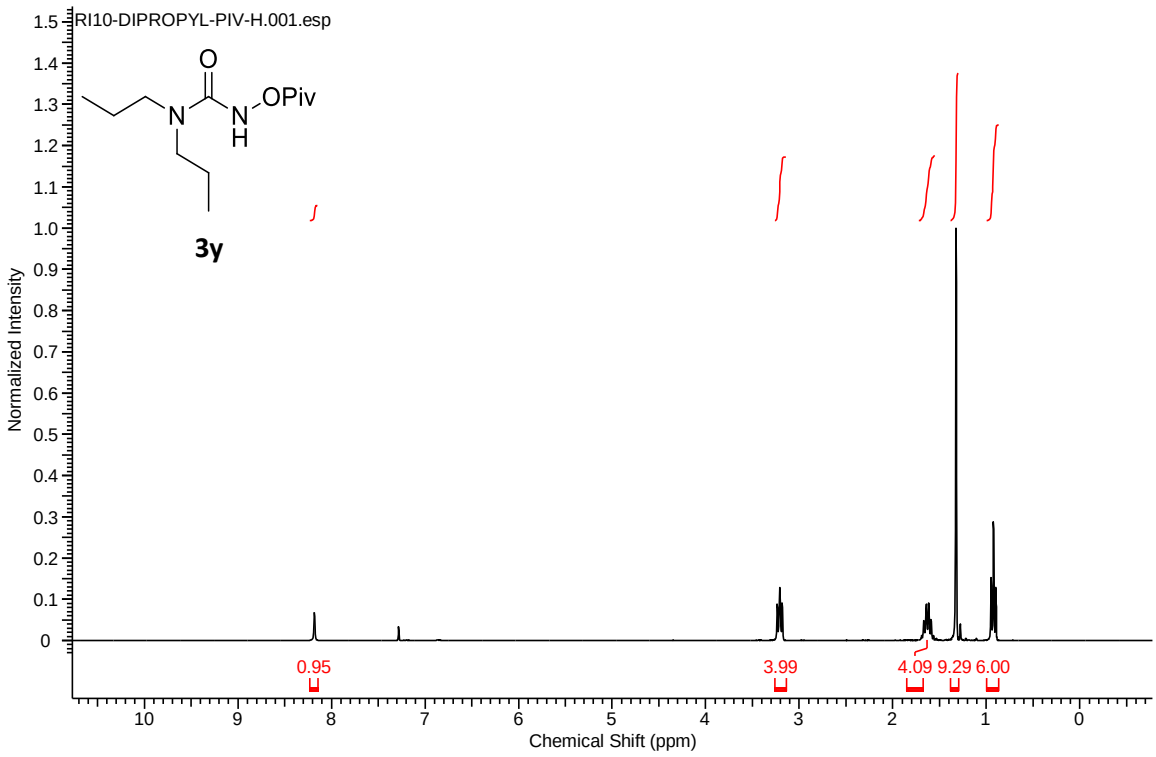

RI10-168-C.001.esp
158.97
132.96
119.58
77.00
48.82
21.42
11.21
Normalized Intensity
Chemical Shift (ppm)

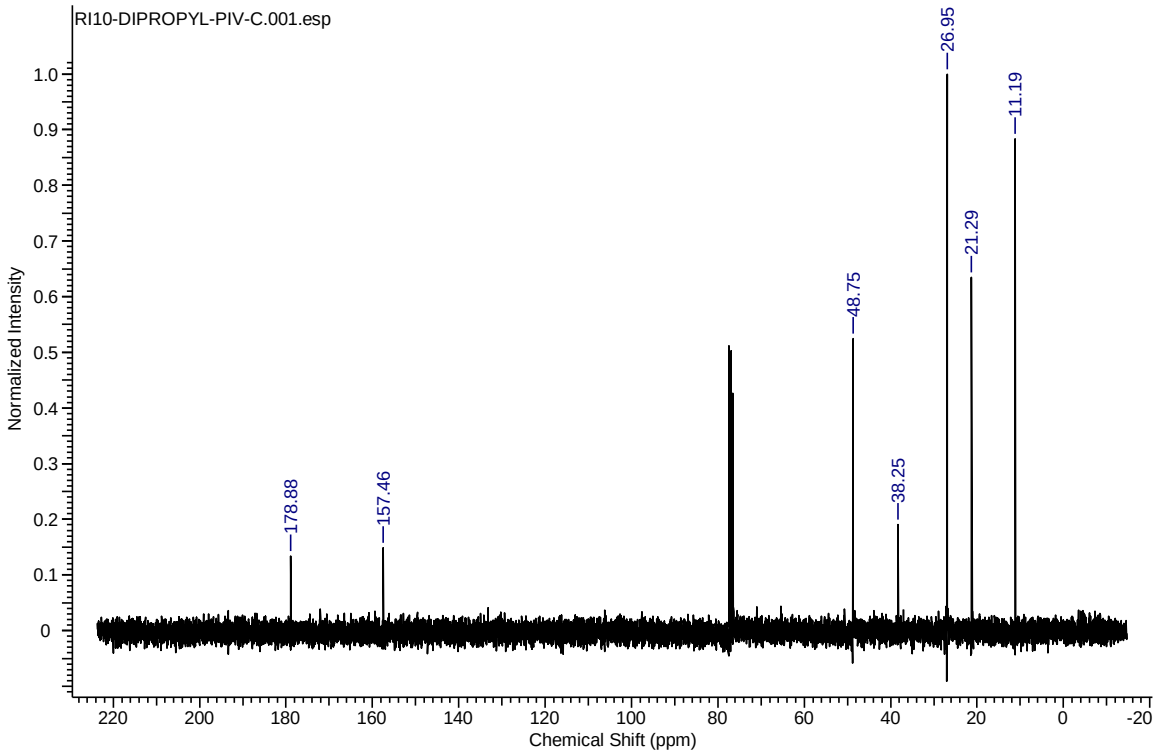

RI10-162.002.esp
O
N
N
H
O
TMS
3w
Normalized Intensity
0.90
1.98
3.99
4.17
2.06
6.15
9.00
Chemical Shift (ppm)

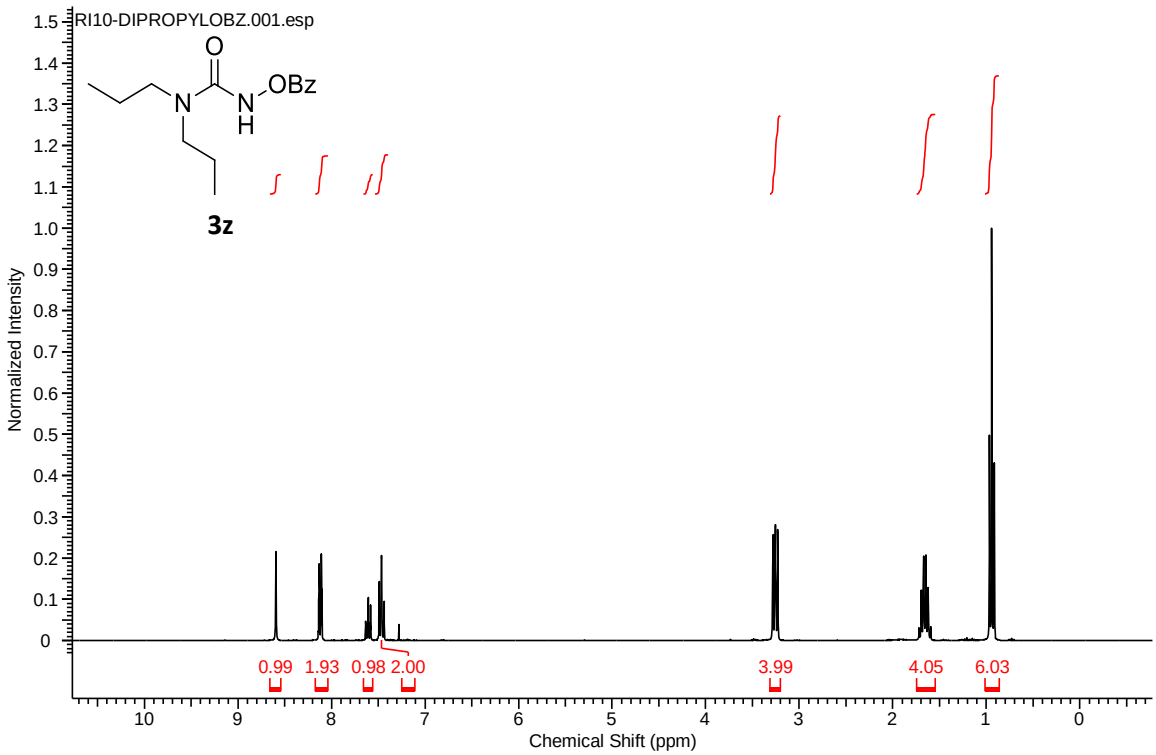

RI10-162.003.esp
Normalized Intensity
159.23
73.90
48.93
21.51
16.77
11.29
-1.45
Chemical Shift (ppm)

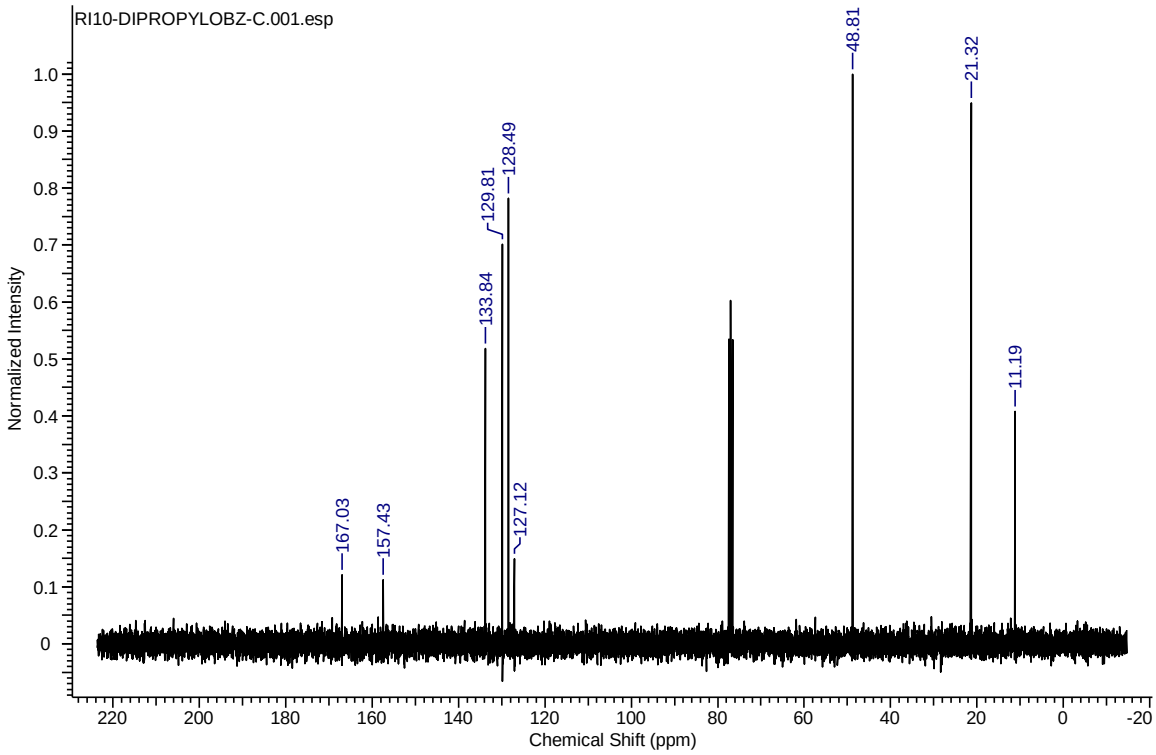

RI10-DIPROPYL-OAC.001.esp
O
N
N
H
OAc
3x
Normalized Intensity
0.87
3.92
2.68
4.01
6.00
Chemical Shift (ppm)

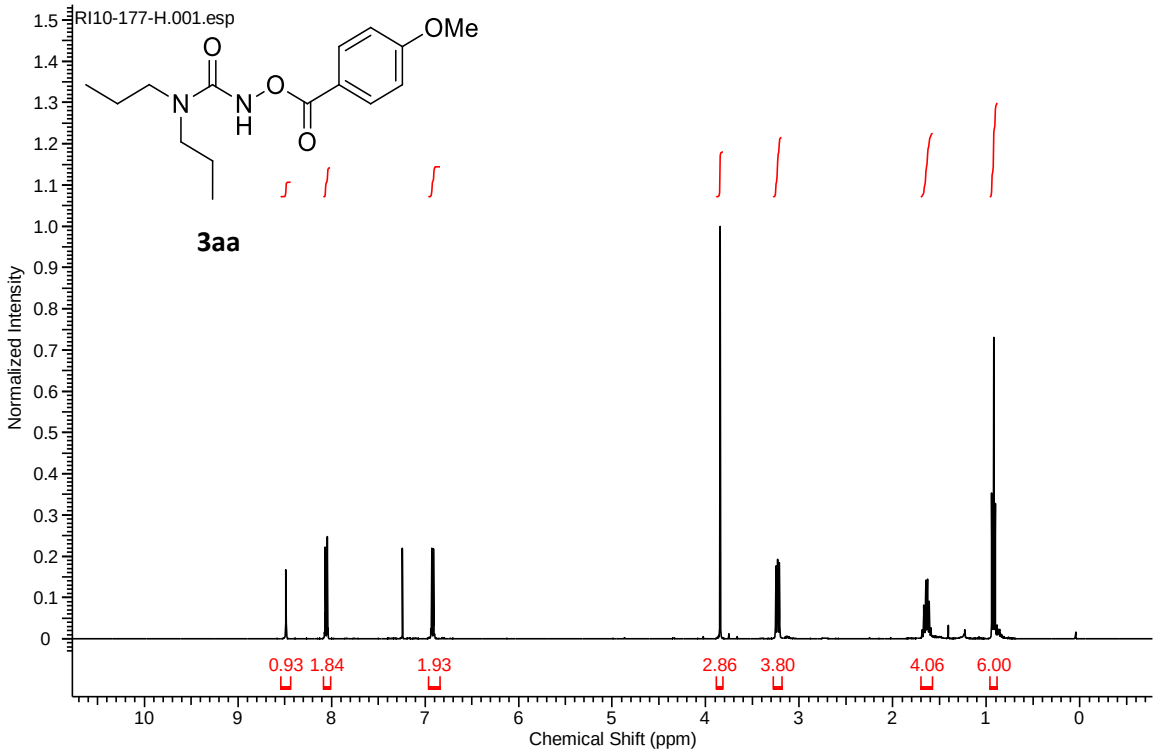

RI10-DIPROPYLOAC-C.001.esp
170.91
157.37
48.73
21.25
18.43
11.11
Normalized Intensity
Chemical Shift (ppm)

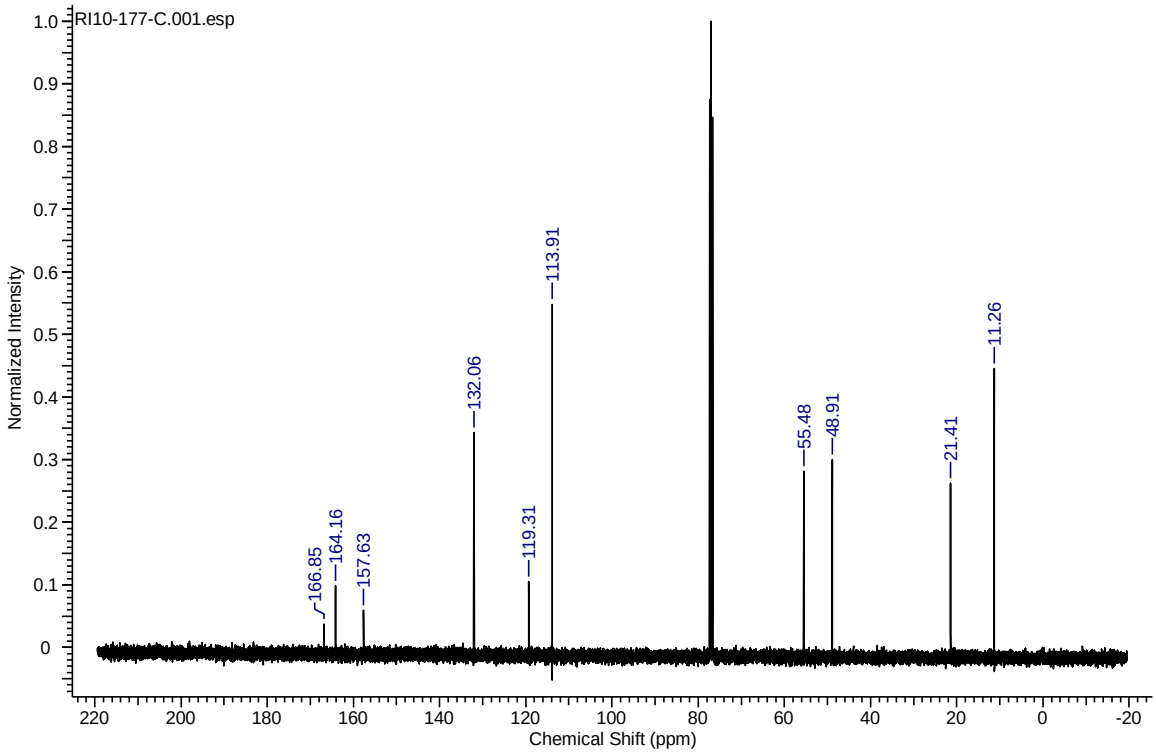

RI10-DIPROPYL-PIV-H.001.esp
O
N
N
H
OPiv
3y
Normalized Intensity
0.95
3.99
4.09
9.29
6.00
Chemical Shift (ppm)

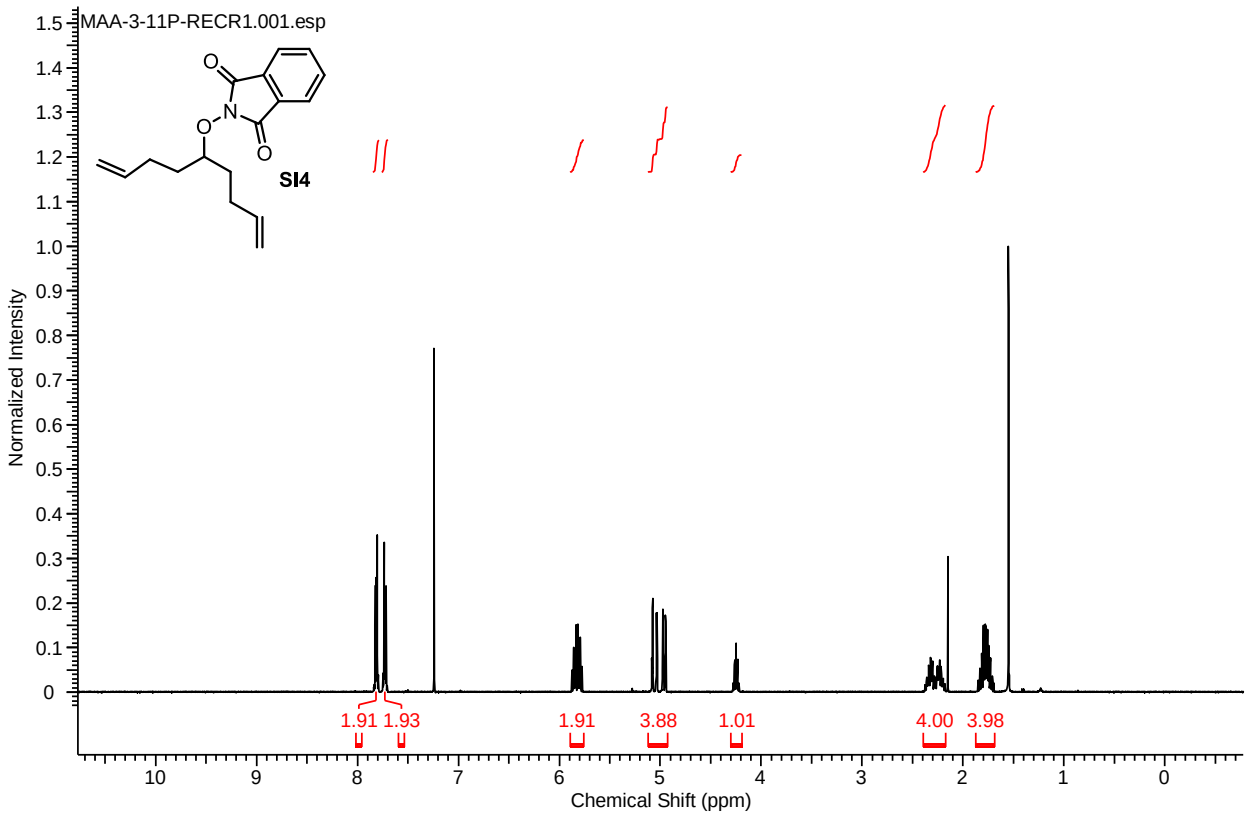

RI10-DIPROPYL-PIV-C.001.esp
178.88
157.46
48.75
38.25
26.95
21.29
11.19
Normalized Intensity
Chemical Shift (ppm)

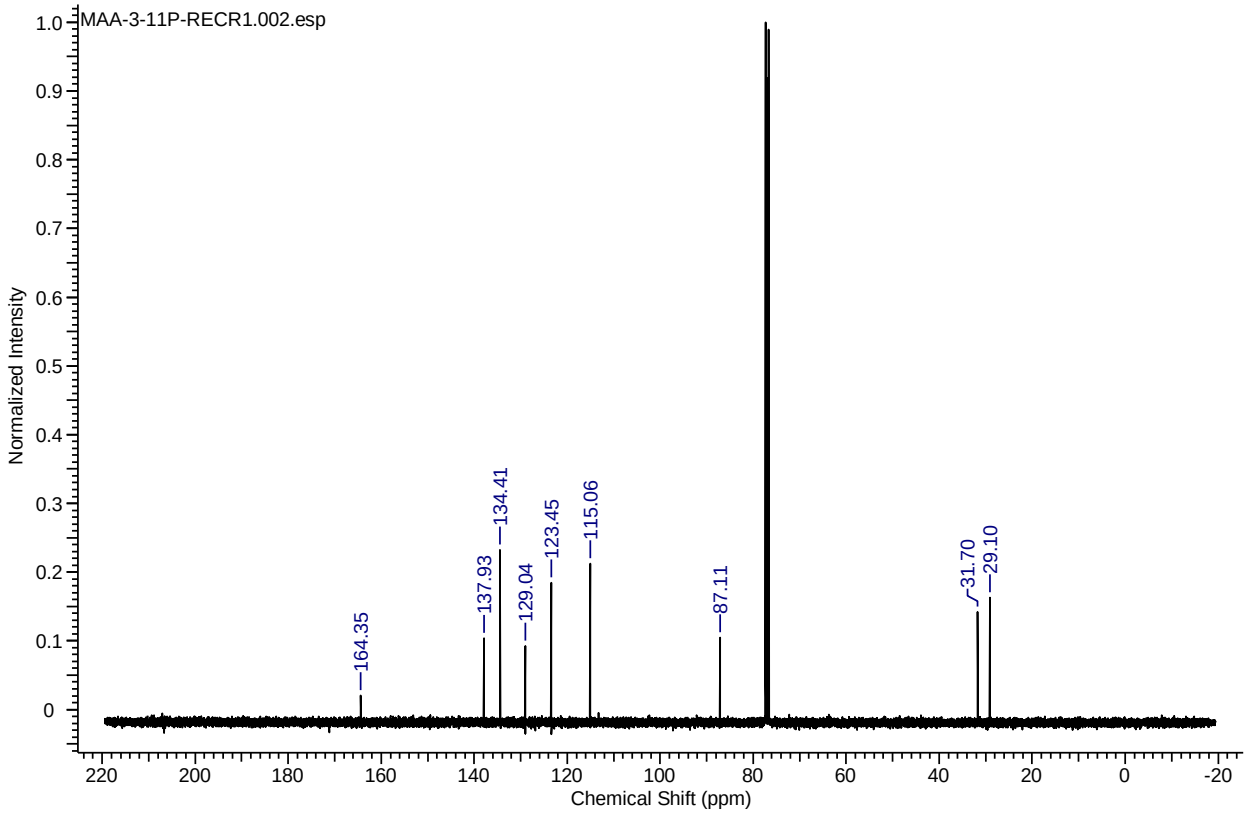

RI10-DIPROPYLOBZ.001.esp
O
N
N
H
OBz
3z
Normalized Intensity
0.99
1.93
0.98
2.00
3.99
4.05
6.03
Chemical Shift (ppm)

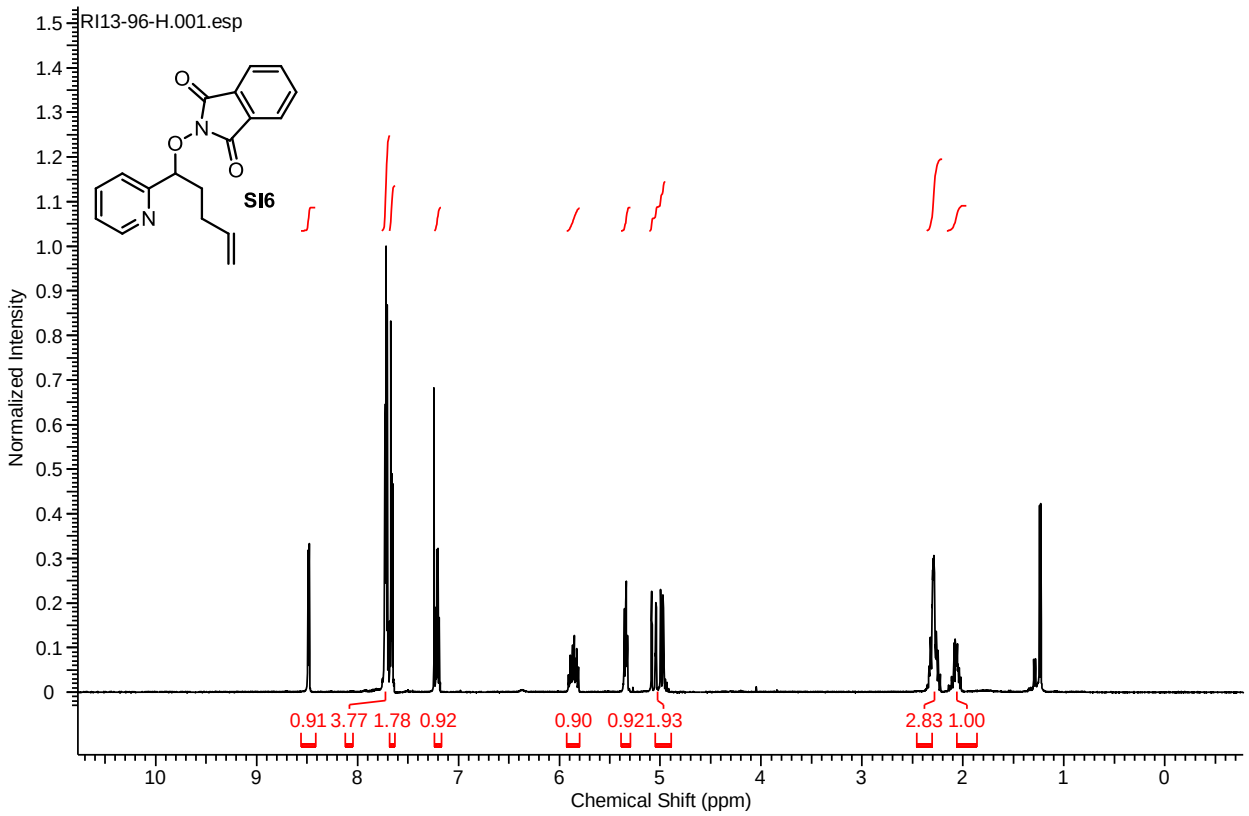

RI10-DIPROPYLOBZ-C.001.esp
48.81
21.32
129.81
128.49
133.84
11.19
167.03
157.43
127.12
Normalized Intensity
Chemical Shift (ppm)

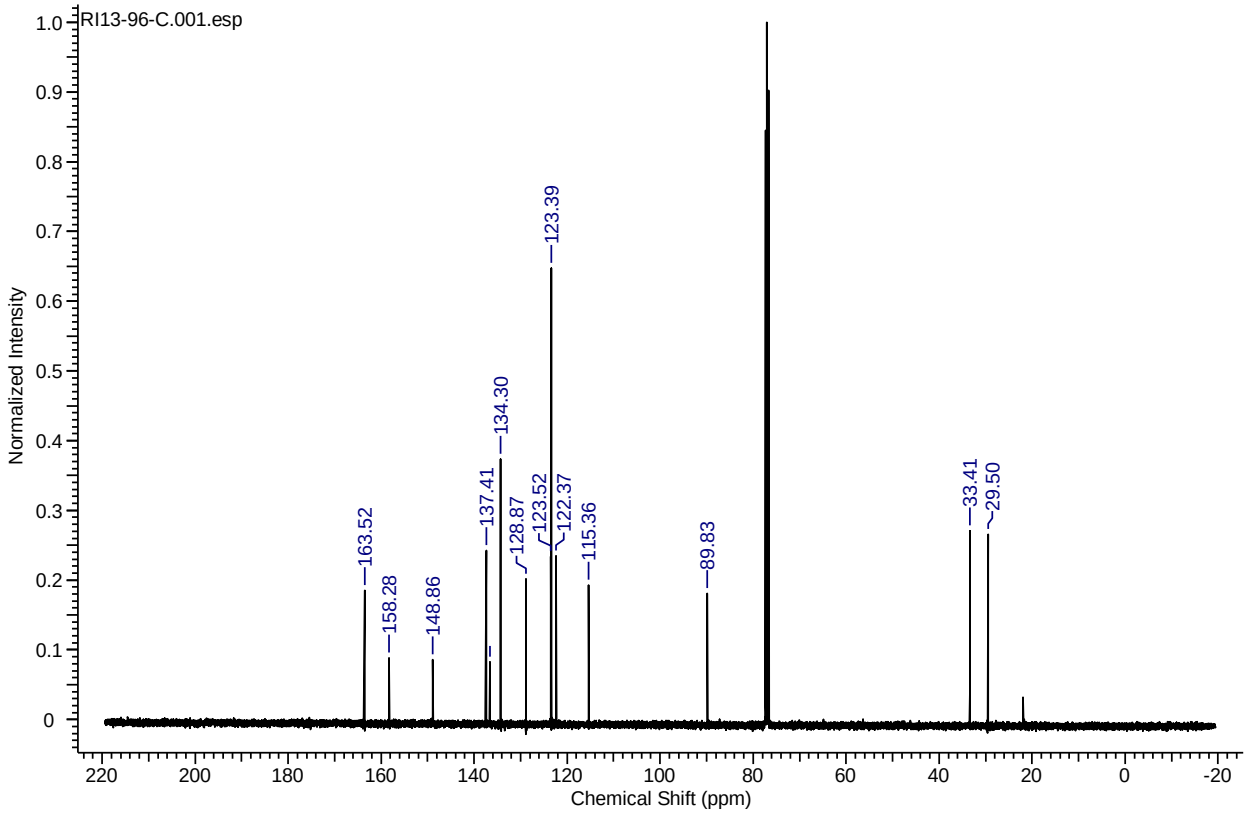

RI10-177-H.001.esp
OMe
O
N
N
H
O
O
3aa
Normalized Intensity
0.93
1.84
1.93
2.86
3.80
4.06
6.00
Chemical Shift (ppm)

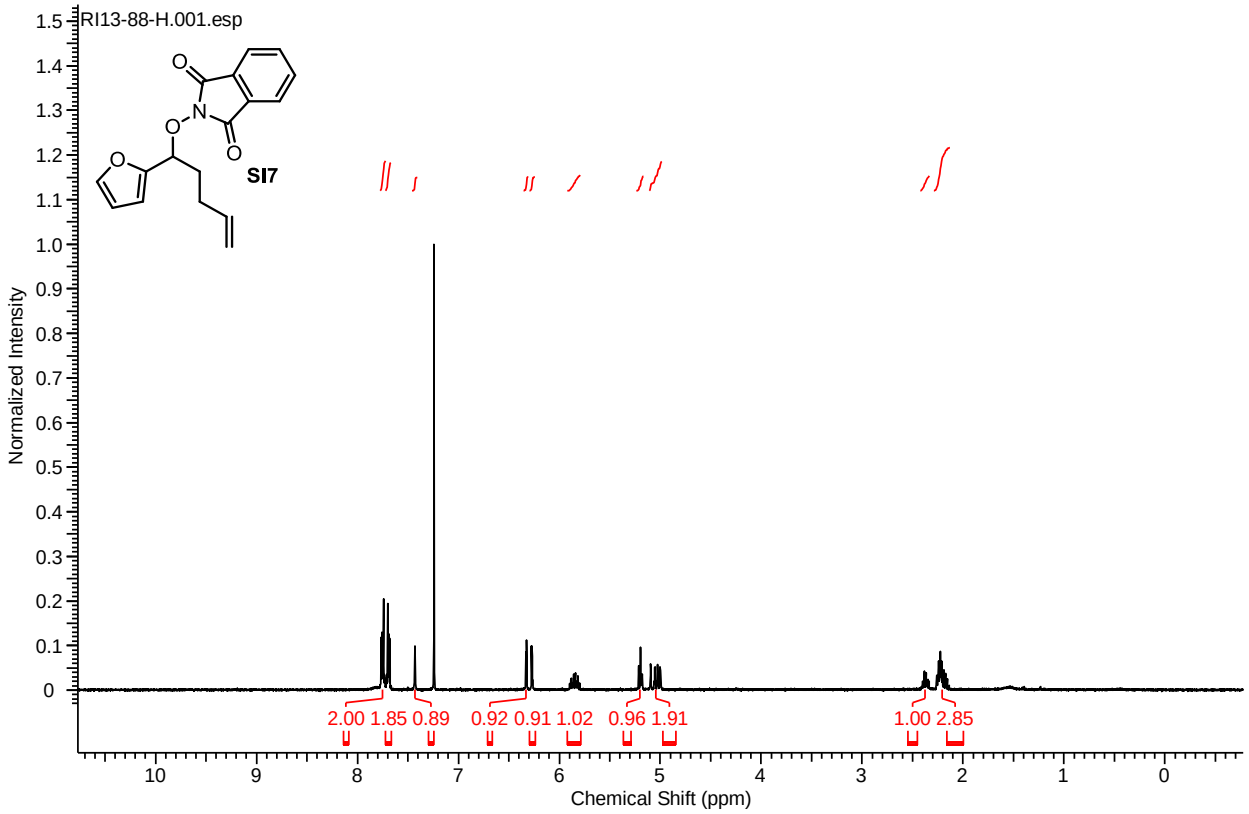

RI10-177-C.001.esp
Normalized Intensity
166.85
164.16
157.63
132.06
119.31
113.91
55.48
48.91
21.41
11.26
Chemical Shift (ppm)

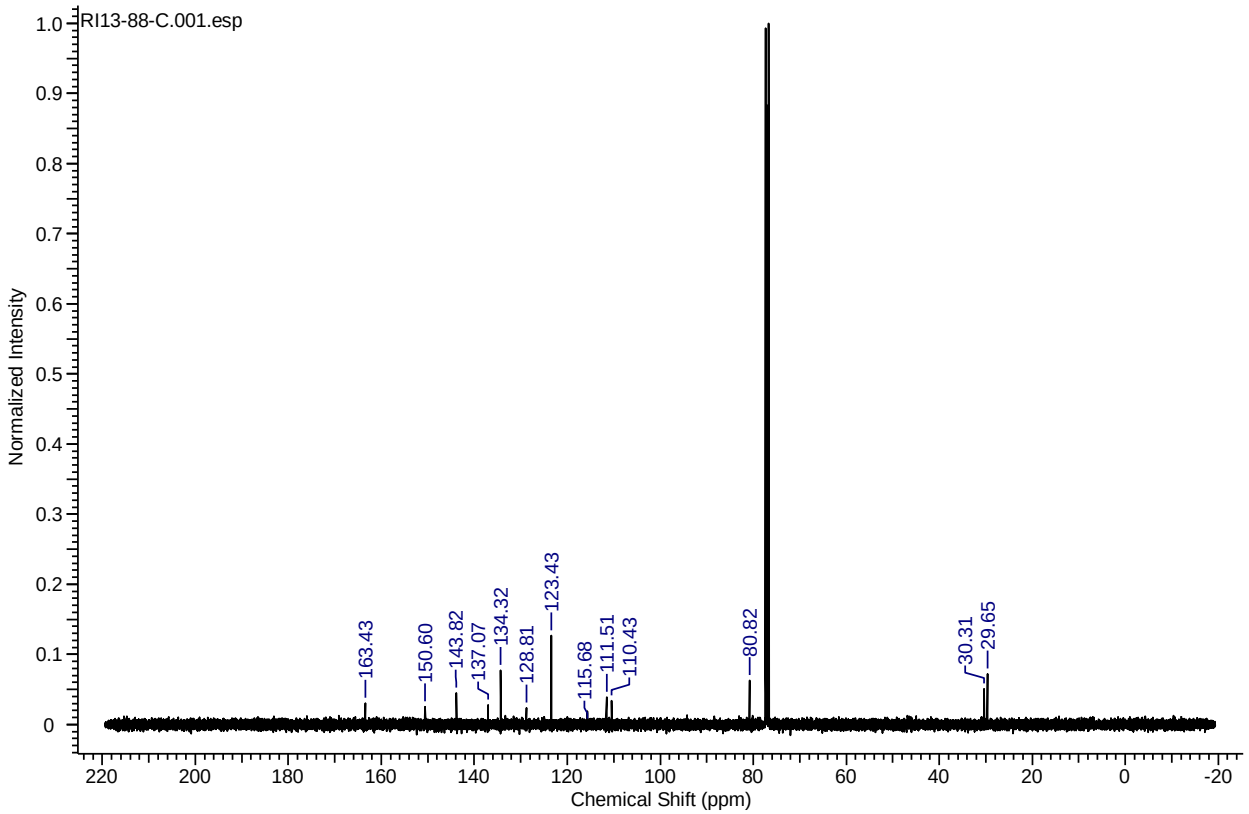

MAA-3-11P-RECR1.001.esp
SI4
Normalized Intensity
1.91
1.93
1.91
3.88
1.01
4.00
3.98
Chemical Shift (ppm)

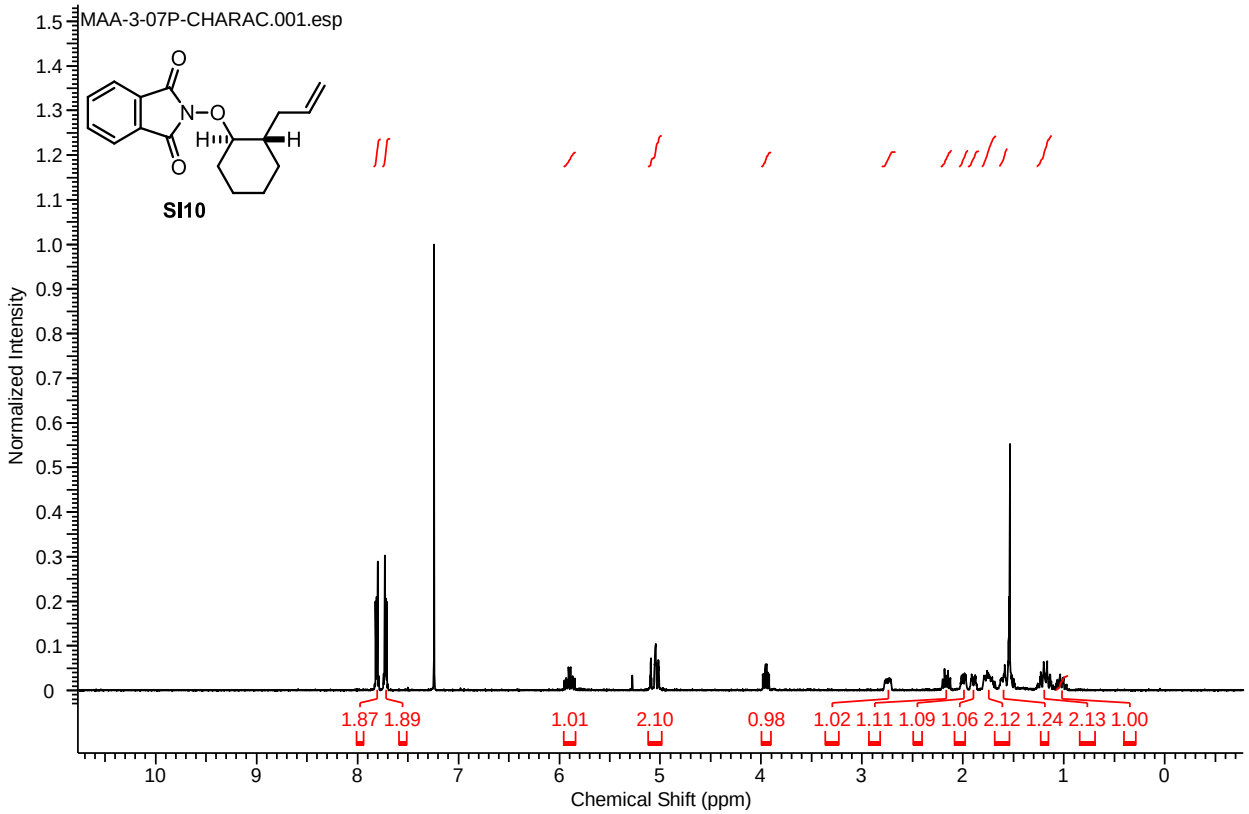

MAA-3-11P-RECR1.002.esp
Normalized Intensity
164.35
137.93
134.41
129.04
123.45
115.06
87.11
31.70
29.10
Chemical Shift (ppm)

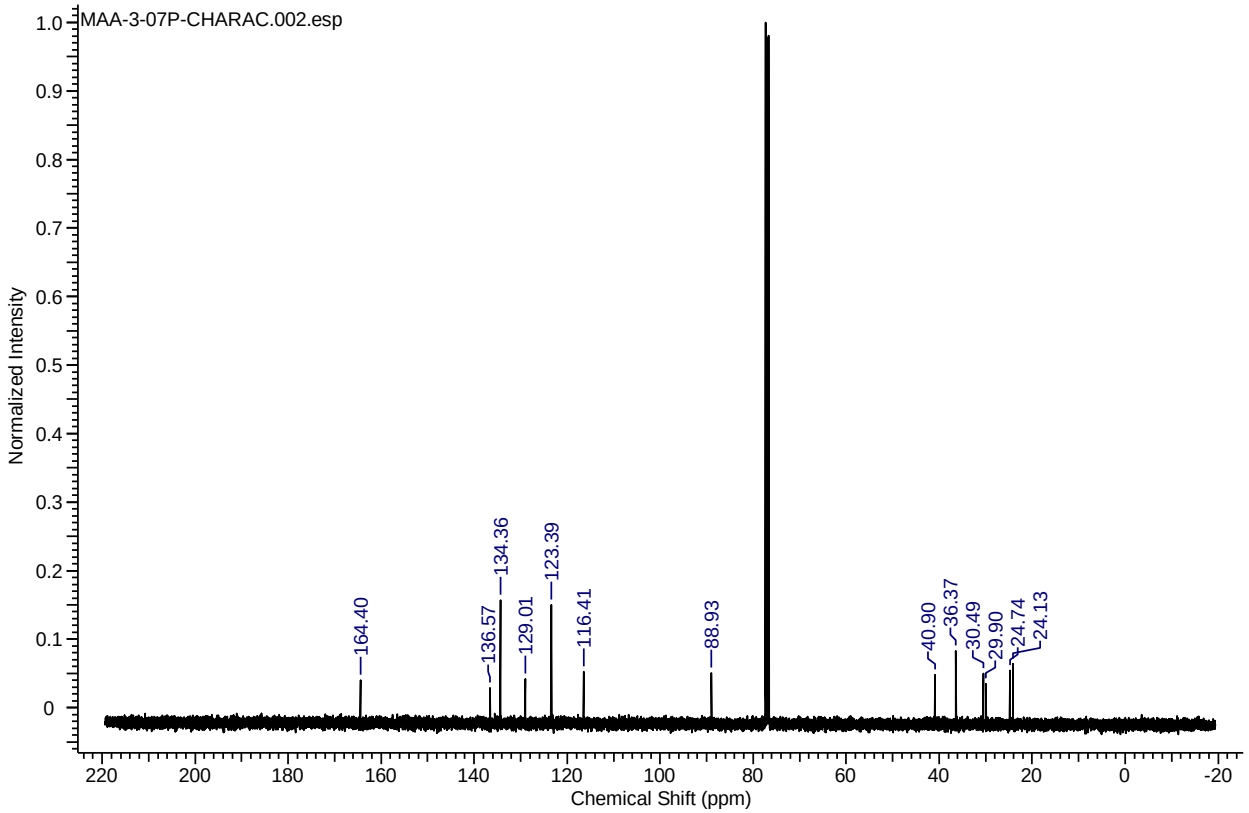

RI13-96-H.001.esp
SI6
Normalized Intensity
0.91 3.77 1.78 0.92 0.90 0.92 1.93 2.83 1.00
Chemical Shift (ppm)

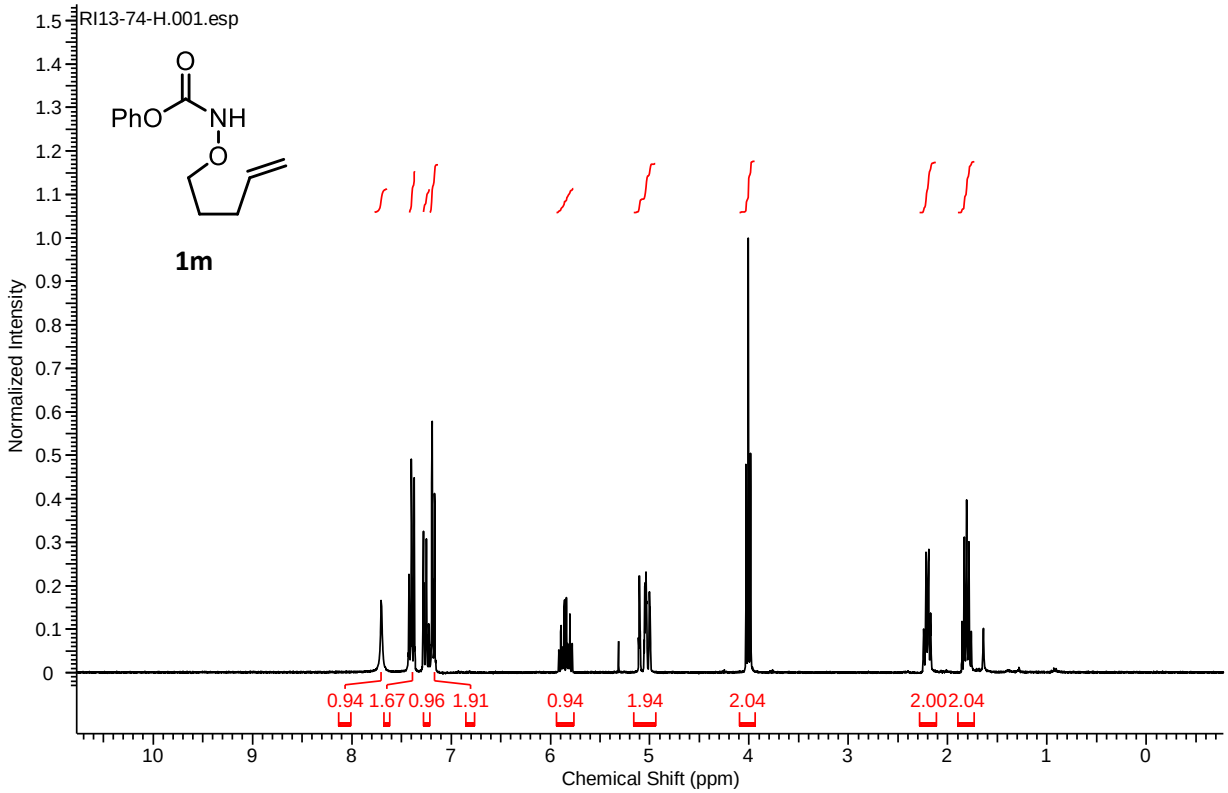

RI13-96-C.001.esp
Normalized Intensity
163.52
158.28
148.86
137.41
134.30
128.87
123.52
123.39
122.37
115.36
89.83
33.41
29.50
Chemical Shift (ppm)

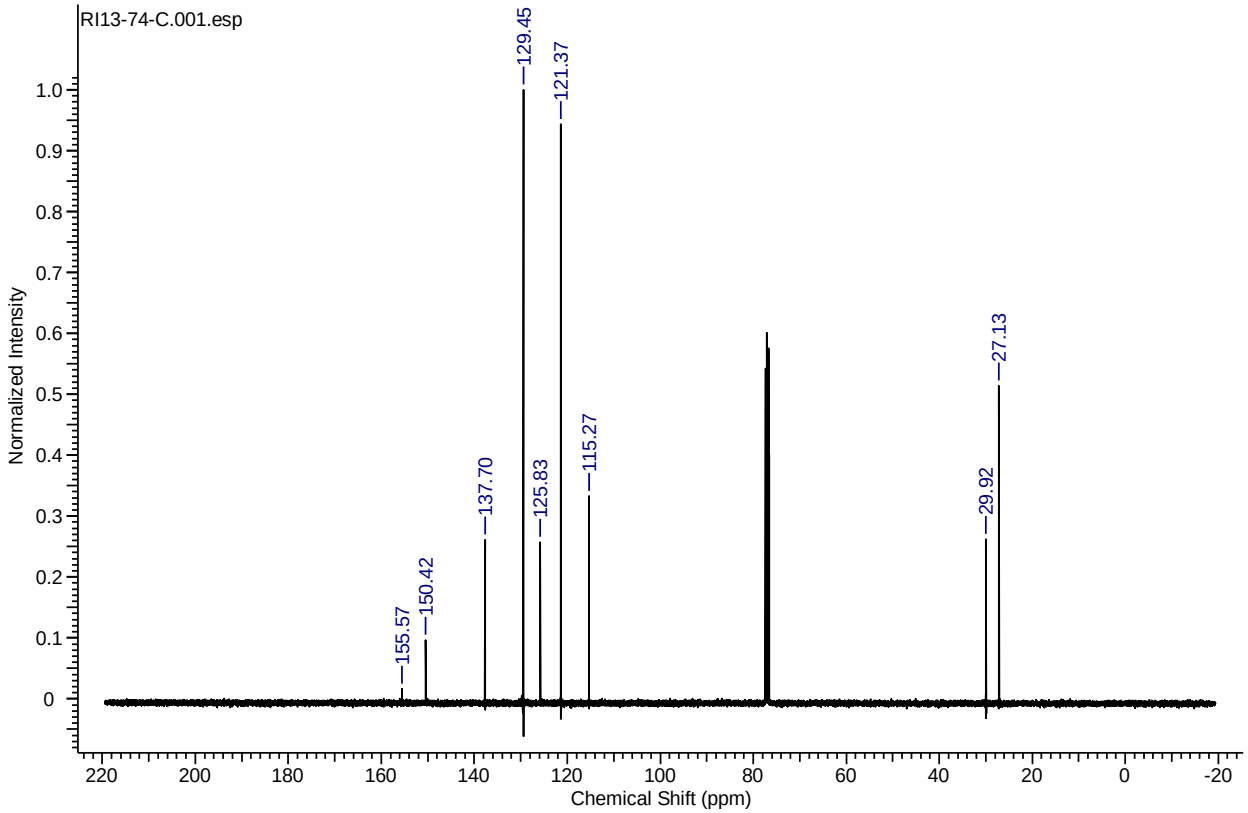

RI13-88-H.001.esp
SI7
Normalized Intensity
Chemical Shift (ppm)
2.00 1.85 0.89 0.92 0.91 1.02 0.96 1.91 1.00 2.85

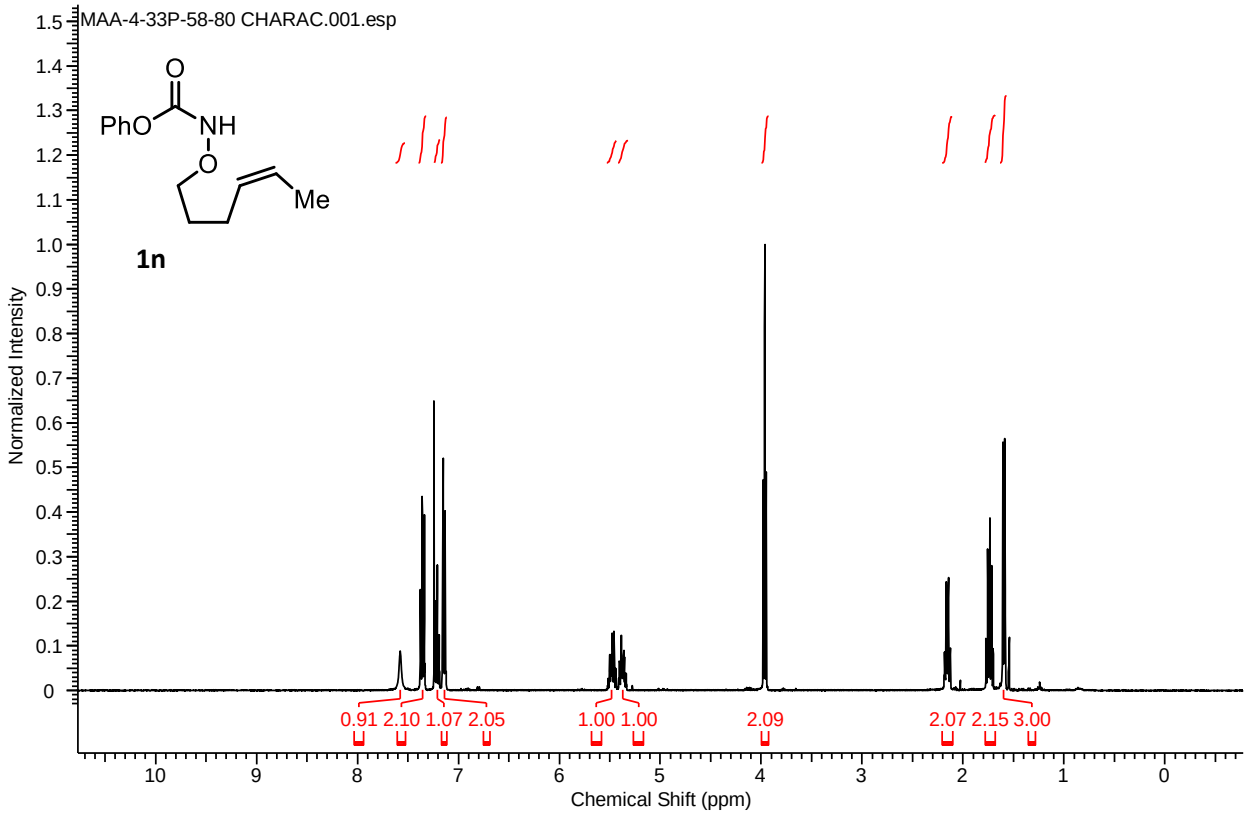

RI13-88-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
163.43
150.60
143.82
137.07
134.32
128.81
123.43
115.68
111.51
110.43
80.82
30.31
29.65

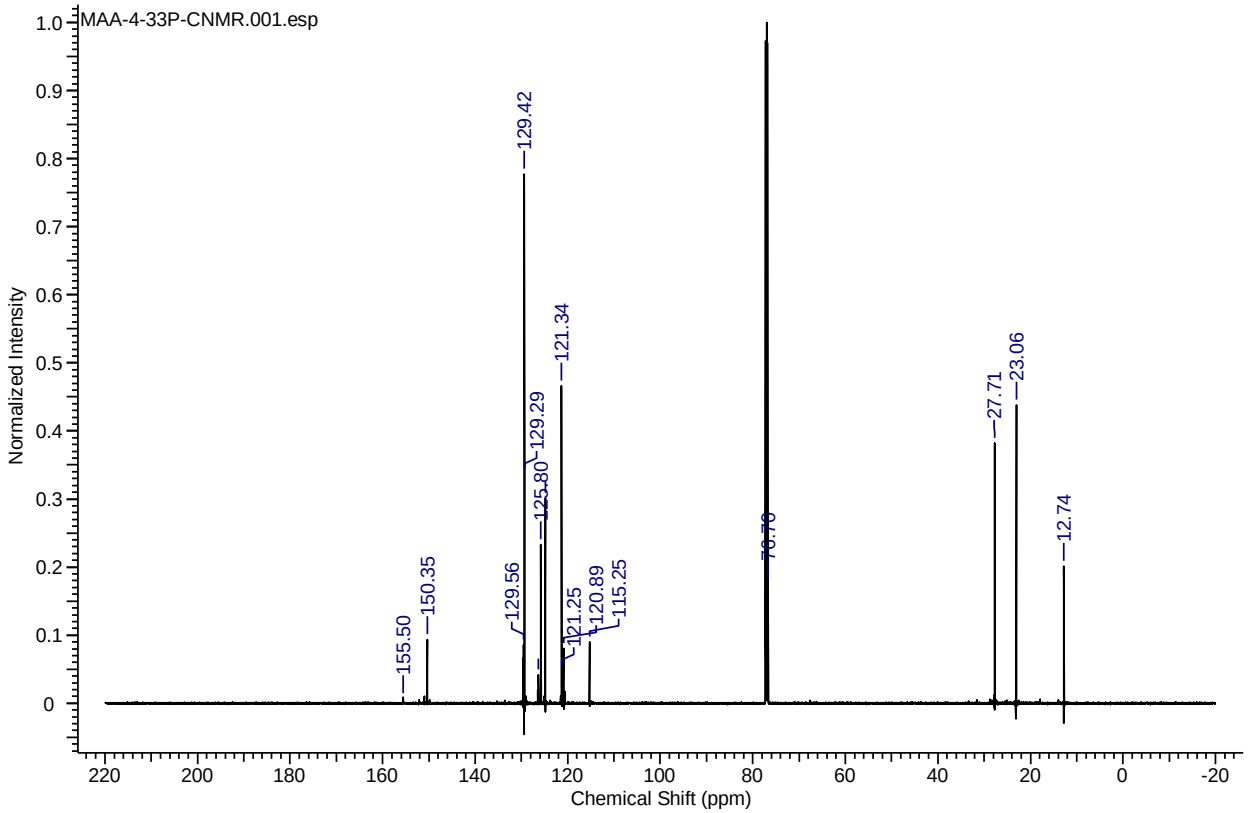

MAA-3-07P-CHARAC.001.esp
SI10
Normalized Intensity
Chemical Shift (ppm)
1.87 1.89
1.01
2.10
0.98
1.02 1.11 1.09 1.06 2.12 1.24 2.13 1.00

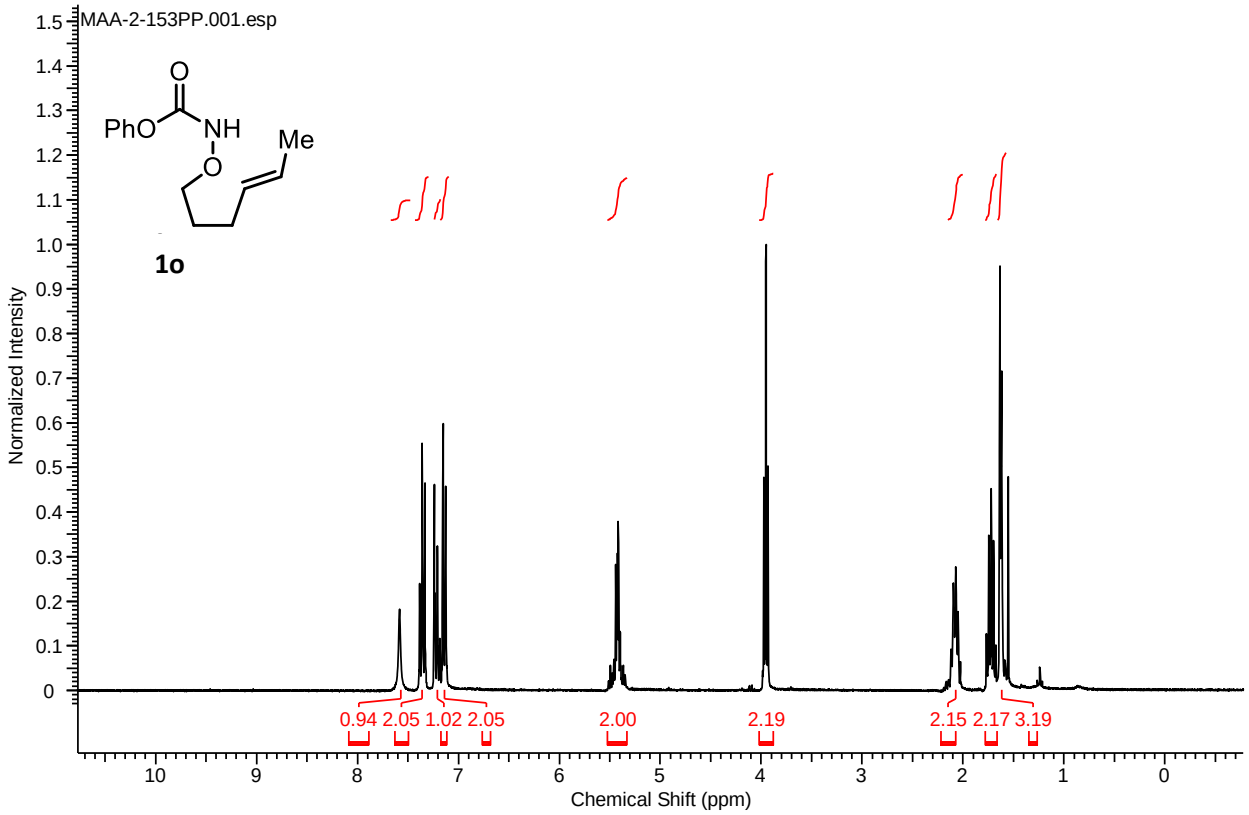

MAA-3-07P-CHARAC.002.esp
Normalized Intensity
Chemical Shift (ppm)
164.40
136.57
134.36
129.01
123.39
116.41
88.93
40.90
36.37
30.49
29.90
24.74
24.13

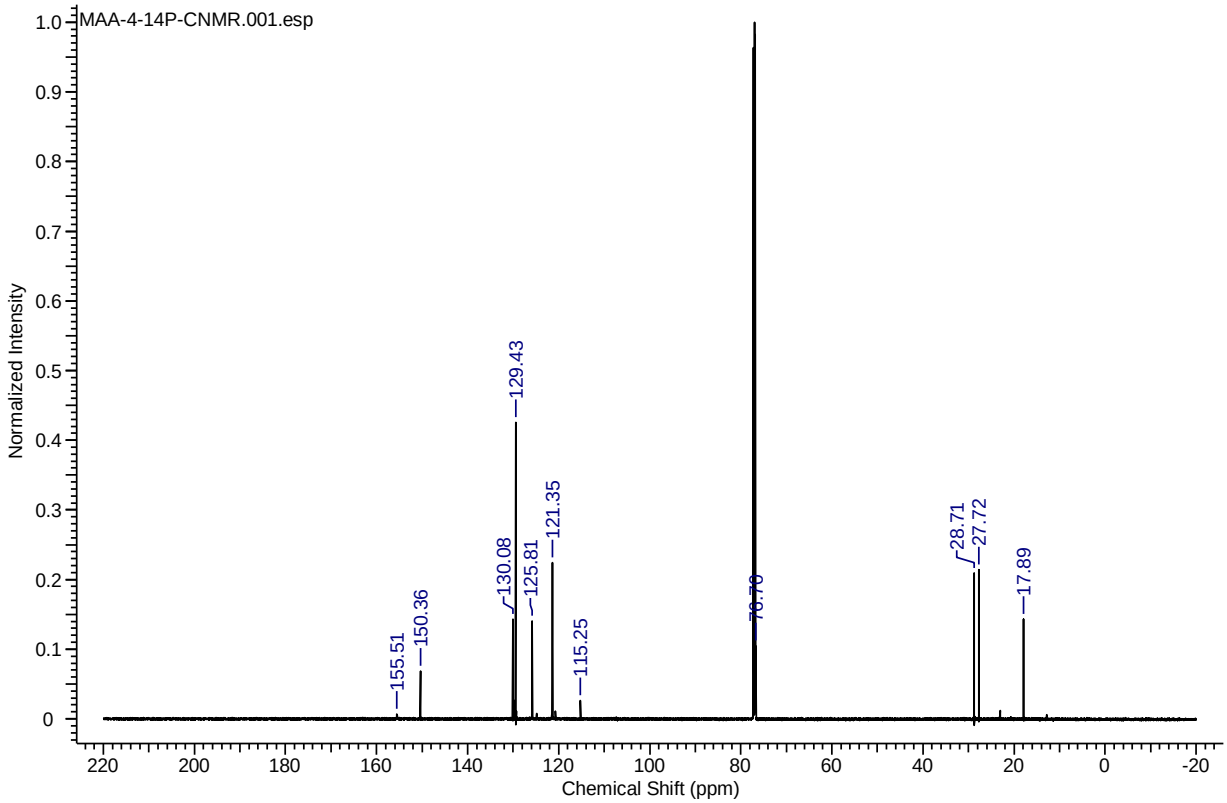

RI13-74-H.001.esp
PhO
O
NH
O
1m
Normalized Intensity
0.94 1.67 0.96 1.91 0.94 1.94 2.04 2.00 2.04
Chemical Shift (ppm)

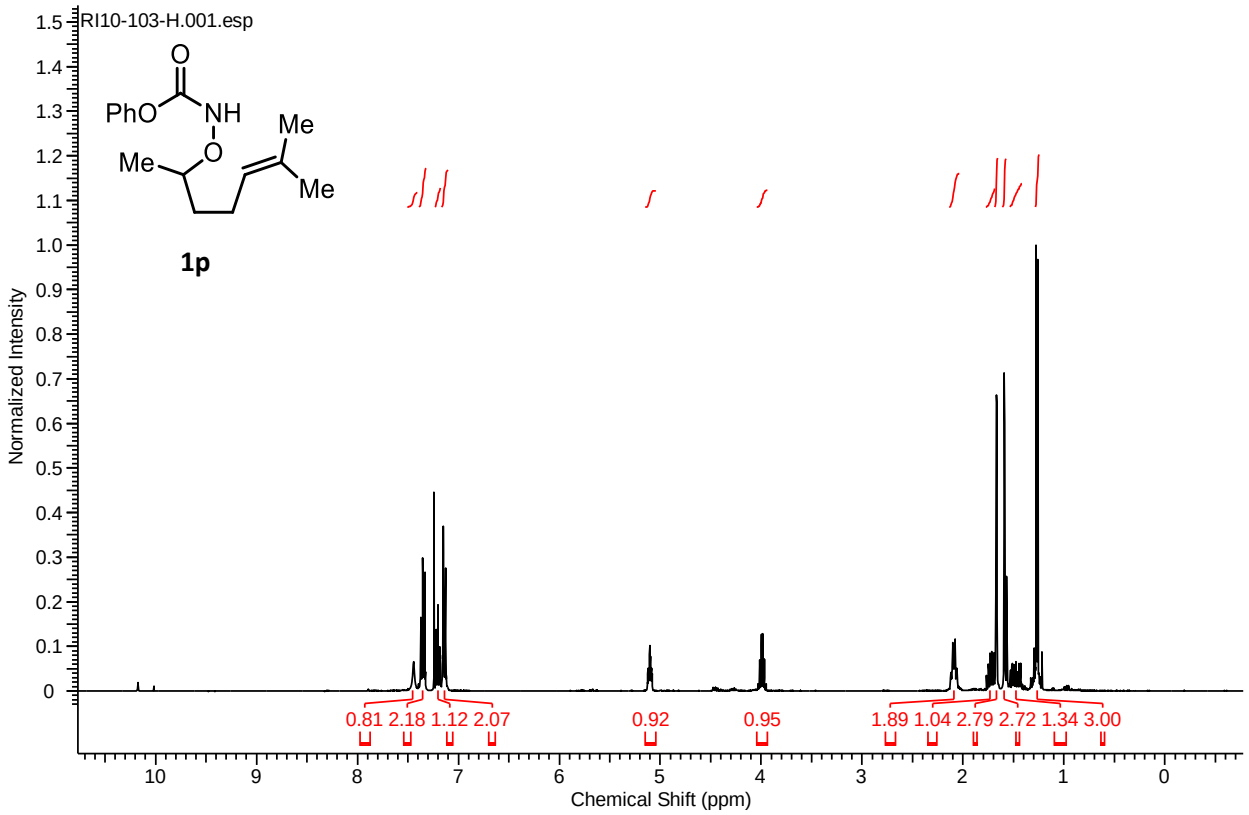

RI13-74-C.001.esp
129.45
121.37
137.70
125.83
115.27
155.57
150.42
29.92
27.13
Normalized Intensity
Chemical Shift (ppm)

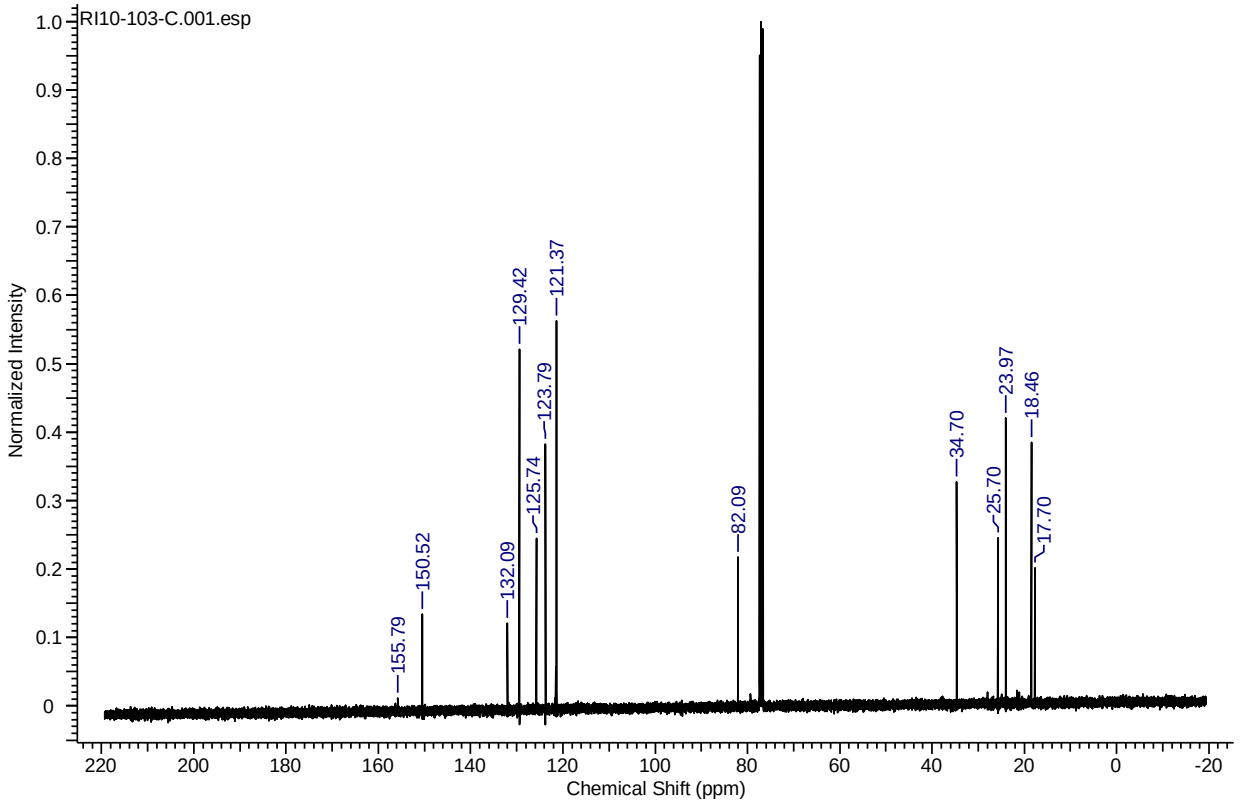

MAA-4-33P-58-80 CHARAC.001.esp
PhO
NH
O
O
Me
1n
Normalized Intensity
0.91 2.10 1.07 2.05
1.00 1.00
2.09
2.07 2.15 3.00
Chemical Shift (ppm)

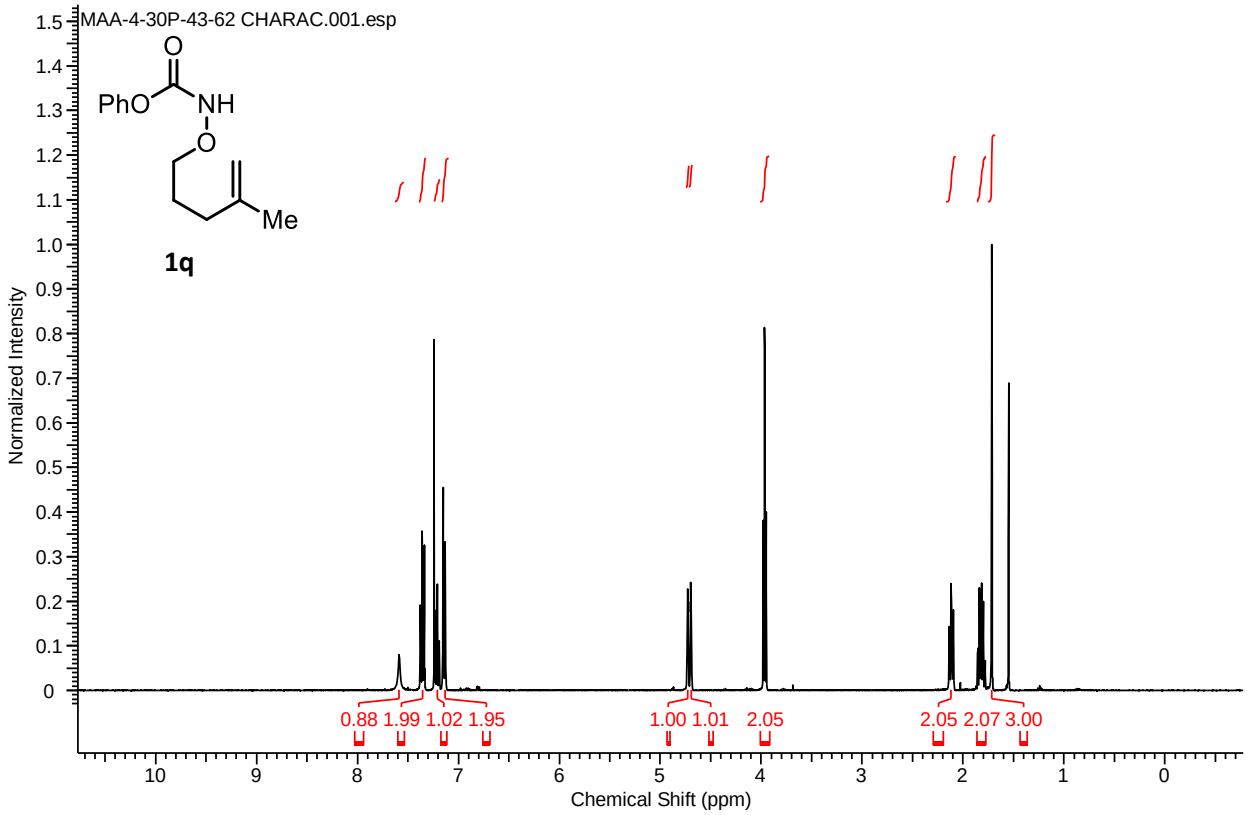

MAA-4-33P-CNMR.001.esp
Normalized Intensity
129.42
129.29
125.80
121.34
155.50
150.35
129.56
121.25
120.89
115.25
76.76
27.71
23.06
12.74
Chemical Shift (ppm)

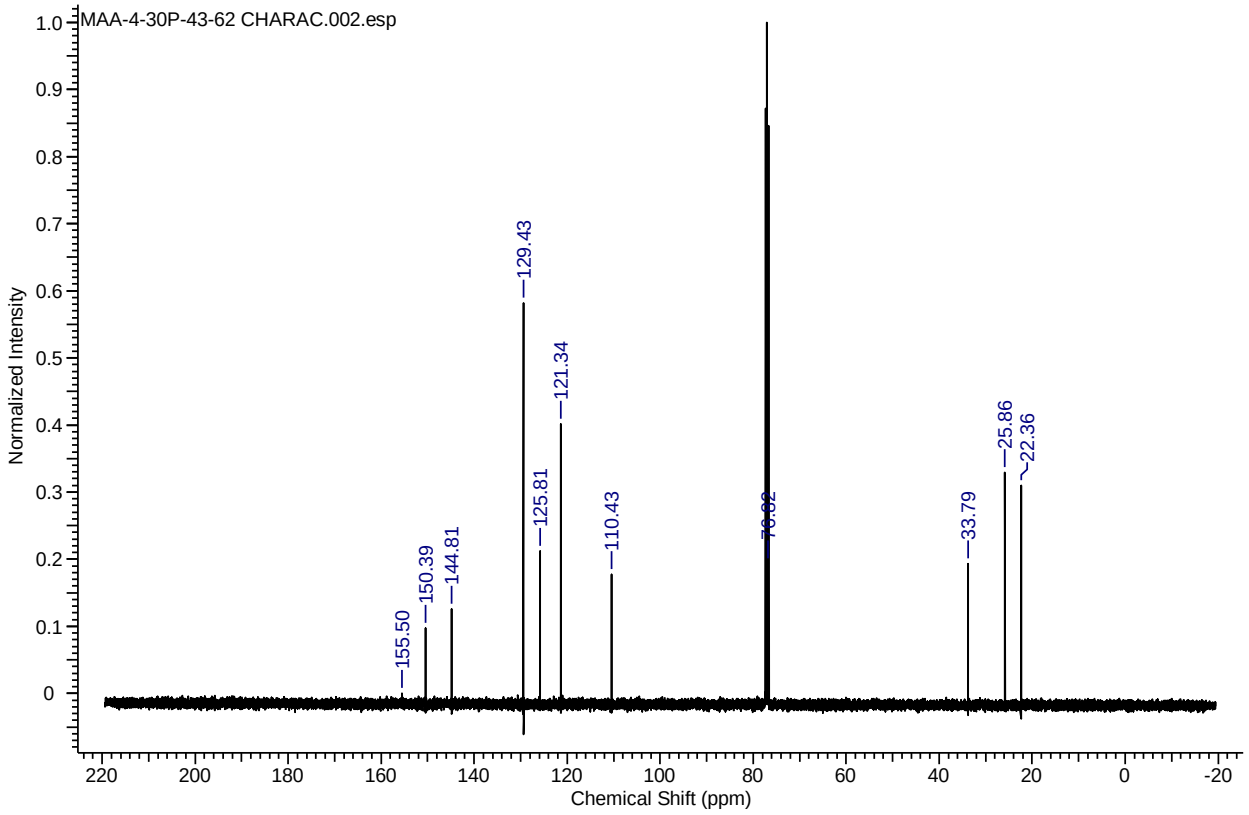

MAA-2-153PP.001.esp
PhO
NH
O
O
Me
1o
Normalized Intensity
0.94 2.05 1.02 2.05 2.00 2.19 2.15 2.17 3.19
Chemical Shift (ppm)

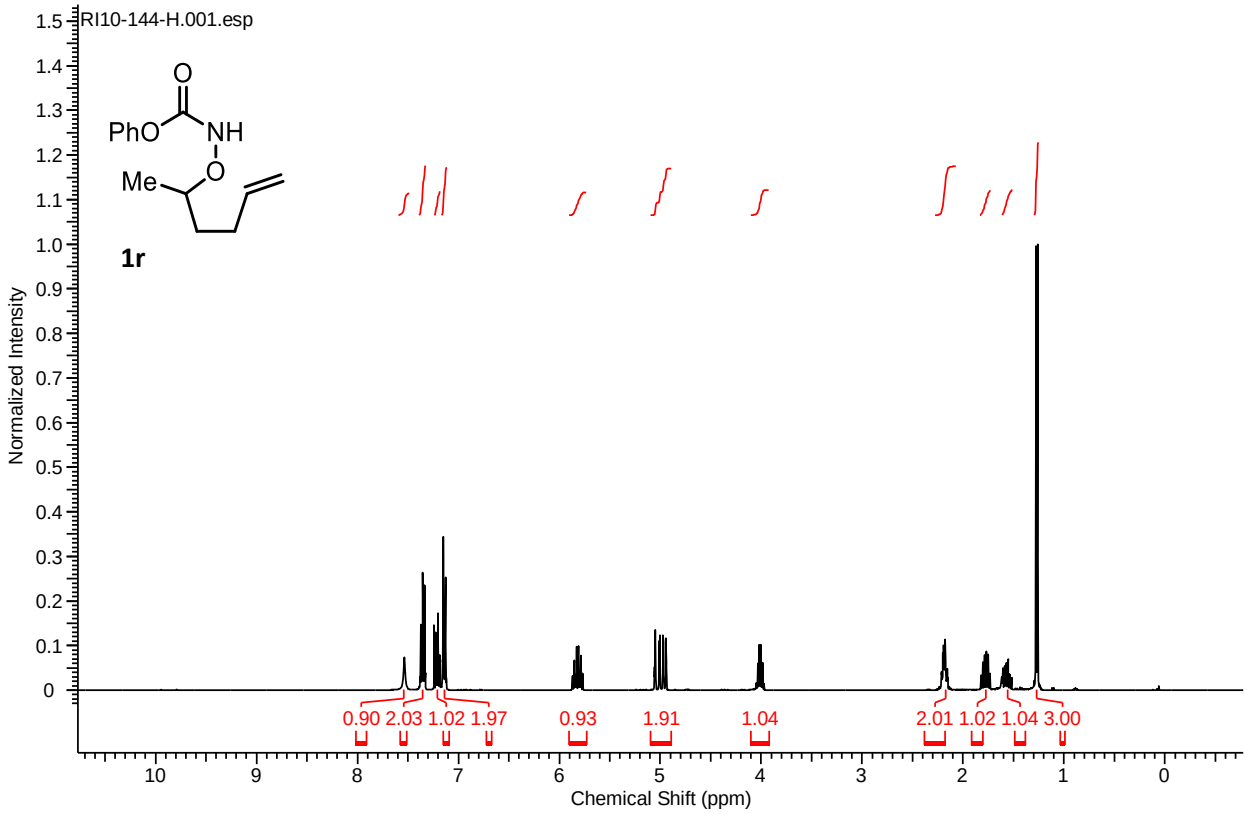

MAA-4-14P-CNMR.001.esp
Normalized Intensity
155.51
150.36
130.08
129.43
125.81
121.35
115.25
76.76
28.71
27.72
17.89
Chemical Shift (ppm)

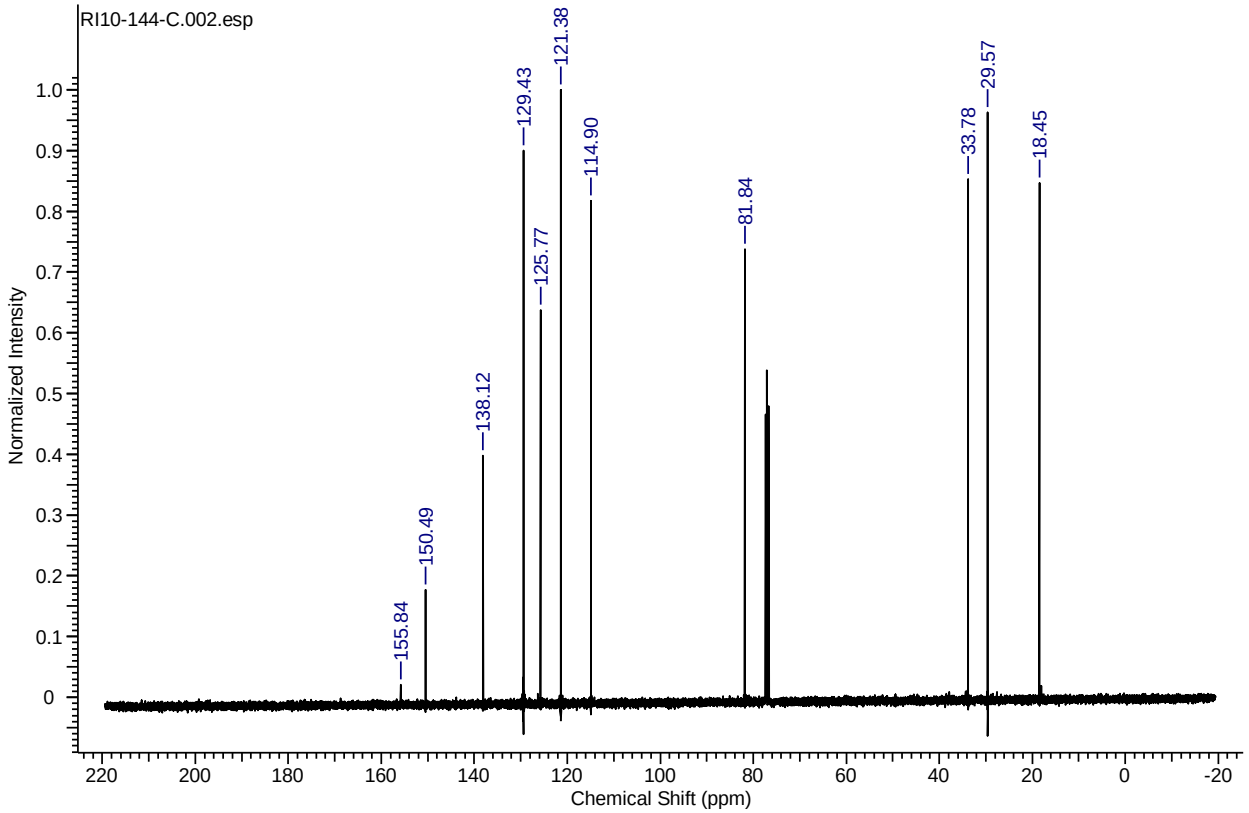

RI10-103-H.001.esp
PhO
NH
O
Me
Me
O
Me
1p
Normalized Intensity
Chemical Shift (ppm)
0.81 2.18 1.12 2.07
0.92
0.95
1.89 1.04 2.79 2.72 1.34 3.00

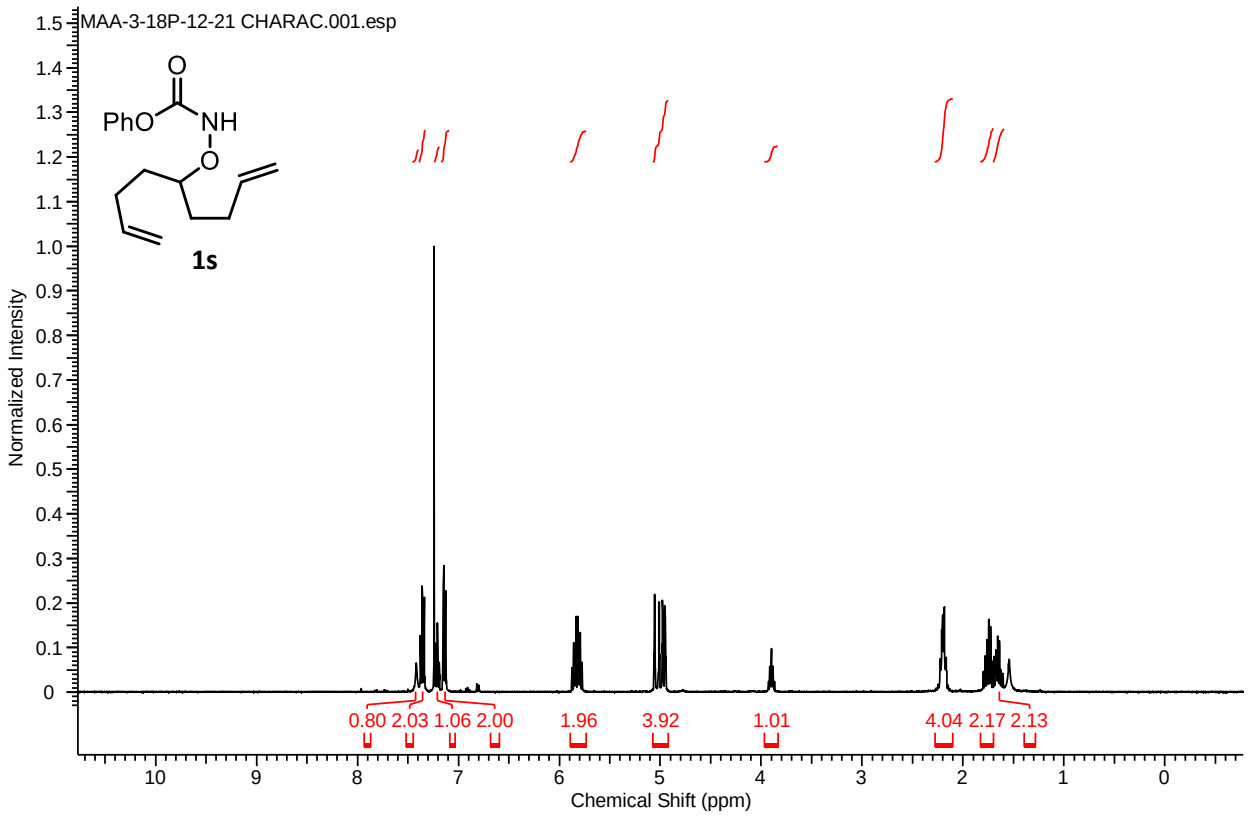

RI10-103-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
155.79
150.52
132.09
129.42
125.74
123.79
121.37
82.09
34.70
25.70
23.97
18.46
17.70

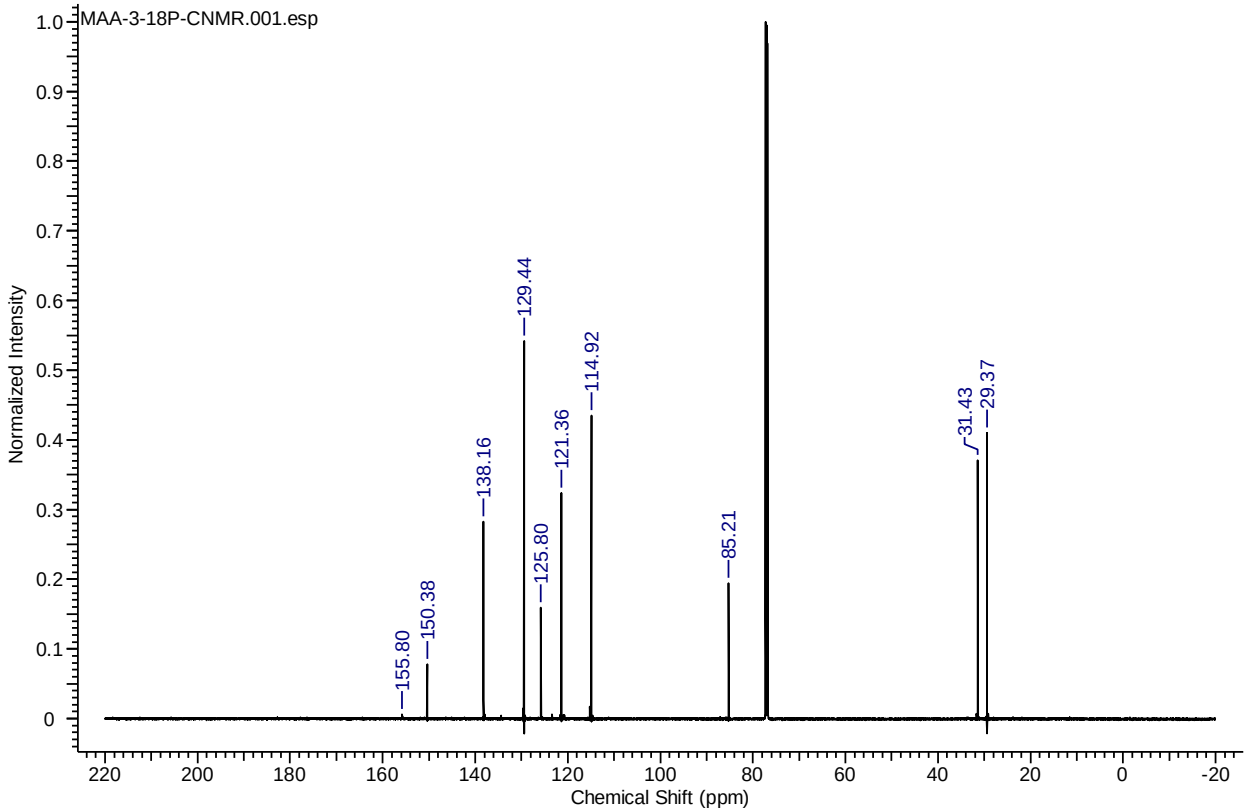

MAA-4-30P-43-62 CHARAC.001.esp
PhO
NH
O
O
Me
1q
Normalized Intensity
0.88 1.99 1.02 1.95
1.00 1.01 2.05
2.05 2.07 3.00
Chemical Shift (ppm)

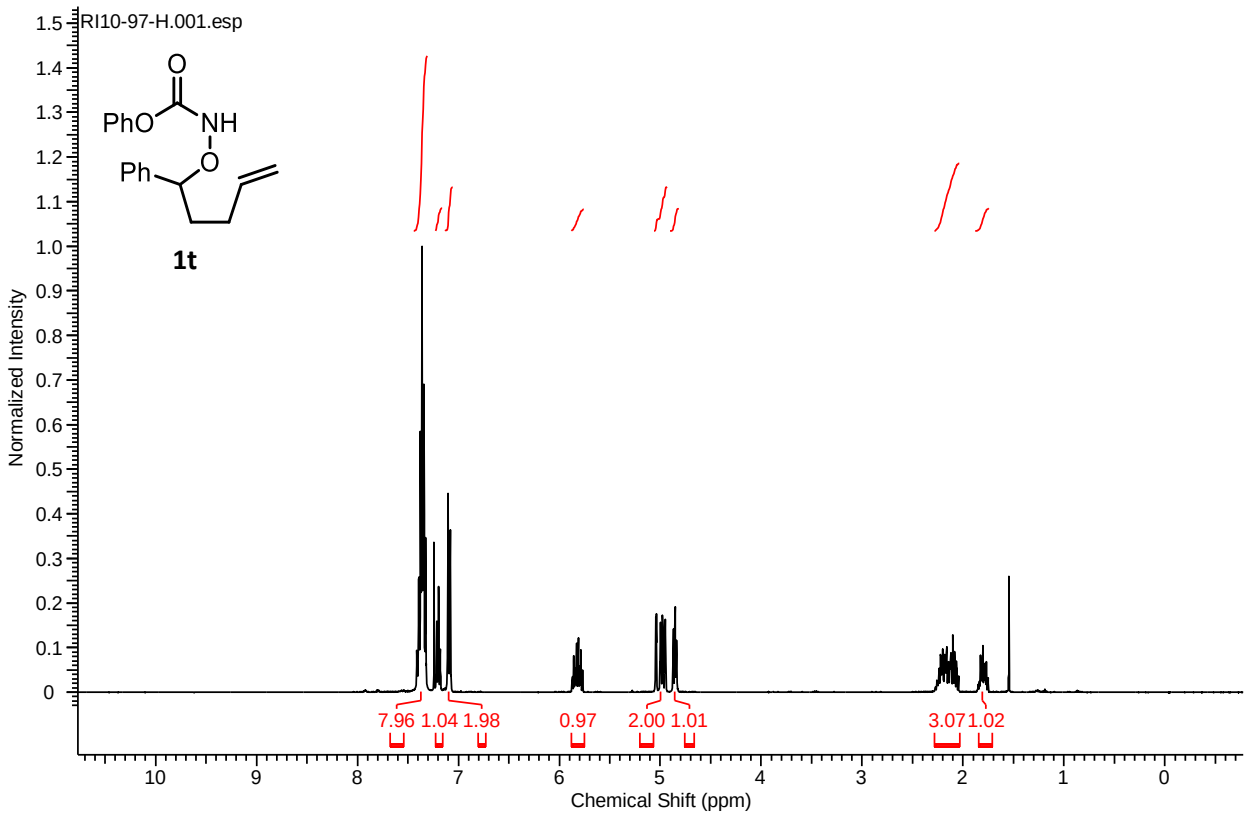

MAA-4-30P-43-62 CHARAC.002.esp
Normalized Intensity
155.50
150.39
144.81
129.43
125.81
121.34
110.43
76.92
33.79
25.86
22.36
Chemical Shift (ppm)

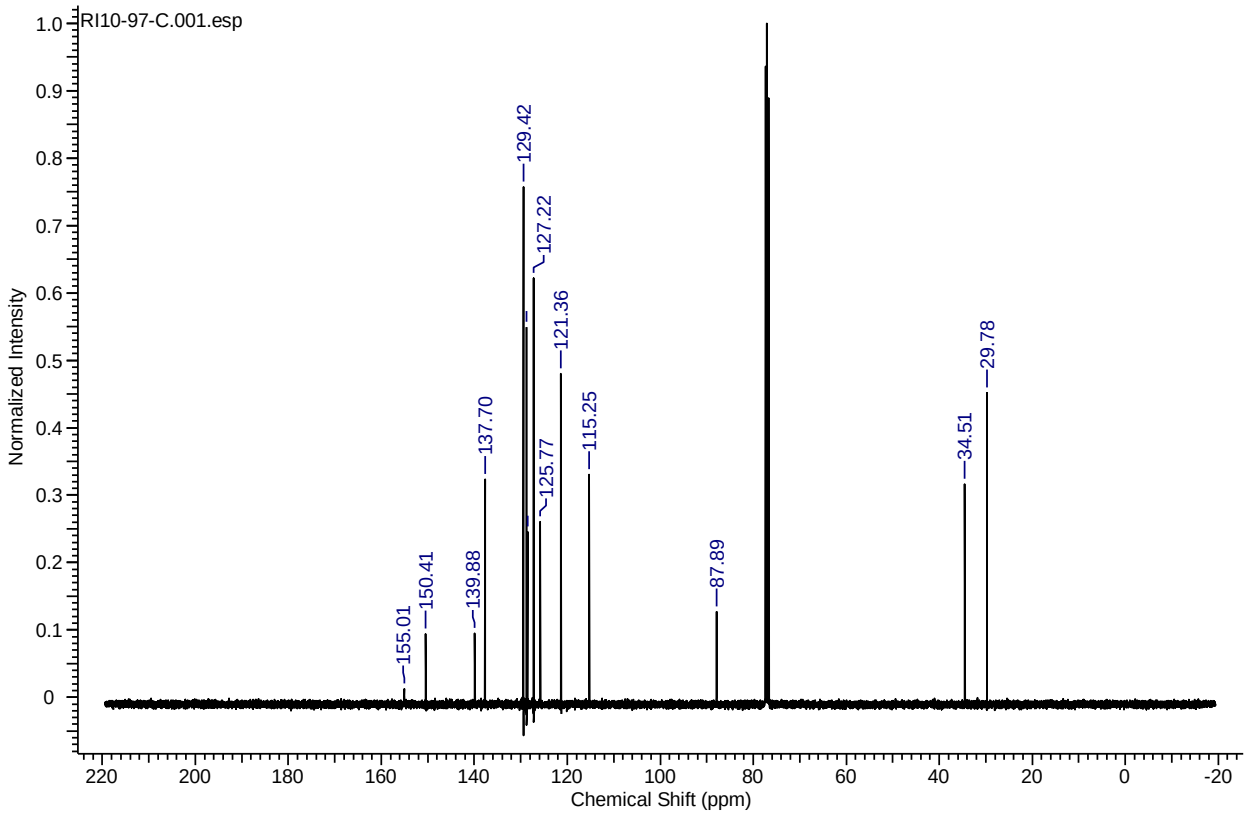

RI10-144-H.001.esp
PhO
NH
O
Me
O
1r
Normalized Intensity
0.90 2.03 1.02 1.97
0.93
1.91
1.04
2.01 1.02 1.04 3.00
Chemical Shift (ppm)

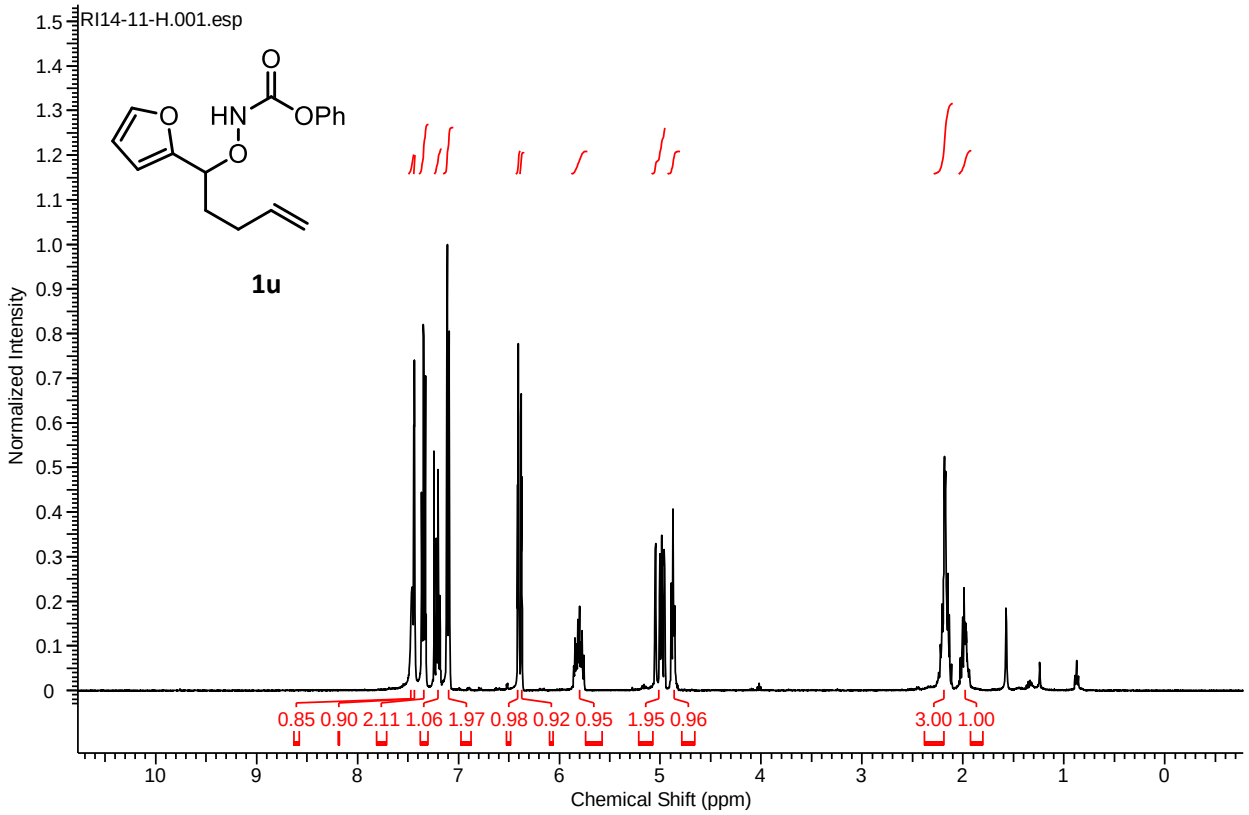

RI10-144-C.002.esp
155.84
150.49
138.12
129.43
125.77
121.38
114.90
81.84
33.78
29.57
18.45
Normalized Intensity
Chemical Shift (ppm)

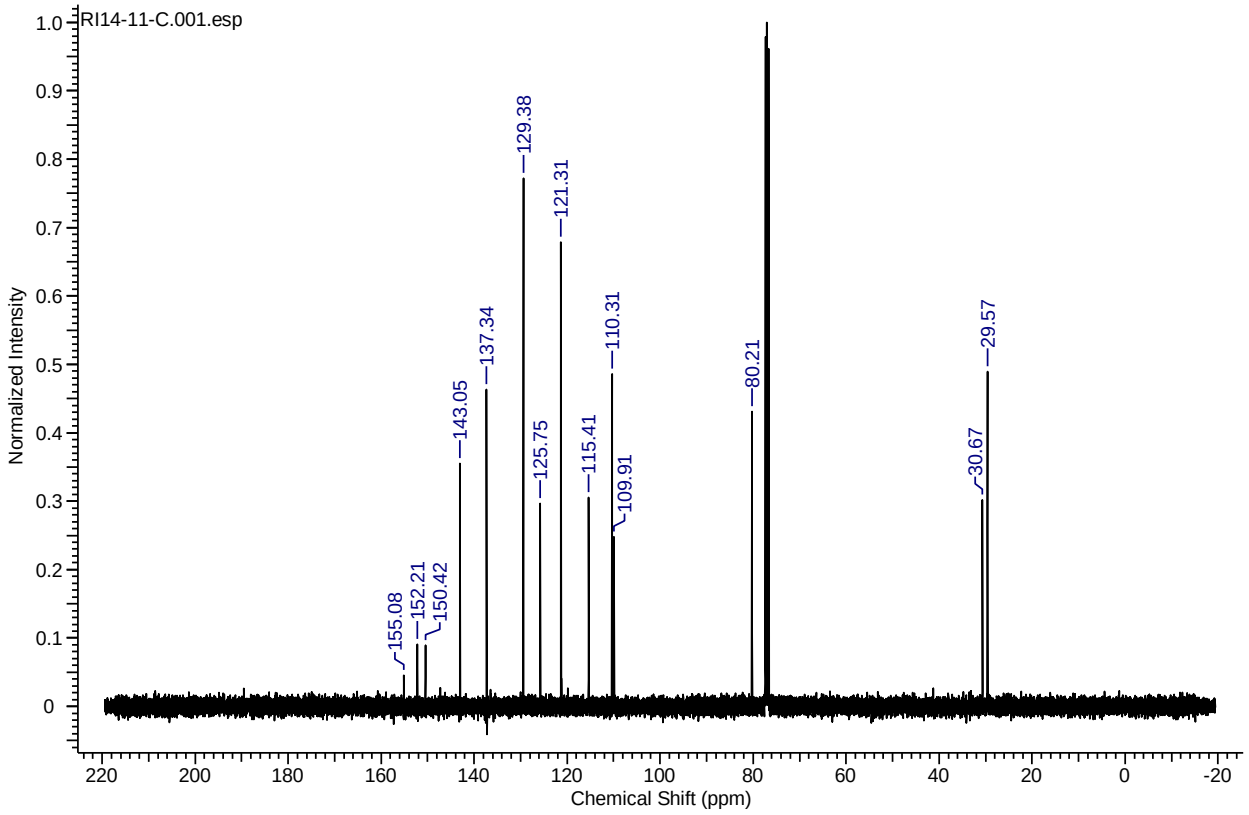

MAA-3-18P-12-21 CHARAC.001.esp
PhO
O
NH
O
1s
Normalized Intensity
0.80 2.03 1.06 2.00
1.96
3.92
1.01
4.04 2.17 2.13
Chemical Shift (ppm)

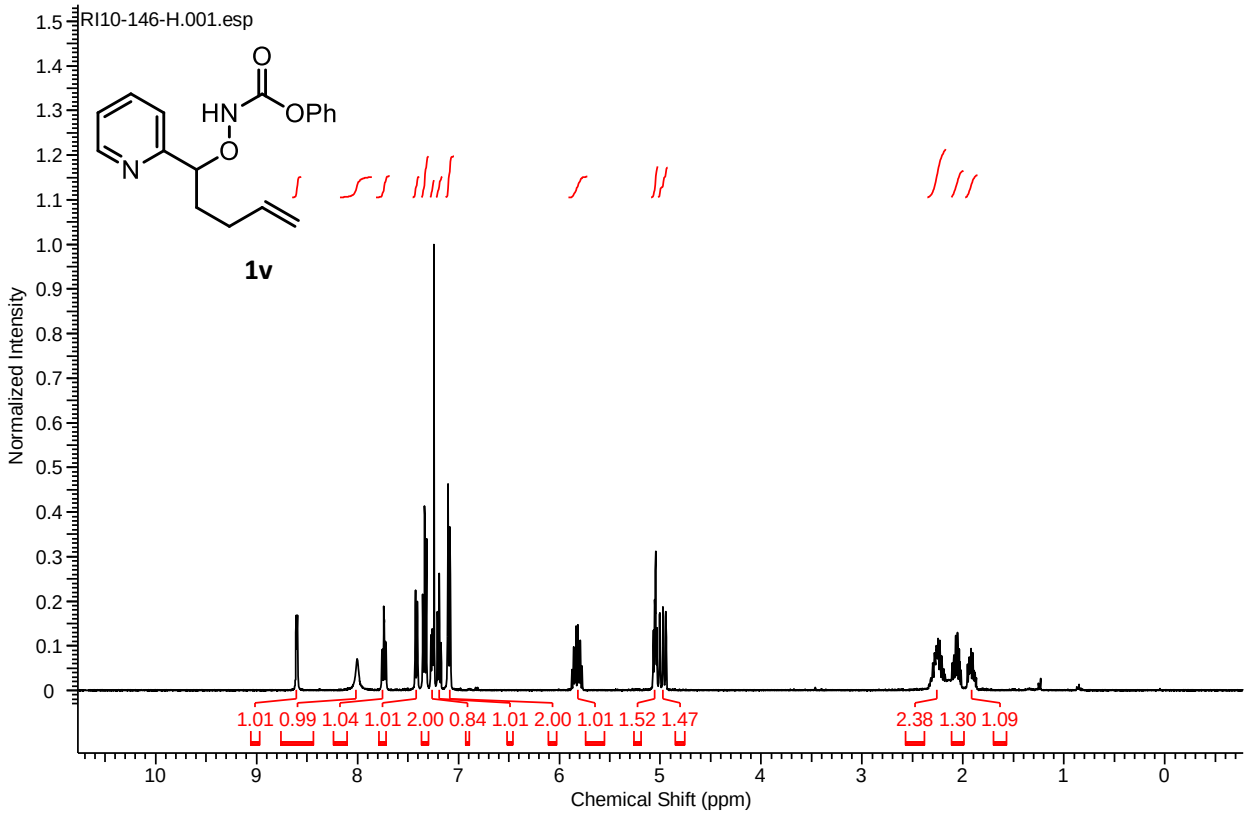

MAA-3-18P-CNMR.001.esp
Normalized Intensity
155.80
150.38
138.16
129.44
125.80
121.36
114.92
85.21
31.43
29.37
Chemical Shift (ppm)

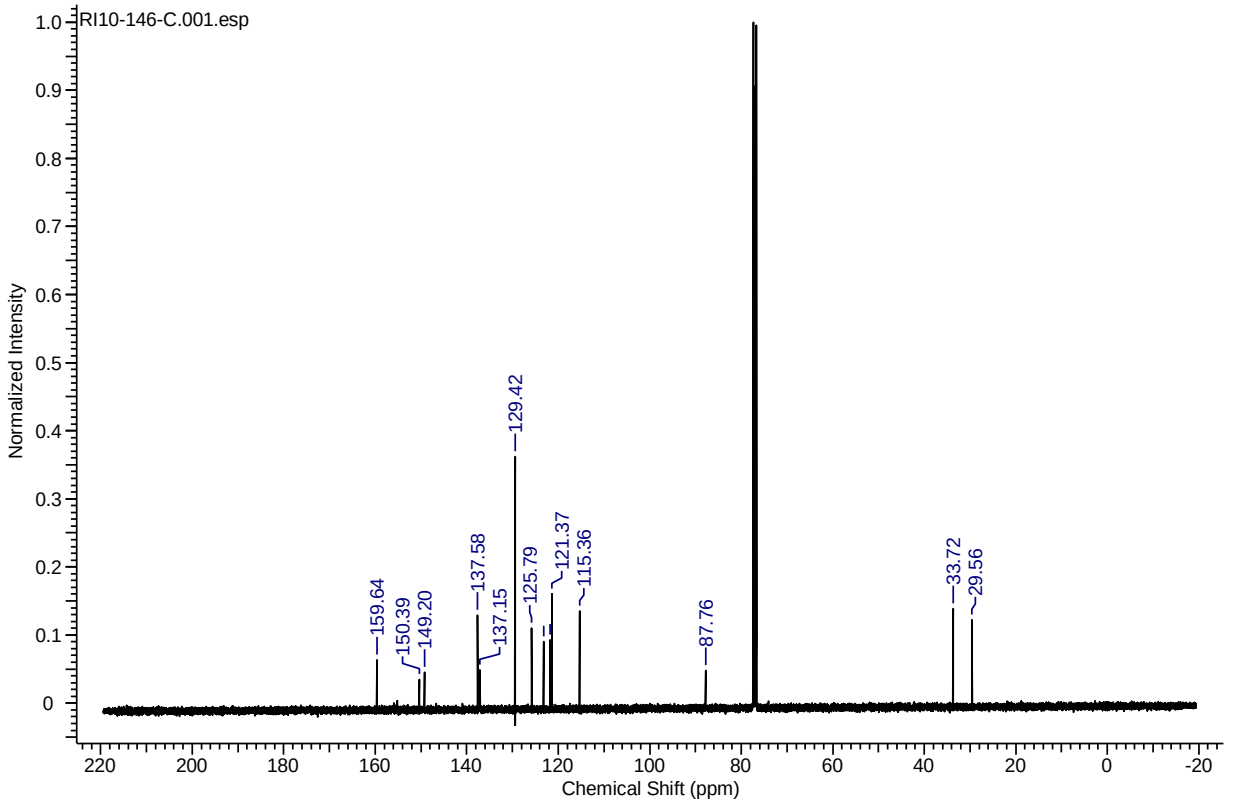

RI10-97-H.001.esp
PhO
NH
O
Ph
O
1t
Normalized Intensity
Chemical Shift (ppm)
7.96 1.04 1.98
0.97
2.00 1.01
3.07 1.02

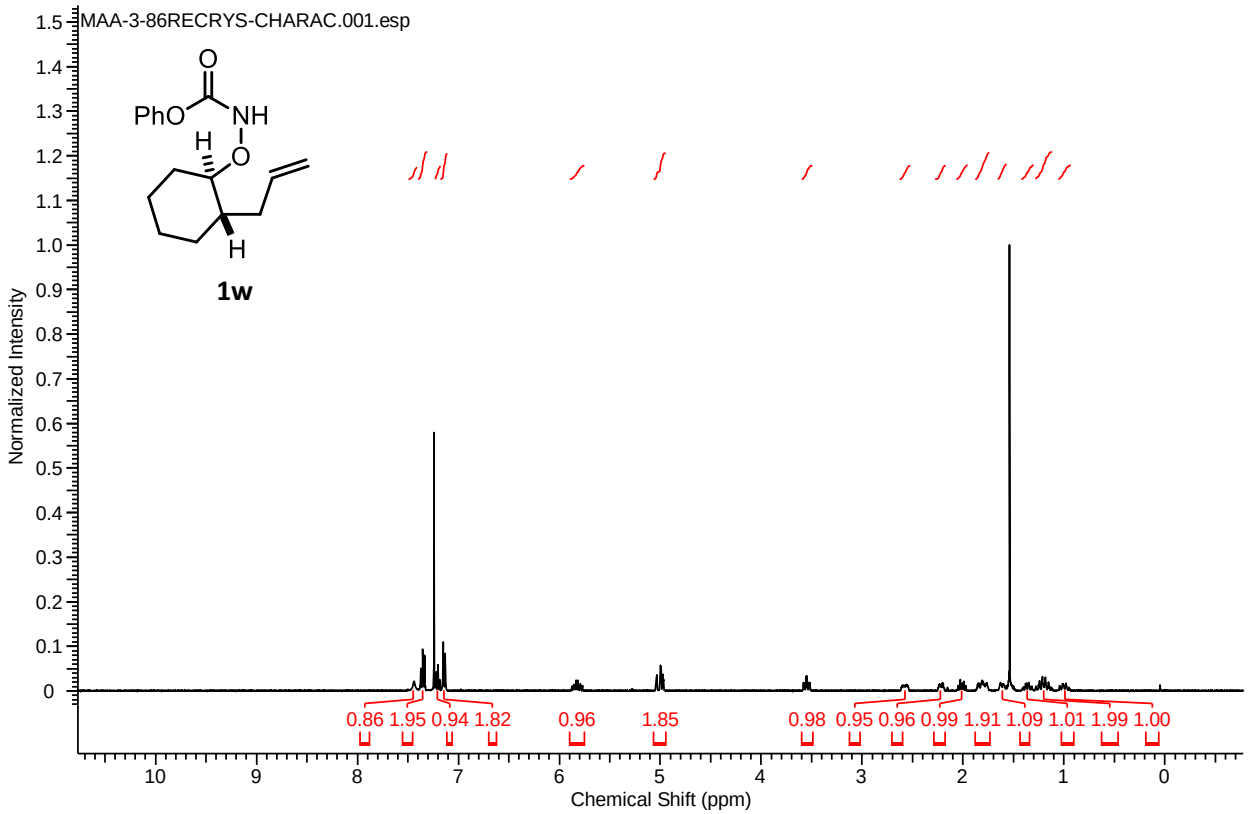

RI10-97-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
155.01
150.41
139.88
137.70
129.42
127.22
125.77
121.36
115.25
87.89
34.51
29.78

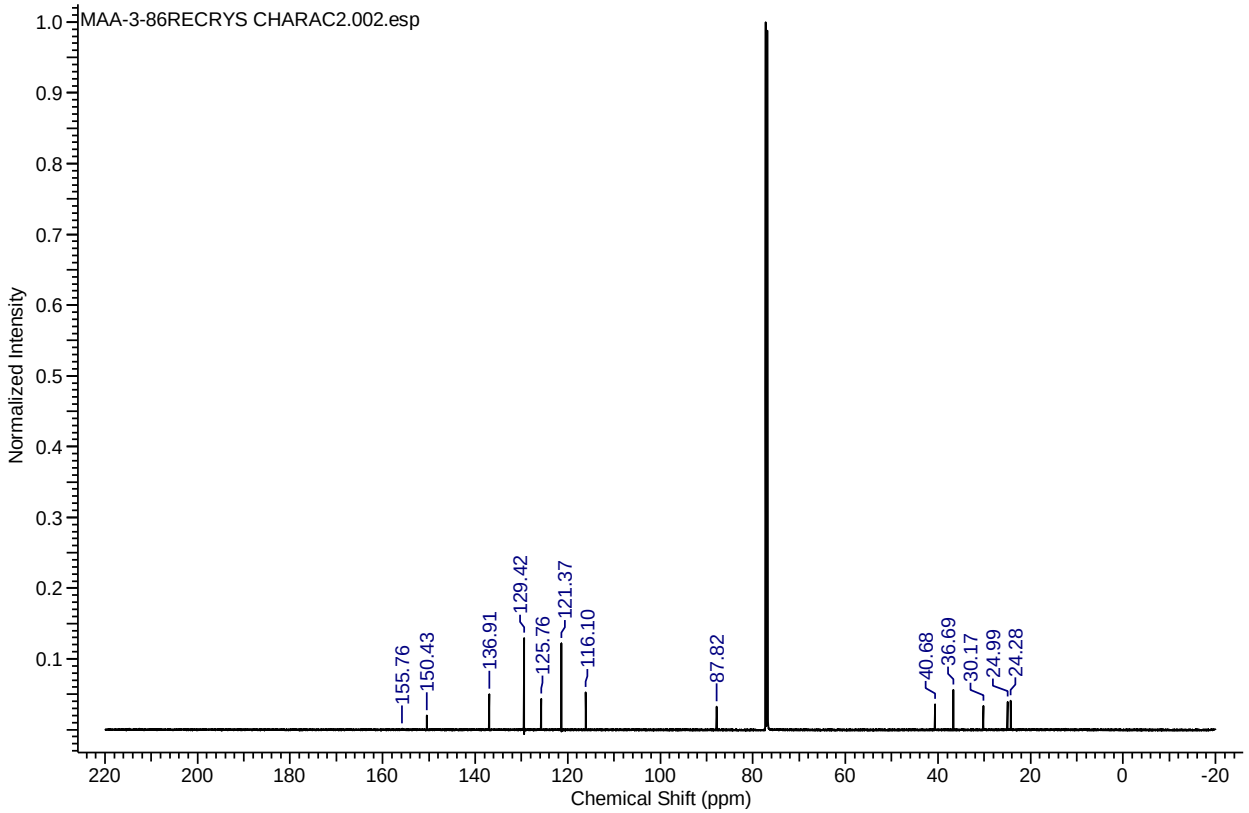

RI14-11-H.001.esp
O
HN
OPh
O
1u
Normalized Intensity
0.85 0.90 2.11 1.06 1.97 0.98 0.92 0.95 1.95 0.96
3.00 1.00
Chemical Shift (ppm)

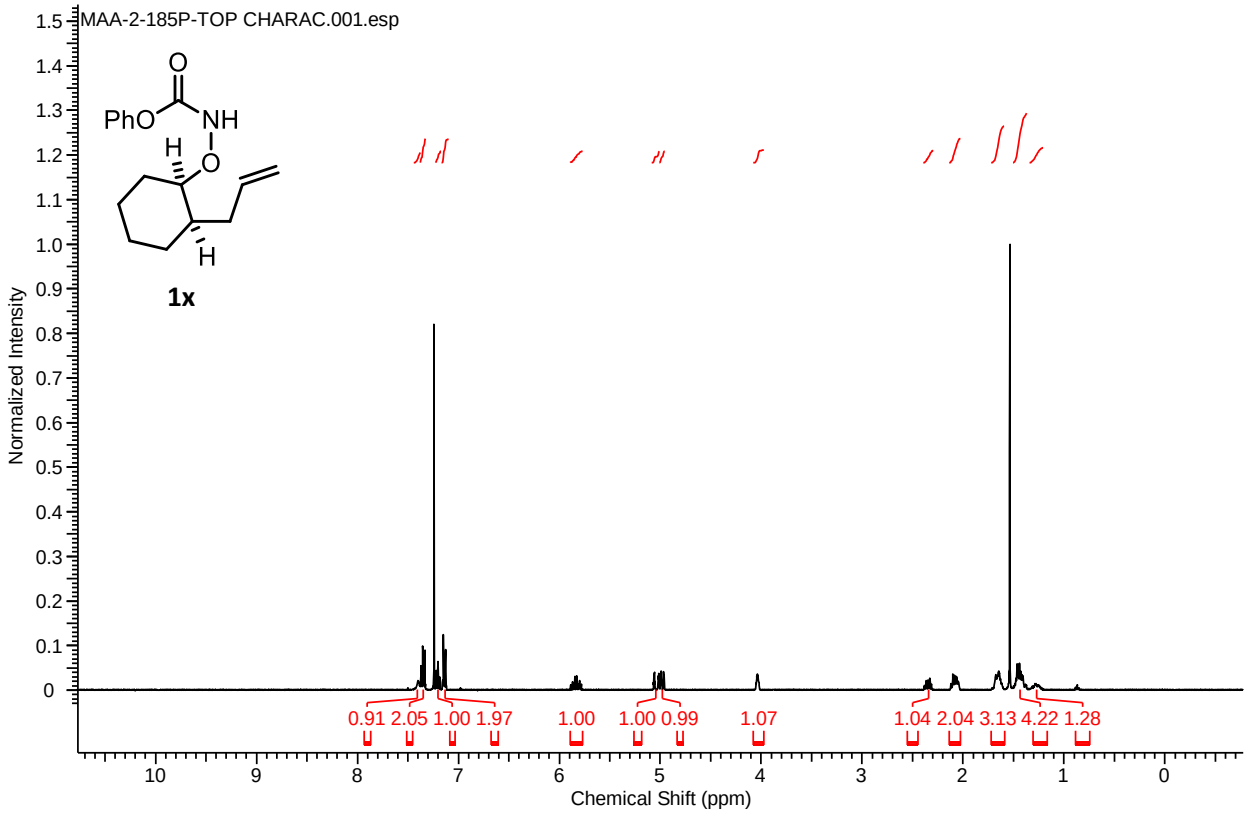

RI14-11-C.001.esp
Normalized Intensity
155.08
152.21
150.42
143.05
137.34
129.38
125.75
121.31
115.41
110.31
109.91
80.21
30.67
29.57
Chemical Shift (ppm)

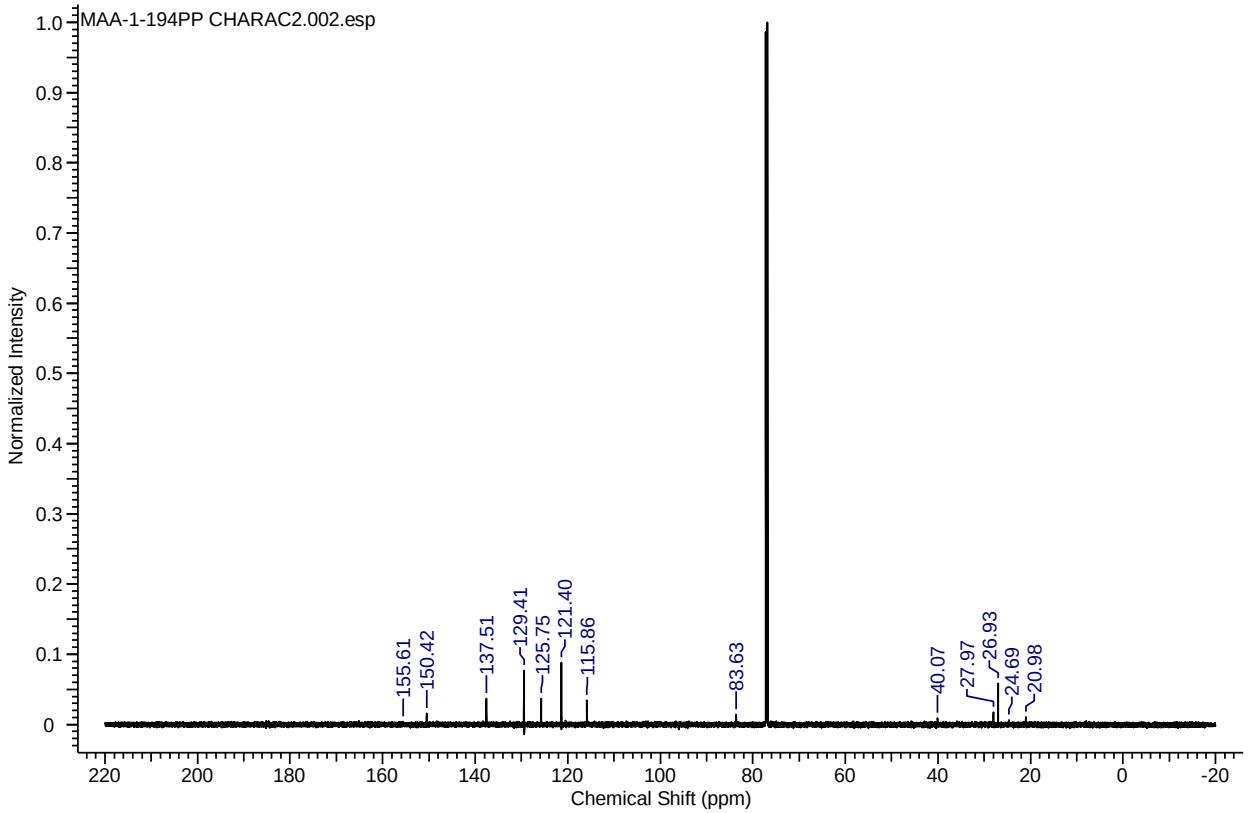

RI10-146-H.001.esp
HN
O
OPh
N
O
1v
Normalized Intensity
1.01 0.99 1.04 1.01 2.00 0.84 1.01 2.00 1.01 1.52 1.47
2.38 1.30 1.09
Chemical Shift (ppm)

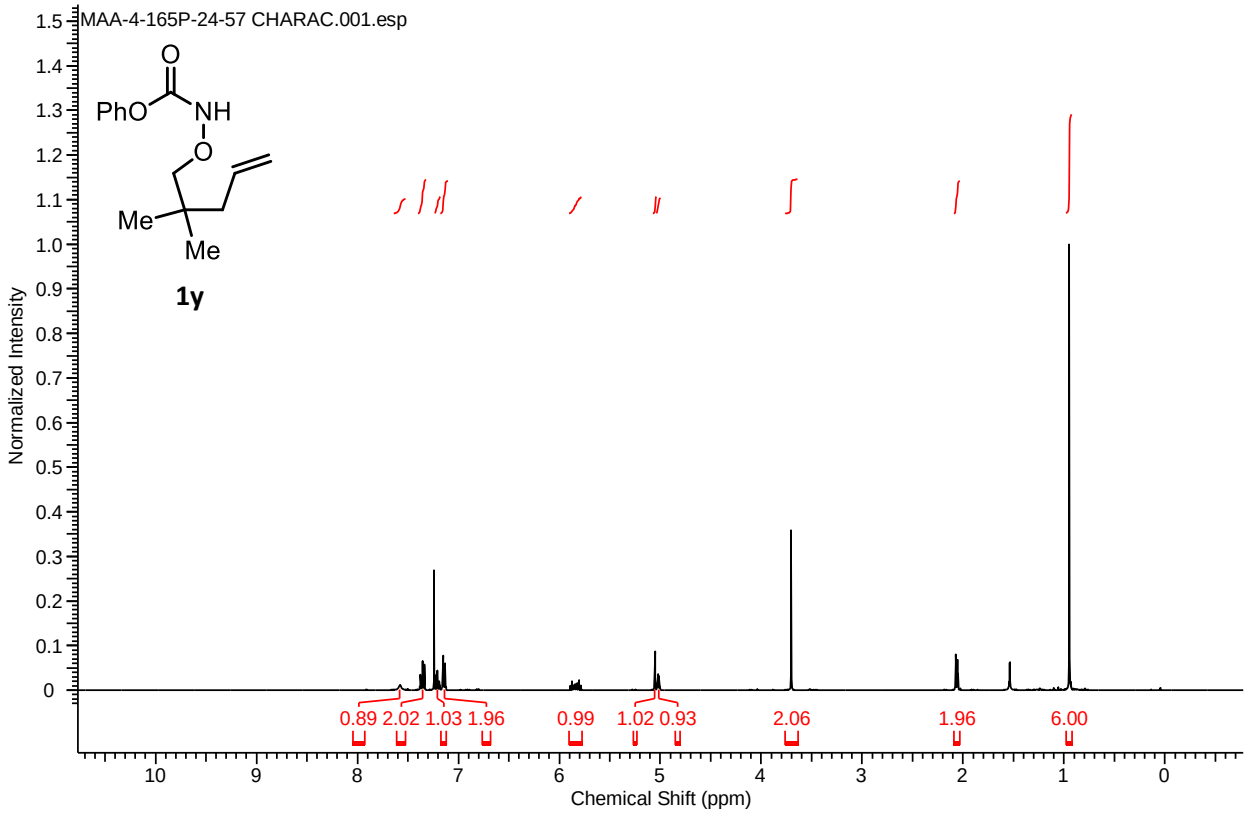

RI10-146-C.001.esp
Normalized Intensity
159.64
150.39
149.20
137.58
137.15
129.42
125.79
121.37
115.36
87.76
33.72
29.56
Chemical Shift (ppm)

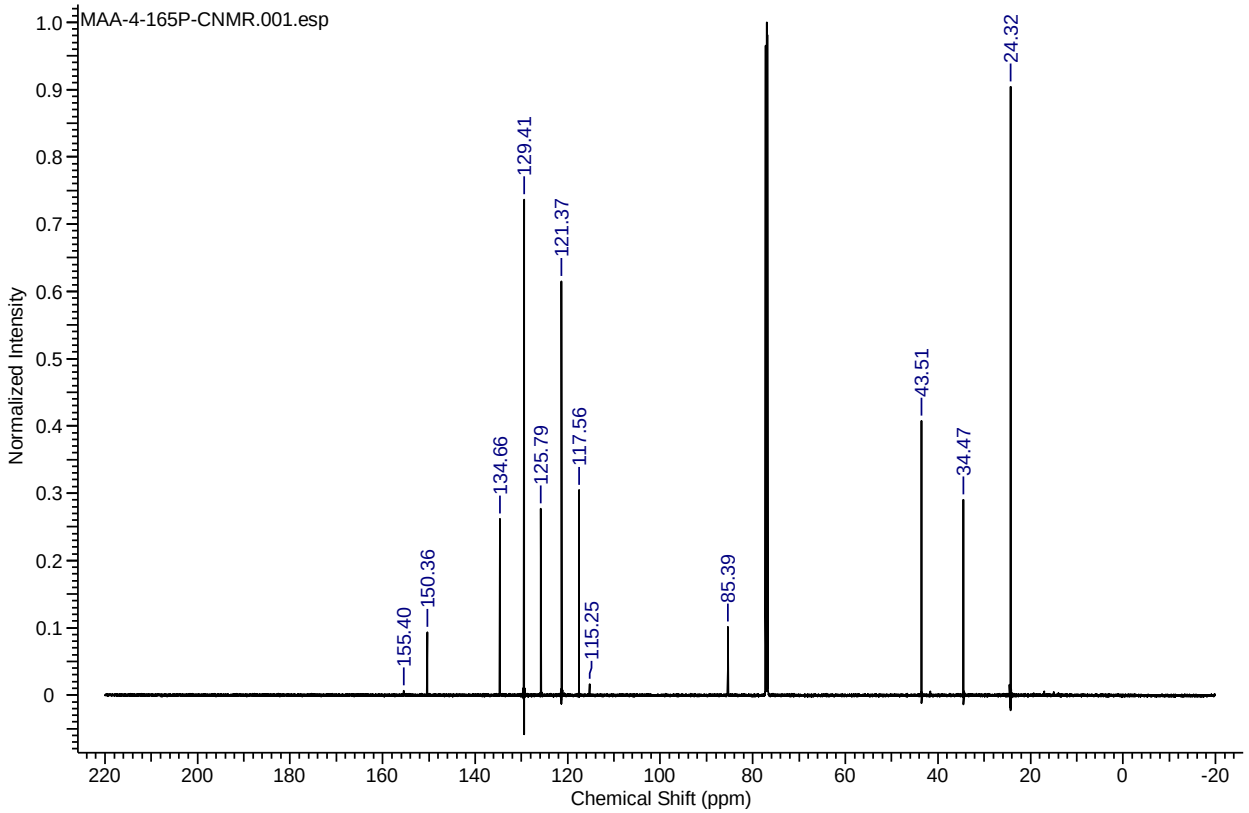

MAA-3-86RECRYS-CHARAC.001.esp
PhO
O
NH
H
O
H
1w
Normalized Intensity
0.86 1.95 0.94 1.82
0.96
1.85
0.98 0.95 0.96 0.99 1.91 1.09 1.01 1.99 1.00
Chemical Shift (ppm)

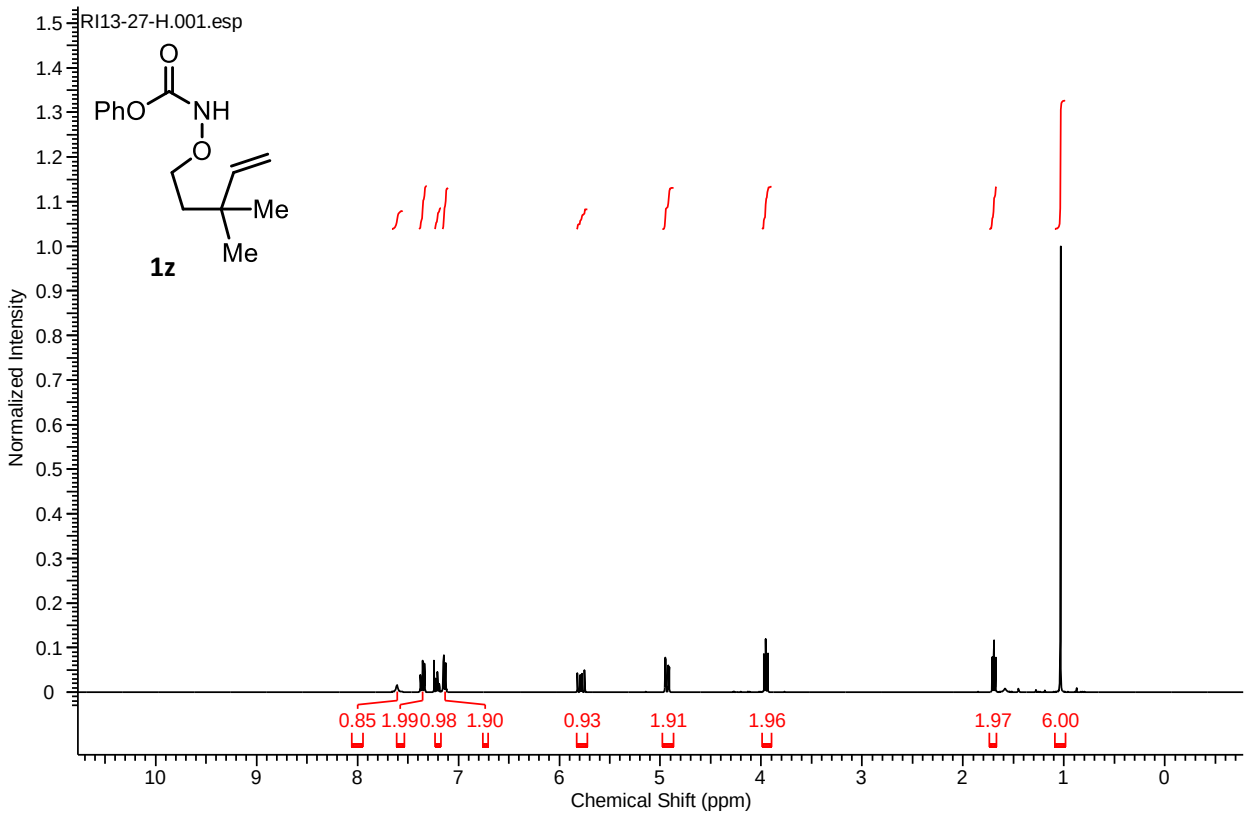

MAA-3-86RECRYS CHARAC2.002.esp
Normalized Intensity
155.76
150.43
136.91
129.42
125.76
121.37
116.10
87.82
40.68
36.69
30.17
24.99
24.28
Chemical Shift (ppm)

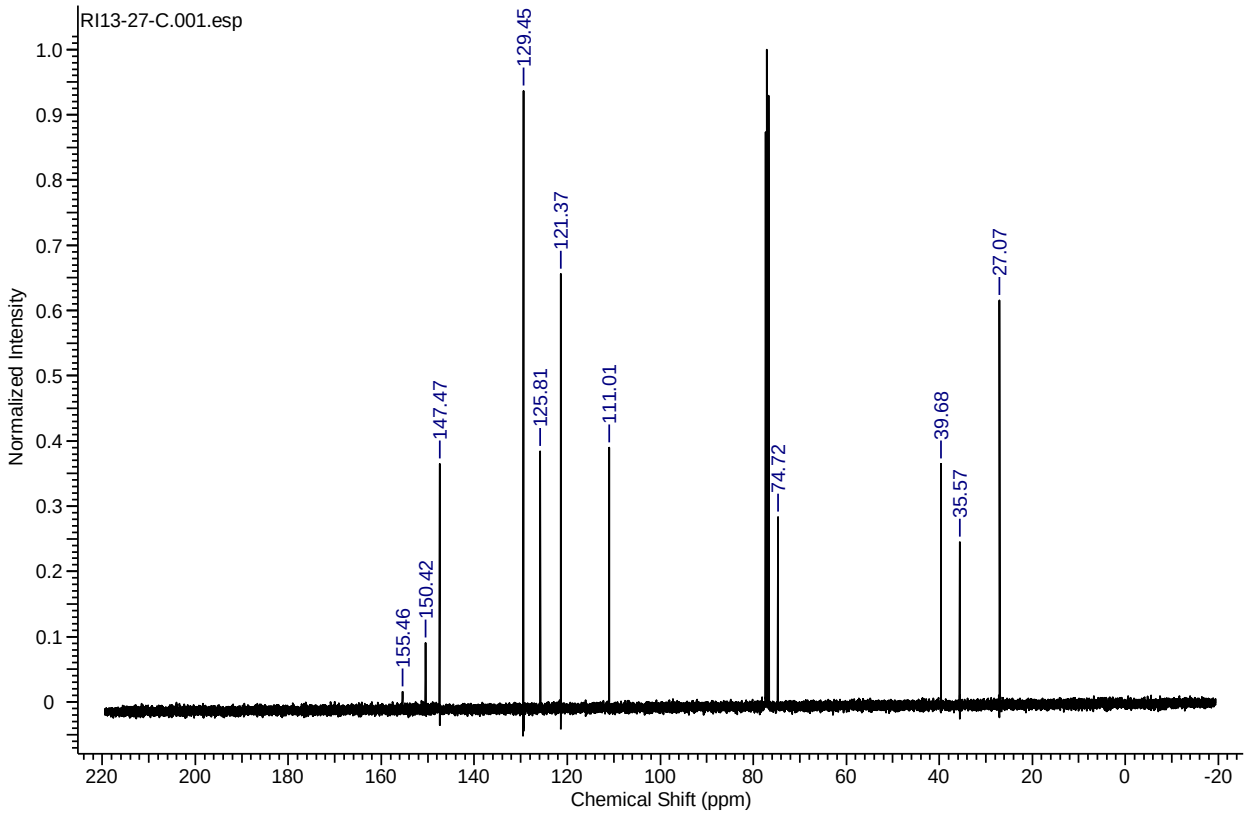

MAA-2-185P-TOP CHARAC.001.esp
PhO
O
NH
H
O
H
1x
Normalized Intensity
0.91 2.05 1.00 1.97
1.00
1.00 0.99
1.07
1.04 2.04 3.13 4.22 1.28
Chemical Shift (ppm)

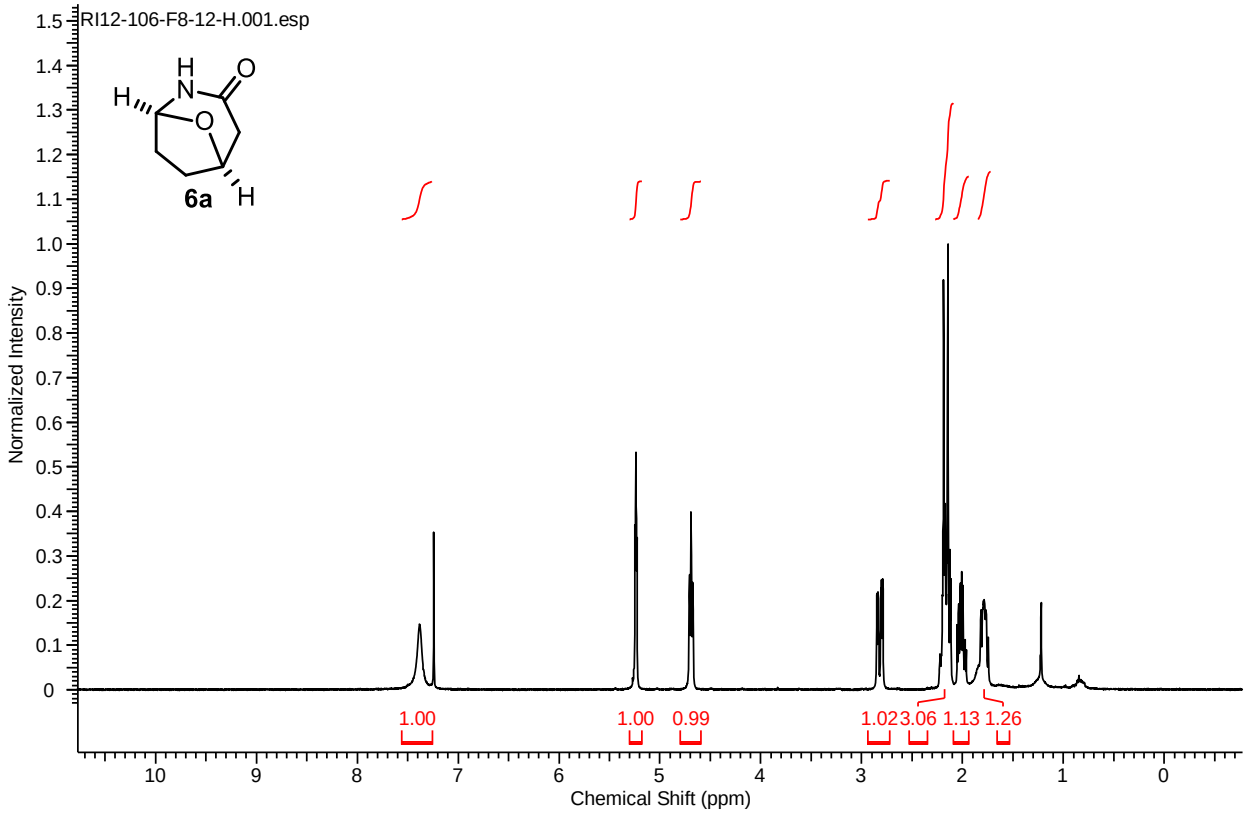

MAA-1-194PP CHARAC2.002.esp
Normalized Intensity
155.61
150.42
137.51
129.41
125.75
121.40
115.86
83.63
40.07
27.97
26.93
24.69
20.98
Chemical Shift (ppm)

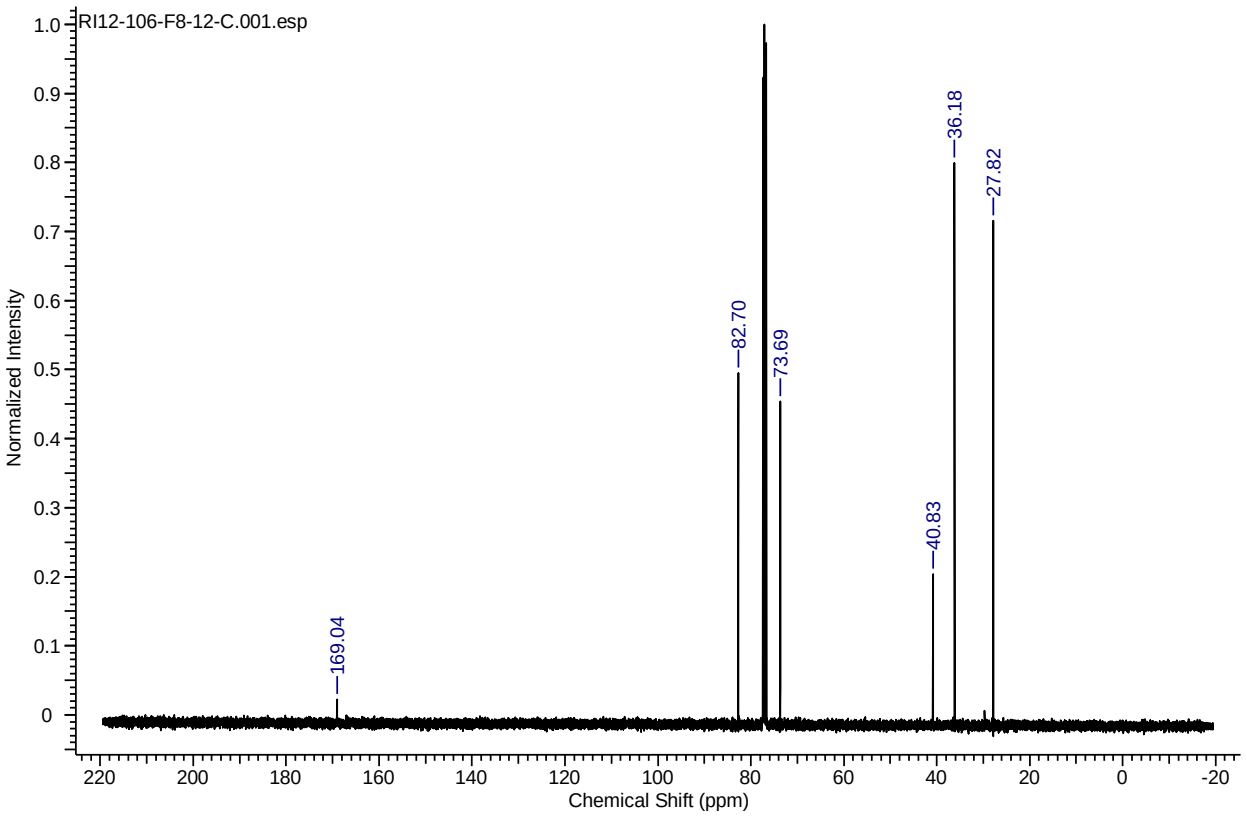

MAA-4-165P-24-57 CHARAC.001.esp
PhO
NH
O
O
Me
Me
1y
Normalized Intensity
0.89 2.02 1.03 1.96
0.99
1.02 0.93
2.06
1.96
6.00
Chemical Shift (ppm)

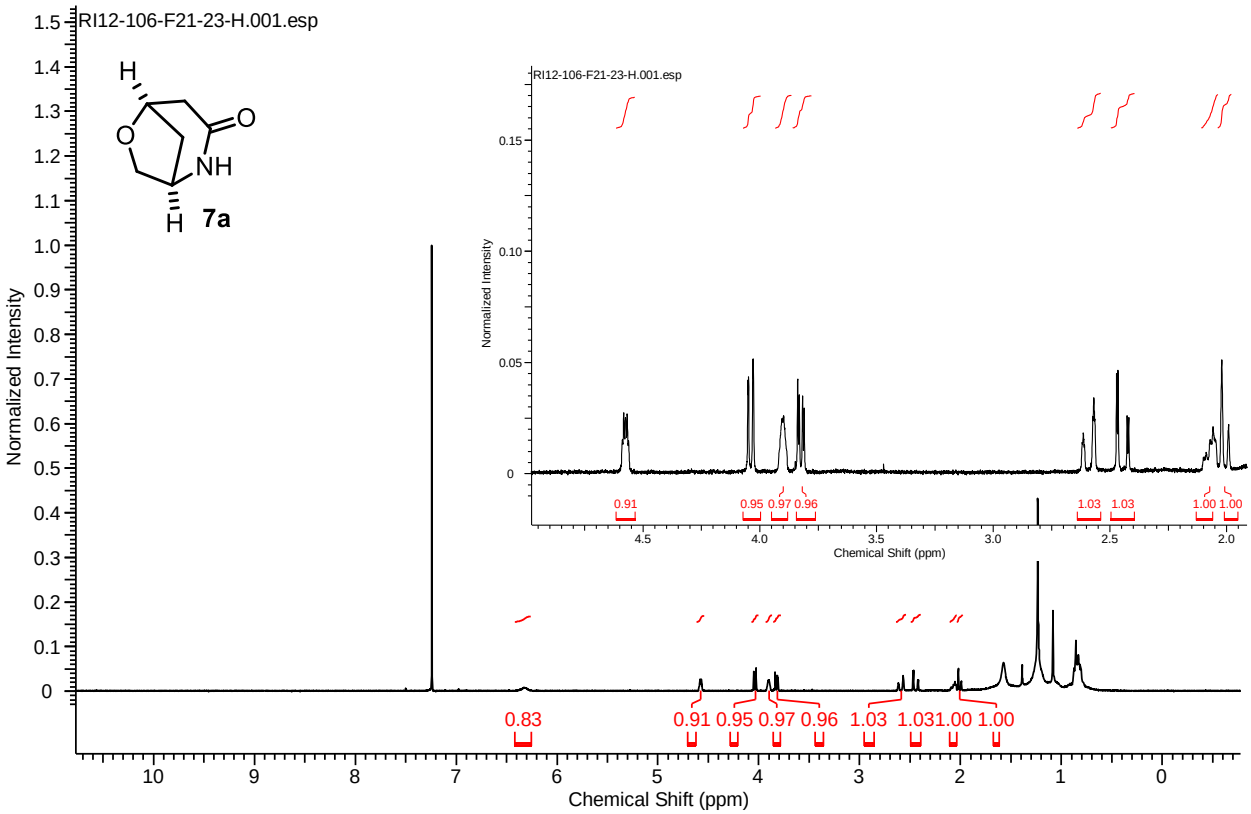

MAA-4-165P-CNMR.001.esp
Normalized Intensity
155.40
150.36
134.66
129.41
125.79
121.37
117.56
115.25
85.39
43.51
34.47
24.32
Chemical Shift (ppm)

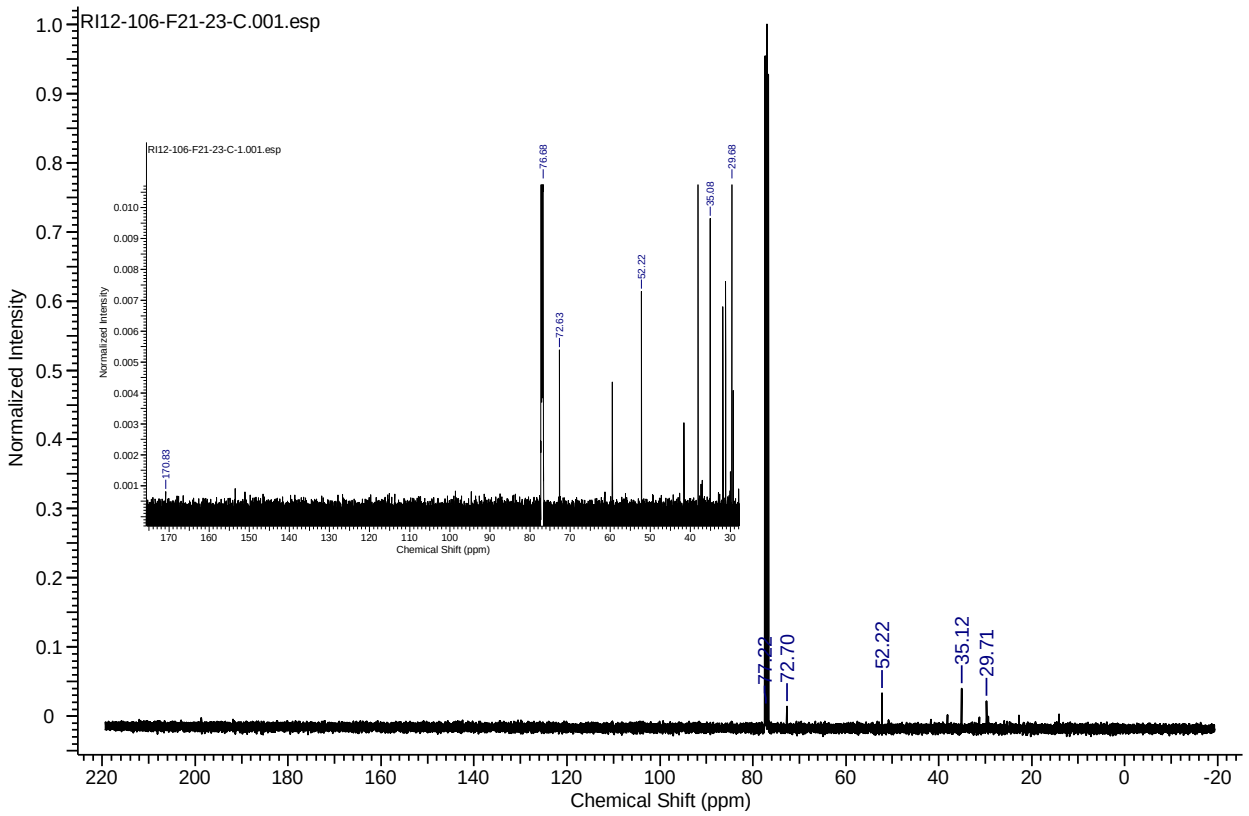

RI13-27-H.001.esp
PhO
O
NH
O
Me
Me
1z
Normalized Intensity
Chemical Shift (ppm)
0.85
1.99
0.98
1.90
0.93
1.91
1.96
1.97
6.00

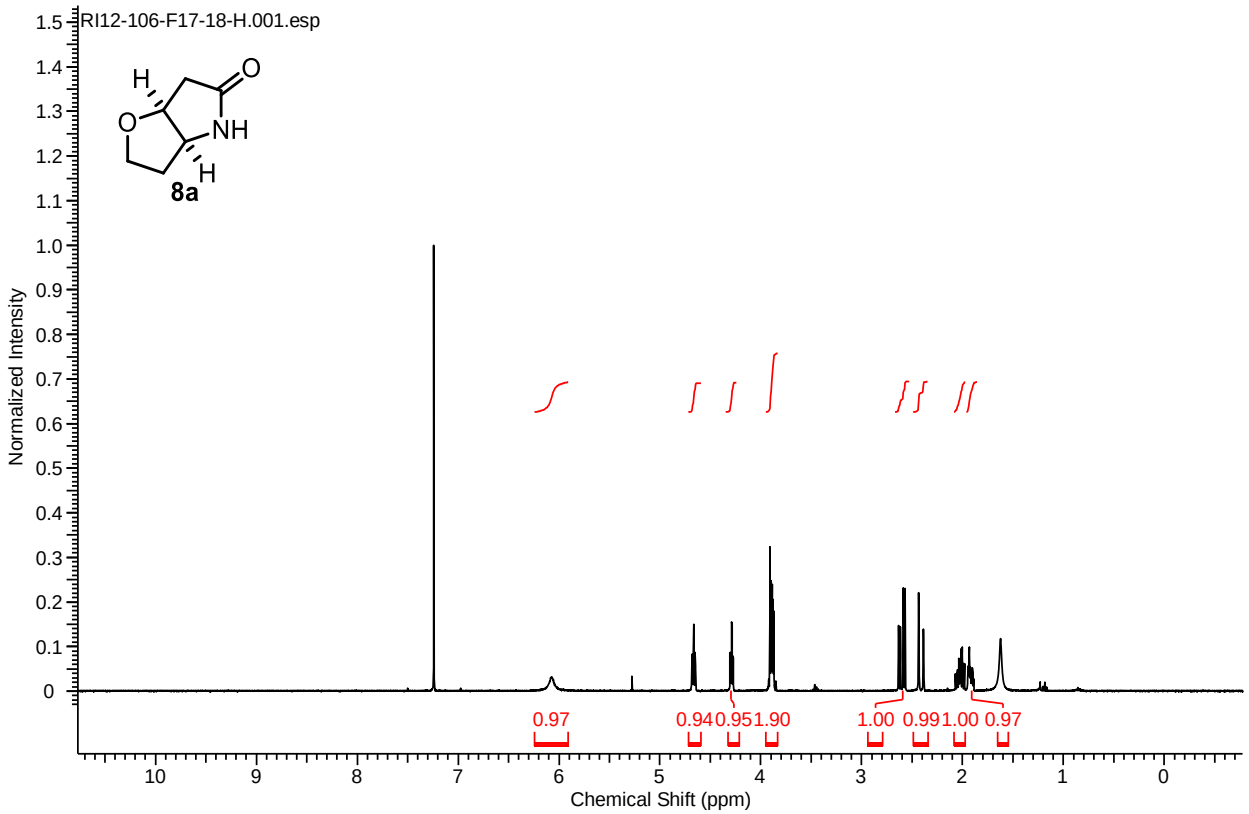

RI13-27-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
155.46
150.42
147.47
129.45
125.81
121.37
111.01
74.72
39.68
35.57
27.07

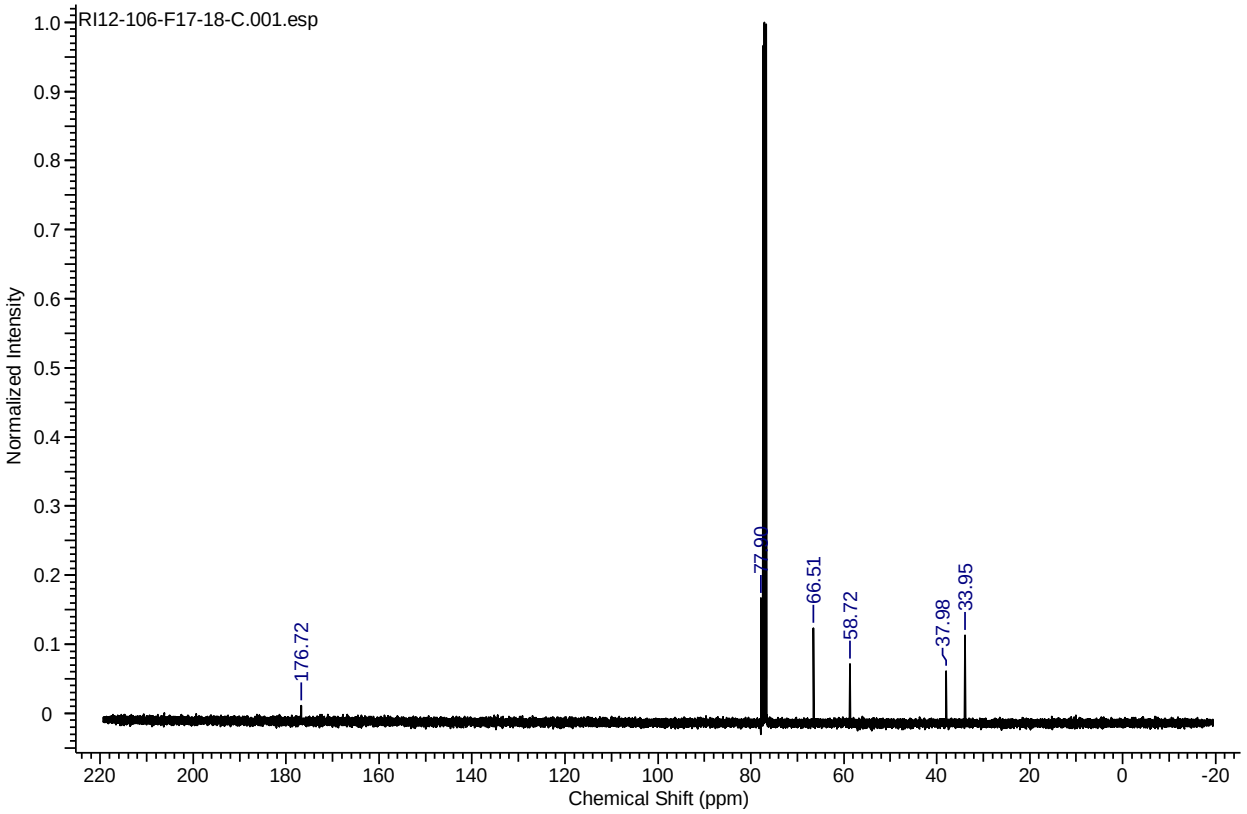

RI12-106-F8-12-H.001.esp
H
N
O
H
O
6a
H
Normalized Intensity
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
1.00
1.00
0.99
1.02
3.06
1.13
1.26
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

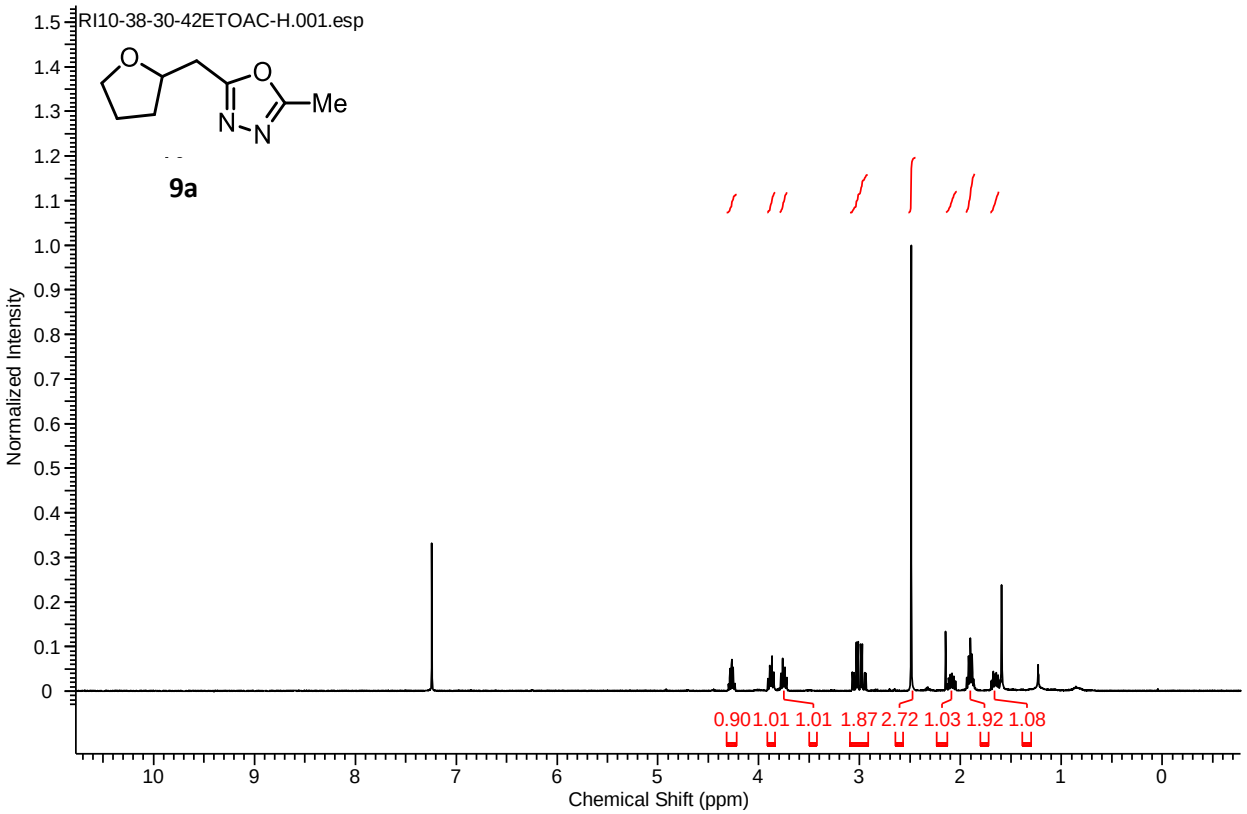

RI12-106-F8-12-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
169.04
82.70
73.69
40.83
36.18
27.82


RI12-106-F21-23-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.83
0.91 0.95 0.97 0.96 1.03 1.03 1.00 1.00
7a

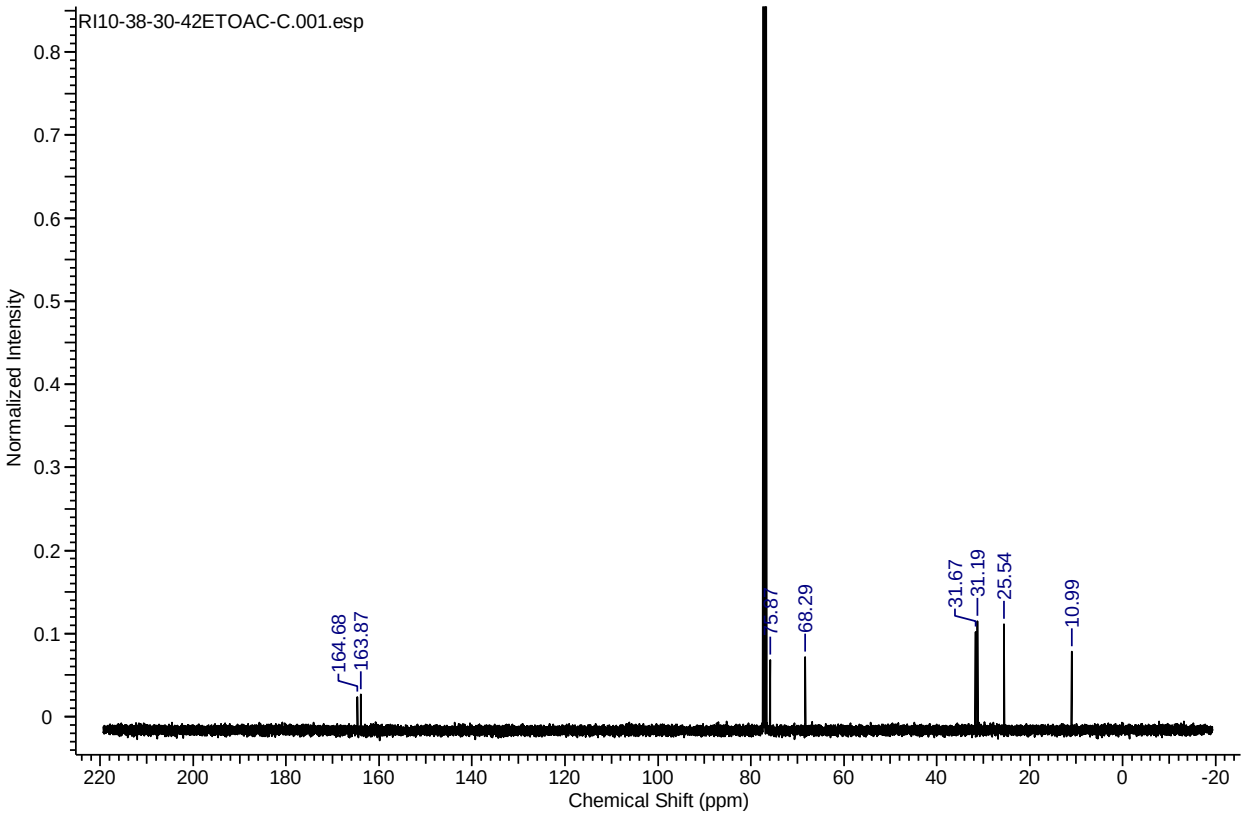

RI12-106-F21-23-C.001.esp
RI12-106-F21-23-C-1.001.esp
Normalized Intensity
Chemical Shift (ppm)
77.22
72.70
52.22
35.12
29.71

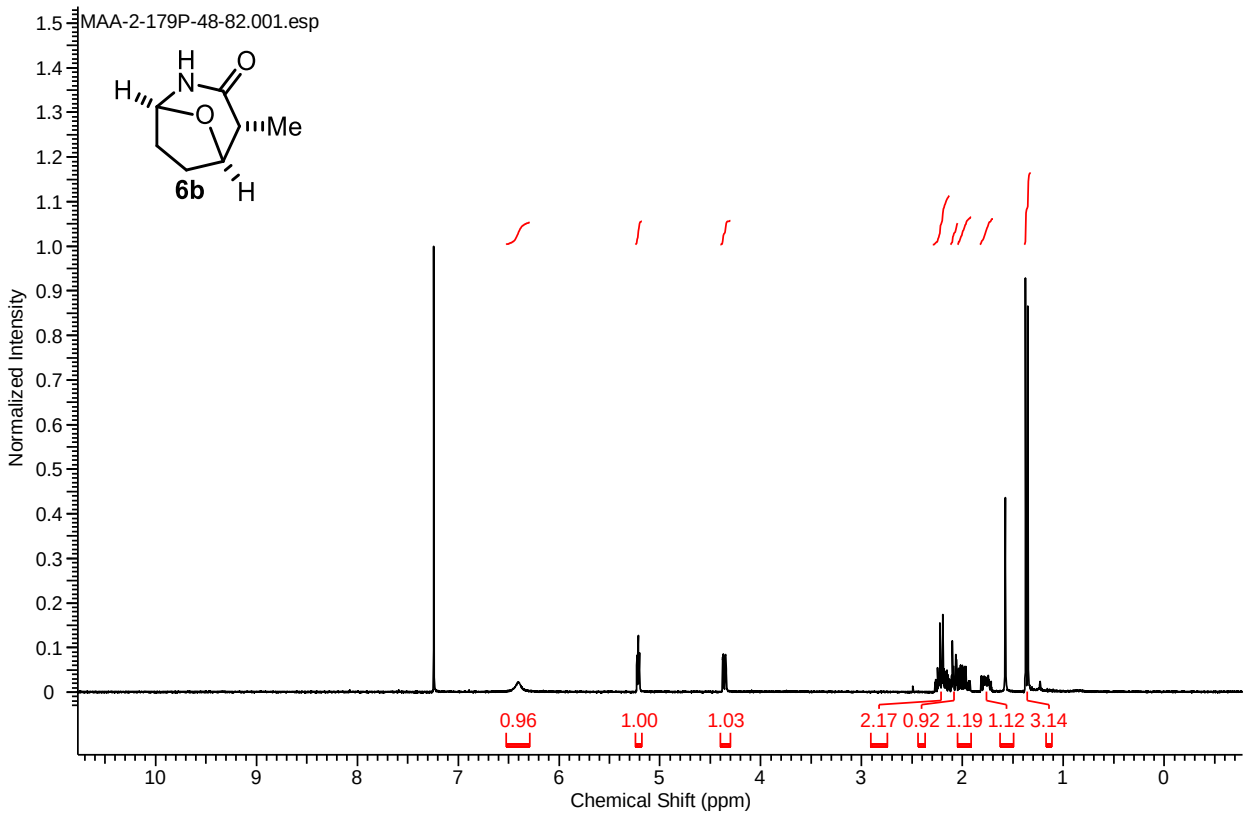

RI12-106-F17-18-H.001.esp
8a
Normalized Intensity
Chemical Shift (ppm)
0.97
0.94
0.95
1.90
1.00
0.99
1.00
0.97

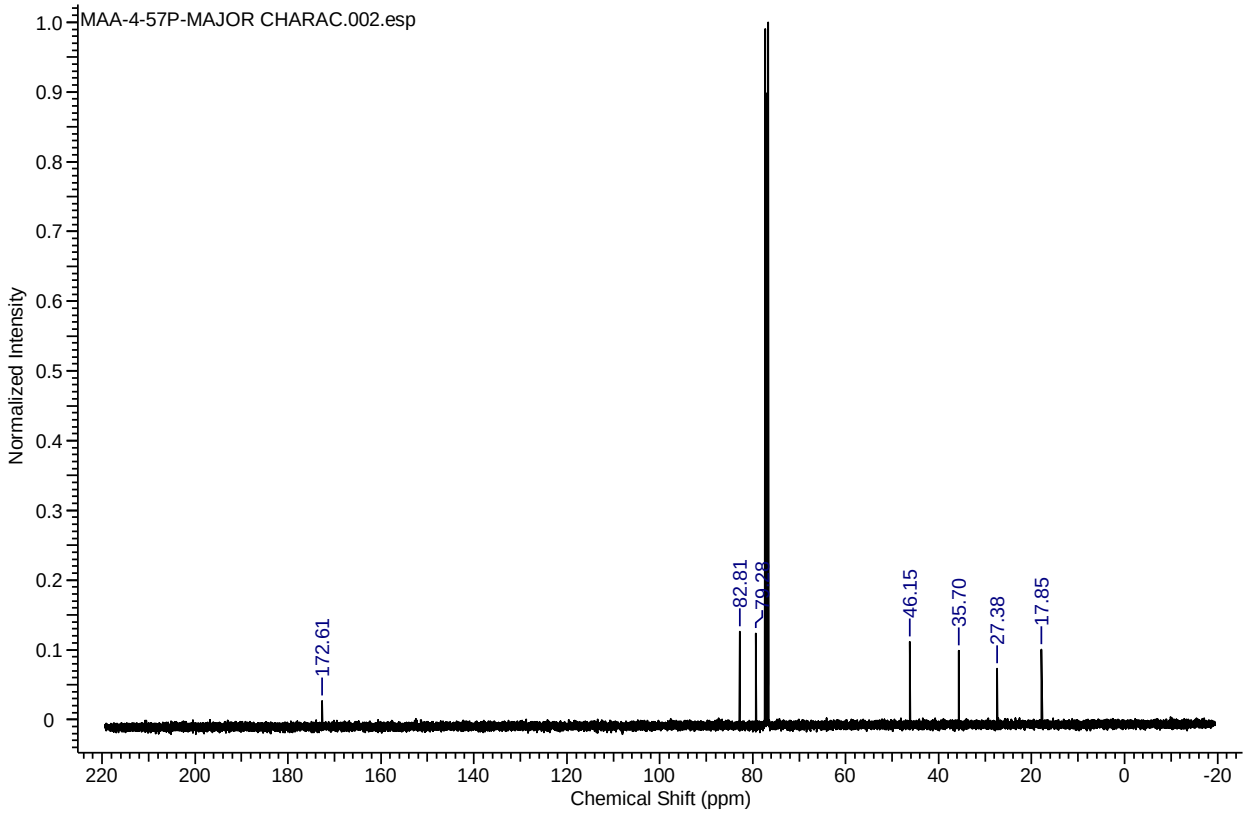

RI12-106-F17-18-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
176.72
77.00
66.51
58.72
37.98
33.95

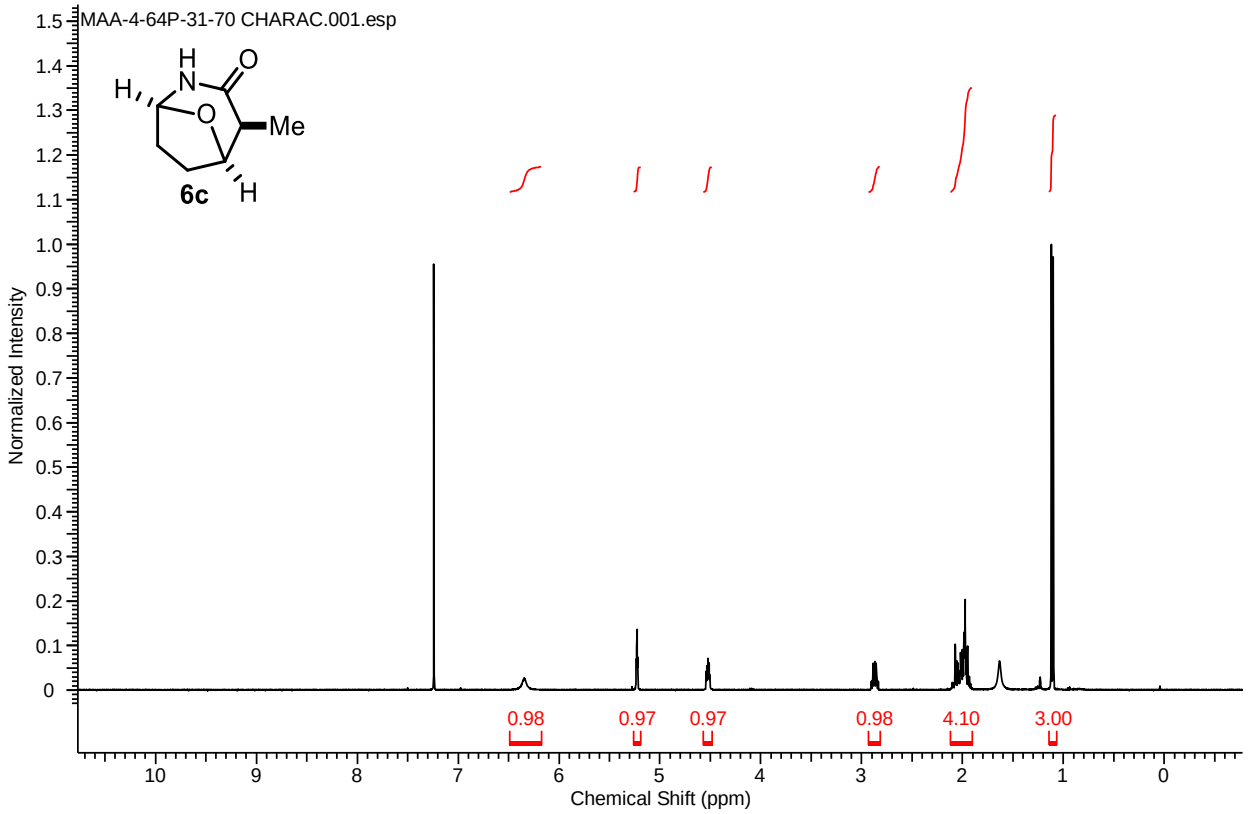

RI10-38-30-42ETOAC-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
Me
0.90 1.01 1.01 1.87 2.72 1.03 1.92 1.08

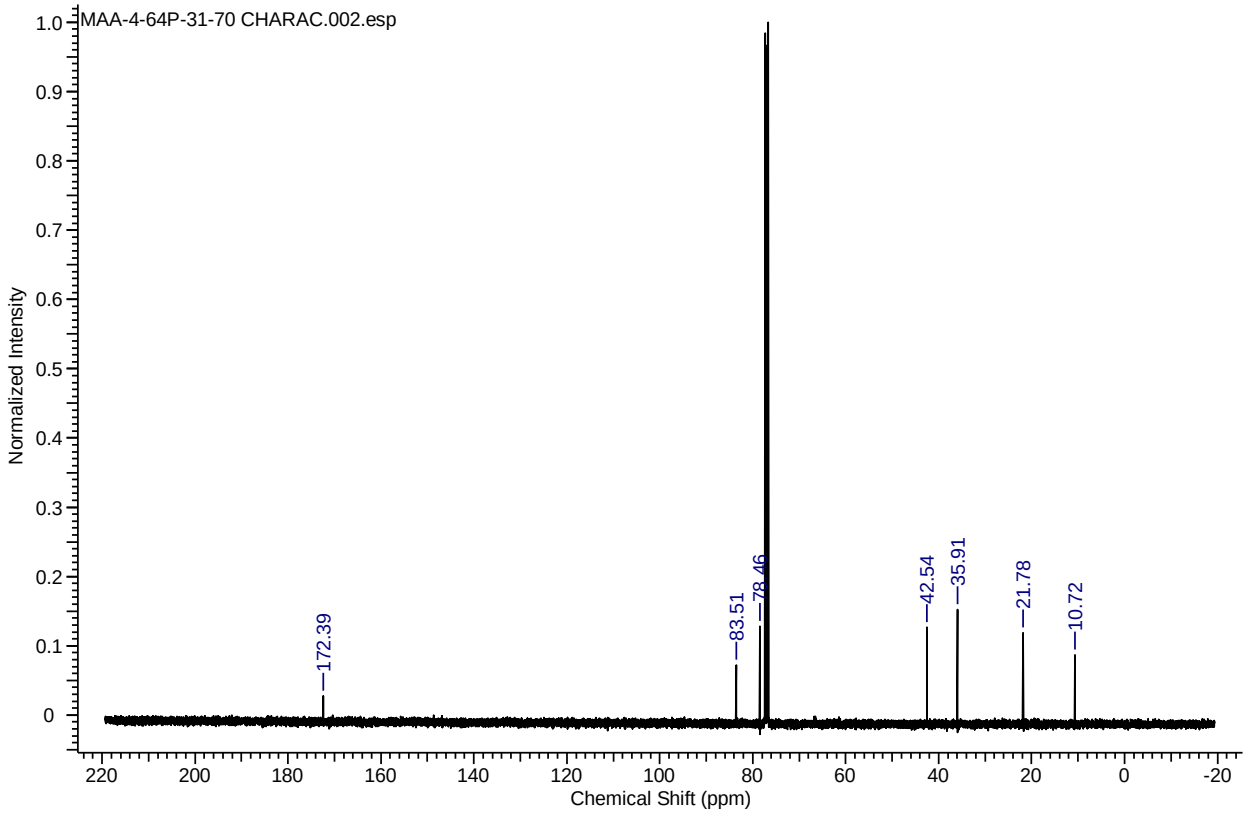
9a

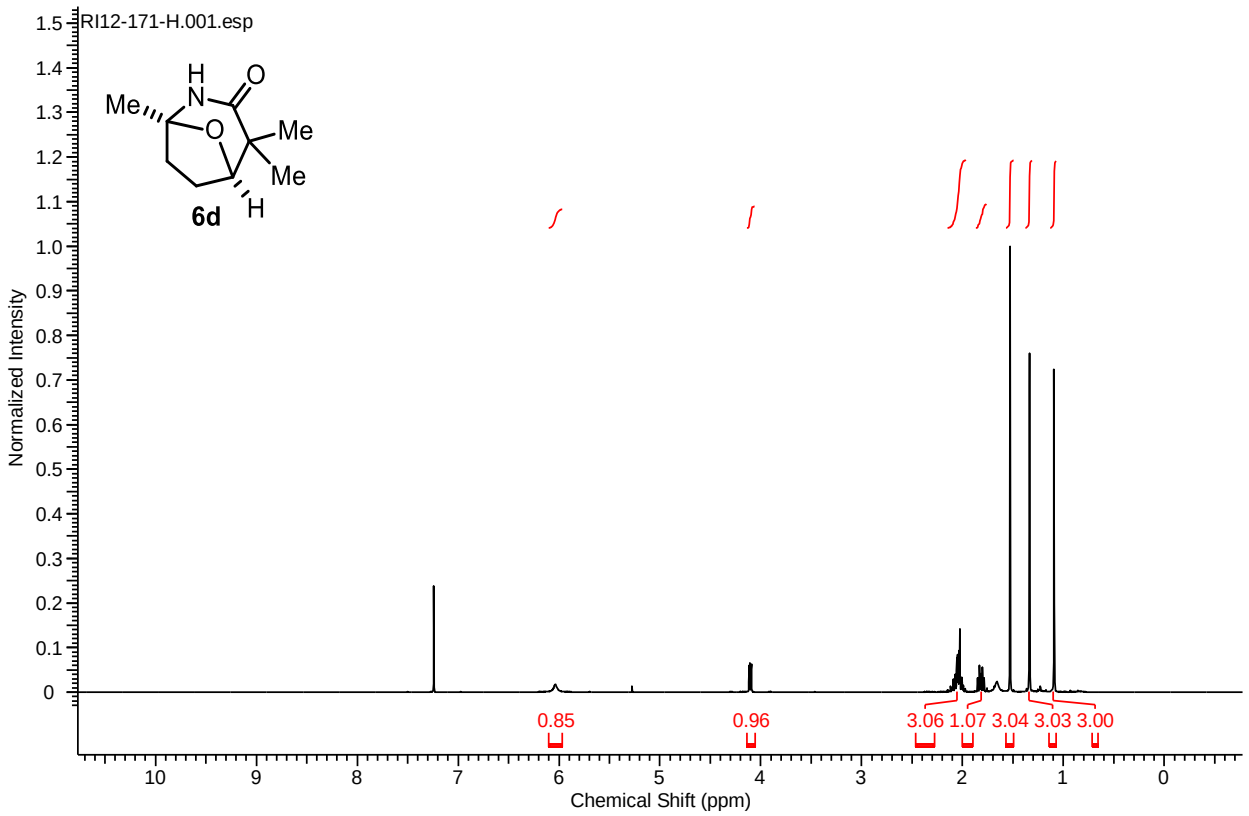

RI10-38-30-42ETOAC-C.001.esp
Normalized Intensity
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
164.68
163.87
77.87
68.29
31.67
31.19
25.54
10.99
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

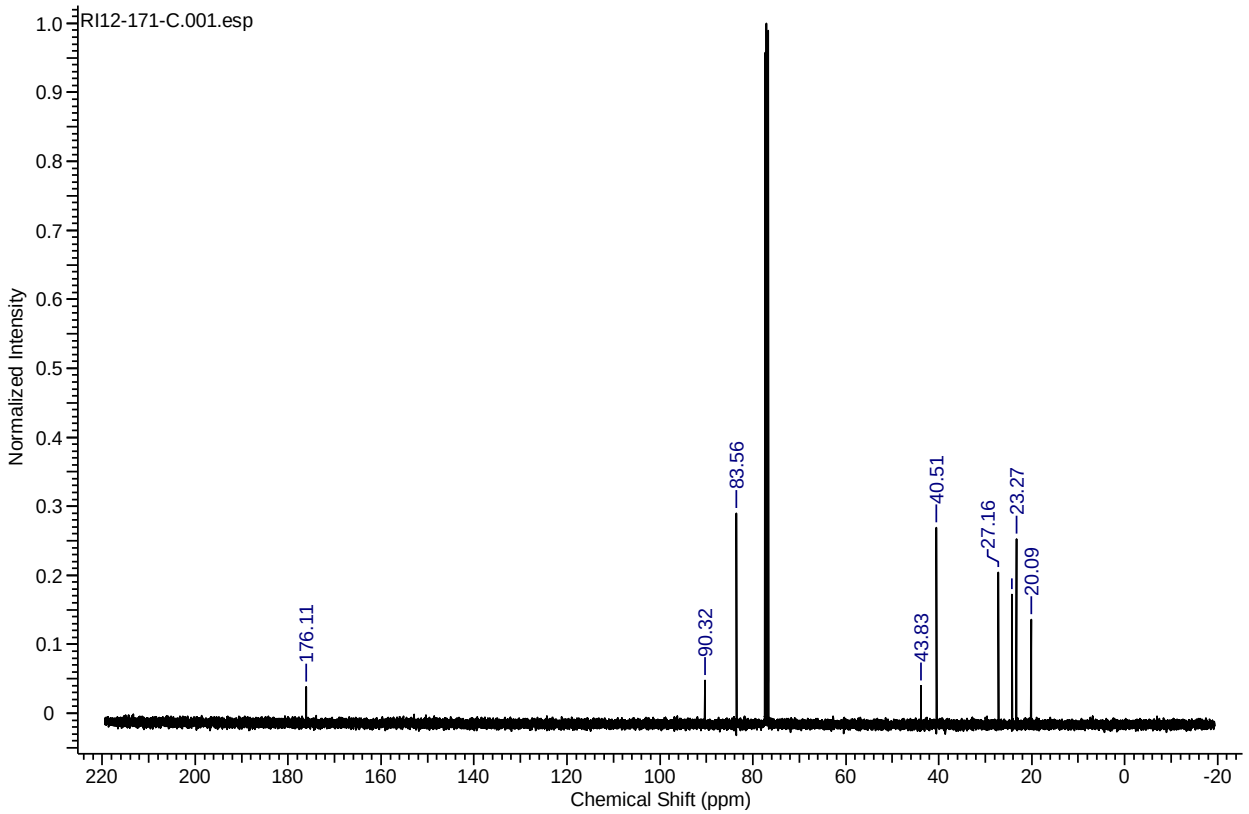

MAA-2-179P-48-82.001.esp
H
N
O
H
O
Me
6b
H
Normalized Intensity
0.96
1.00
1.03
2.17
0.92
1.19
1.12
3.14
Chemical Shift (ppm)

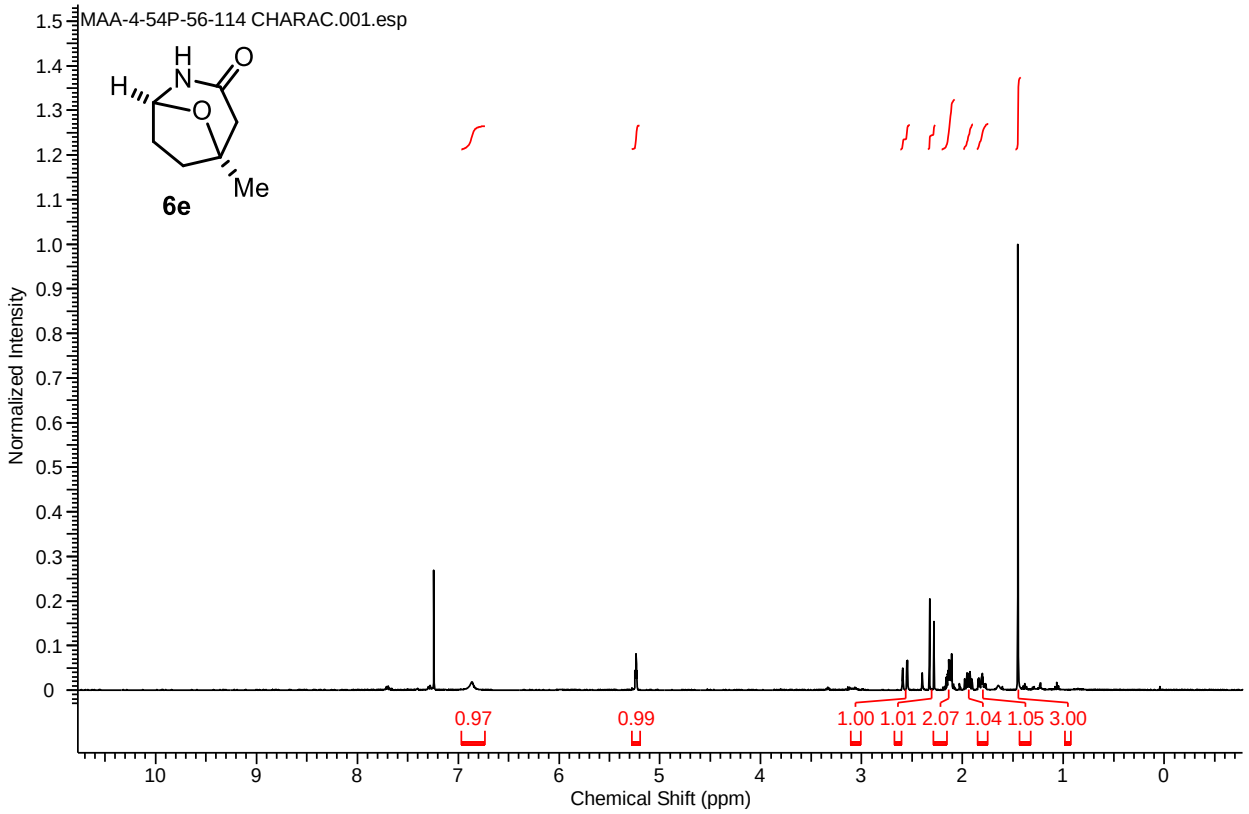

MAA-4-57P-MAJOR CHARAC.002.esp
Normalized Intensity
172.61
82.81
79.28
46.15
35.70
27.38
17.85
Chemical Shift (ppm)

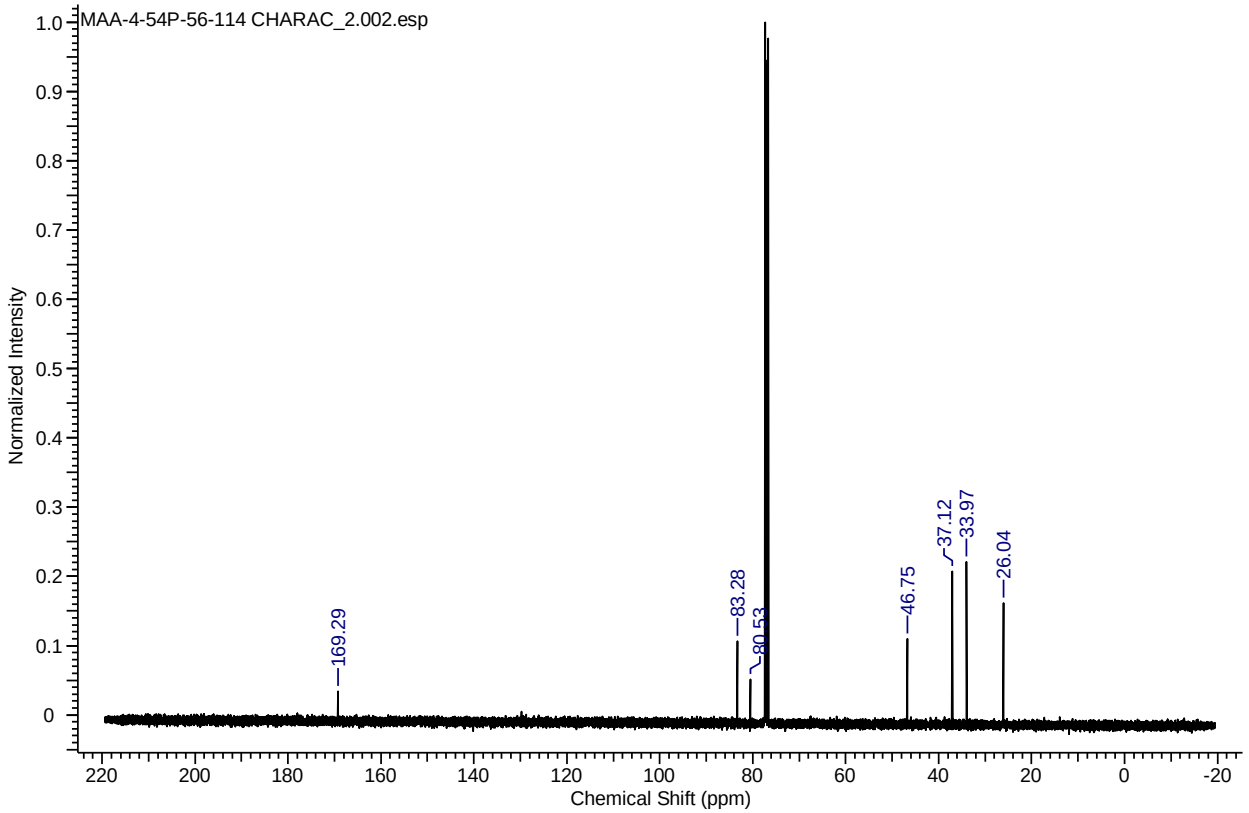

MAA-4-64P-31-70 CHARAC.001.esp
H
N
O
H
O
Me
6c
H
Normalized Intensity
0.98
0.97
0.97
0.98
4.10
3.00
Chemical Shift (ppm)

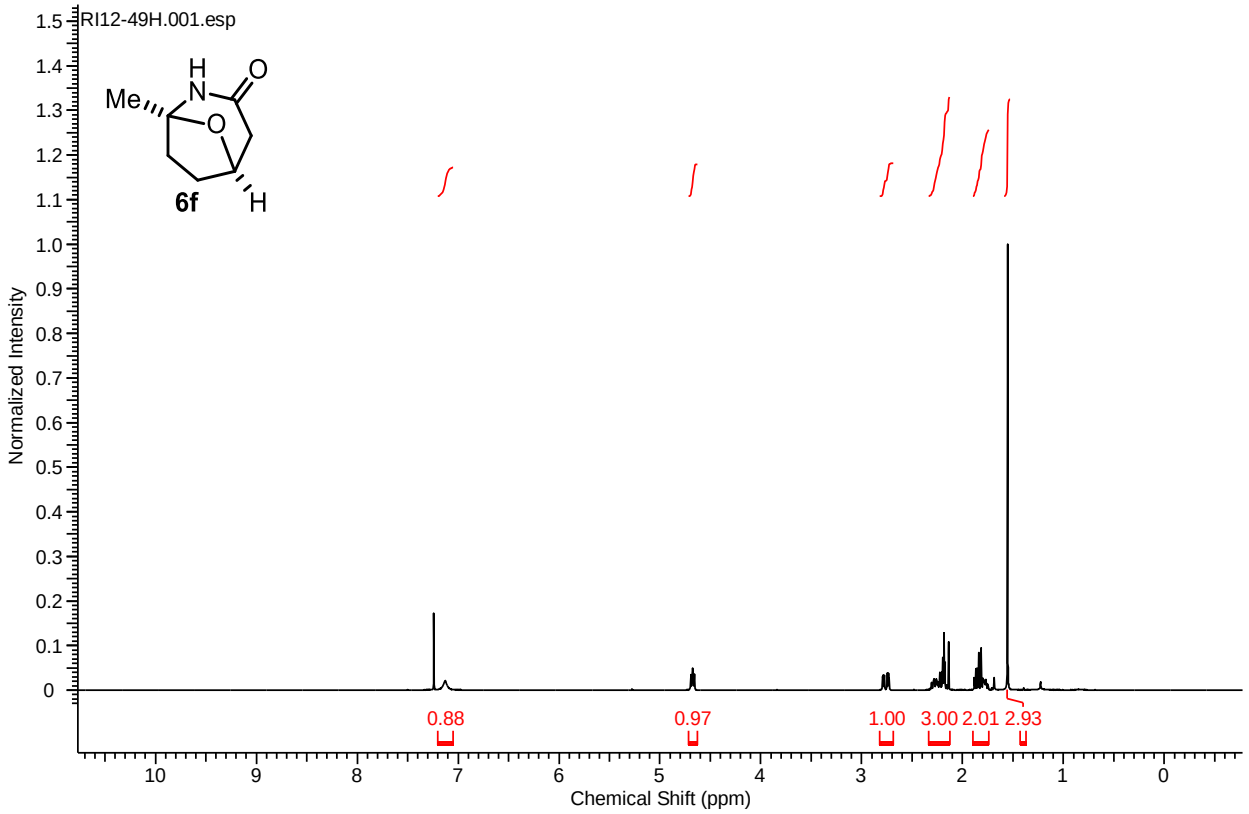

MAA-4-64P-31-70 CHARAC.002.esp
172.39
83.51
78.46
42.54
35.91
21.78
10.72
Normalized Intensity
Chemical Shift (ppm)

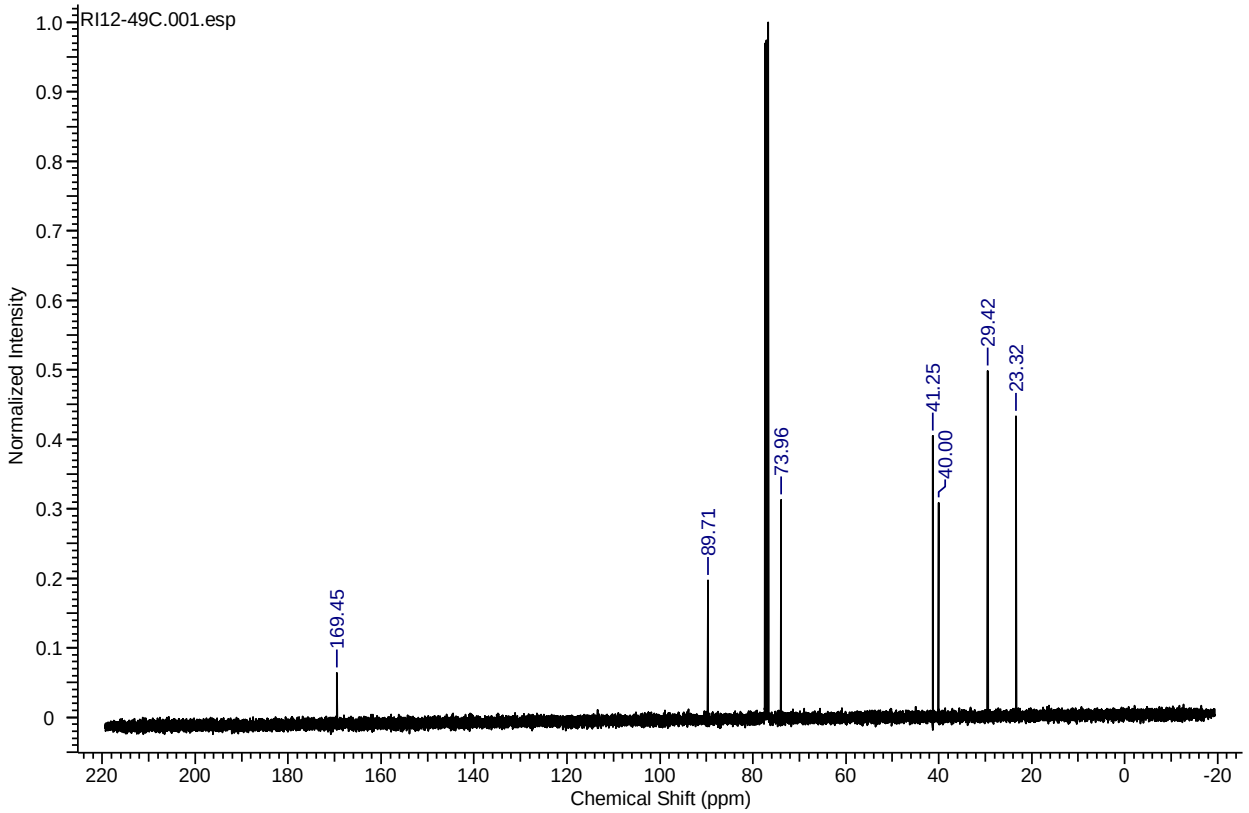

RI12-171-H.001.esp
Me
H
N
O
O
Me
Me
H
6d
Normalized Intensity
0.85
0.96
3.06 1.07 3.04 3.03 3.00
Chemical Shift (ppm)

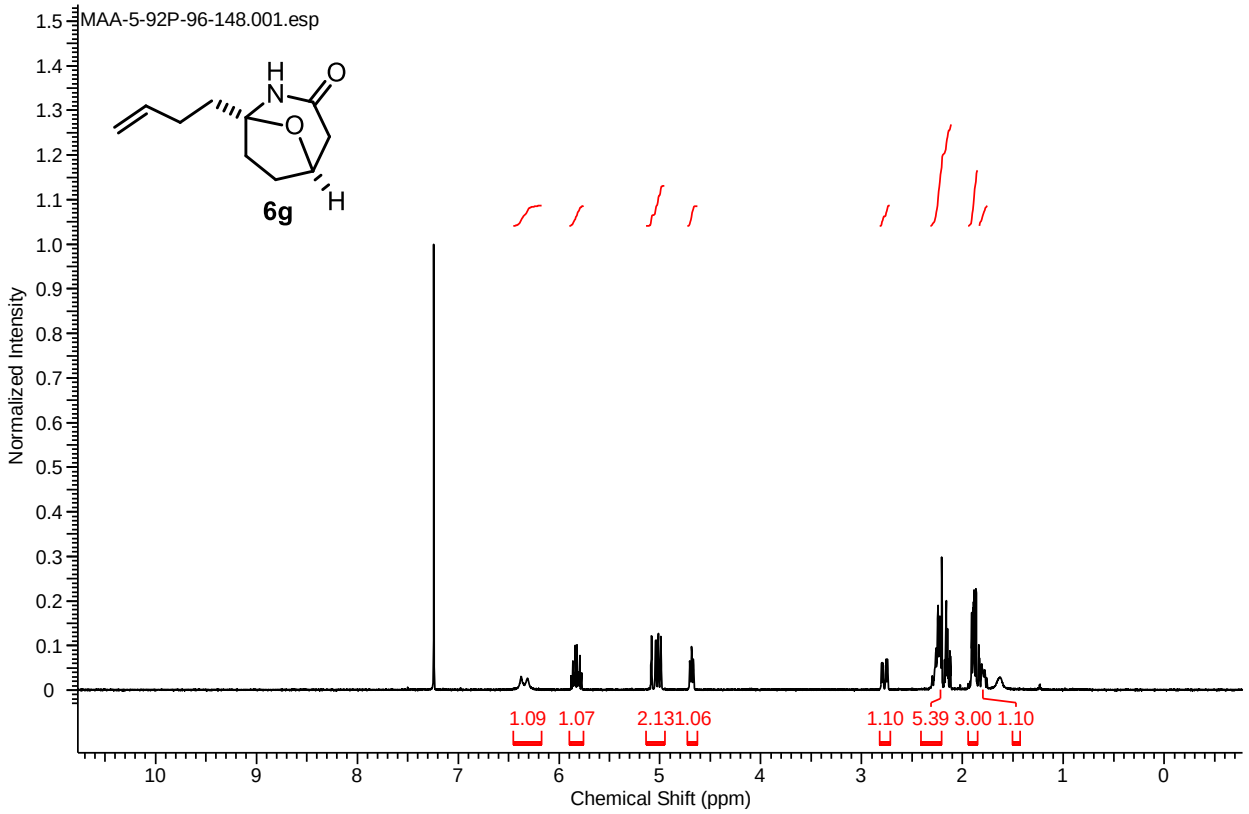

RI12-171-C.001.esp
Normalized Intensity
176.11
90.32
83.56
43.83
40.51
27.16
23.27
20.09
Chemical Shift (ppm)

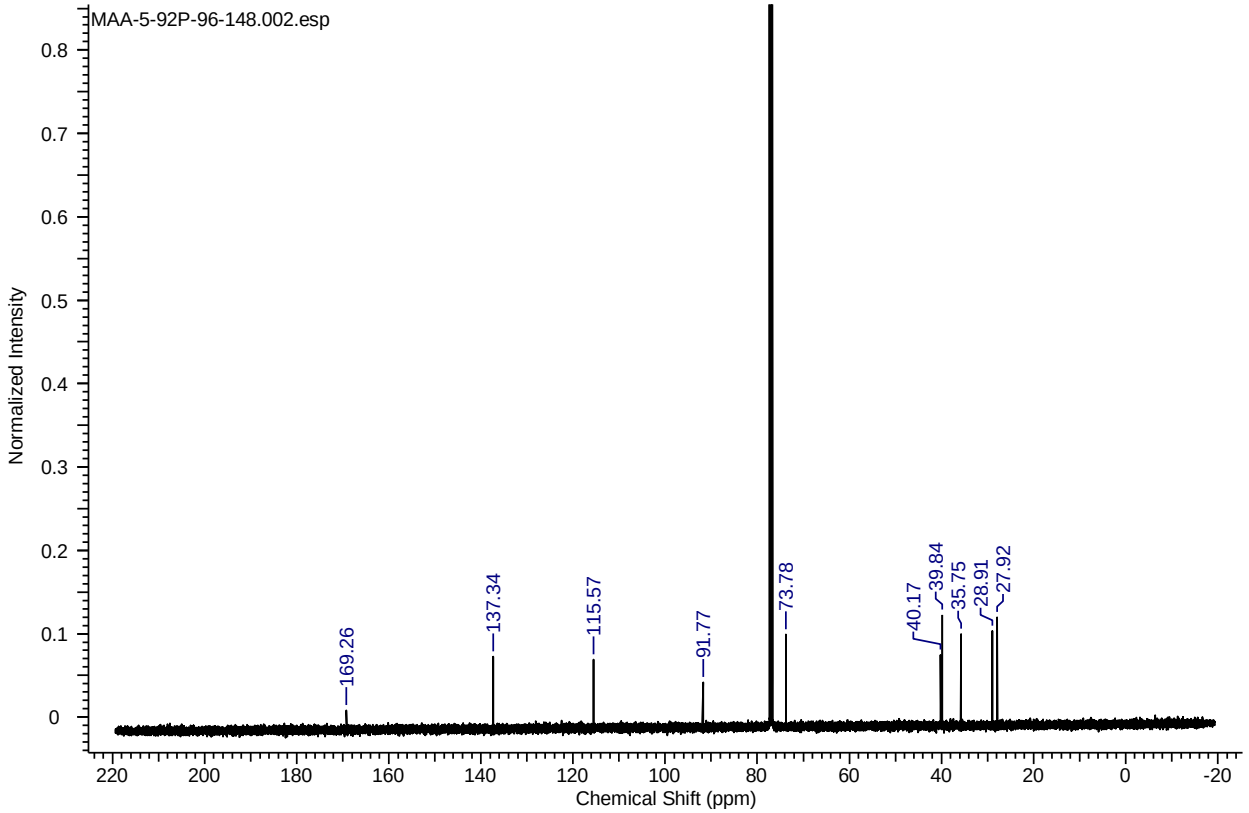

MAA-4-54P-56-114 CHARAC.001.esp
H
N
O
H
O
Me
6e
Normalized Intensity
0.97
0.99
1.00 1.01 2.07 1.04 1.05 3.00
Chemical Shift (ppm)

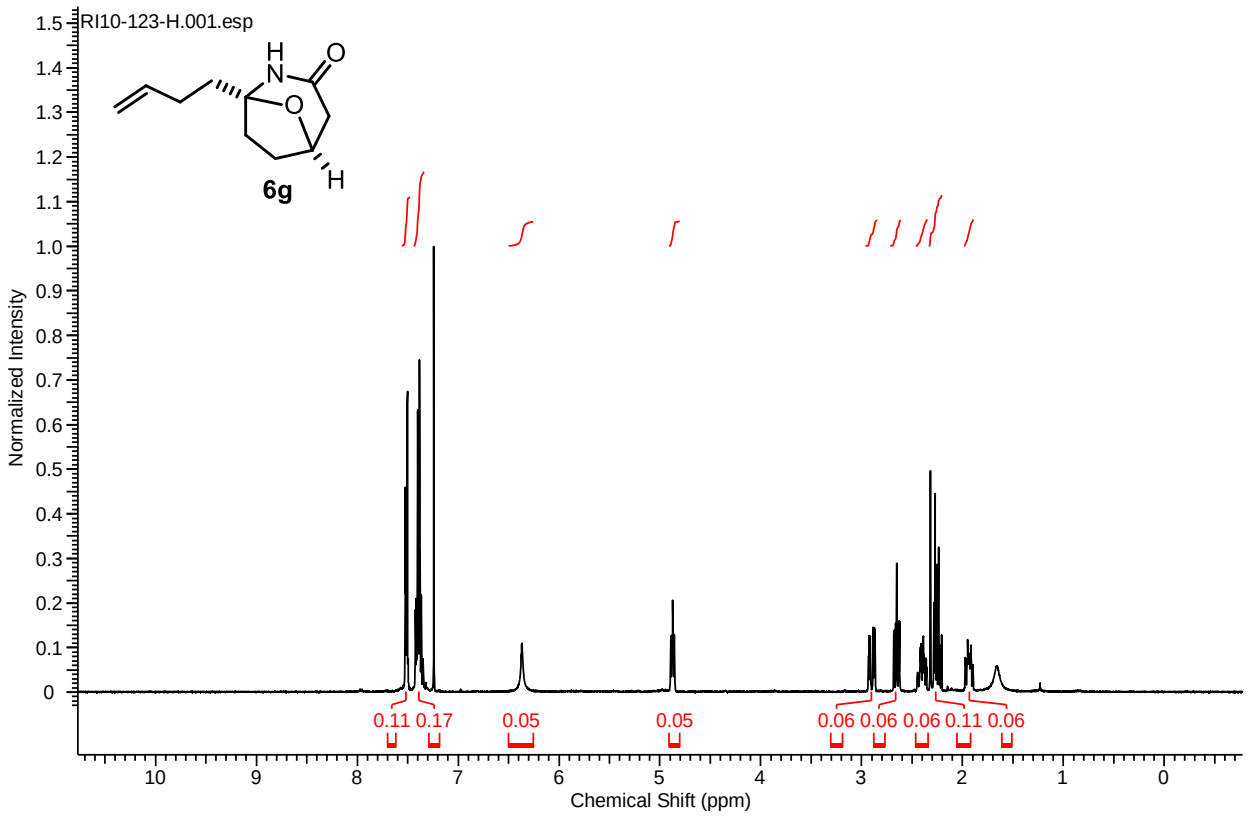

MAA-4-54P-56-114 CHARAC_2.002.esp
Normalized Intensity
169.29
83.28
80.53
46.75
37.12
33.97
26.04
Chemical Shift (ppm)

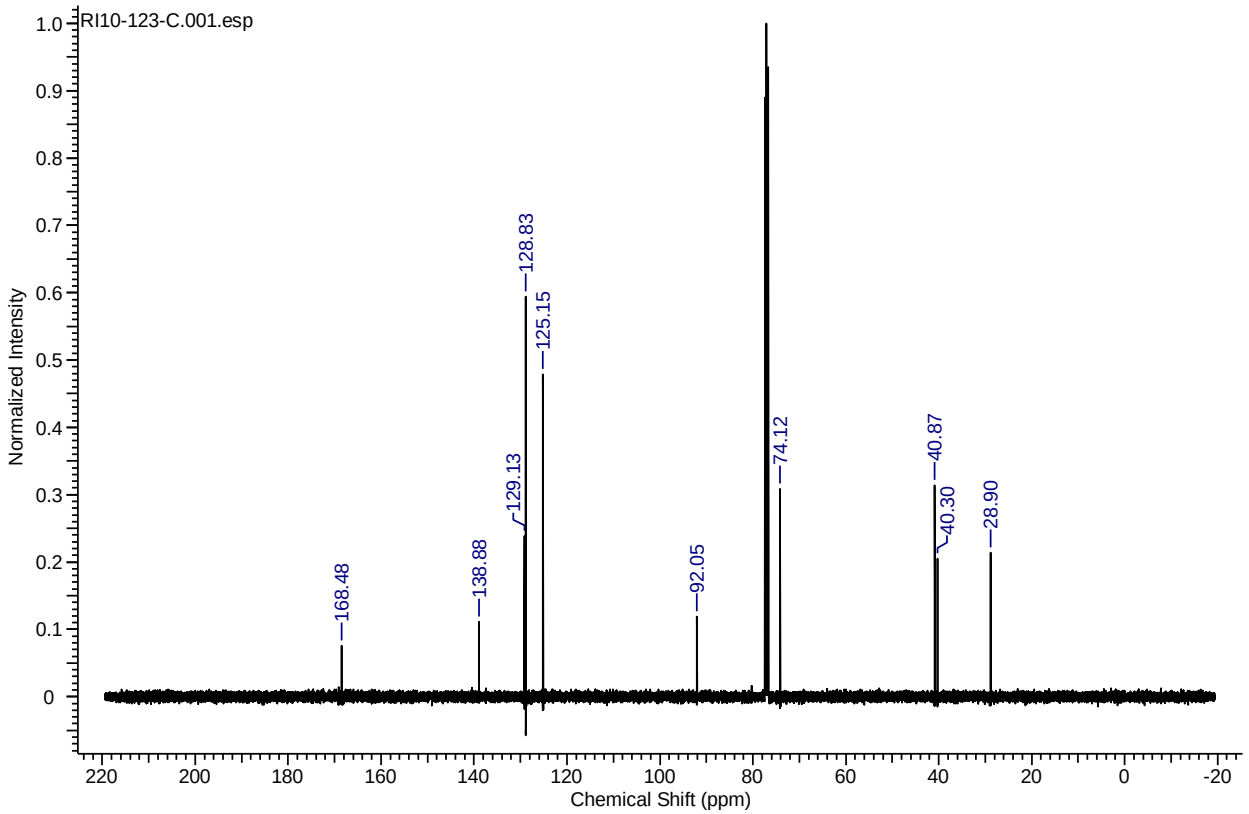

RI12-49H.001.esp
Me
H
N
O
O
6f
H
Normalized Intensity
0.88
0.97
1.00
3.00
2.01
2.93
Chemical Shift (ppm)

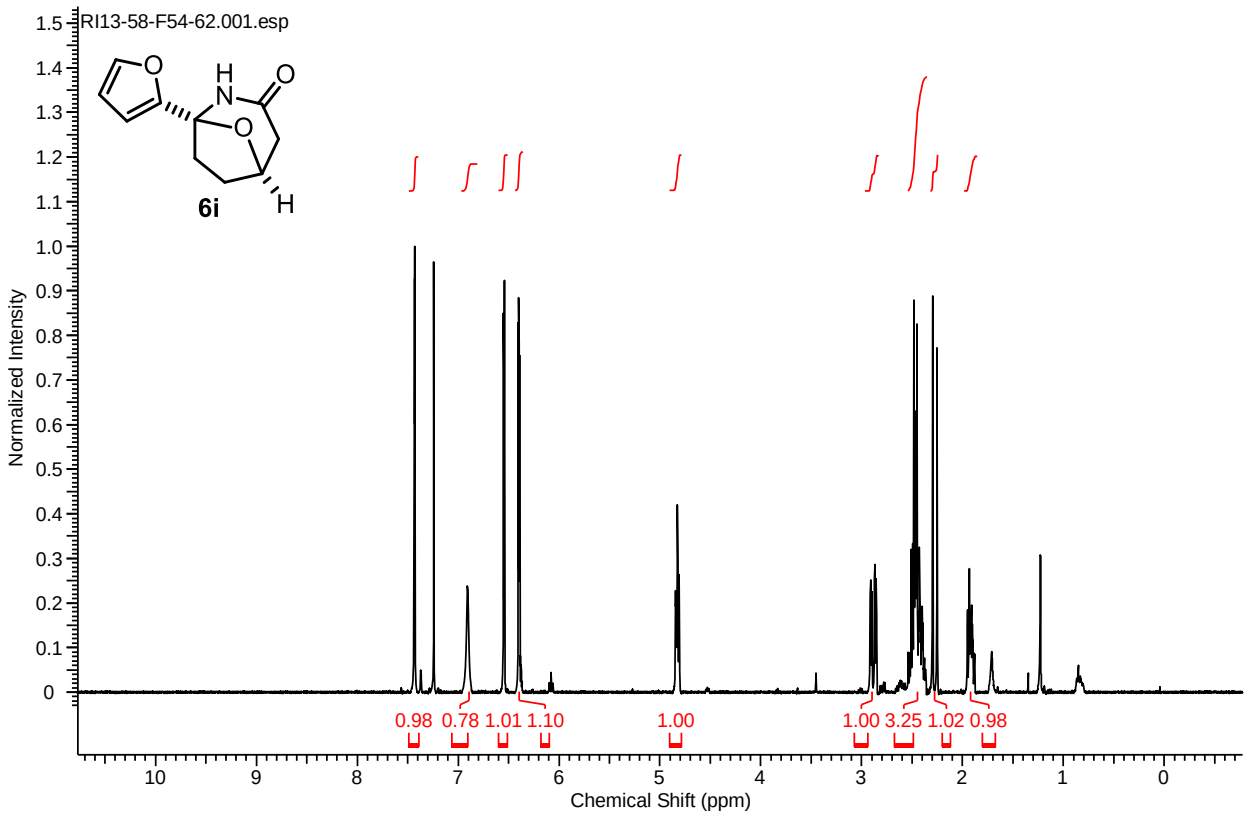

RI12-49C.001.esp
Normalized Intensity
169.45
89.71
73.96
41.25
40.00
29.42
23.32
Chemical Shift (ppm)

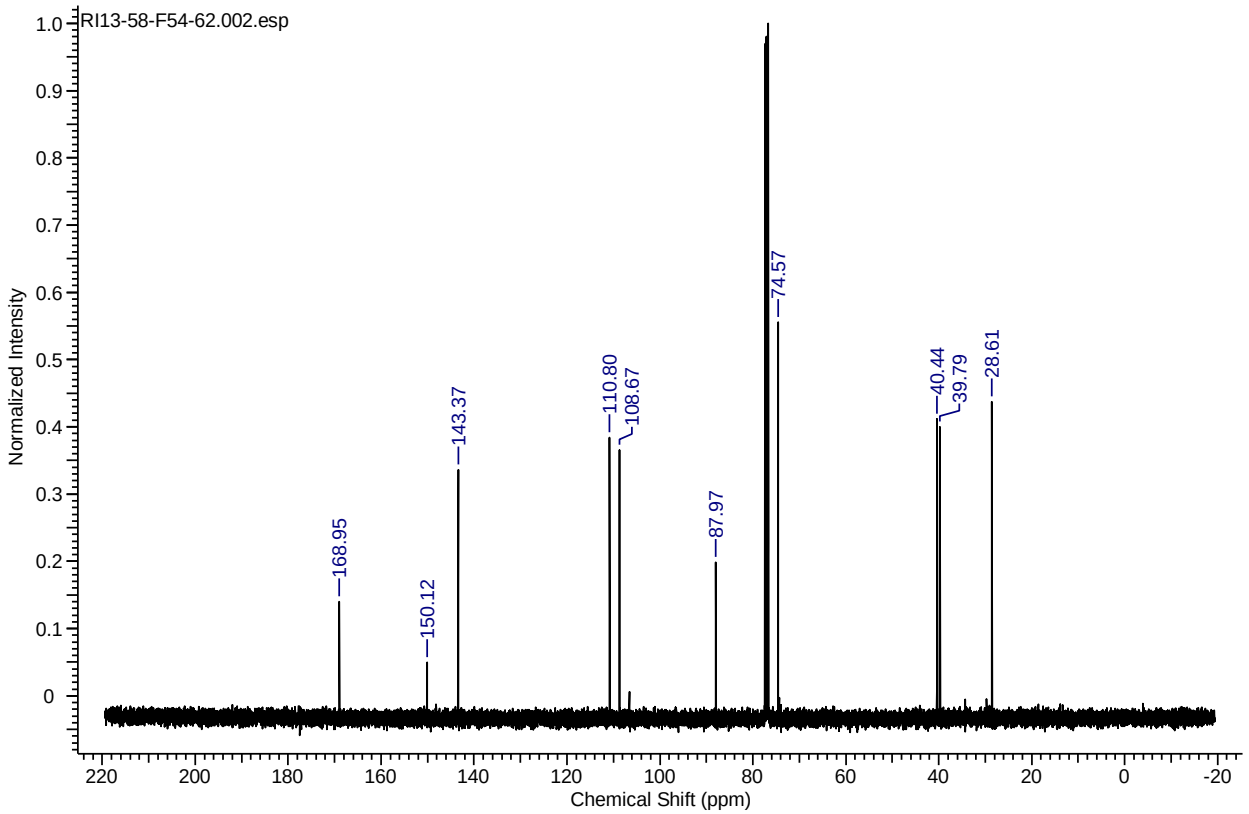

MAA-5-92P-96-148.001.esp
H
N
O
O
H
6g
Normalized Intensity
1.09
1.07
2.13
1.06
1.10
5.39
3.00
1.10
Chemical Shift (ppm)

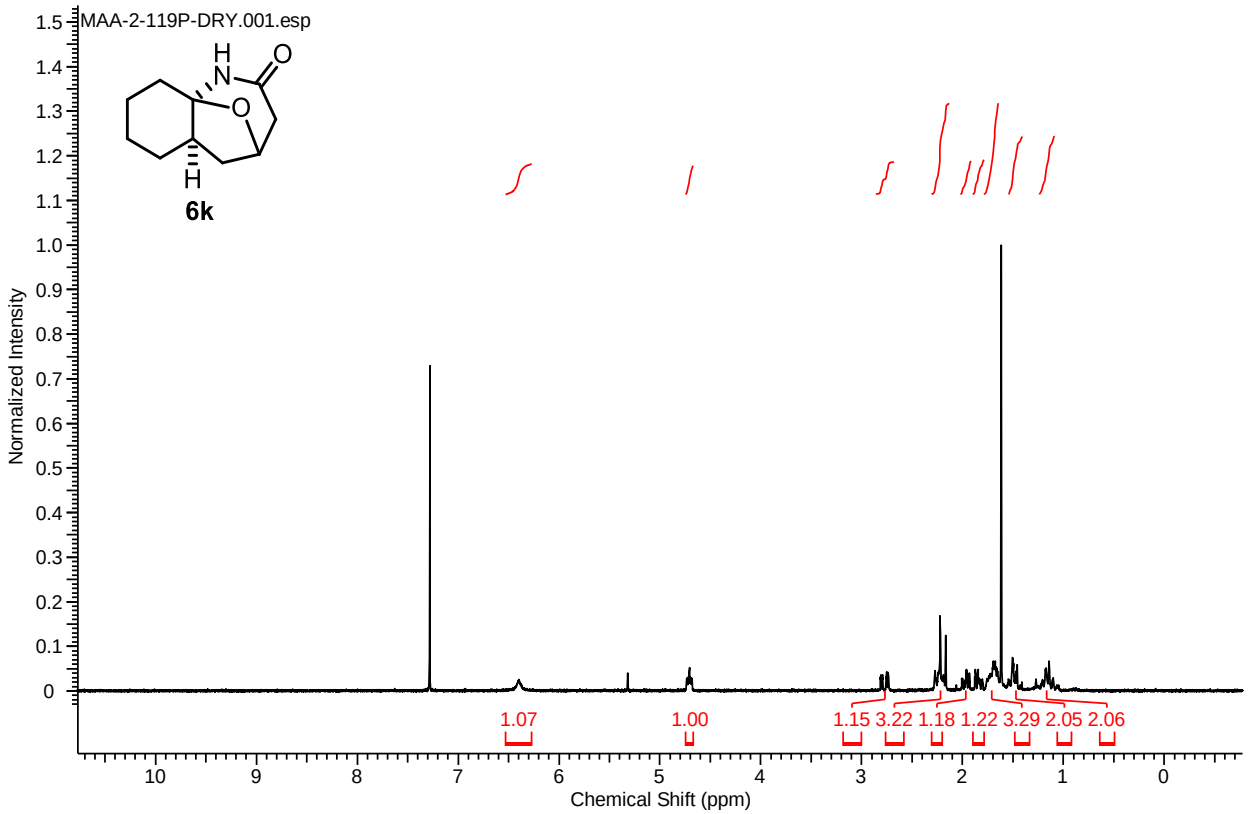

MAA-5-92P-96-148.002.esp
Normalized Intensity
169.26
137.34
115.57
91.77
73.78
40.17
39.84
35.75
28.91
27.92
Chemical Shift (ppm)

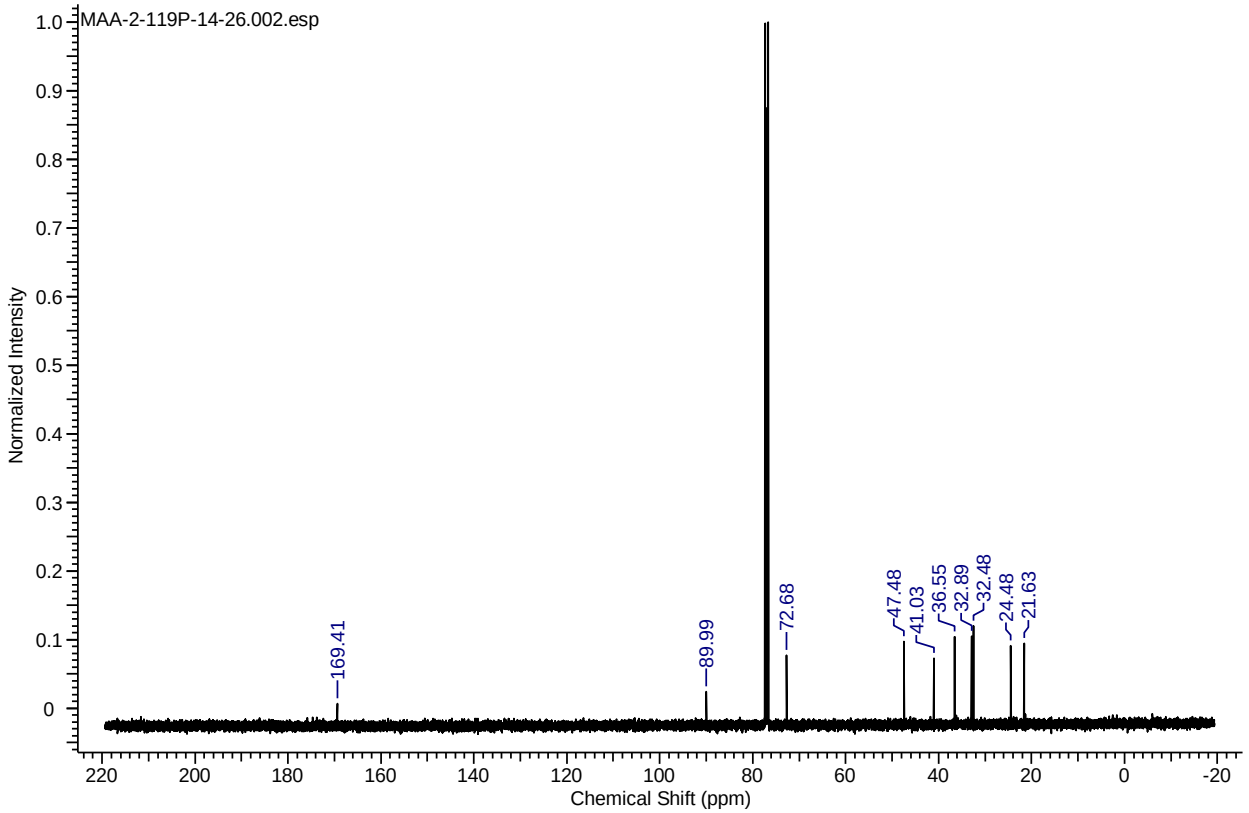

RI10-123-H.001.esp
H
N
O
O
H
6g
Normalized Intensity
Chemical Shift (ppm)
0.11 0.17 0.05 0.05 0.06 0.06 0.06 0.11 0.06

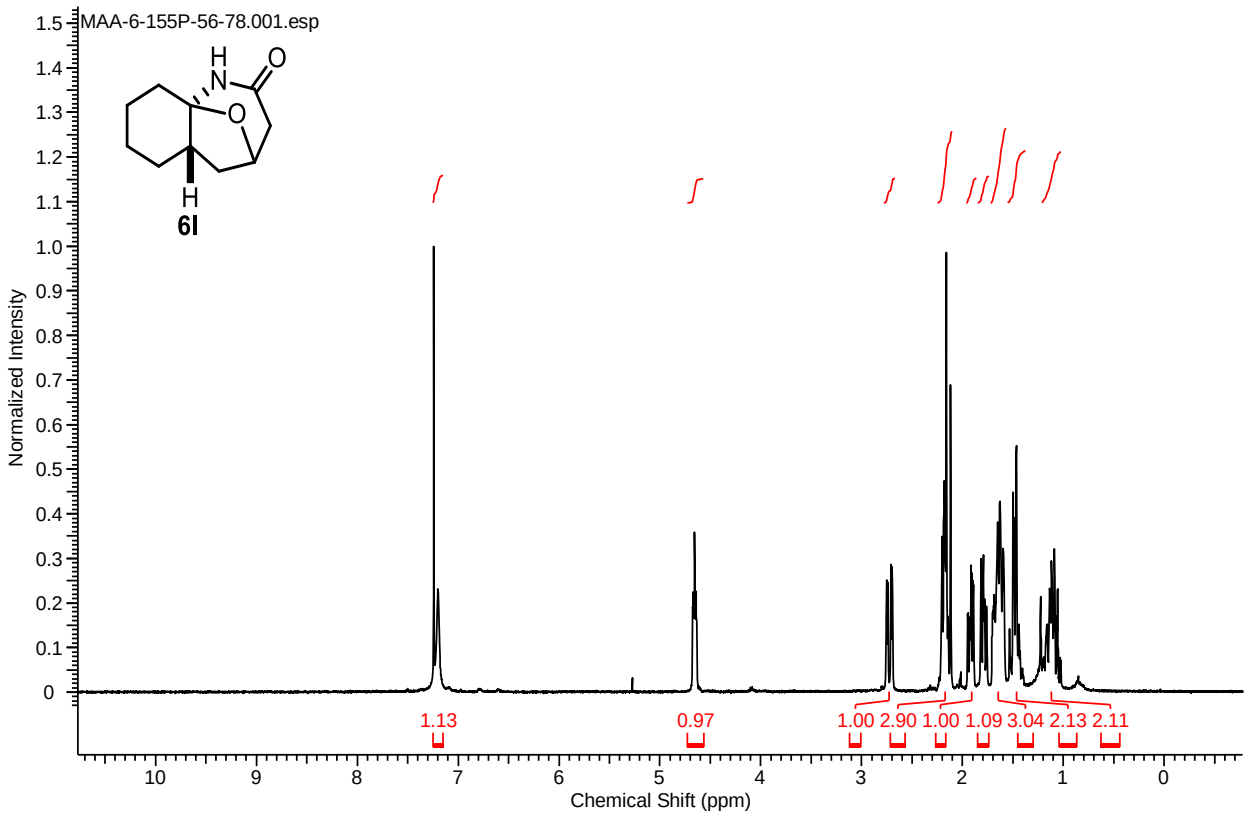

RI10-123-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
168.48
138.88
129.13
128.83
125.15
92.05
74.12
40.87
40.30
28.90

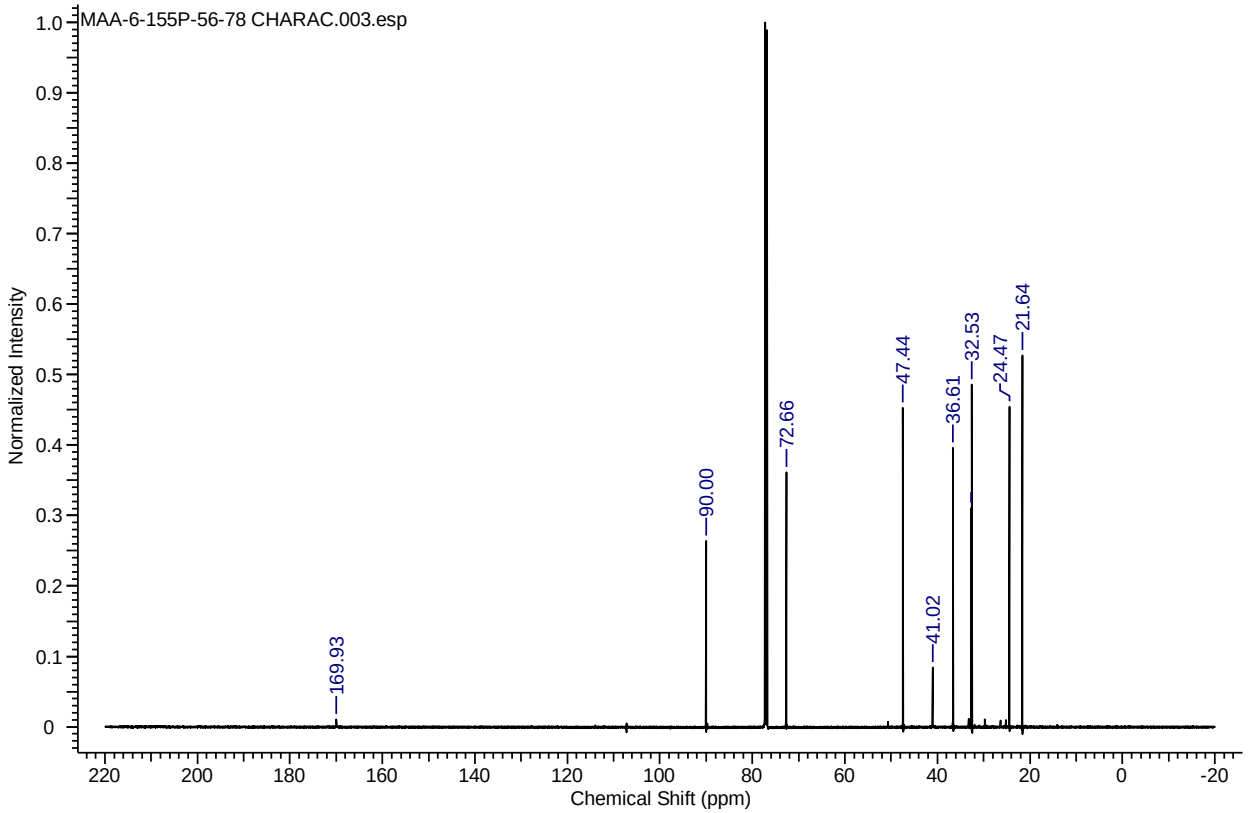

RI13-58-F54-62.001.esp
6i
Normalized Intensity
Chemical Shift (ppm)
0.98 0.78 1.01 1.10 1.00 1.00 3.25 1.02 0.98

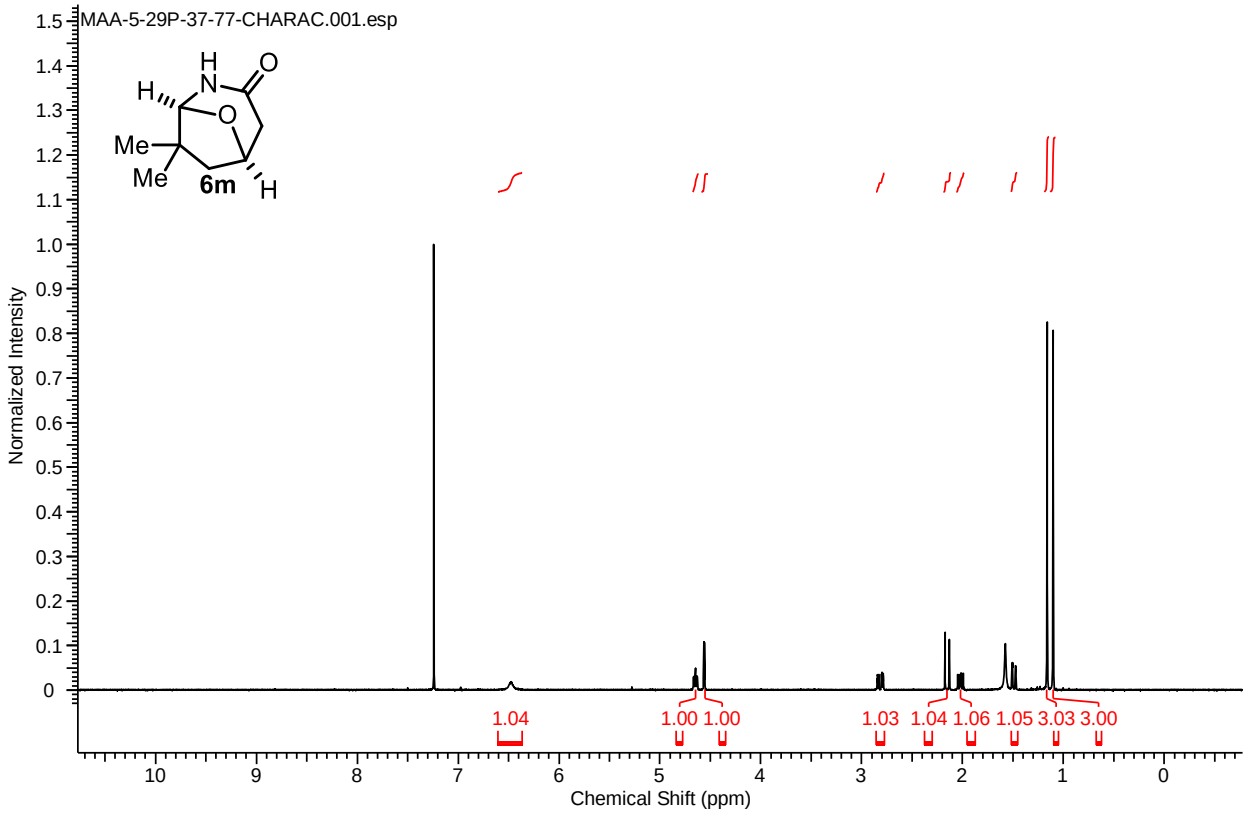

RI13-58-F54-62.002.esp
Normalized Intensity
Chemical Shift (ppm)
168.95
150.12
143.37
110.80
108.67
87.97
74.57
40.44
39.79
28.61

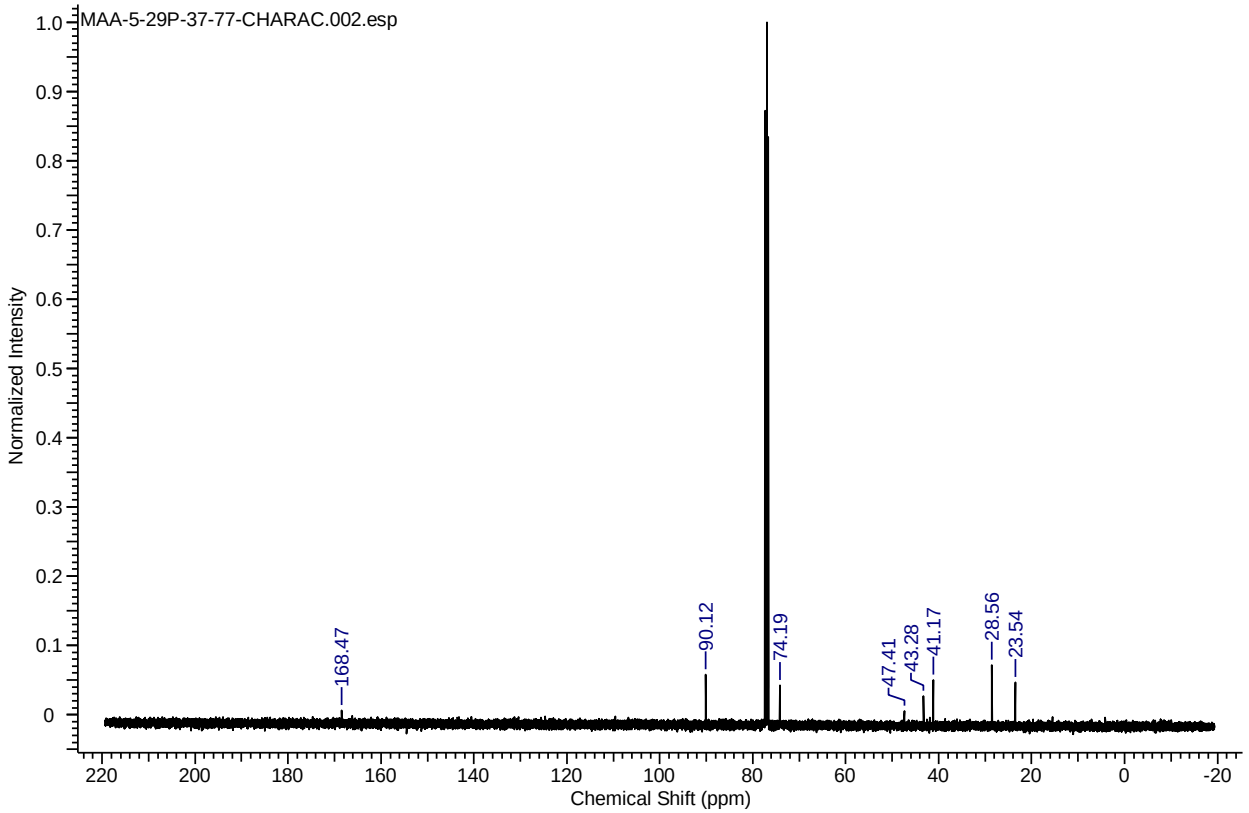

MAA-2-119P-DRY.001.esp
6k
Normalized Intensity
1.07
1.00
1.15 3.22 1.18 1.22 3.29 2.05 2.06
Chemical Shift (ppm)

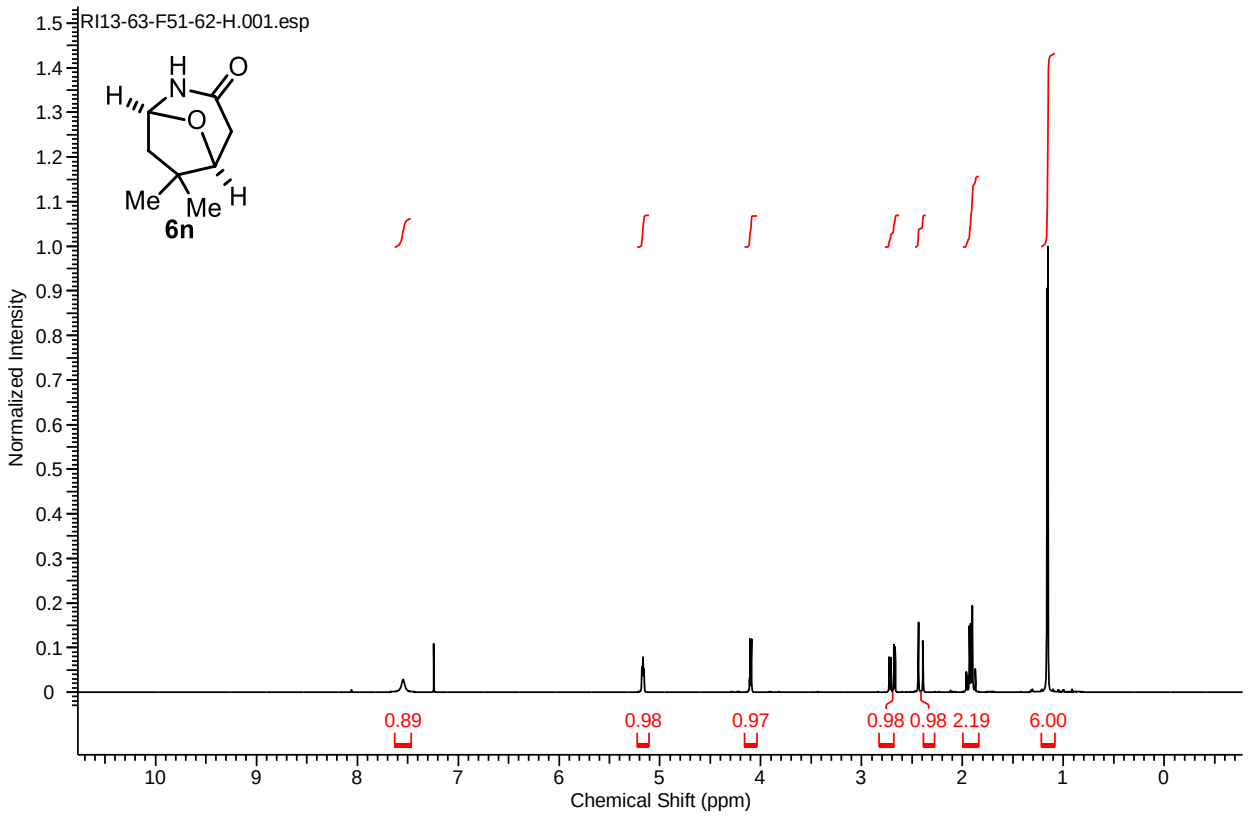

MAA-2-119P-14-26.002.esp
Normalized Intensity
169.41
89.99
72.68
47.48
41.03
36.55
32.89
32.48
24.48
21.63
Chemical Shift (ppm)

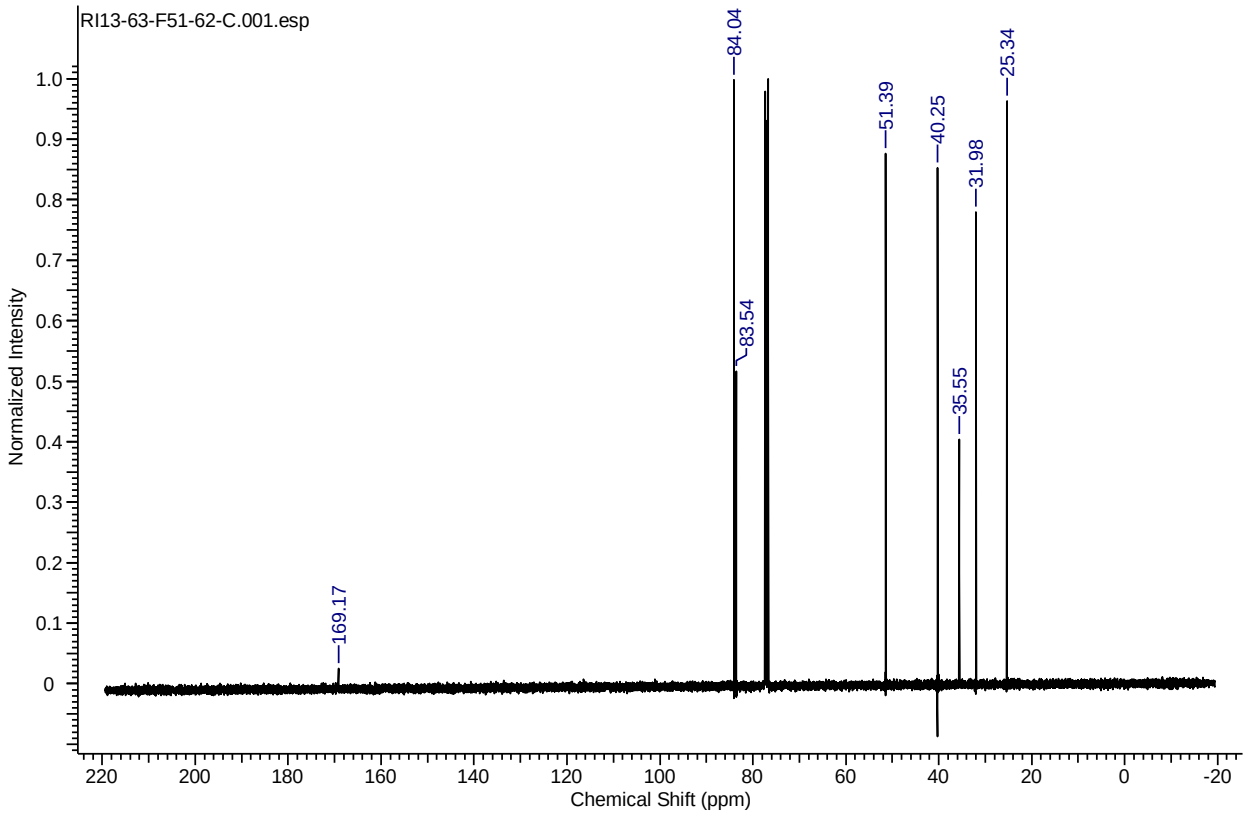

MAA-6-155P-56-78.001.esp
H
N
O
O
H
6l
Normalized Intensity
Chemical Shift (ppm)
1.13
0.97
1.00 2.90 1.00 1.09 3.04 2.13 2.11

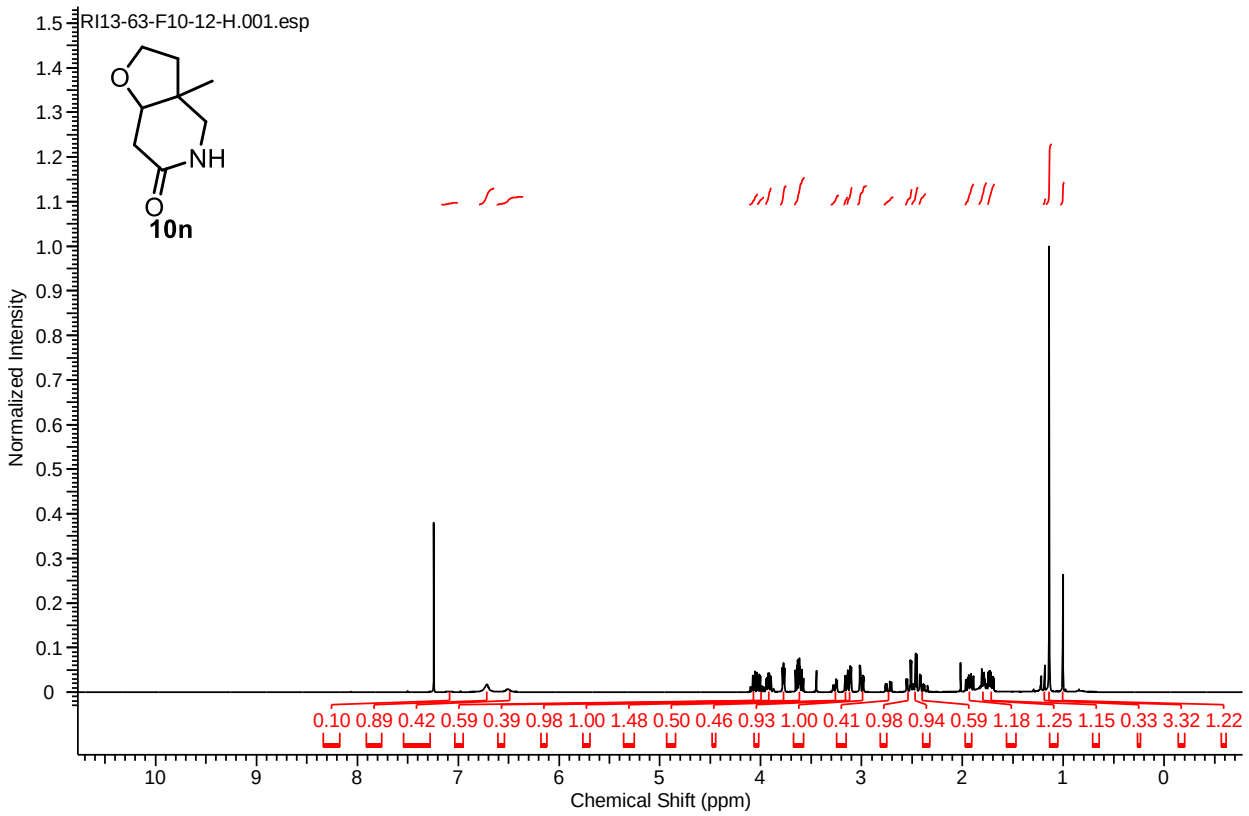

MAA-6-155P-56-78 CHARAC.003.esp
Normalized Intensity
Chemical Shift (ppm)
169.93
90.00
72.66
47.44
41.02
36.61
32.53
24.47
21.64

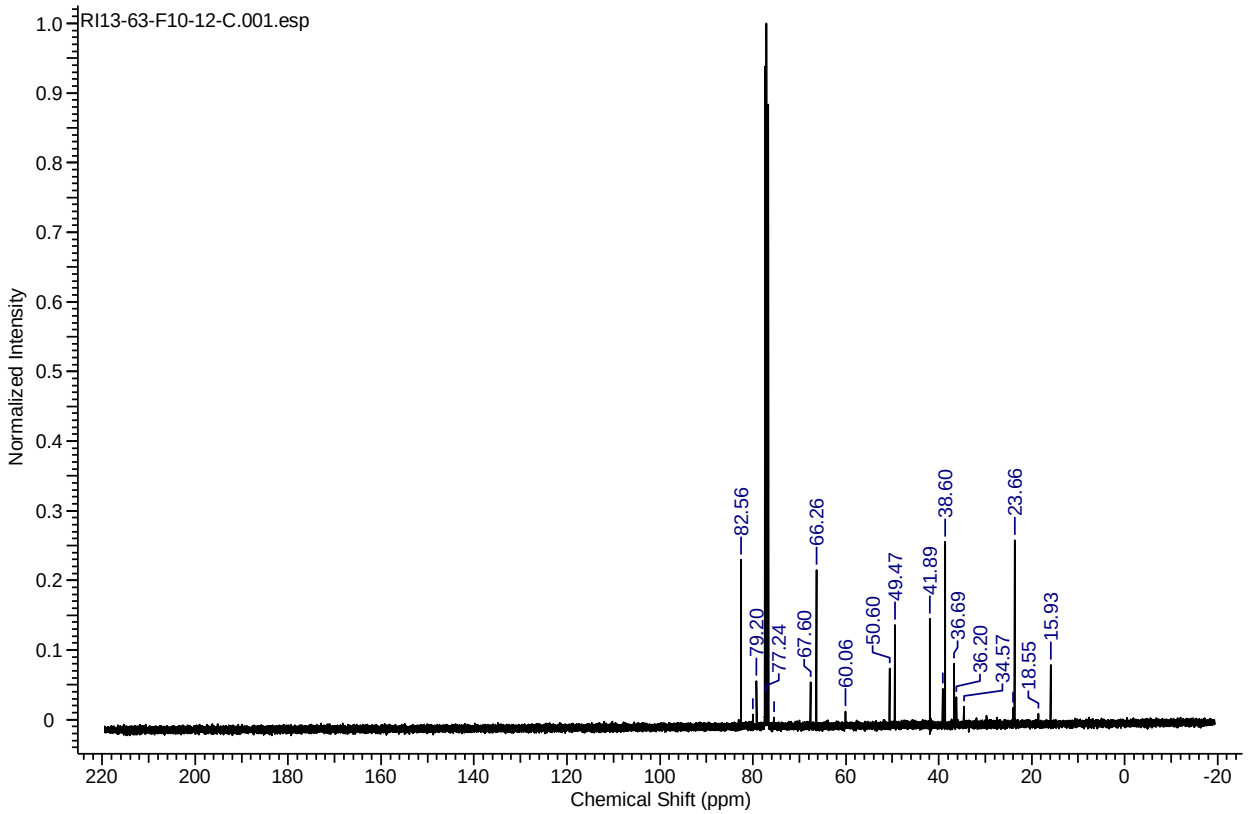

MAA-5-29P-37-77-CHARAC.001.esp
H
N
O
H
O
Me
Me
6m
H
Normalized Intensity
1.04
1.00 1.00
1.03 1.04 1.06 1.05 3.03 3.00
Chemical Shift (ppm)

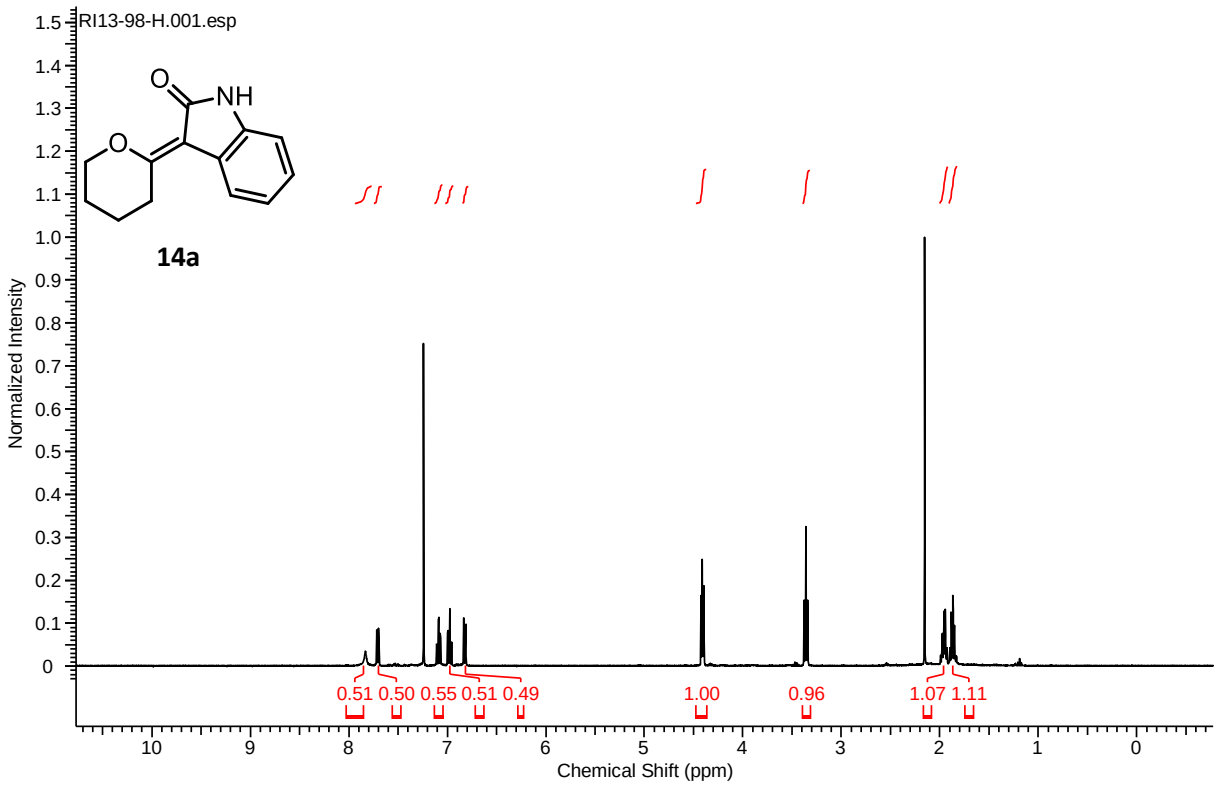

MAA-5-29P-37-77-CHARAC.002.esp
Normalized Intensity
168.47
90.12
74.19
47.41
43.28
41.17
28.56
23.54
Chemical Shift (ppm)

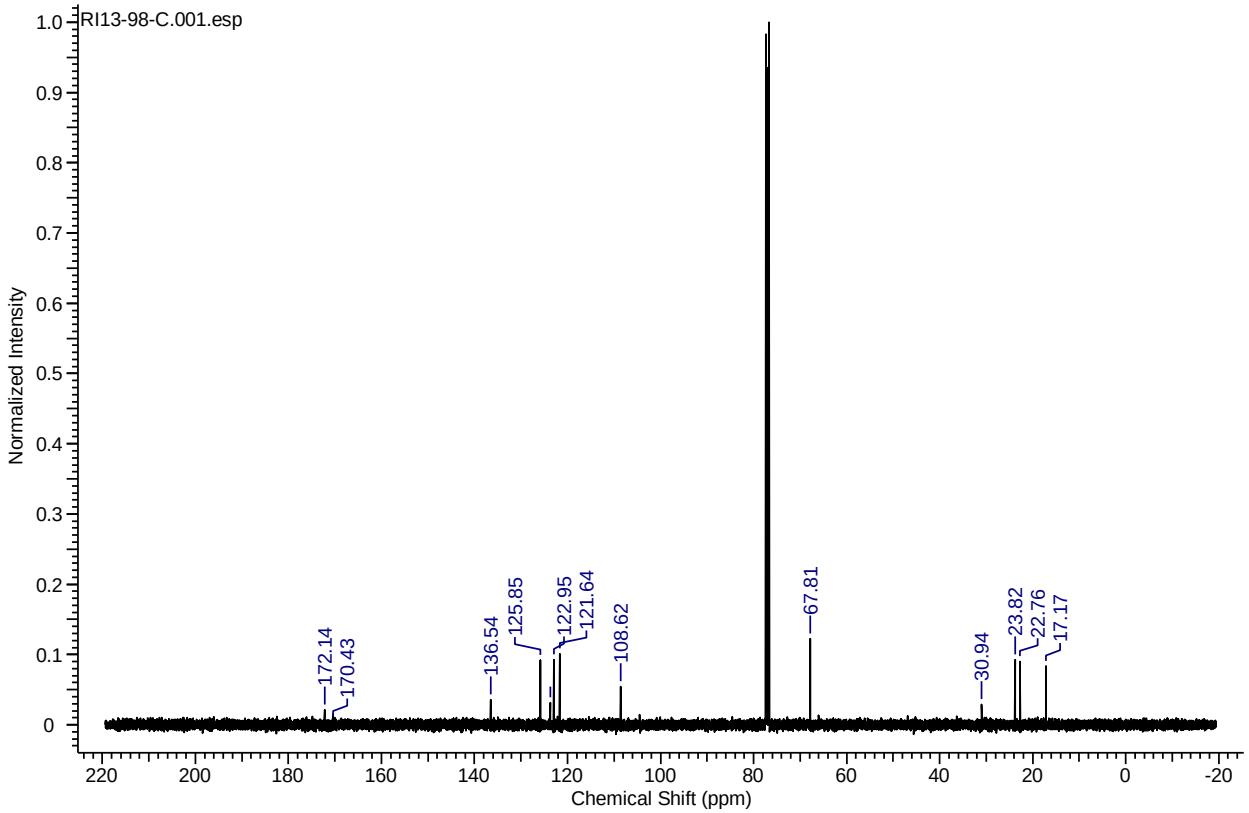

RI13-63-F51-62-H.001.esp
H
N
O
H
O
Me
Me
H
6n
Normalized Intensity
Chemical Shift (ppm)
0.89
0.98
0.97
0.98
0.98
2.19
6.00

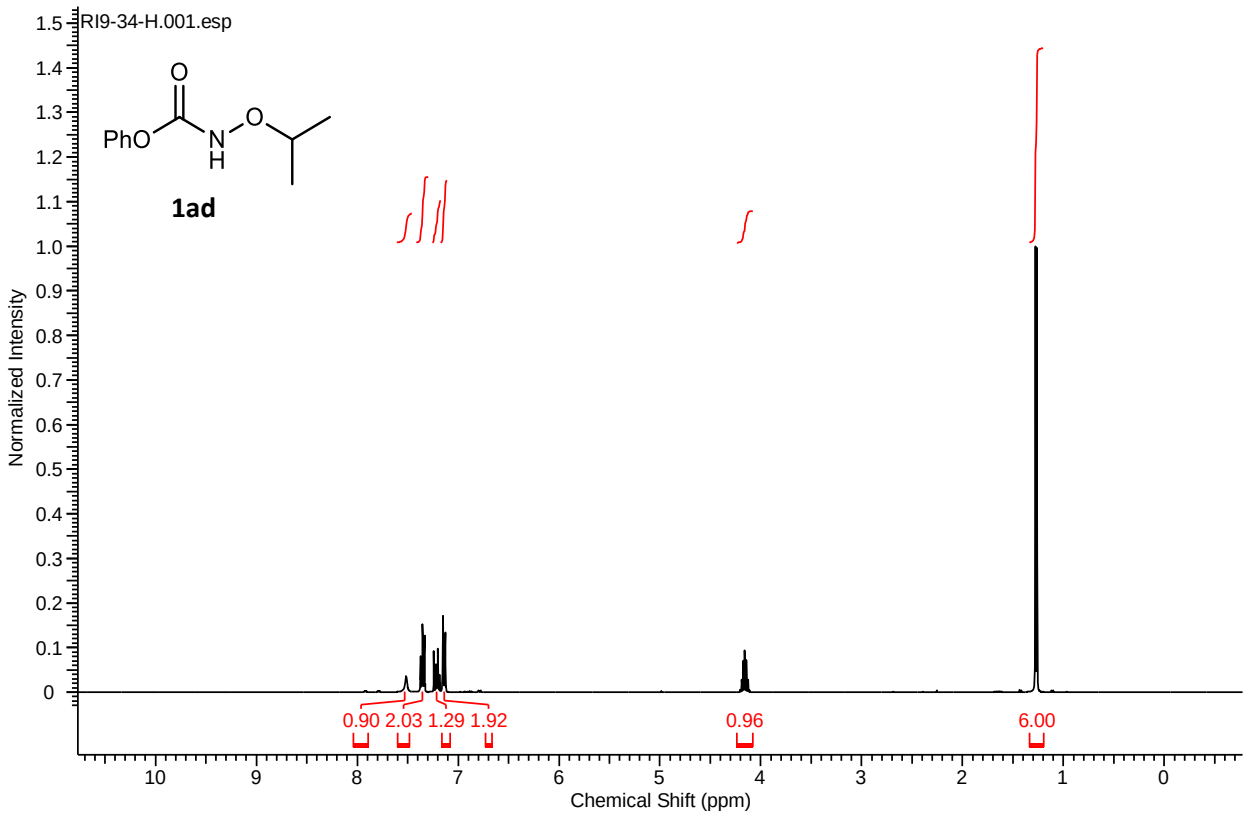

RI13-63-F51-62-C.001.esp
84.04
83.54
51.39
40.25
35.55
31.98
25.34
169.17
Normalized Intensity
Chemical Shift (ppm)

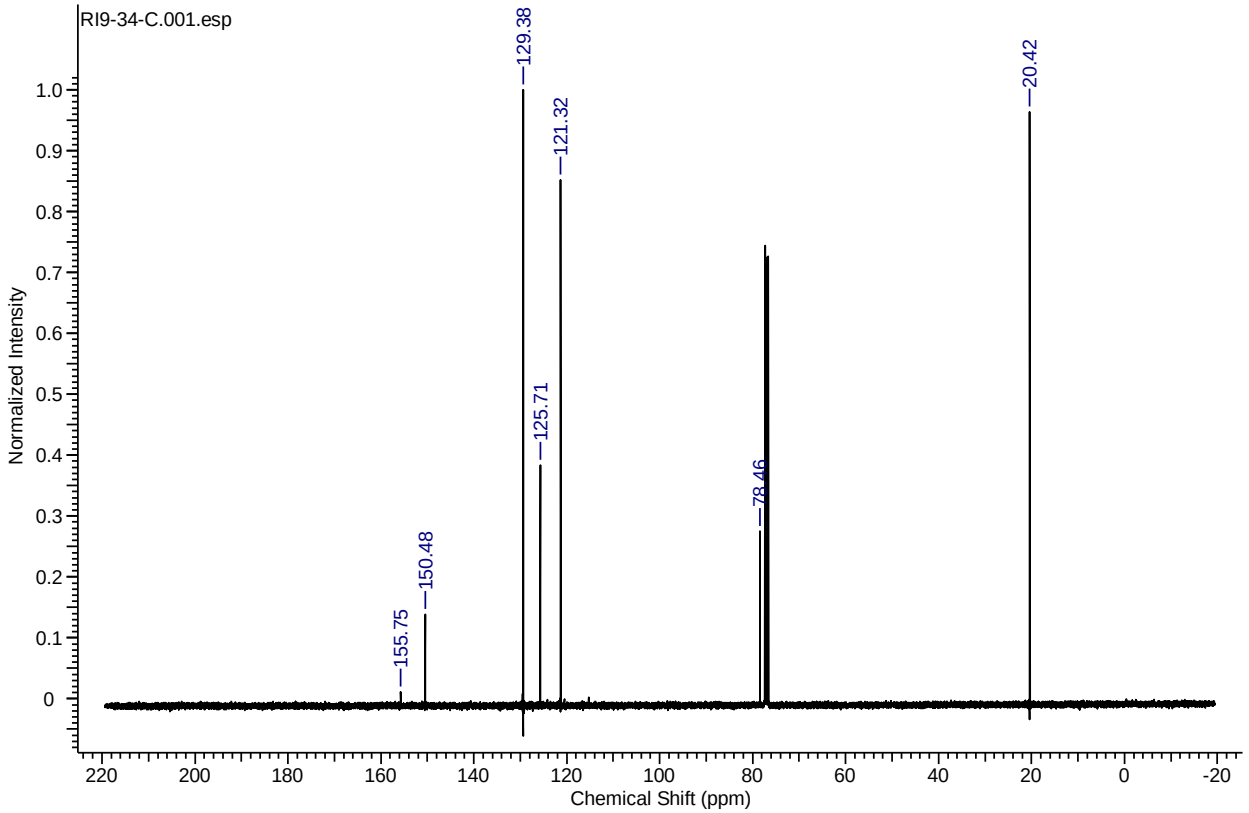

RI13-63-F10-12-H.001.esp
NH
O
O
10n
Normalized Intensity
0.10 0.89 0.42 0.59 0.39 0.98 1.00 1.48 0.50 0.46 0.93 1.00 0.41 0.98 0.94 0.59 1.18 1.25 1.15 0.33 3.32 1.22
Chemical Shift (ppm)

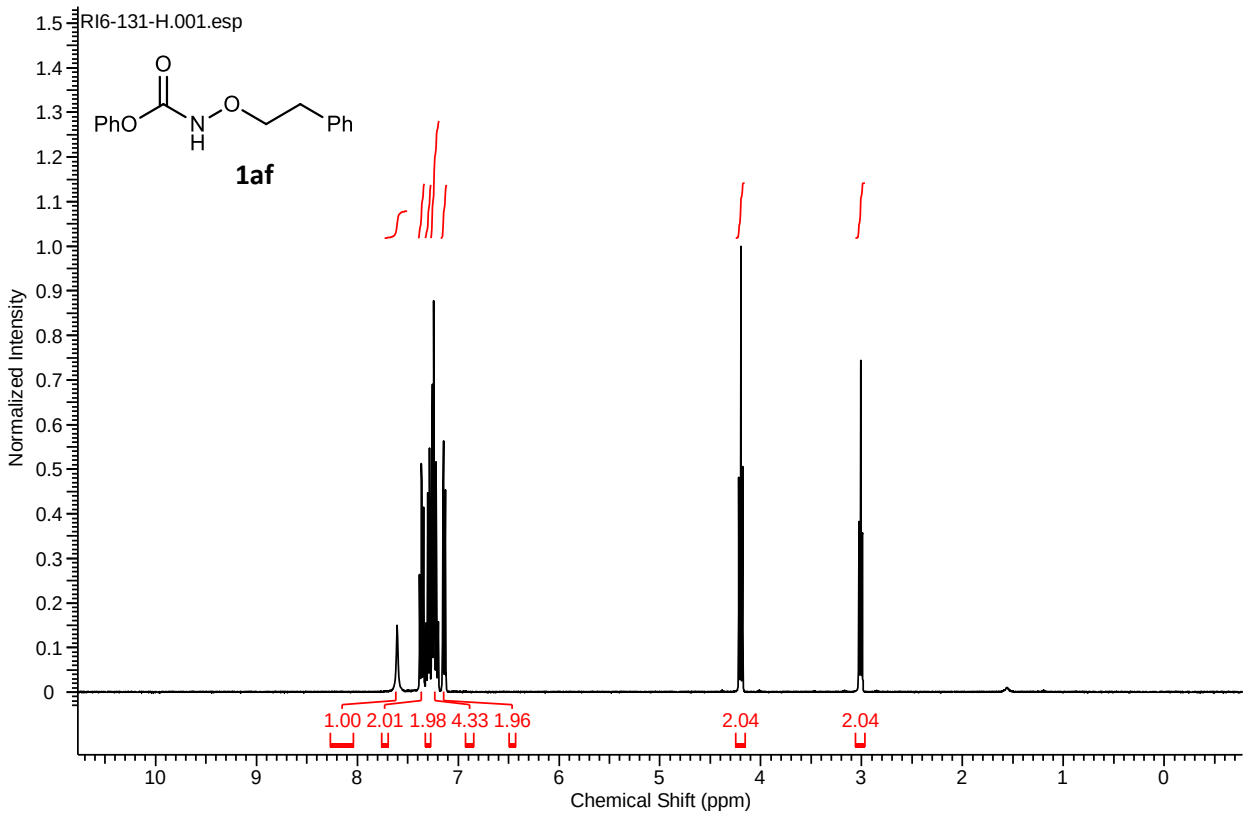

RI13-63-F10-12-C.001.esp
Normalized Intensity
82.56
79.20
77.24
67.60
66.26
60.06
50.60
49.47
41.89
38.60
36.69
36.20
34.57
23.66
18.55
15.93
Chemical Shift (ppm)

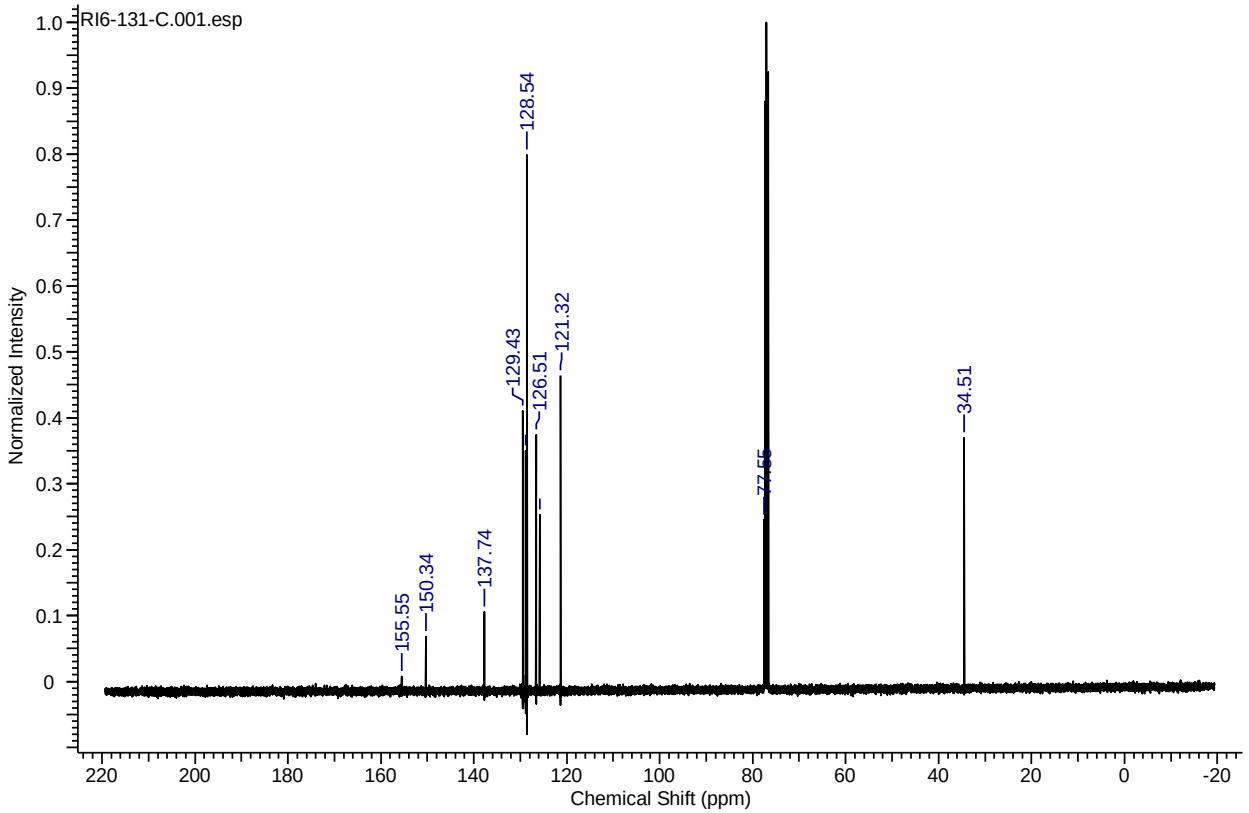

RI13-98-H.001.esp
O
NH
O
14a
Normalized Intensity
0.51 0.50 0.55 0.51 0.49
1.00
0.96
1.07 1.11
Chemical Shift (ppm)

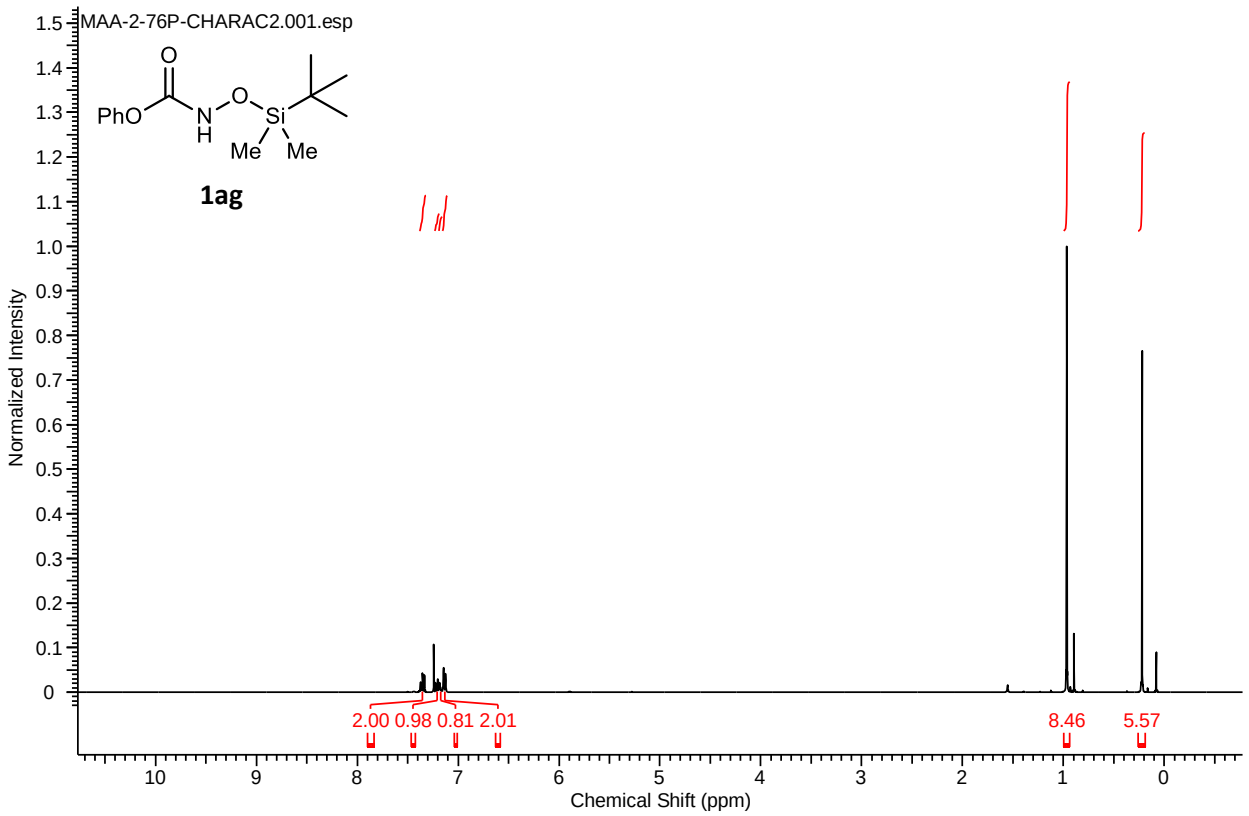

RI13-98-C.001.esp
Normalized Intensity
172.14
170.43
136.54
125.85
122.95
121.64
108.62
67.81
30.94
23.82
22.76
17.17
Chemical Shift (ppm)

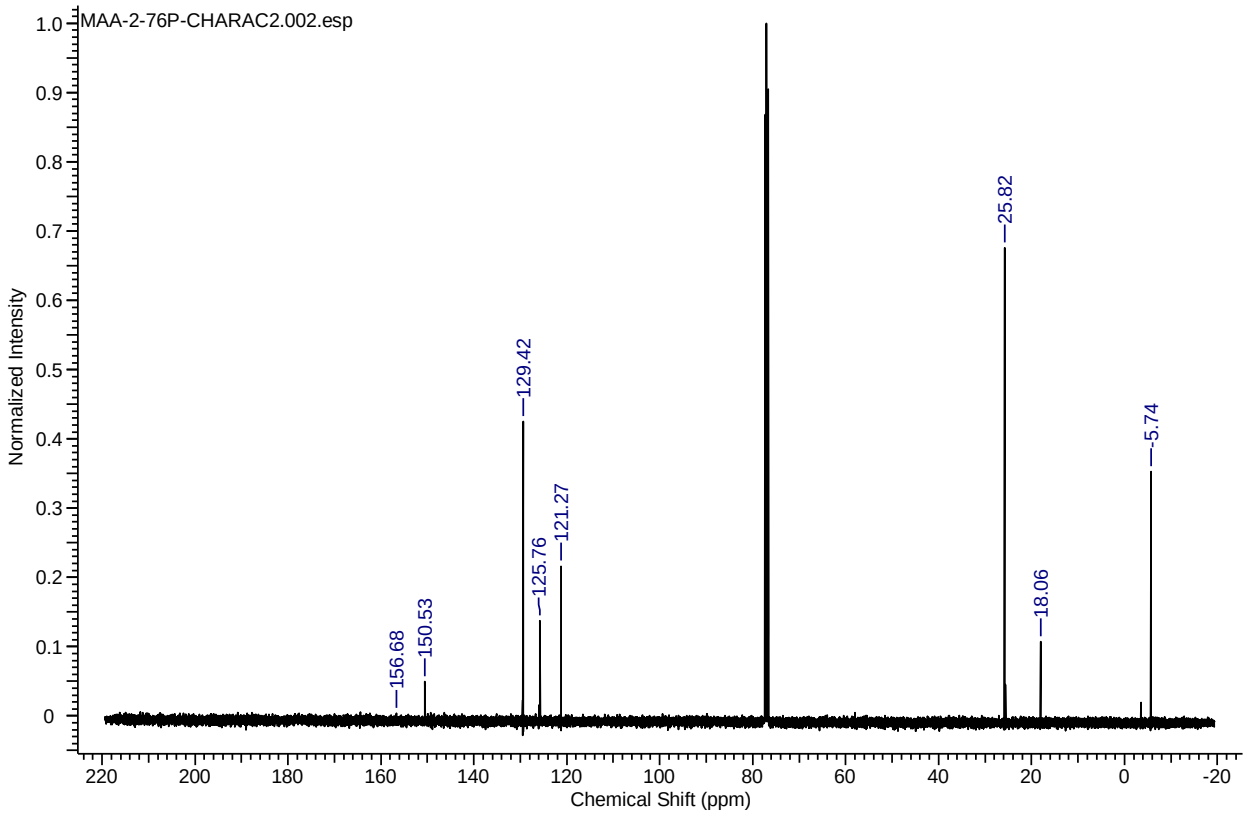

RI9-34-H.001.esp
PhO
O
N
H
O
1ad
Normalized Intensity
0.90 2.03 1.29 1.92
0.96
6.00
Chemical Shift (ppm)

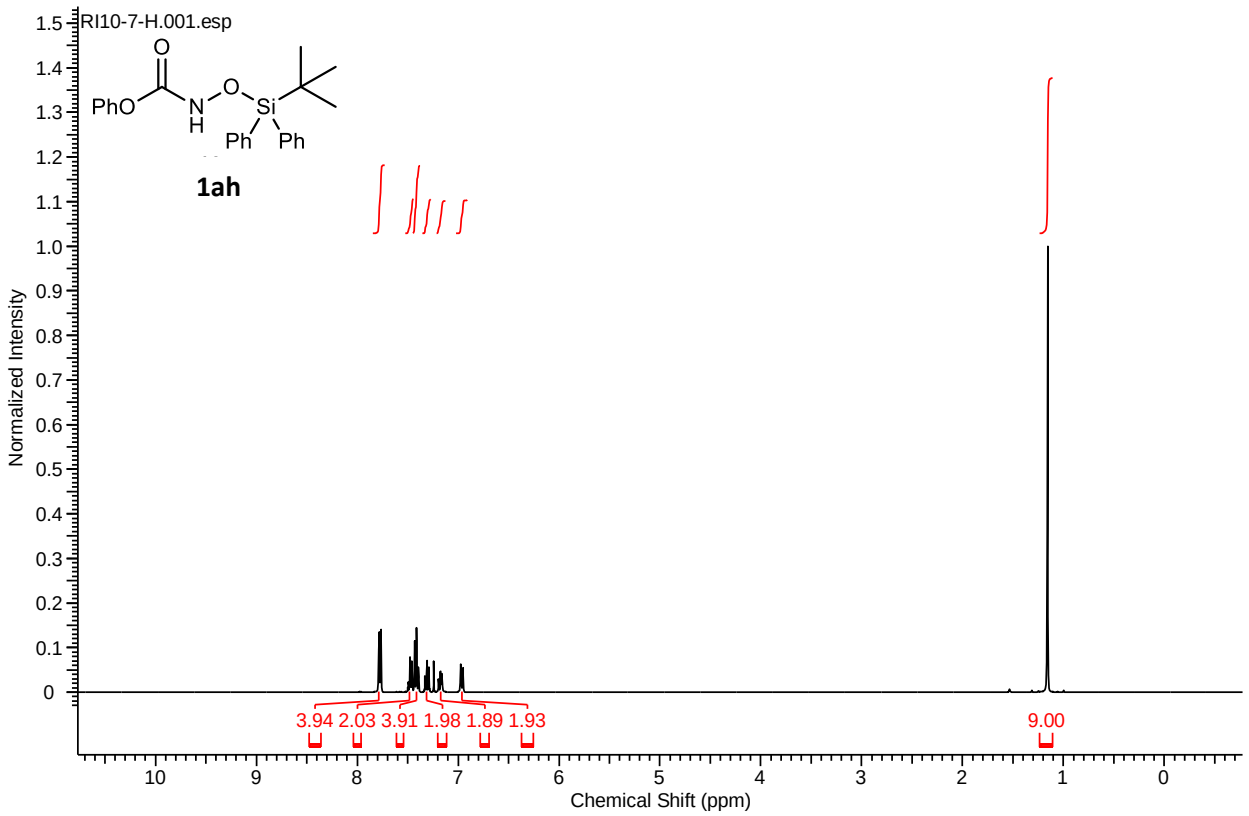

RI9-34-C.001.esp
129.38
121.32
125.71
78.46
150.48
155.75
20.42
Normalized Intensity
Chemical Shift (ppm)

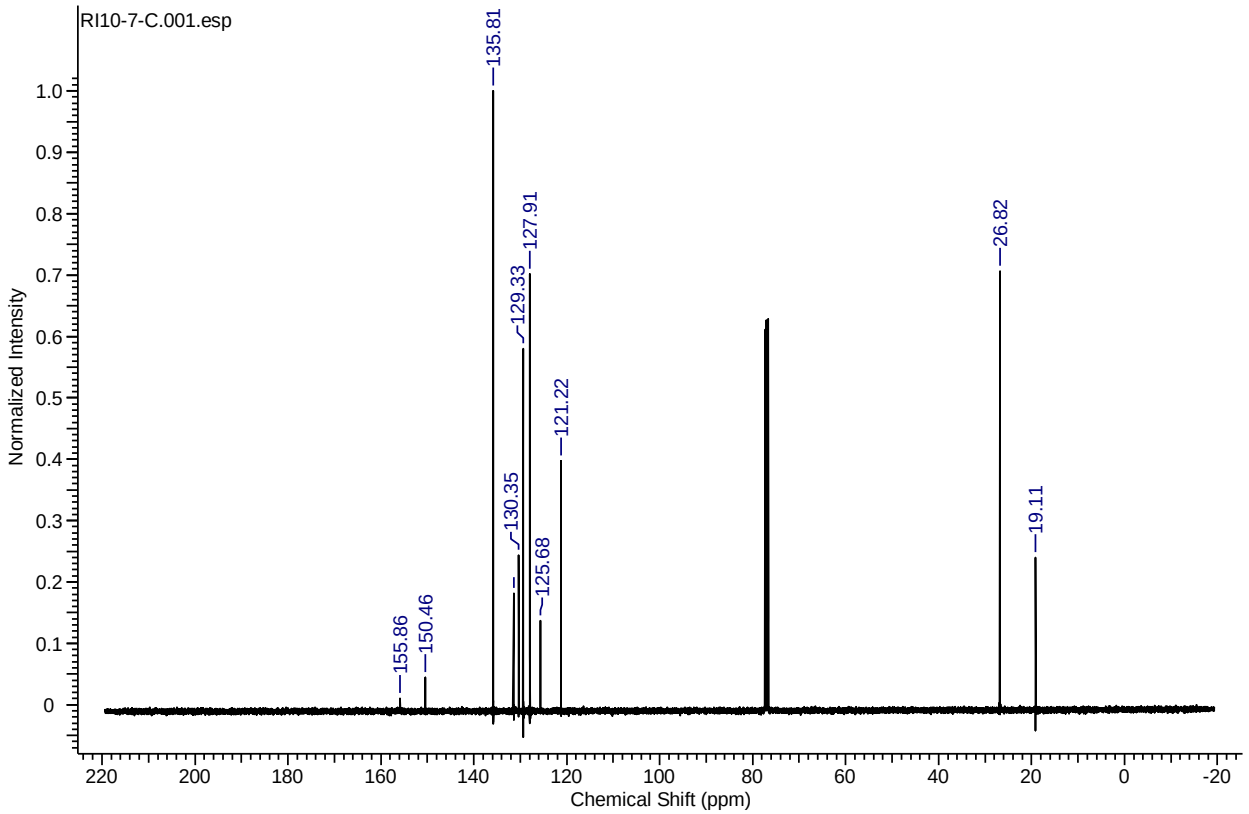

RI6-131-H.001.esp
PhO
O
N
H
O
Ph
1af
Normalized Intensity
1.00 2.01 1.98 4.33 1.96
2.04
2.04
Chemical Shift (ppm)

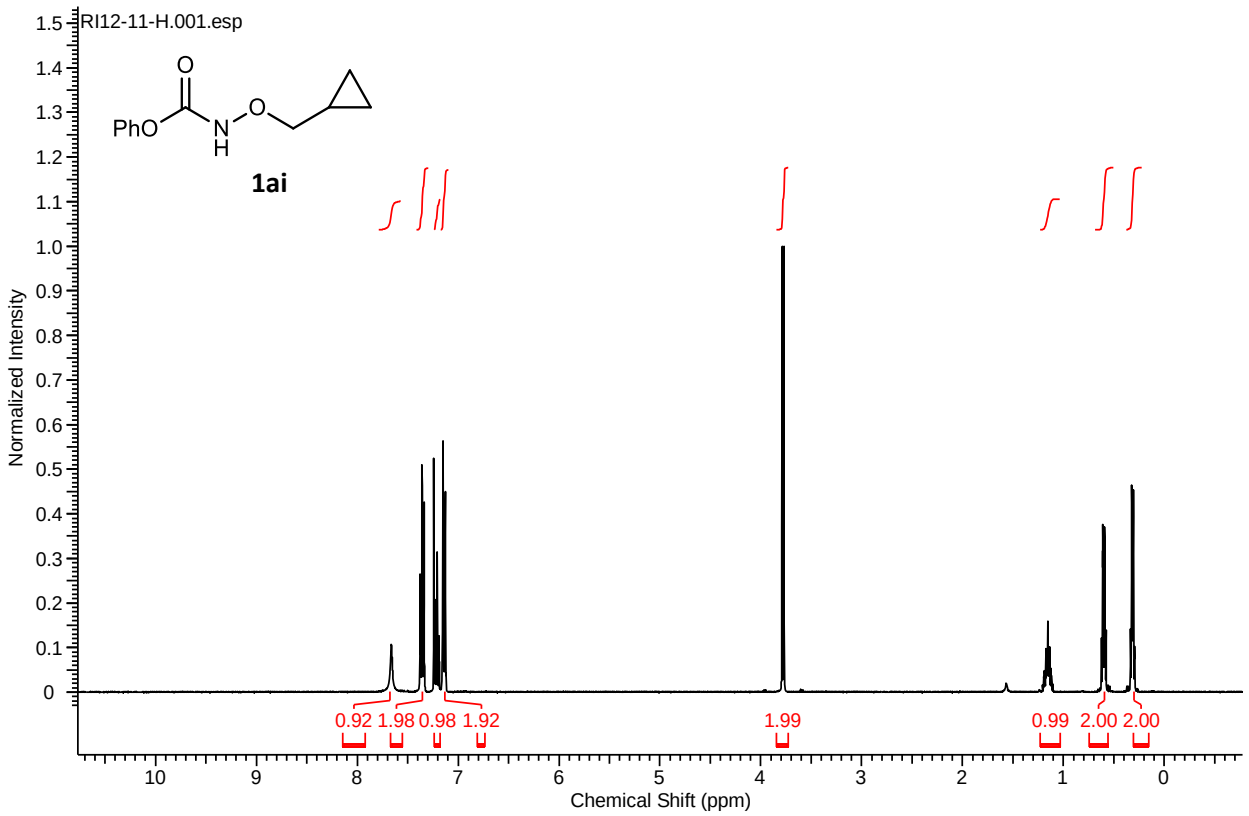

RI6-131-C.001.esp
Normalized Intensity
128.54
129.43
126.51
121.32
77.55
34.51
155.55
150.34
137.74
Chemical Shift (ppm)

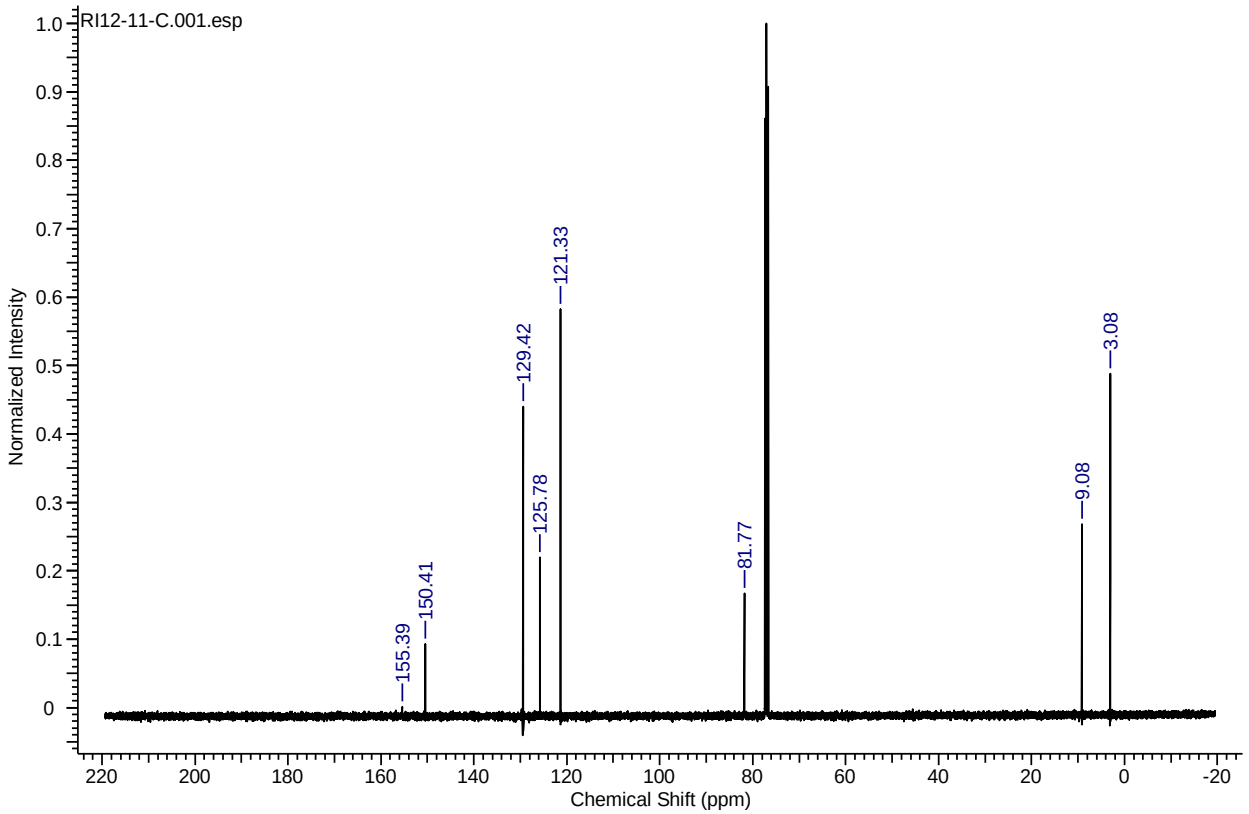

MAA-2-76P-CHARAC2.001.esp
PhO
O
N
H
O
Si
Me
Me
1ag
Normalized Intensity
Chemical Shift (ppm)
2.00 0.98 0.81 2.01
8.46
5.57

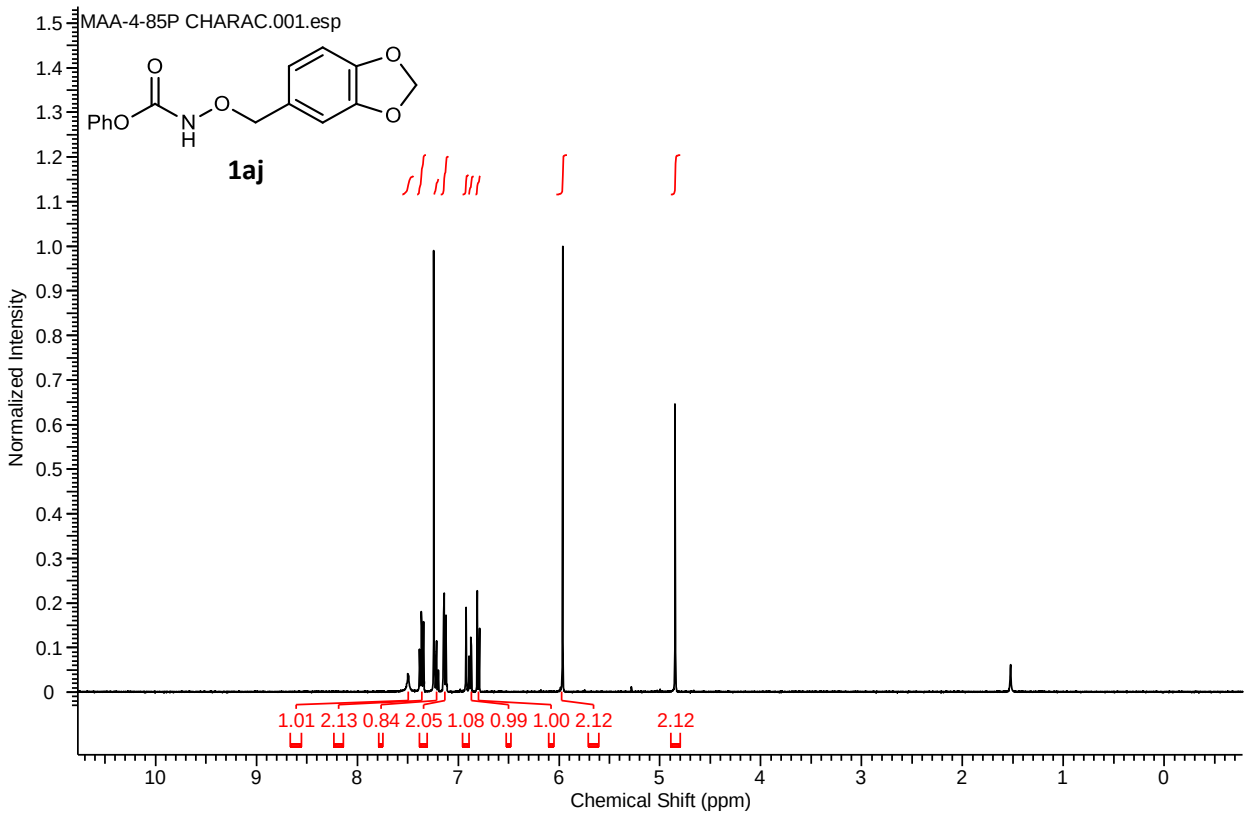

MAA-2-76P-CHARAC2.002.esp
Normalized Intensity
Chemical Shift (ppm)
156.68
150.53
129.42
125.76
121.27
25.82
18.06
5.74

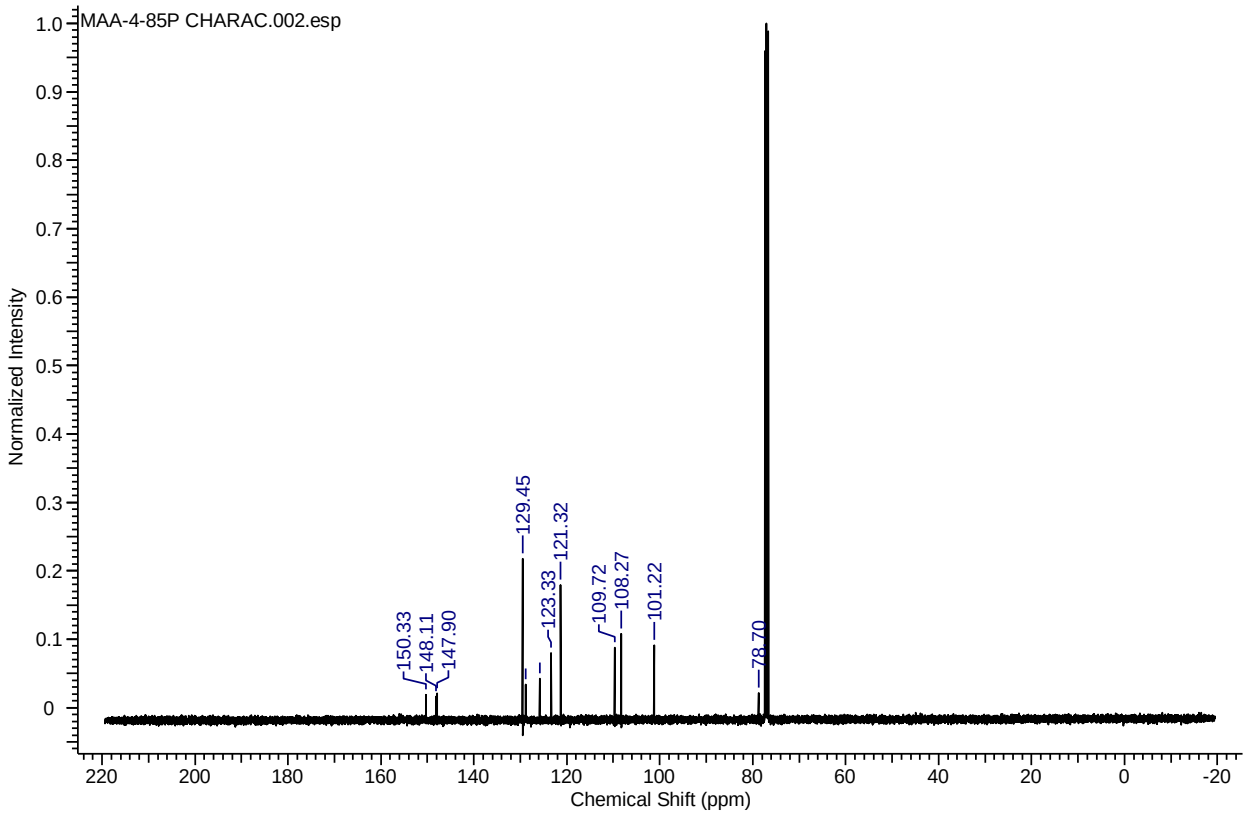

RI10-7-H.001.esp
PhO
O
N
H
O
Si
Ph
Ph
1ah
Normalized Intensity
3.94 2.03 3.91 1.98 1.89 1.93
9.00
Chemical Shift (ppm)

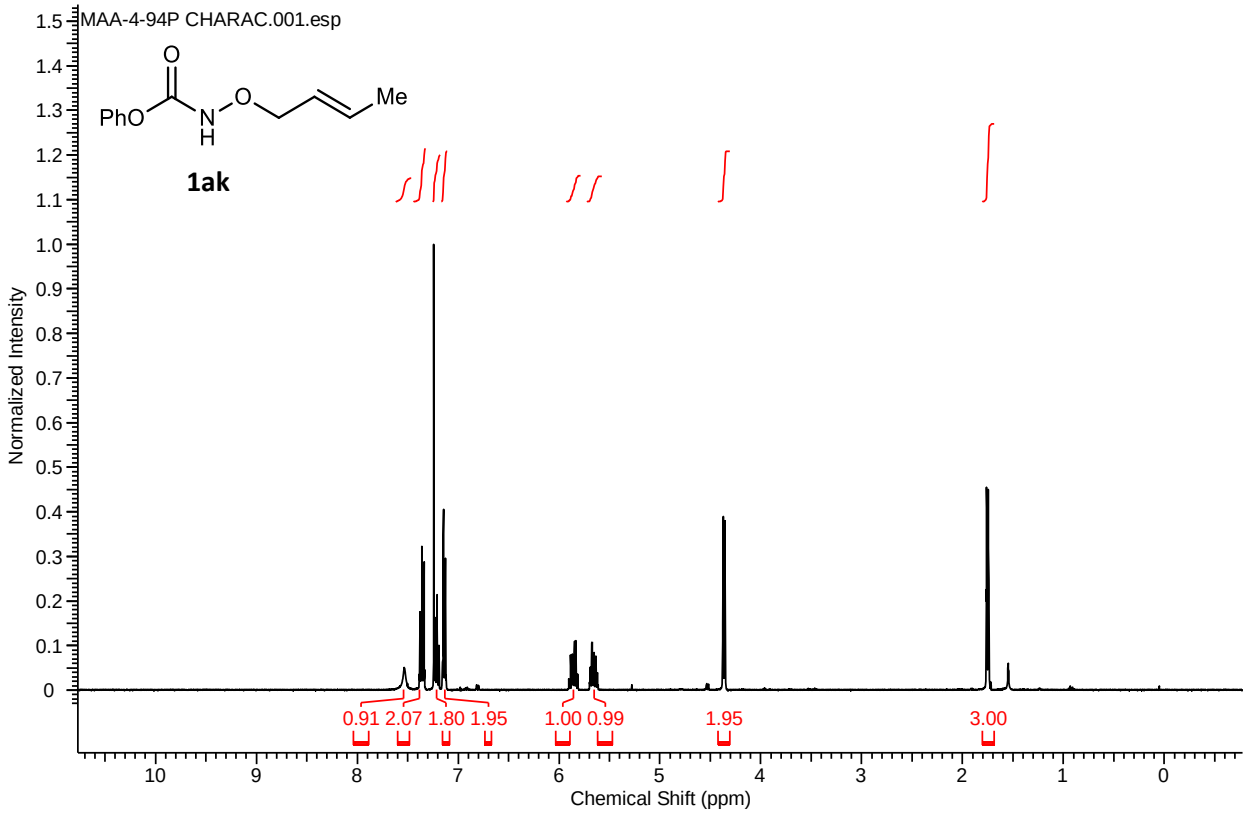

RI10-7-C.001.esp
135.81
129.33
127.91
121.22
130.35
125.68
155.86
150.46
26.82
19.11
Normalized Intensity
Chemical Shift (ppm)

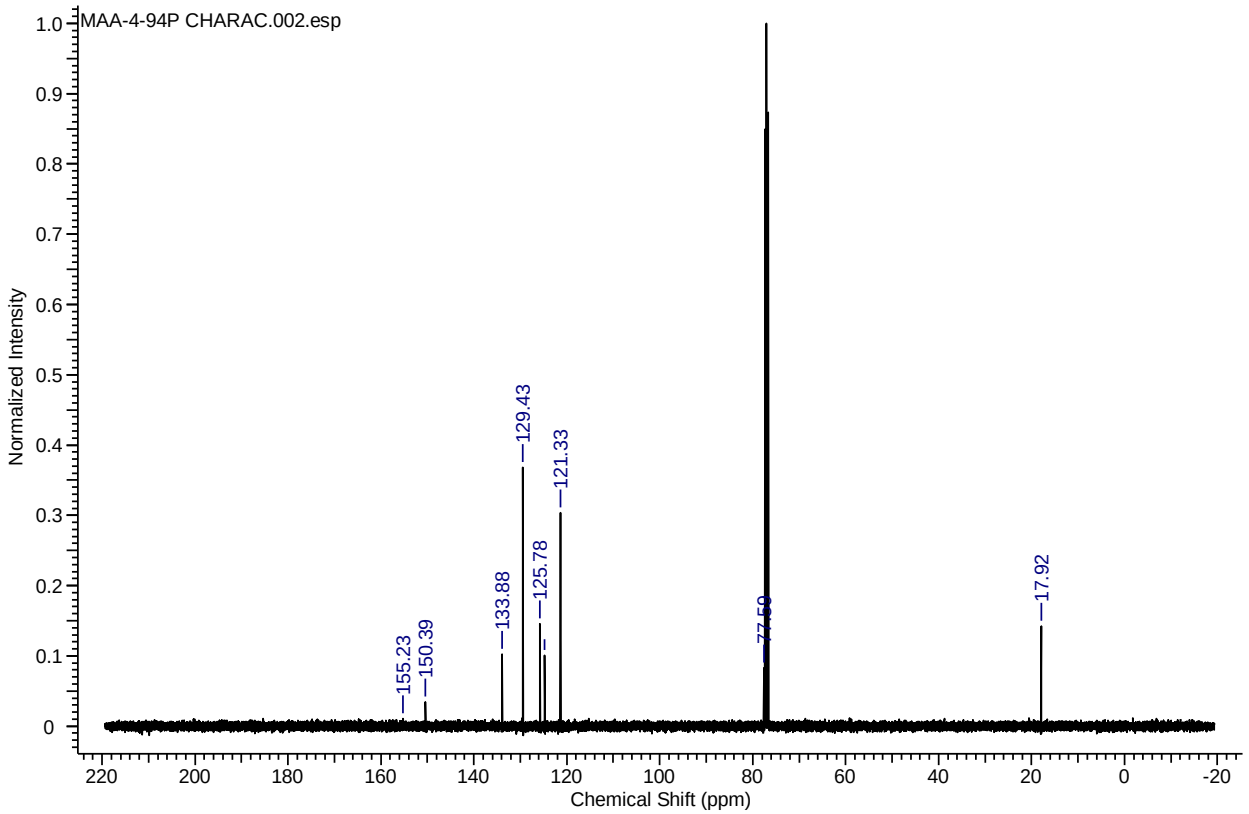

RI12-11-H.001.esp
PhO
O
N
H
O
1ai
Normalized Intensity
Chemical Shift (ppm)
0.92 1.98 0.98 1.92
1.99
0.99 2.00 2.00

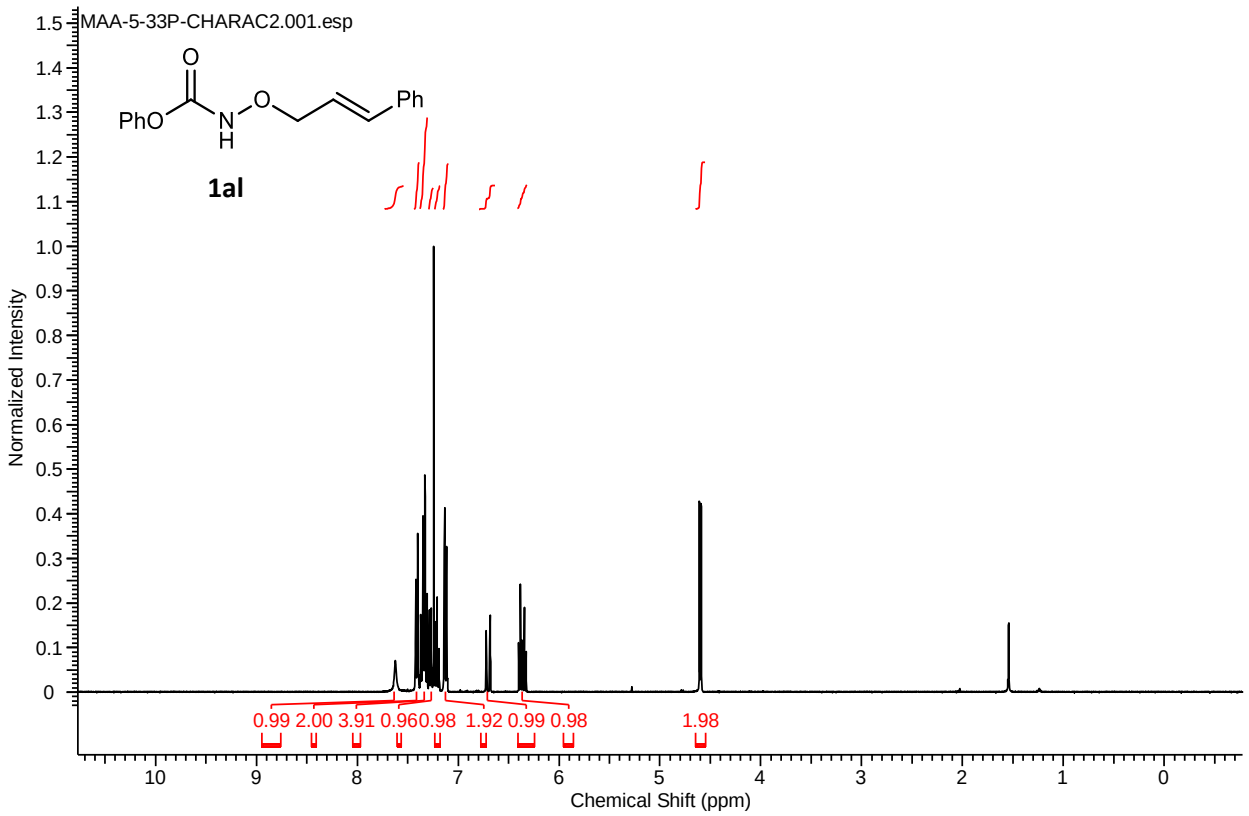

RI12-11-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
155.39
150.41
129.42
125.78
121.33
81.77
9.08
3.08

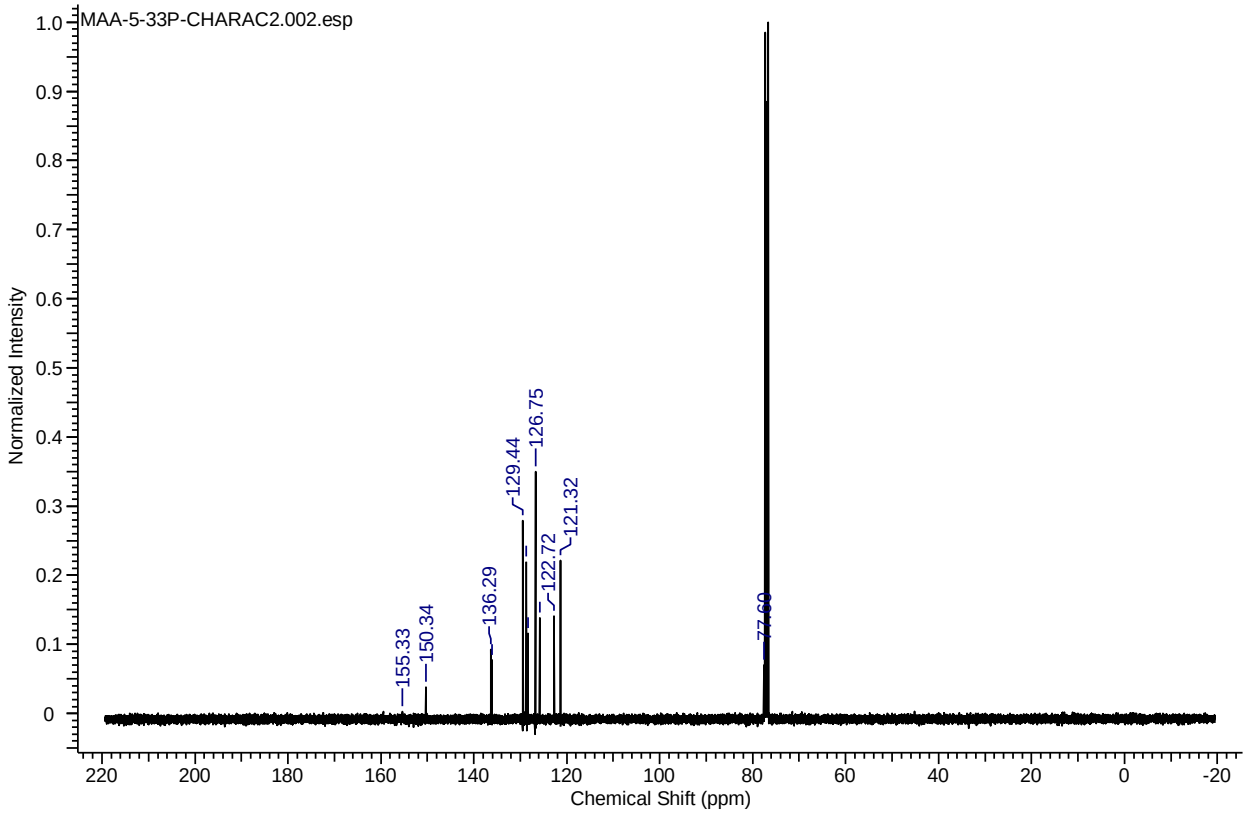

MAA-4-85P CHARAC.001.esp
PhO
O
N
H
O
O
O
1aj
Normalized Intensity
1.01 2.13 0.84 2.05 1.08 0.99 1.00 2.12
2.12
Chemical Shift (ppm)

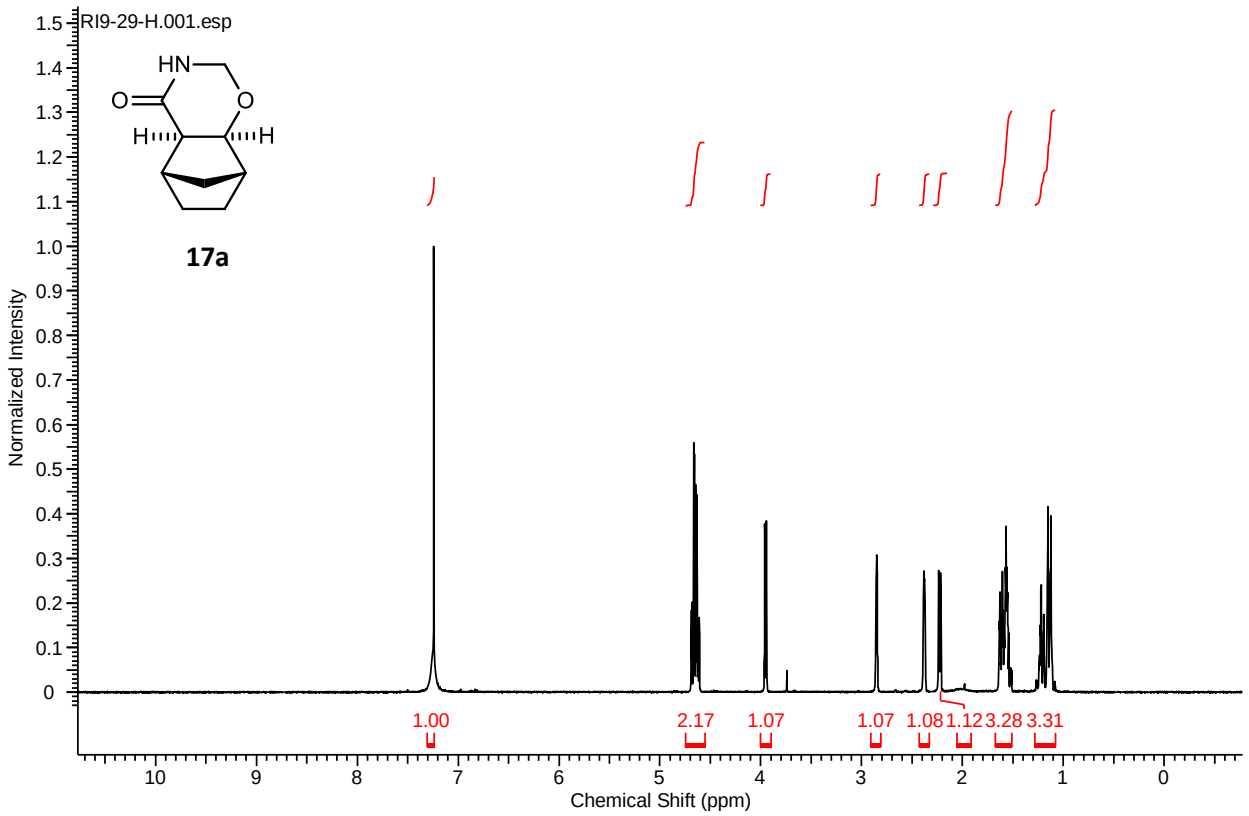

MAA-4-85P CHARAC.002.esp
Normalized Intensity
150.33
148.11
147.90
129.45
123.33
121.32
109.72
108.27
101.22
78.70
Chemical Shift (ppm)

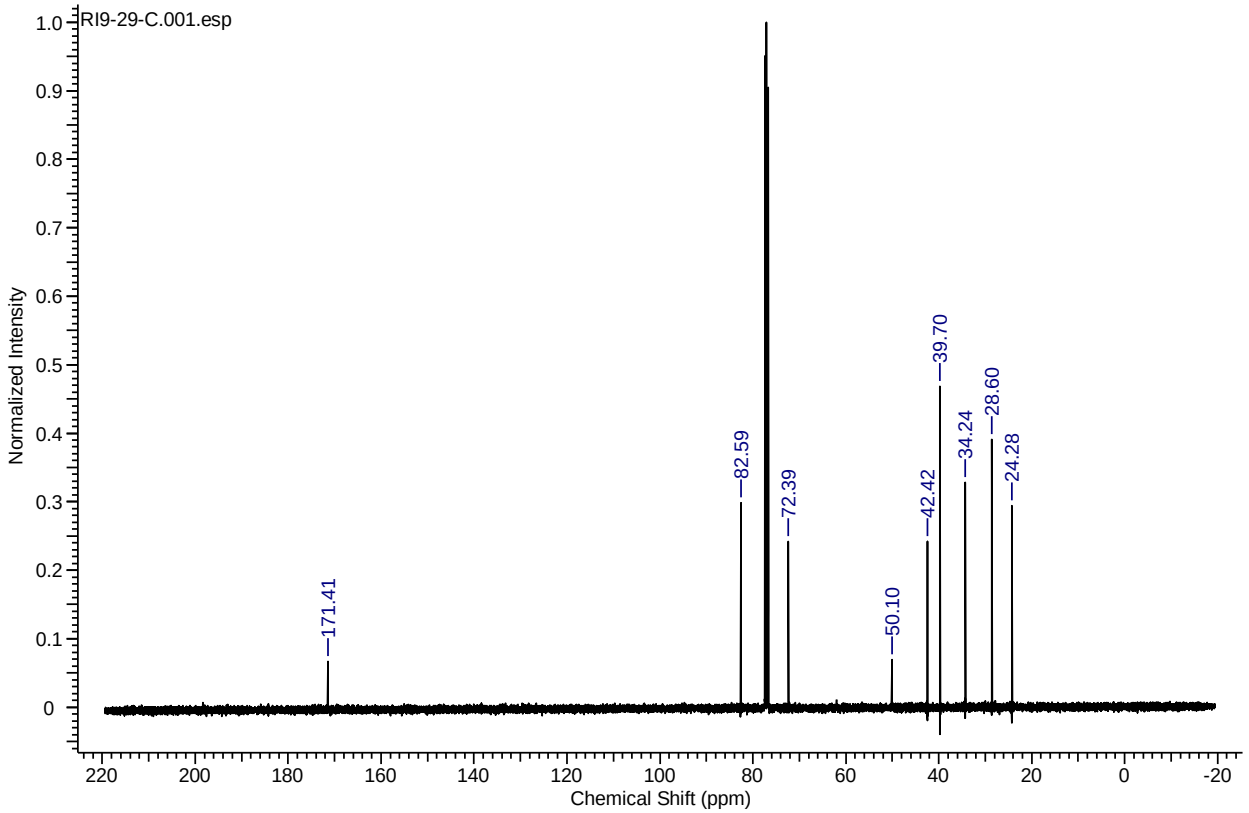

MAA-4-94P CHARAC.001.esp
PhO
O
N
H
O
Me
1ak
Normalized Intensity
0.91 2.07 1.80 1.95 1.00 0.99 1.95 3.00
Chemical Shift (ppm)

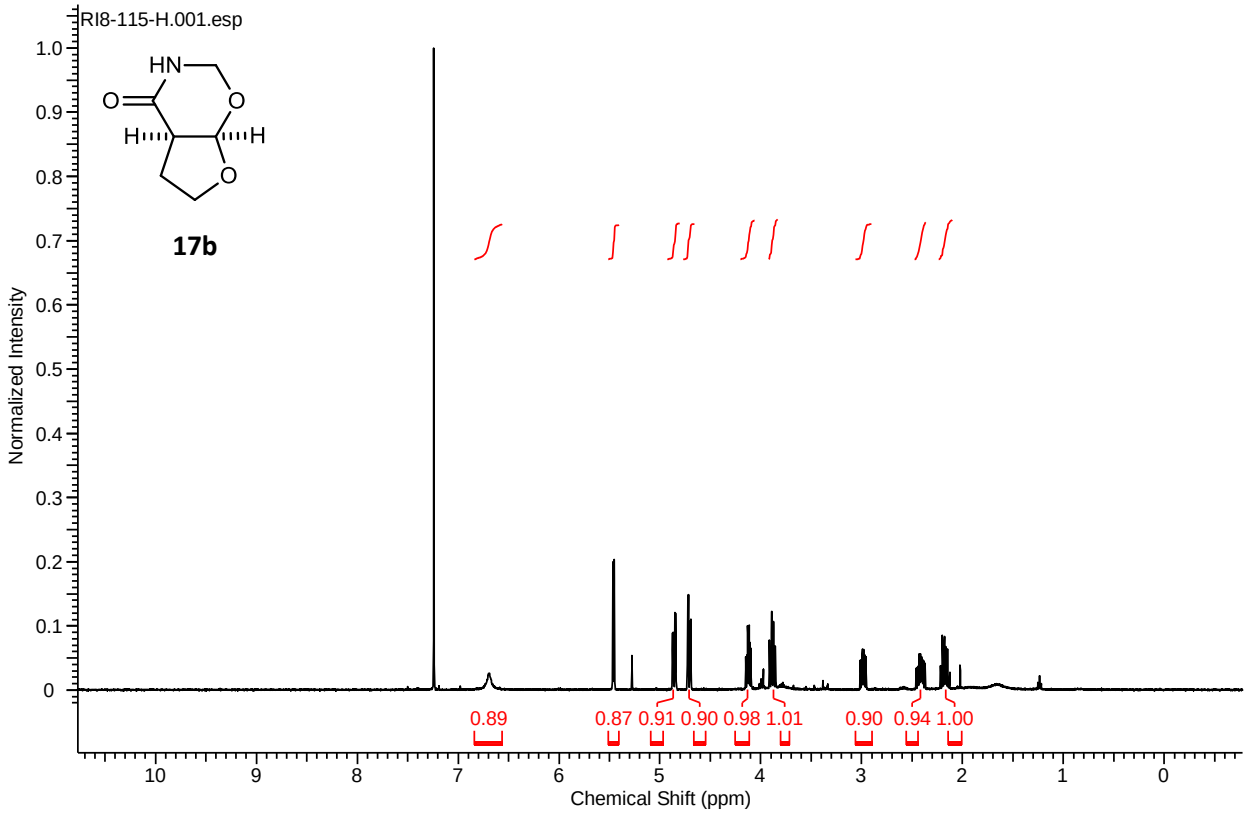

MAA-4-94P CHARAC.002.esp
Normalized Intensity
155.23
150.39
133.88
129.43
125.78
121.33
77.59
17.92
Chemical Shift (ppm)

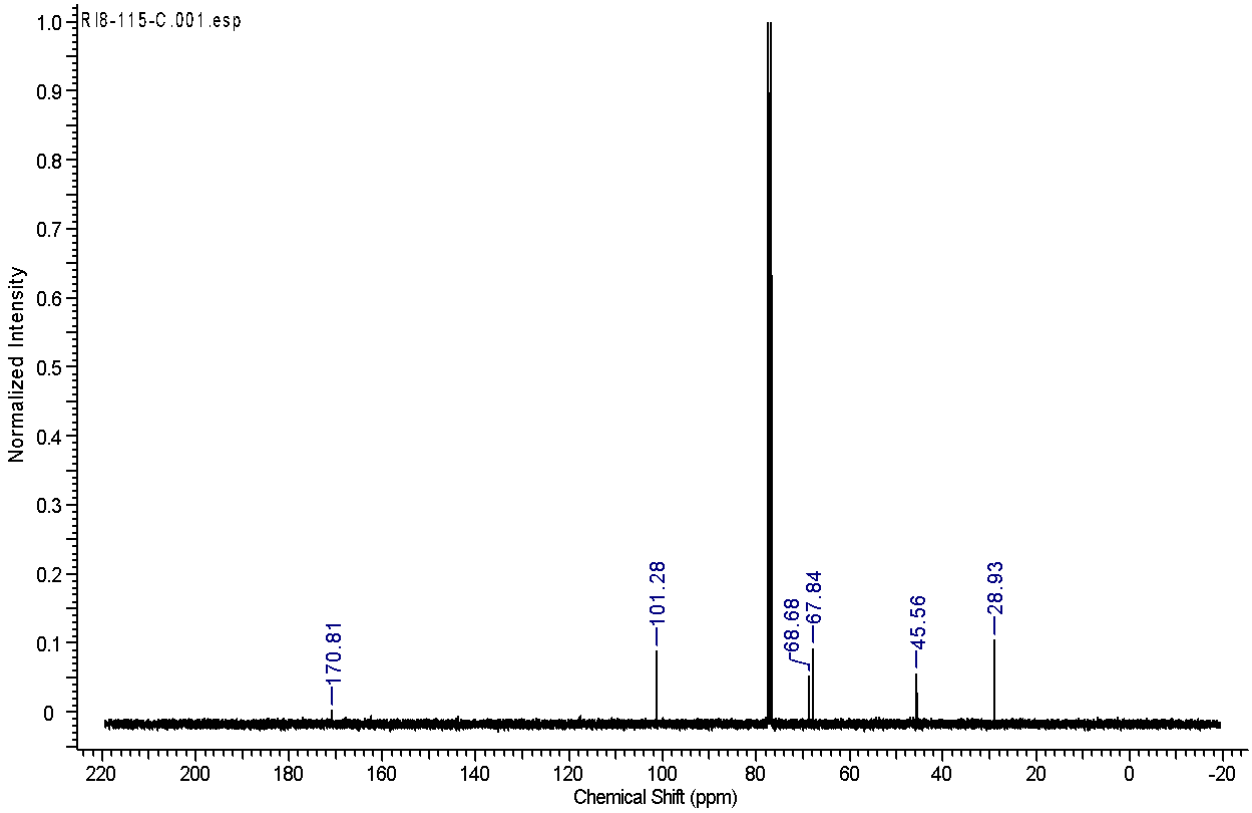

MAA-5-33P-CHARAC2.001.esp
PhO
O
N
H
O
Ph
1al
Normalized Intensity
0.99 2.00 3.91 0.96 0.98 1.92 0.99 0.98
1.98
Chemical Shift (ppm)

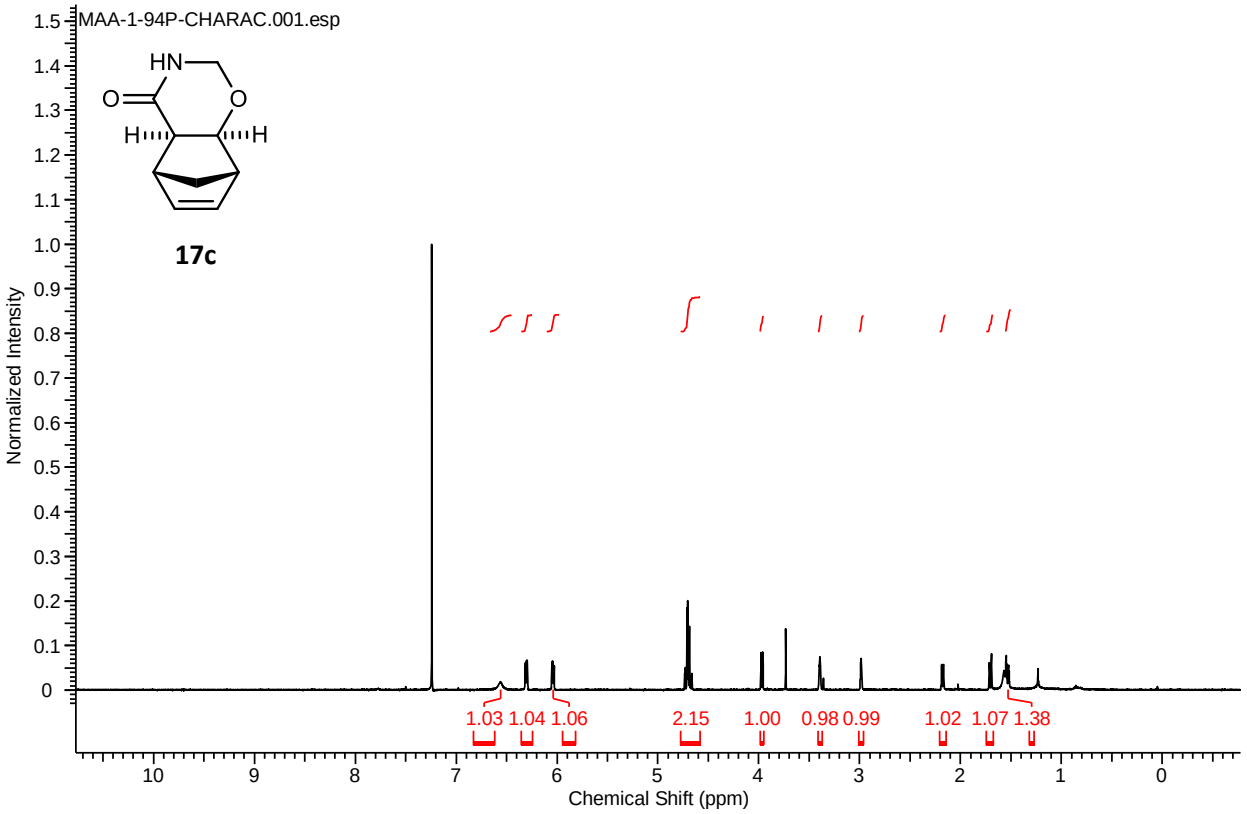

MAA-5-33P-CHARAC2.002.esp
Normalized Intensity
155.33
150.34
136.29
129.44
126.75
122.72
121.32
77.69
Chemical Shift (ppm)

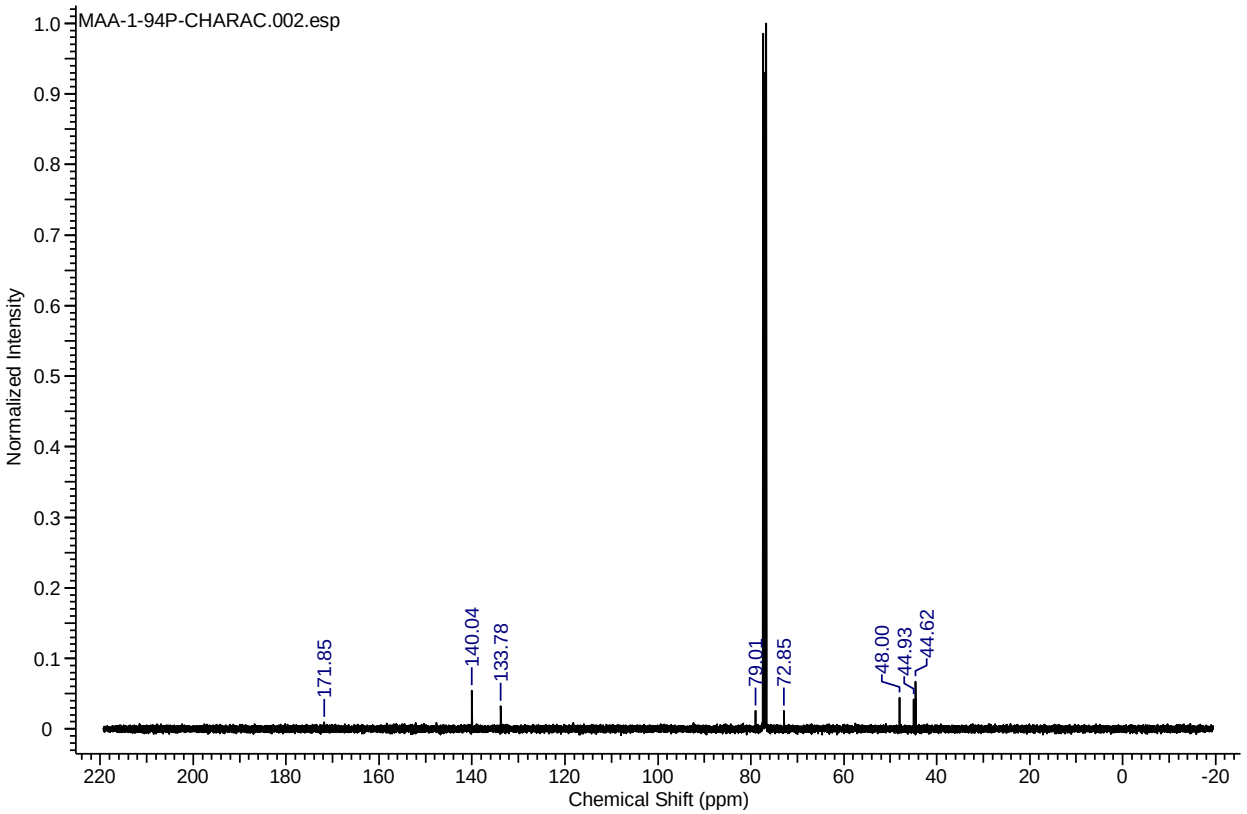

RI9-29-H.001.esp
HN
O
O
H
H
17a
Normalized Intensity
1.00
2.17
1.07
1.07
1.08
1.12
3.28
3.31
Chemical Shift (ppm)

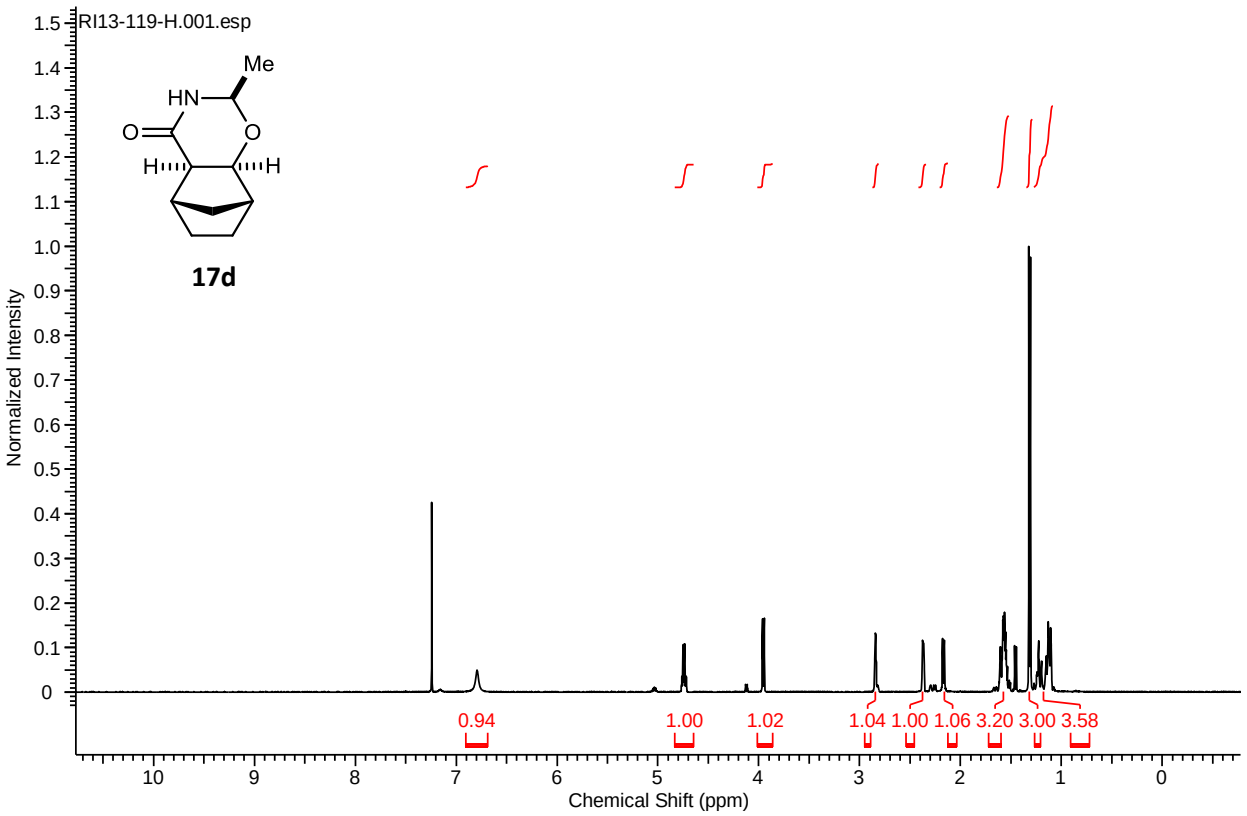

RI9-29-C.001.esp
Normalized Intensity
171.41
82.59
72.39
50.10
42.42
39.70
34.24
28.60
24.28
Chemical Shift (ppm)

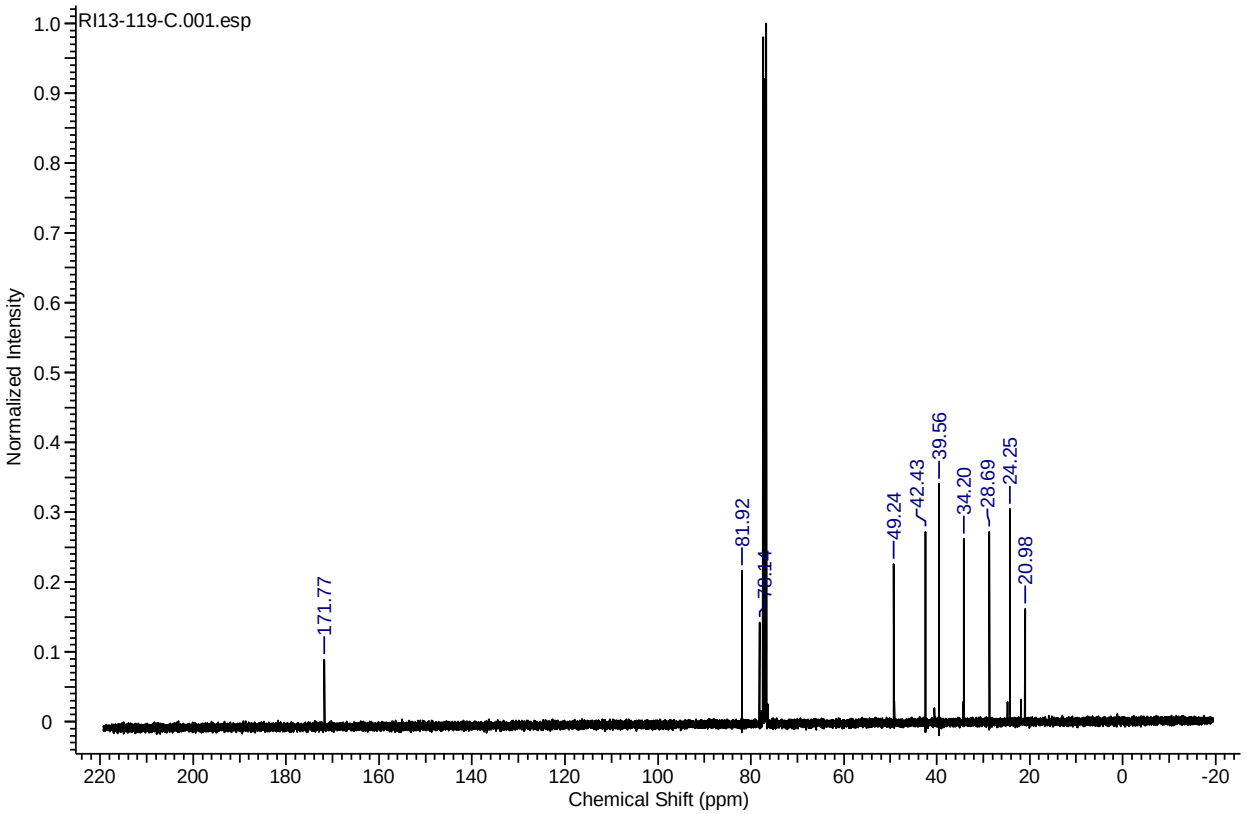

RI8-115-H.001.esp
HN
O
O
H
H
O
17b
Normalized Intensity
0.89
0.87
0.91
0.90
0.98
1.01
0.90
0.94
1.00
Chemical Shift (ppm)

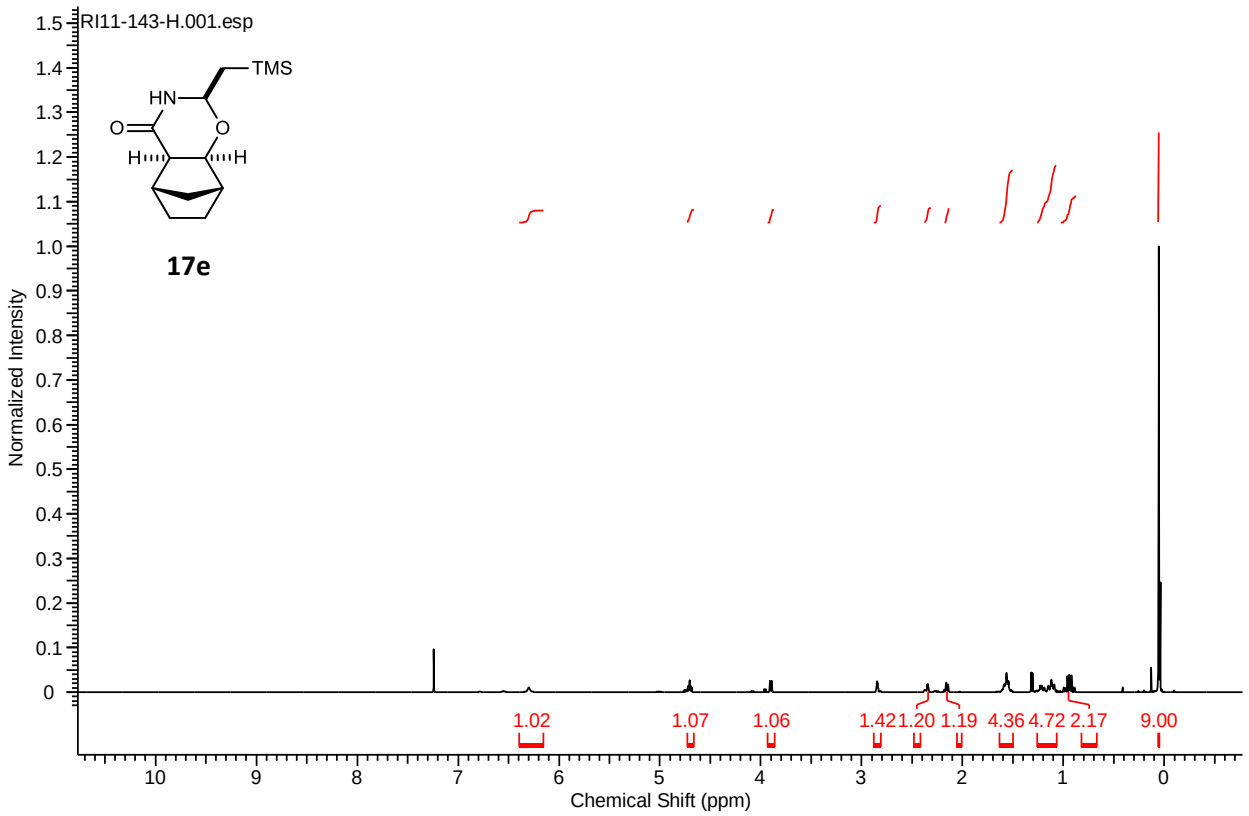

RI8-115-C.001.esp
Normalized Intensity
170.81
101.28
68.68
67.84
45.56
28.93
Chemical Shift (ppm)

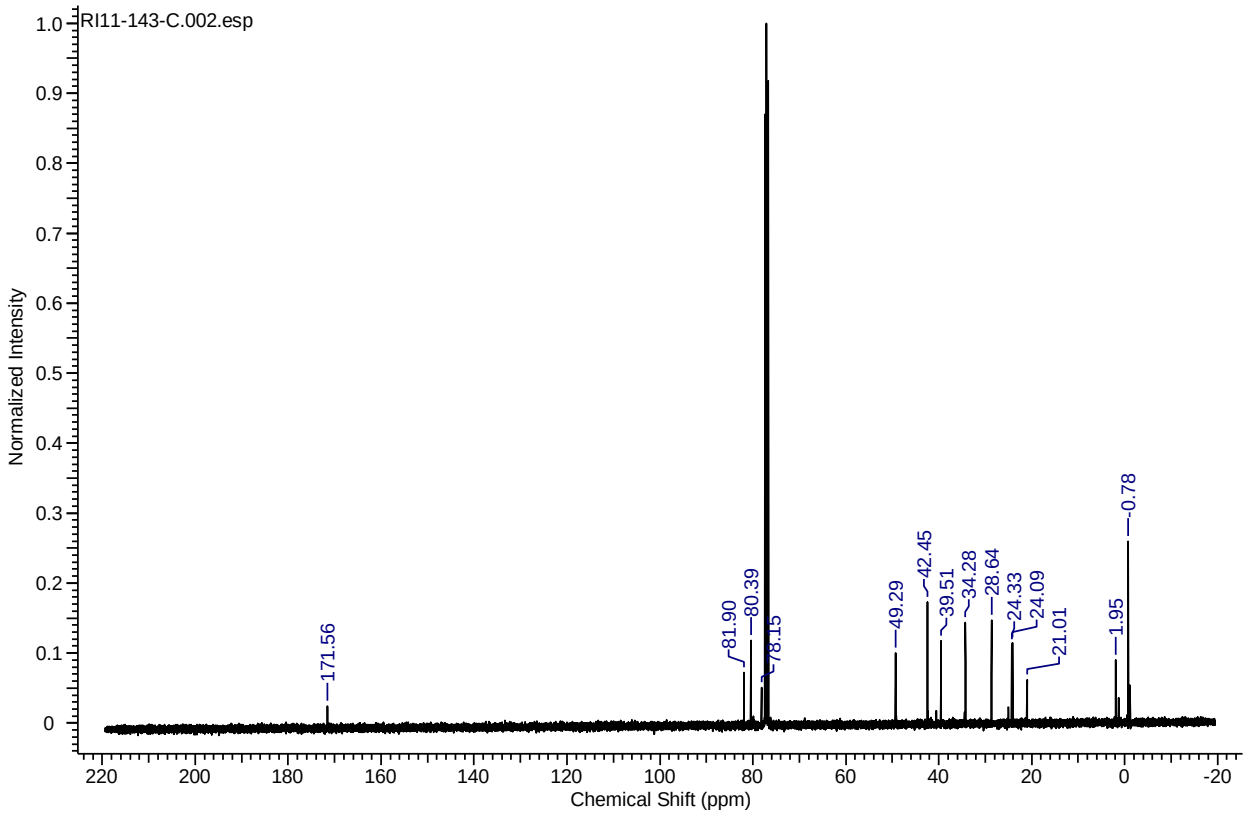

MAA-1-94P-CHARAC.001.esp
HN
O
O
H
H
17c
Normalized Intensity
1.03 1.04 1.06 2.15 1.00 0.98 0.99 1.02 1.07 1.38
Chemical Shift (ppm)

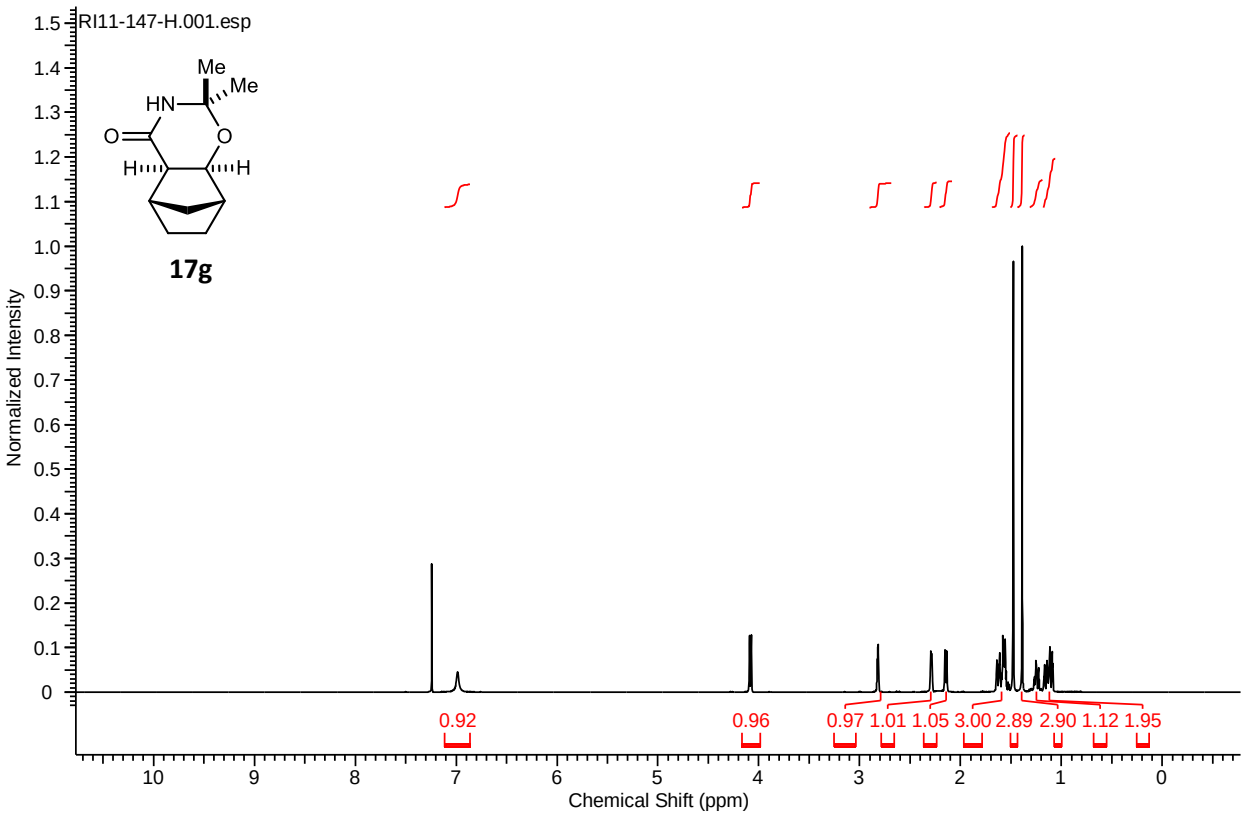

MAA-1-94P-CHARAC.002.esp
Normalized Intensity
171.85
140.04
133.78
79.01
72.85
48.00
44.93
44.62
Chemical Shift (ppm)

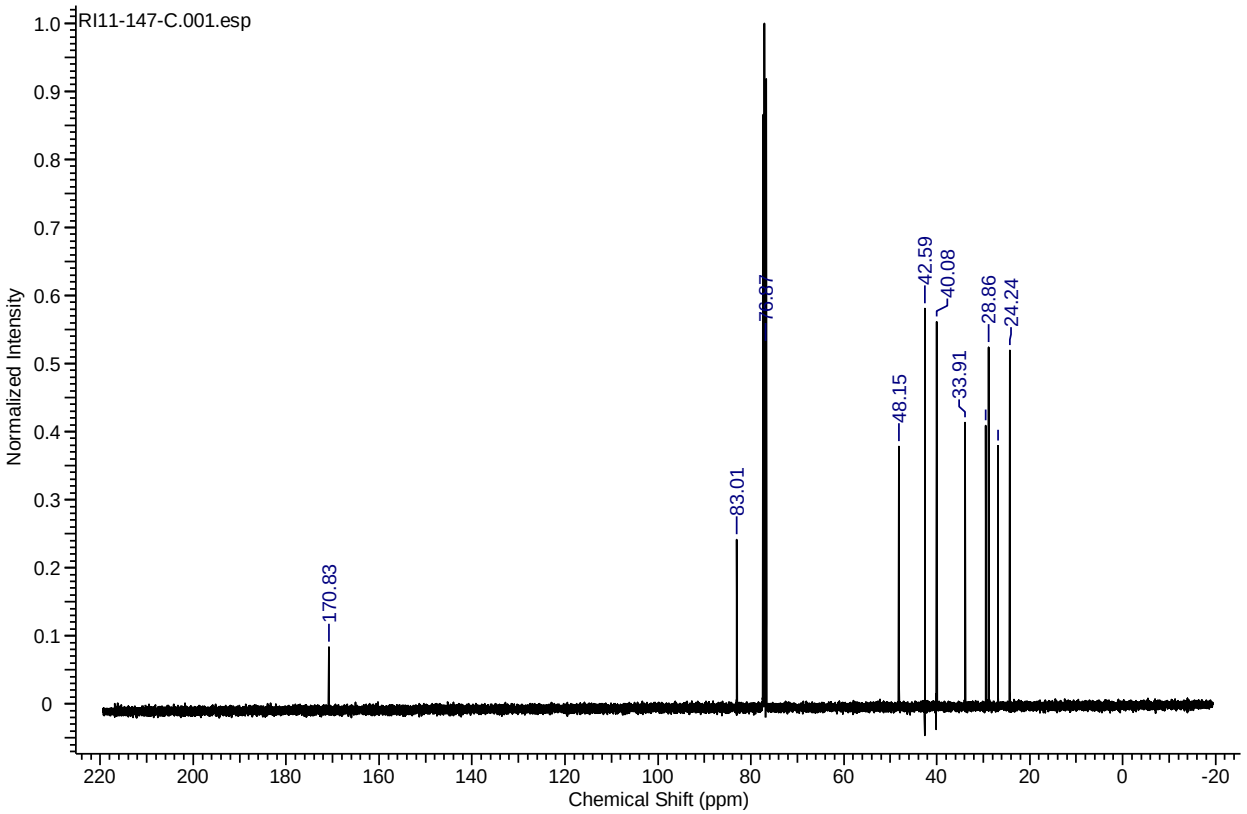

RI13-119-H.001.esp
Me
HN
O
O
H
H
17d
Normalized Intensity
0.94
1.00
1.02
1.04
1.00
1.06
3.20
3.00
3.58
Chemical Shift (ppm)

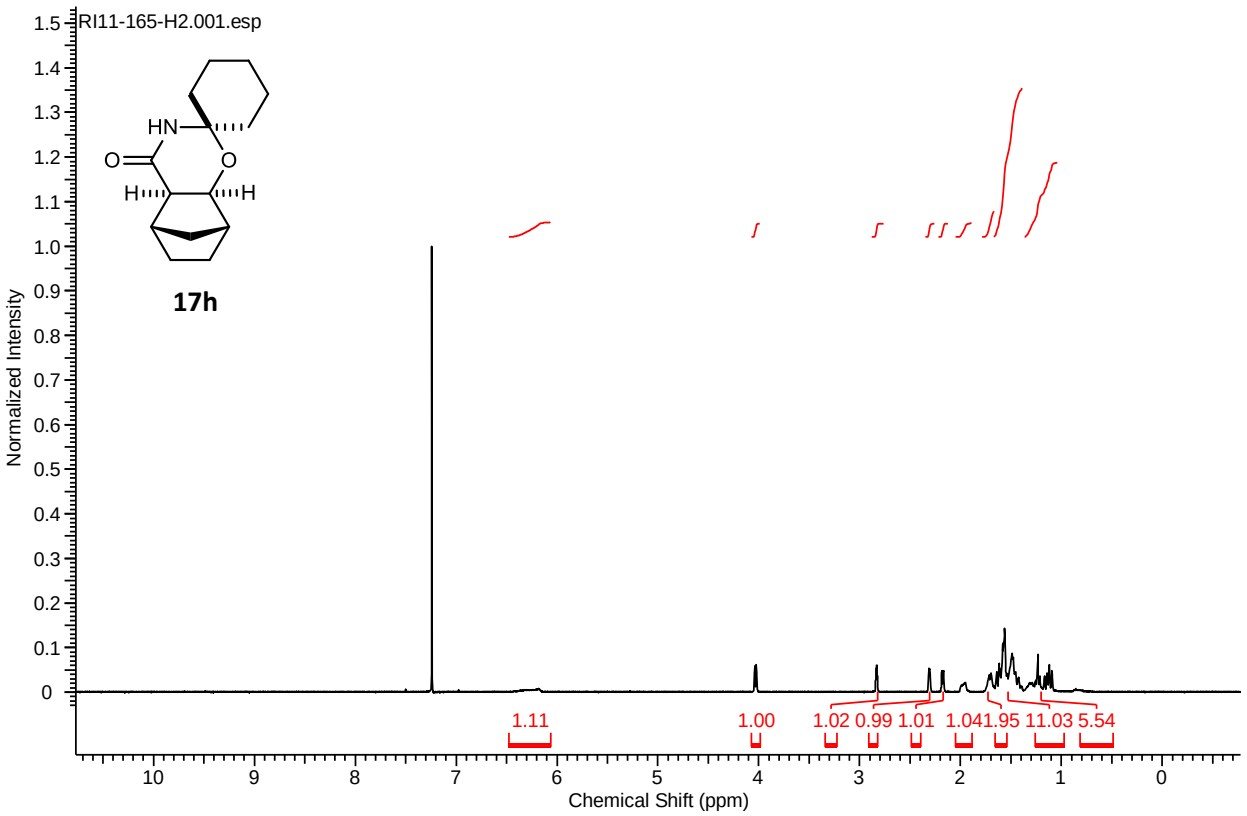

RI13-119-C.001.esp
Normalized Intensity
171.77
81.92
78.14
49.24
42.43
39.56
34.20
28.69
24.25
20.98
Chemical Shift (ppm)

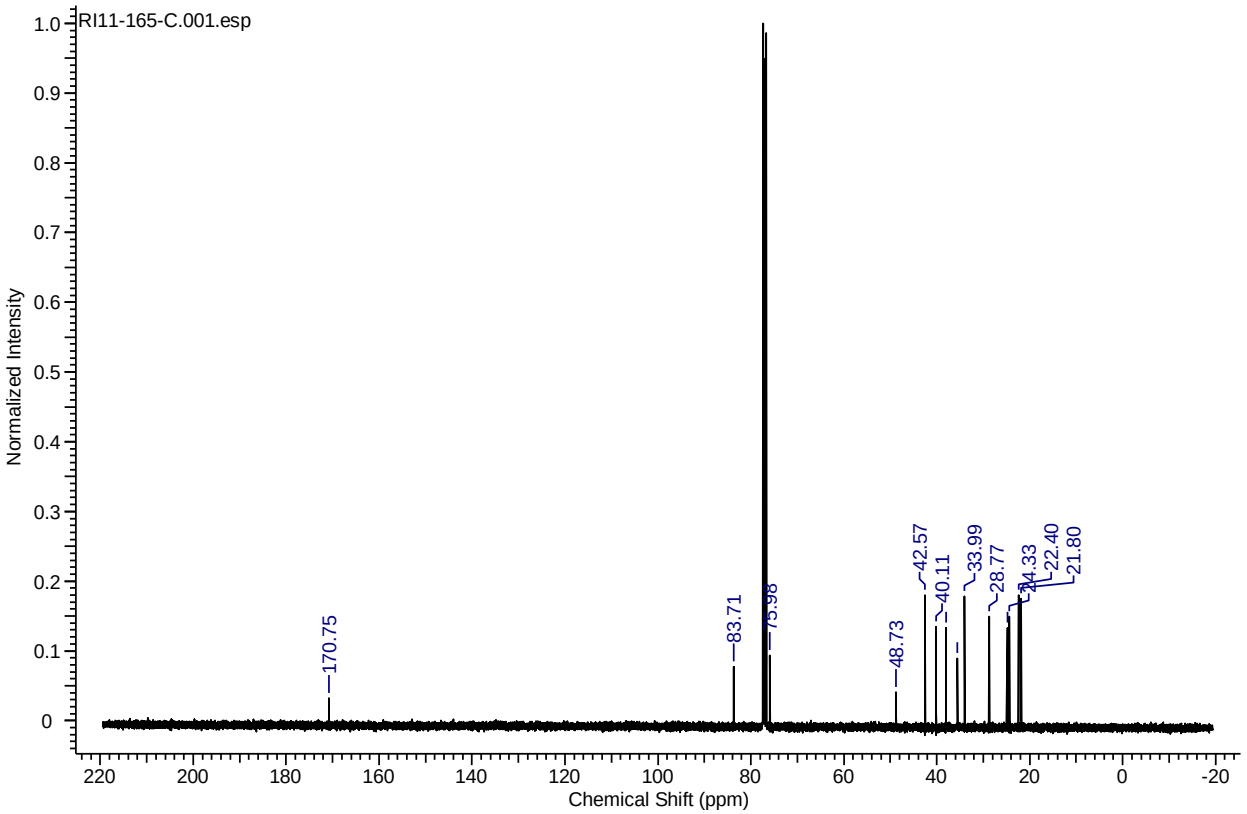

RI11-143-H.001.esp
TMS
HN
O
O
H
H
17e
Normalized Intensity
1.02
1.07
1.06
1.42
1.20
1.19
4.36
4.72
2.17
9.00
Chemical Shift (ppm)

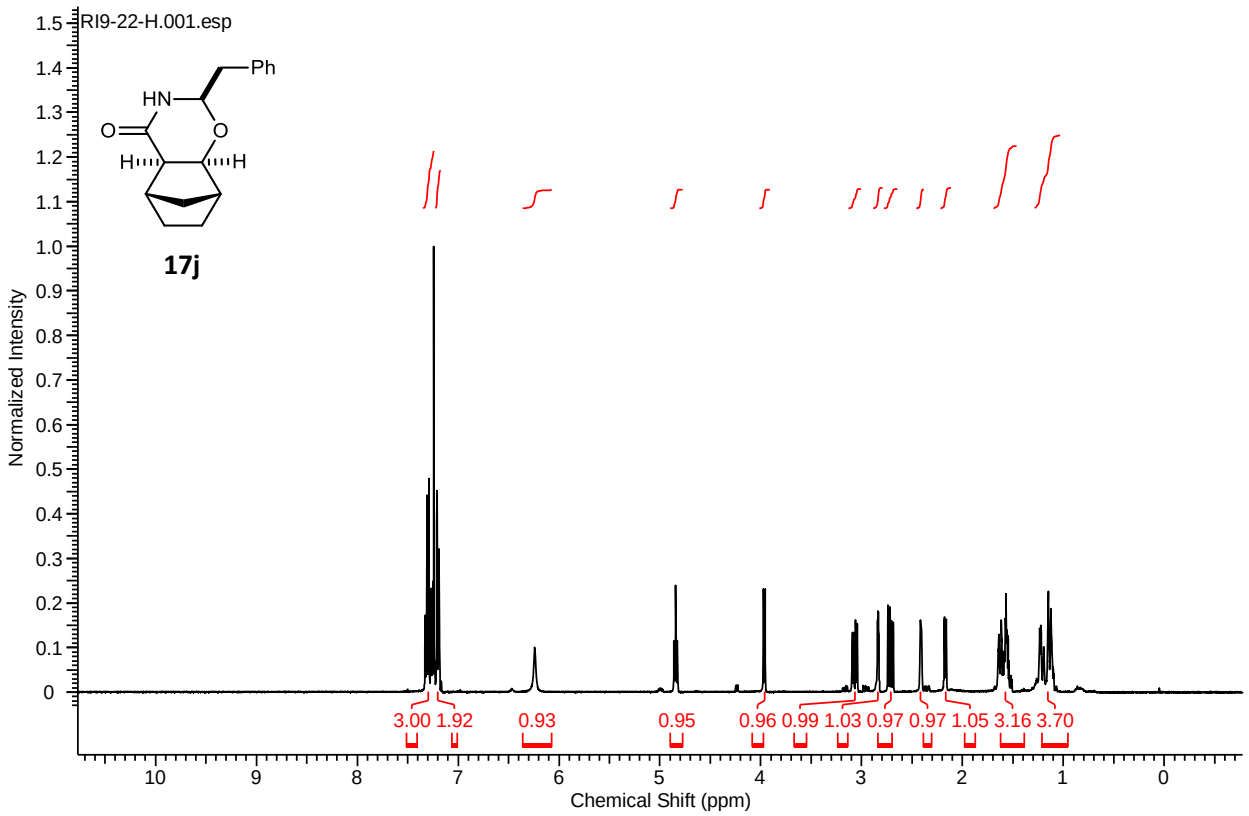

RI11-143-C.002.esp
Normalized Intensity
171.56
81.90
80.39
78.15
49.29
42.45
39.51
34.28
28.64
24.33
24.09
21.01
1.95
0.78
Chemical Shift (ppm)

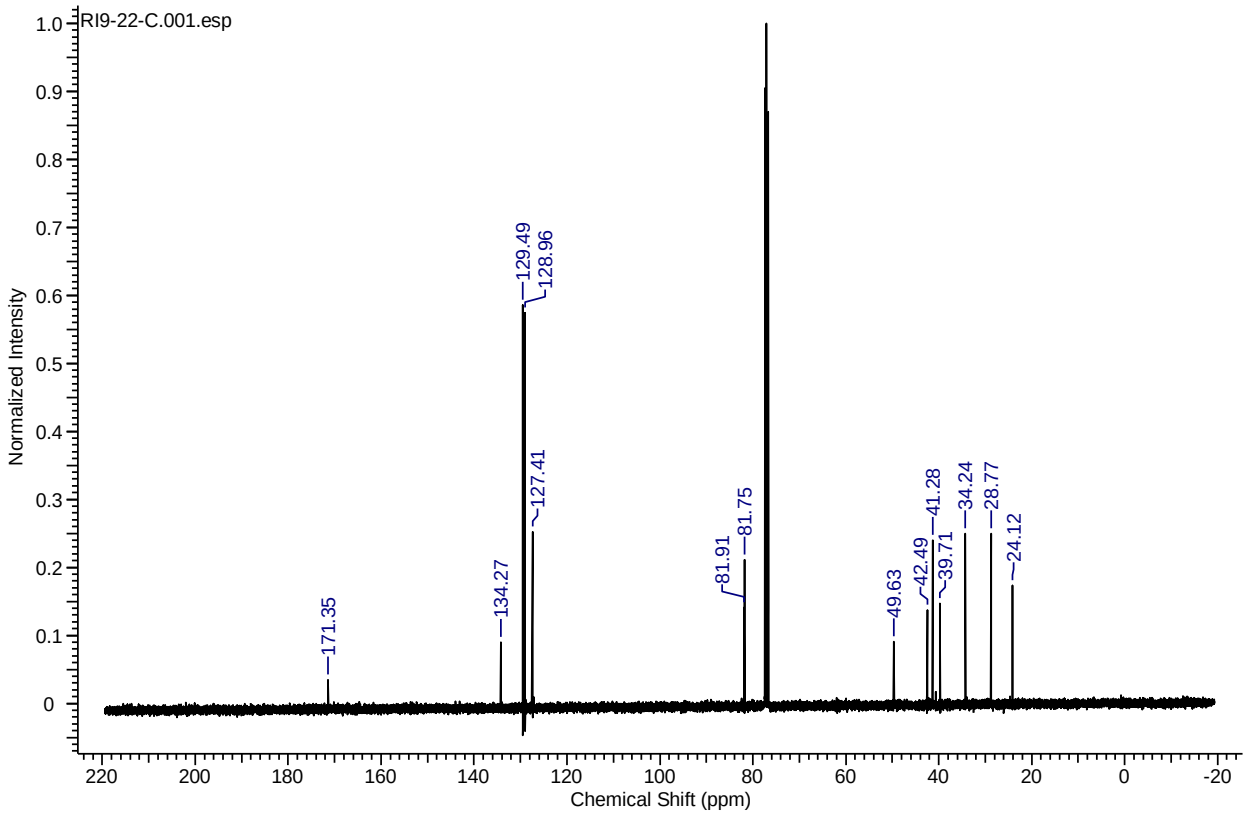

RI11-147-H.001.esp
Me
Me
HN
O
O
H
H
17g
Normalized Intensity
Chemical Shift (ppm)
0.92
0.96
0.97 1.01 1.05 3.00 2.89 2.90 1.12 1.95

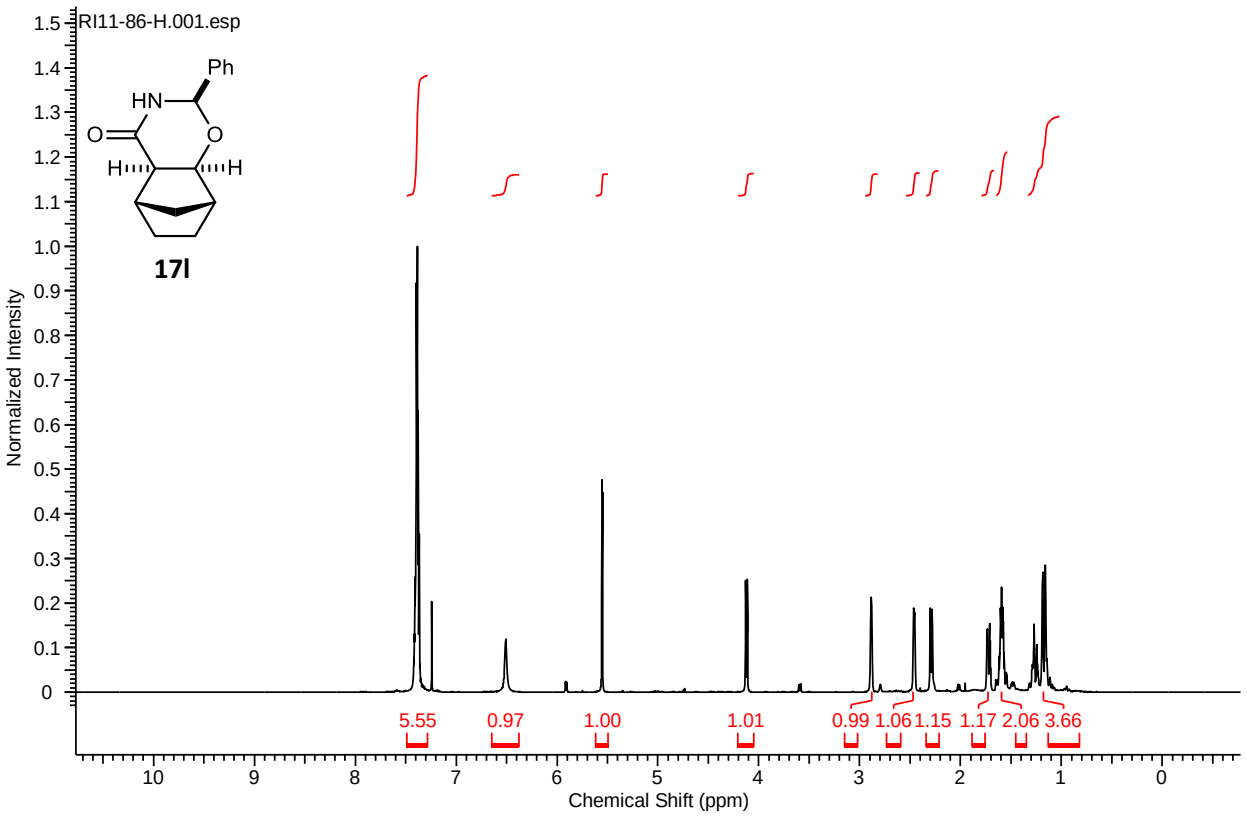

RI11-147-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
170.83
83.01
78.67
48.15
42.59
40.08
33.91
28.86
24.24

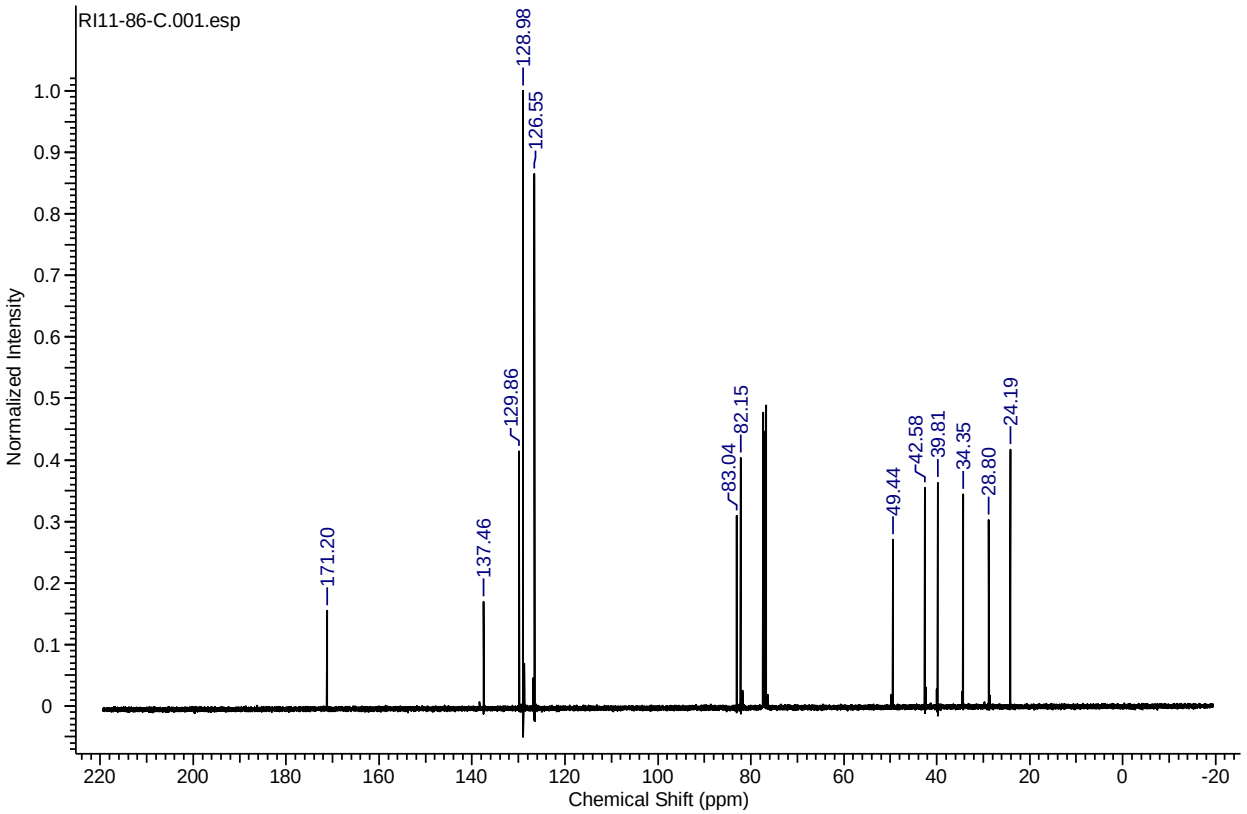

RI11-165-H2.001.esp
HN
O
O
H
H
17h
Normalized Intensity
1.11
1.00
1.02
0.99
1.01
1.04
1.95
11.03
5.54
Chemical Shift (ppm)

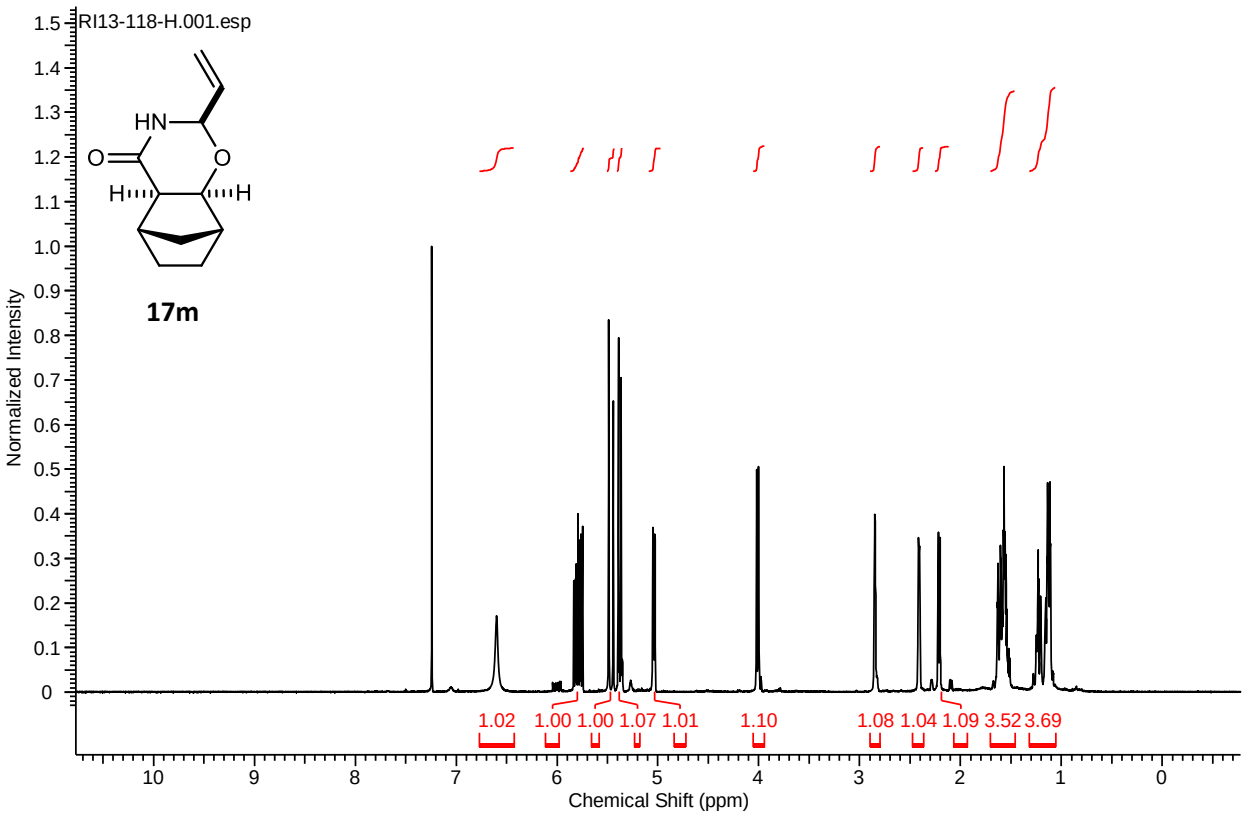

RI11-165-C.001.esp
Normalized Intensity
170.75
83.71
75.98
48.73
42.57
40.11
33.99
28.77
24.33
22.40
21.80
Chemical Shift (ppm)

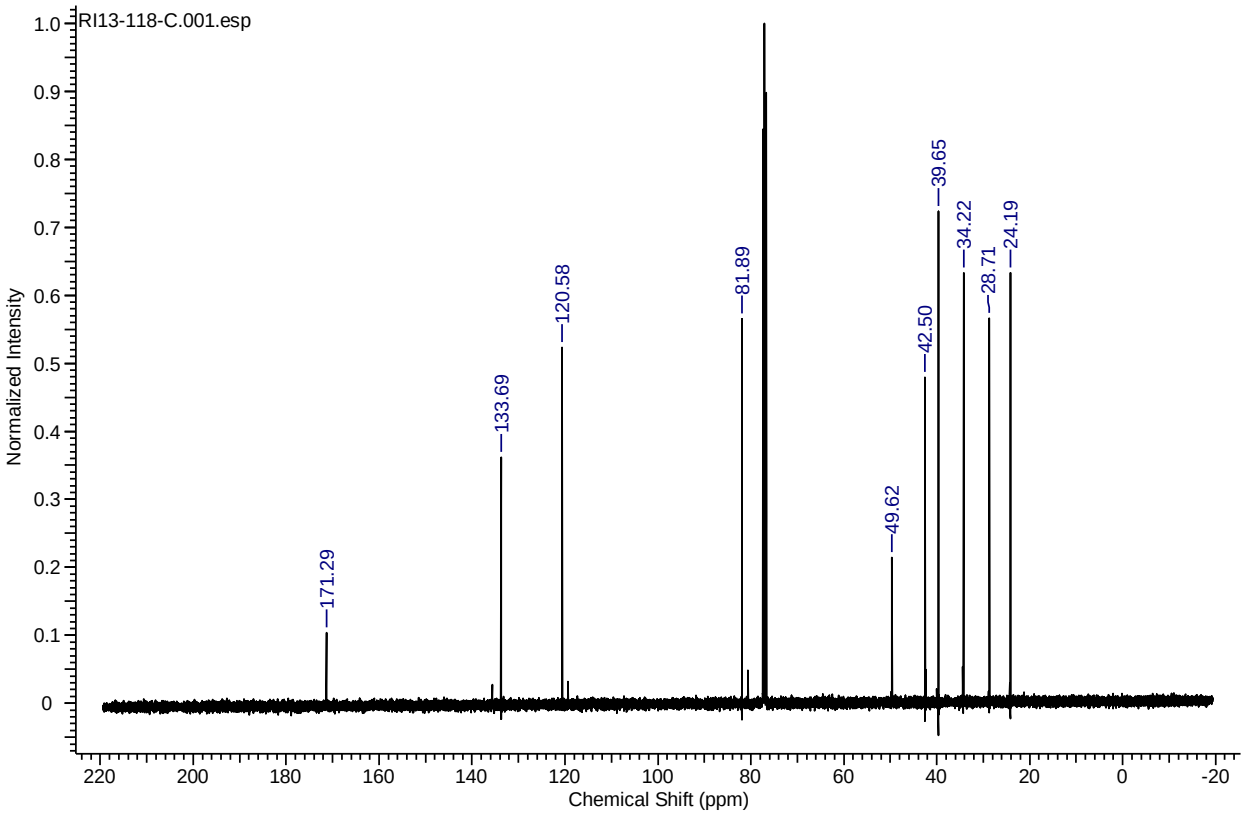

RI9-22-H.001.esp
Ph
HN
O
O
H
H
17j
Normalized Intensity
Chemical Shift (ppm)
3.00 1.92 0.93 0.95 0.96 0.99 1.03 0.97 0.97 1.05 3.16 3.70

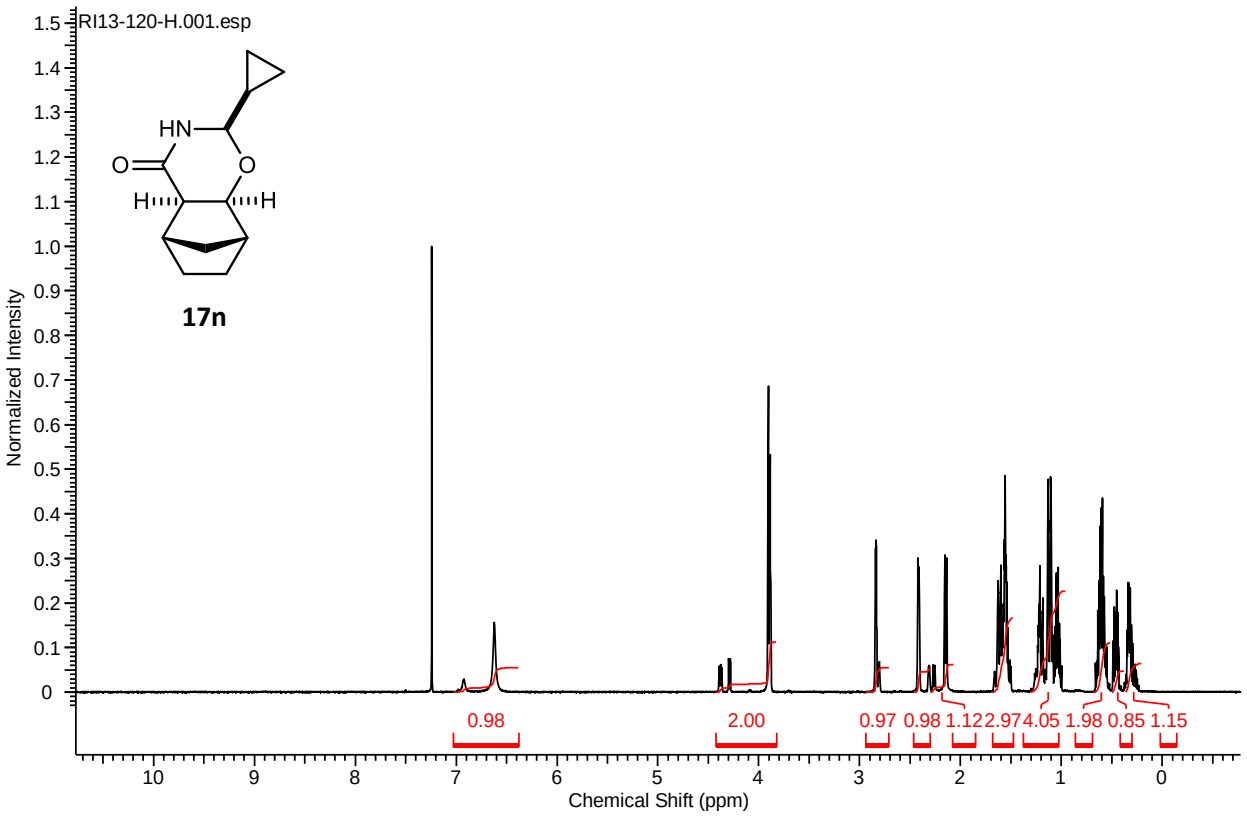

RI9-22-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
171.35
134.27
129.49
128.96
127.41
81.91
81.75
49.63
42.49
41.28
39.71
34.24
28.77
24.12

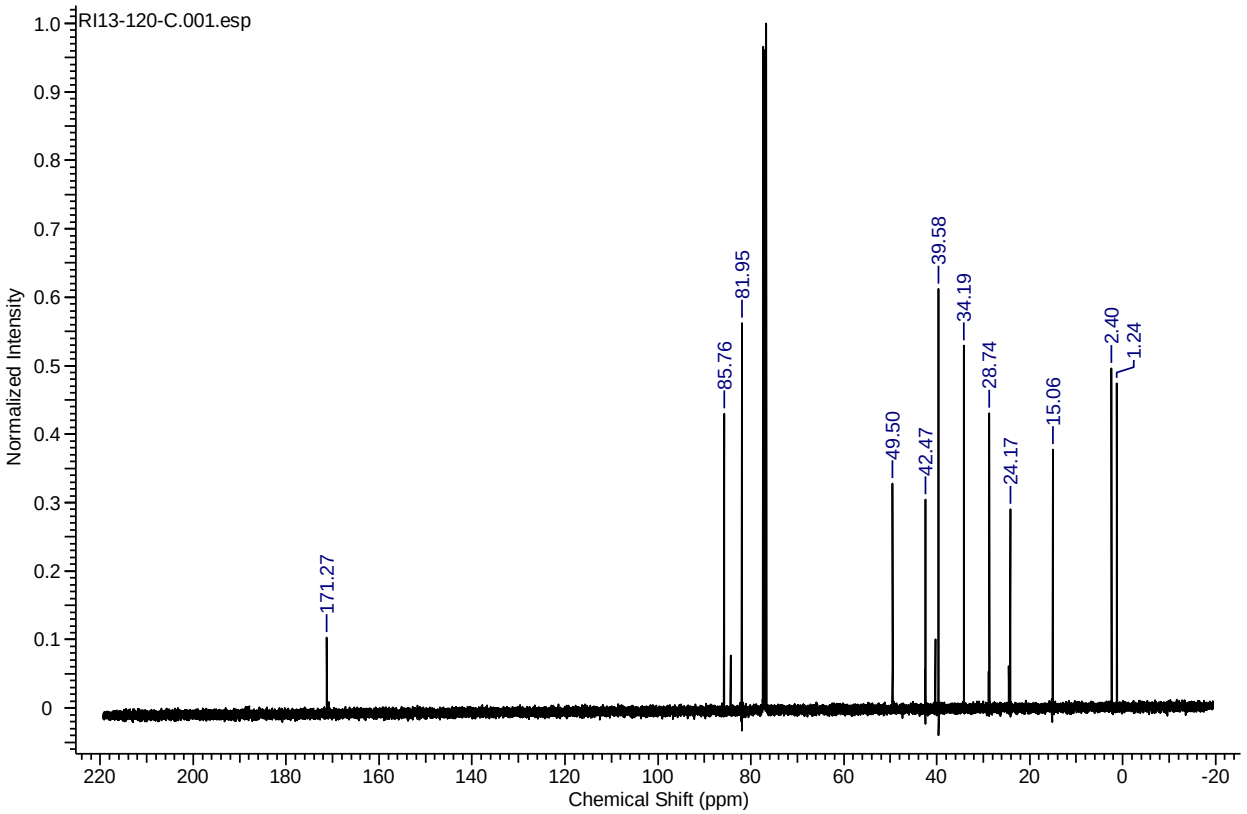

RI11-86-H.001.esp
Ph
HN
O
O
H
H
17l
Normalized Intensity
5.55
0.97
1.00
1.01
0.99
1.06
1.15
1.17
2.06
3.66
Chemical Shift (ppm)

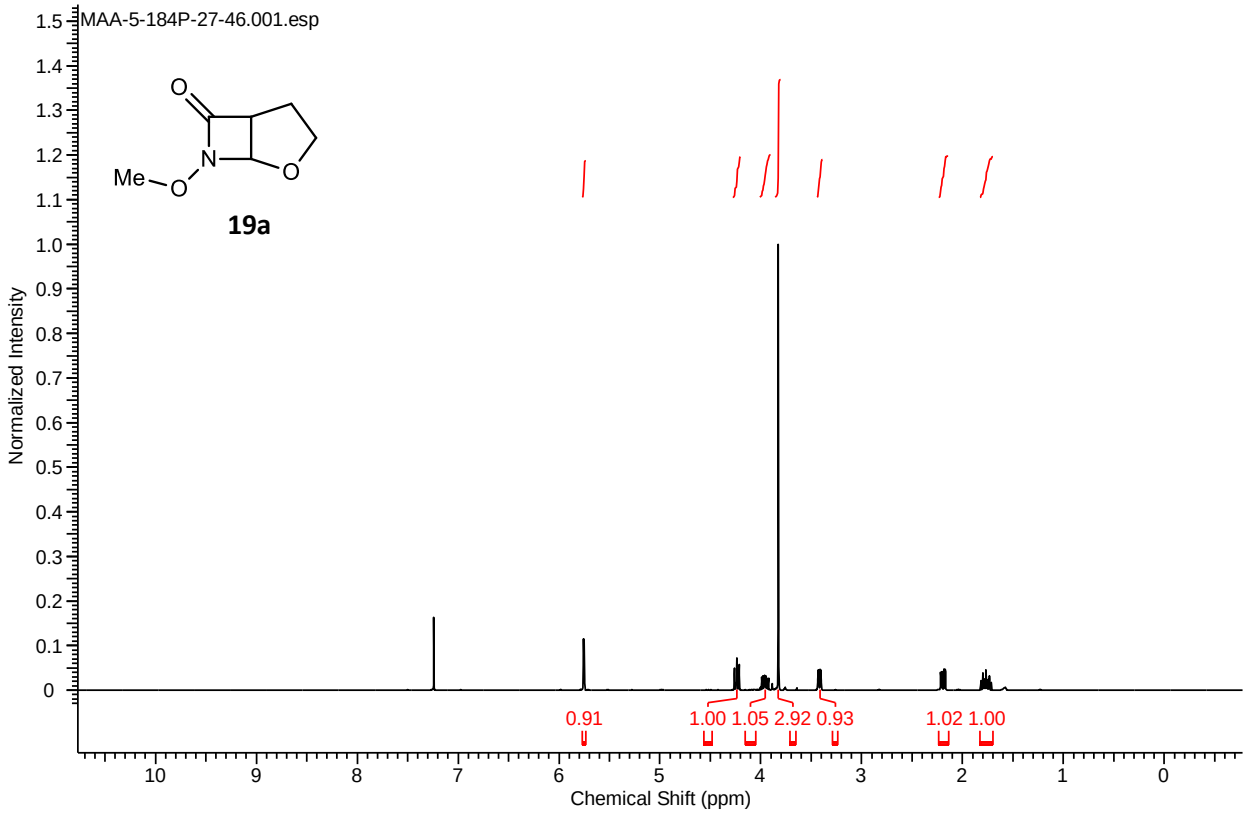

RI11-86-C.001.esp
128.98
126.55
129.86
171.20
137.46
83.04
82.15
49.44
42.58
39.81
34.35
28.80
24.19
Normalized Intensity
Chemical Shift (ppm)

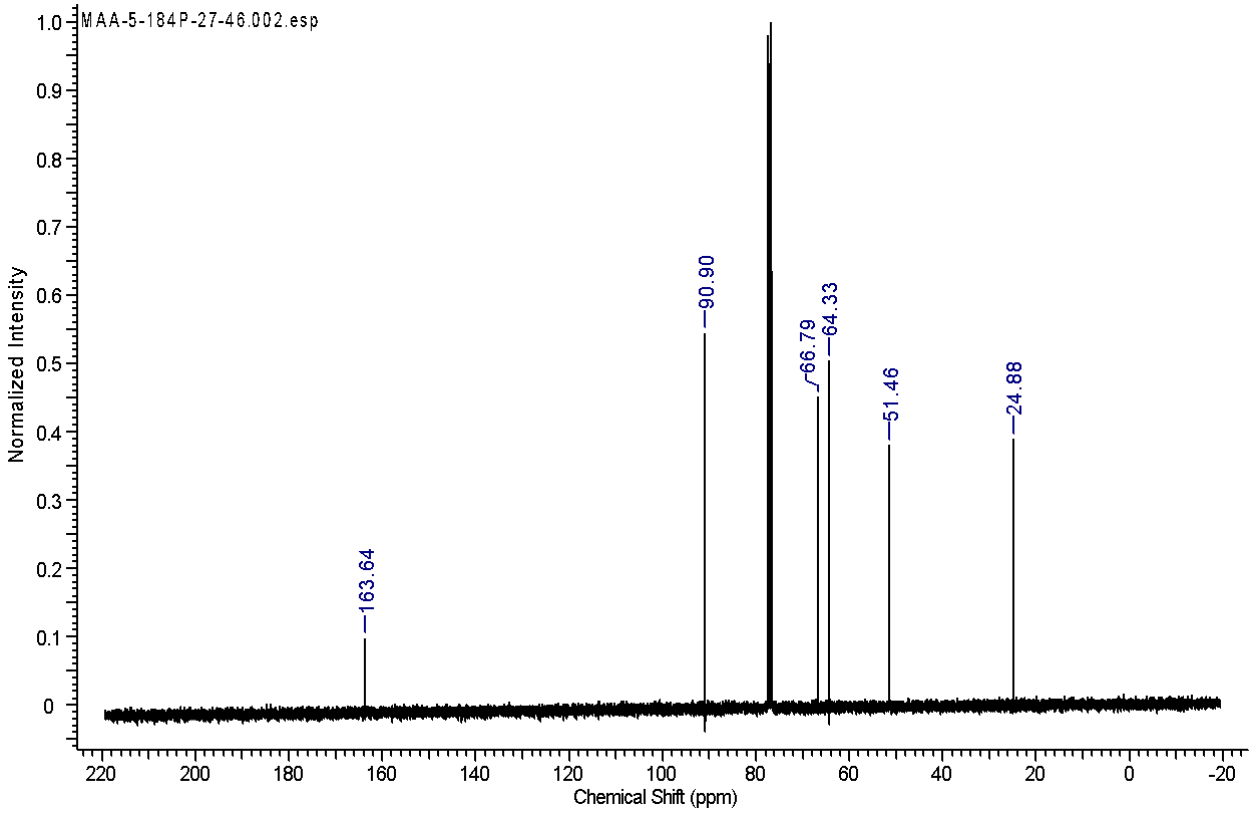

RI13-118-H.001.esp
HN
O
O
H
H
17m
Normalized Intensity
1.02
1.00
1.00
1.07
1.01
1.10
1.08
1.04
1.09
3.52
3.69
Chemical Shift (ppm)

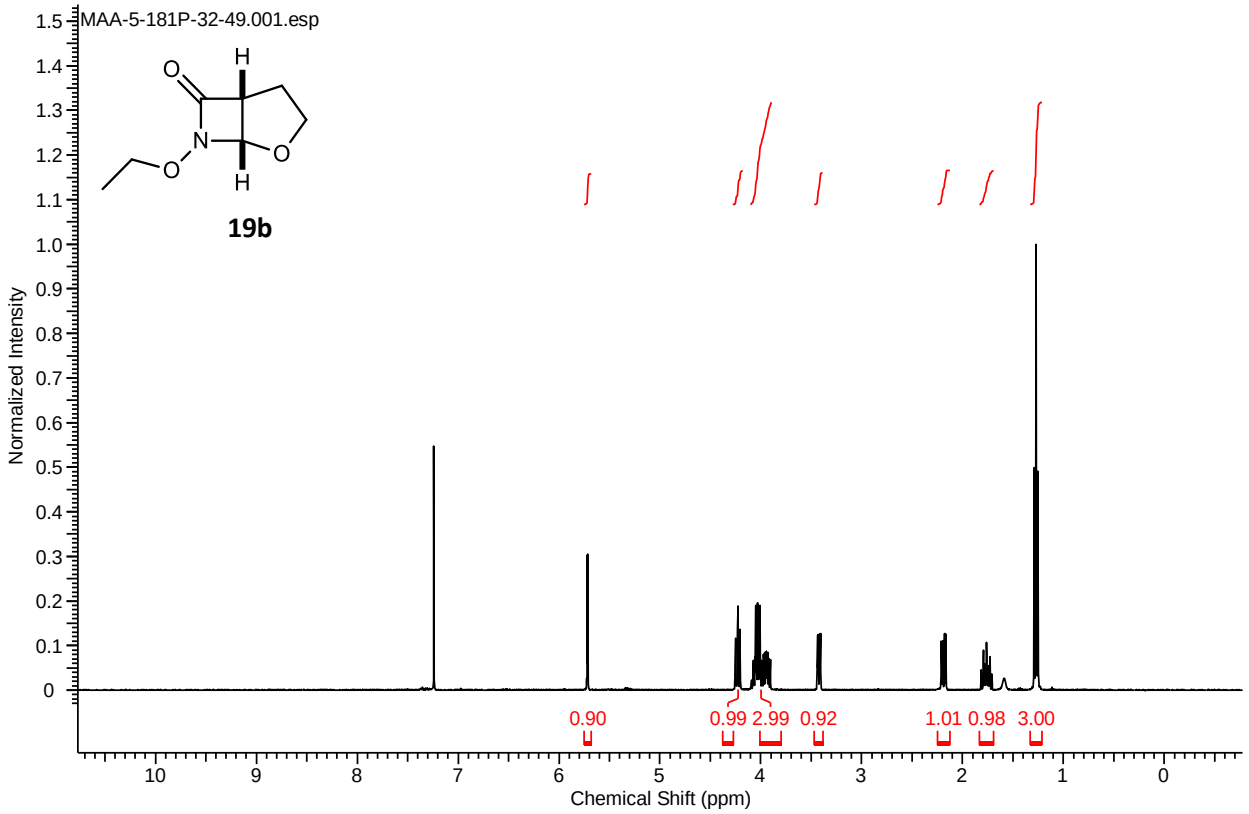

RI13-118-C.001.esp
Normalized Intensity
171.29
133.69
120.58
81.89
49.62
42.50
39.65
34.22
28.71
24.19
Chemical Shift (ppm)

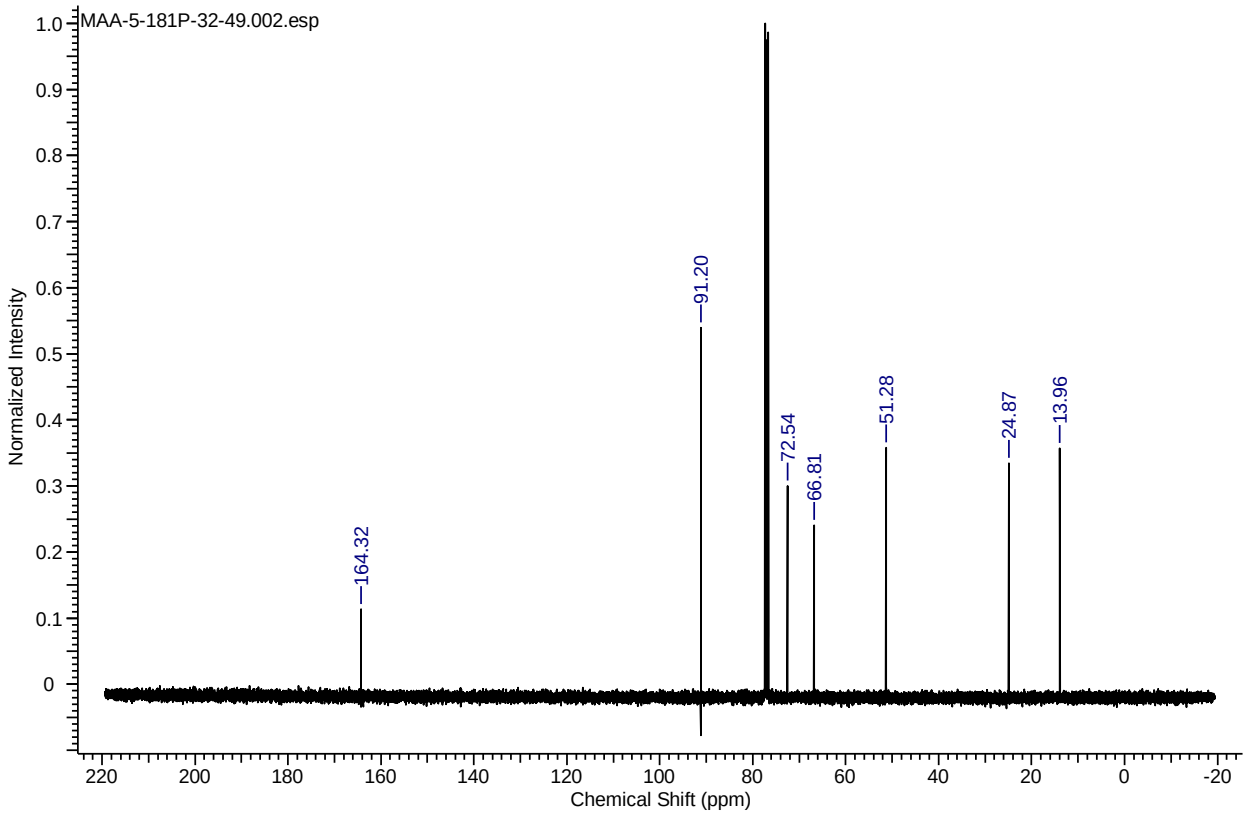

RI13-120-H.001.esp
HN
O
O
H
H
17n
Normalized Intensity
Chemical Shift (ppm)
0.98
2.00
0.97
0.98
1.12
2.97
4.05
1.98
0.85
1.15

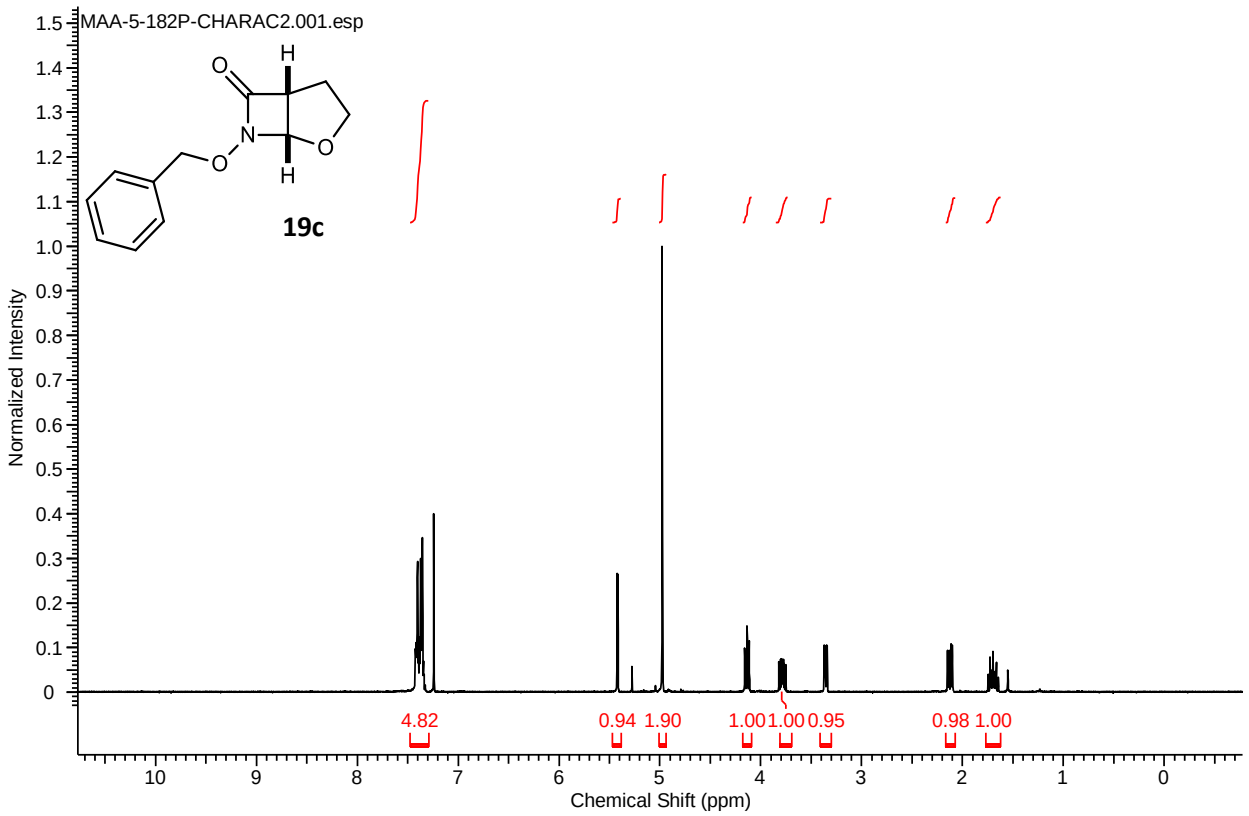

RI13-120-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
171.27
85.76
81.95
49.50
42.47
39.58
34.19
28.74
24.17
15.06
2.40
1.24

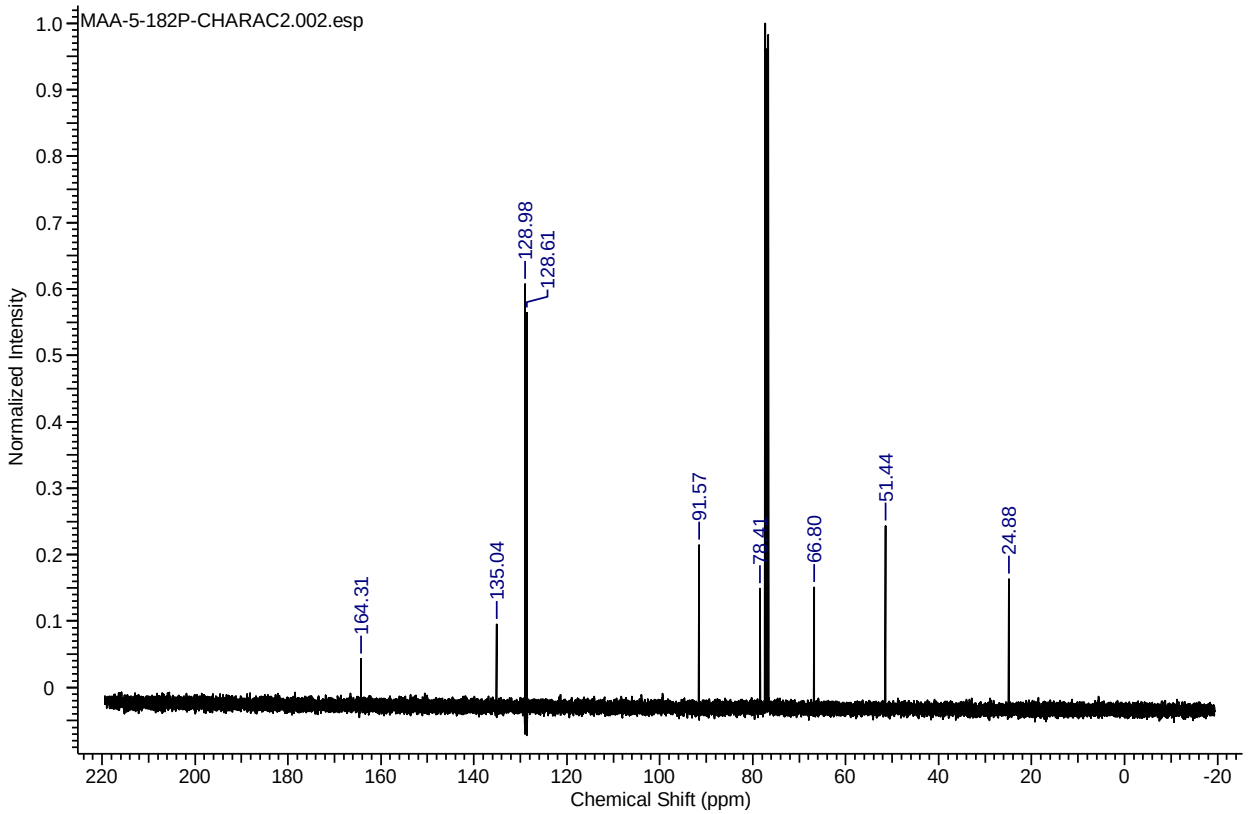

MAA-5-184P-27-46.001.esp
Me
19a
Normalized Intensity
0.91
1.00 1.05 2.92 0.93
1.02 1.00
Chemical Shift (ppm)

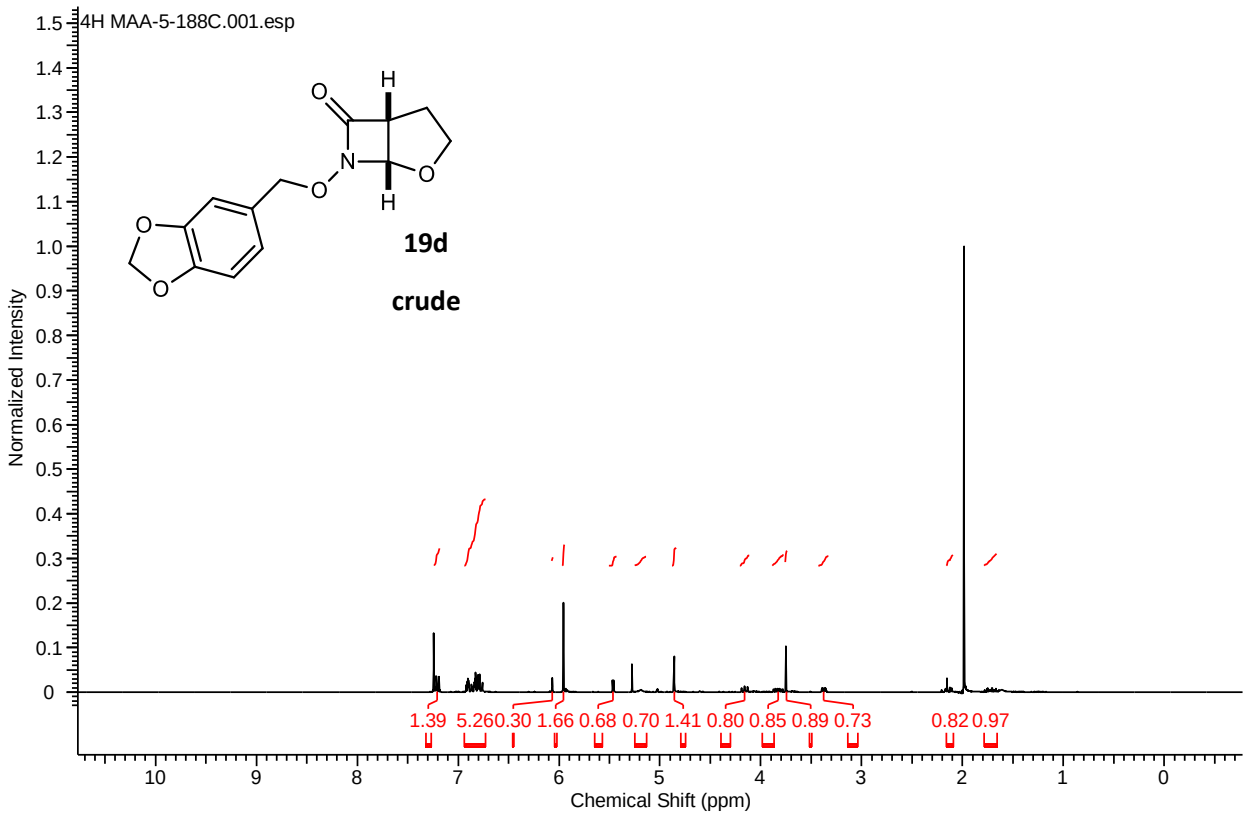

MAA-5-184P-27-46.002.esp
Normalized Intensity
163.64
90.90
66.79
64.33
51.46
24.88
Chemical Shift (ppm)

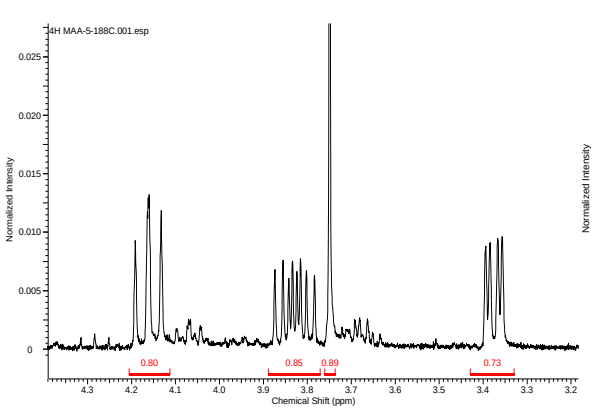

MAA-5-181P-32-49.001.esp
19b
Normalized Intensity
Chemical Shift (ppm)
0.90
0.99
2.99
0.92
1.01
0.98
3.00

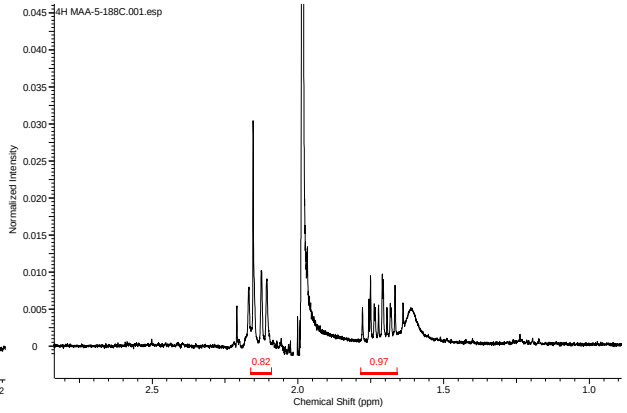

MAA-5-181P-32-49.002.esp
Normalized Intensity
Chemical Shift (ppm)
164.32
91.20
72.54
66.81
51.28
24.87
13.96

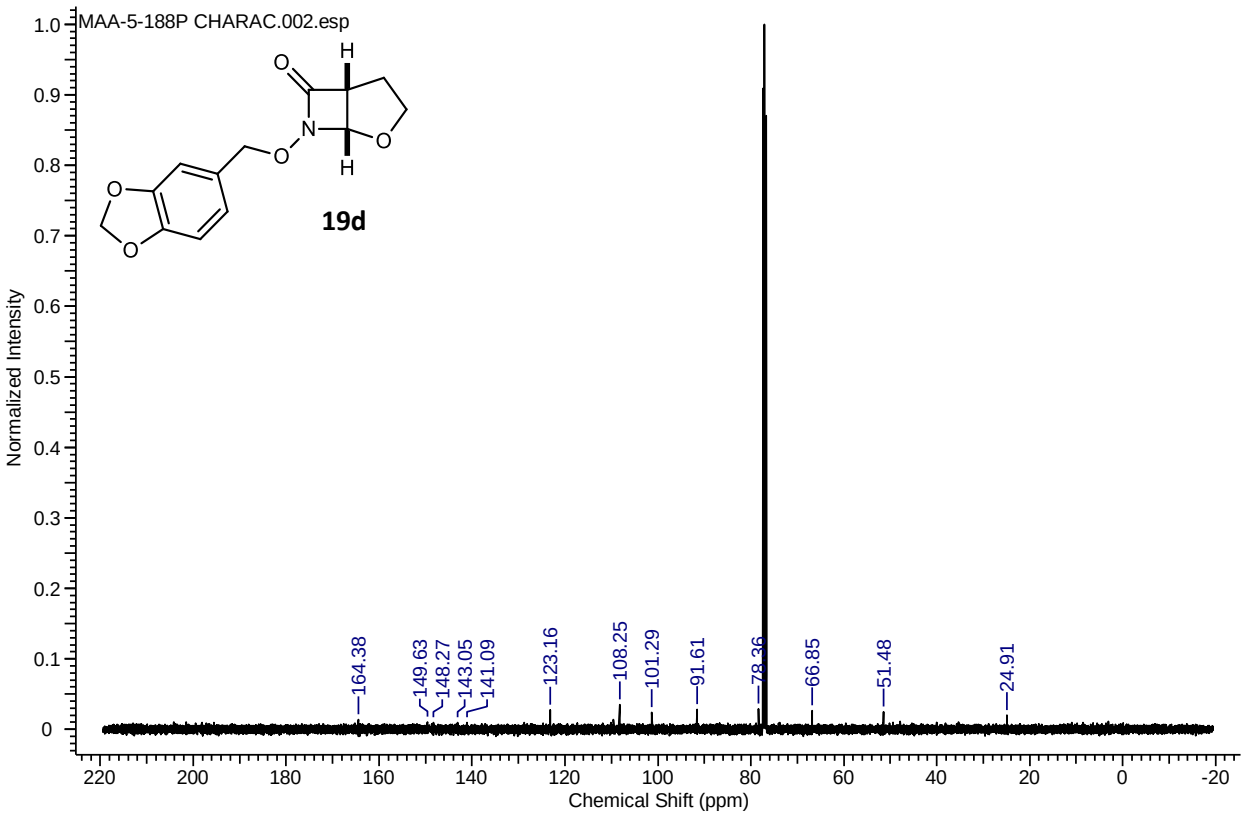

MAA-5-182P-CHARAC2.001.esp
19c
Normalized Intensity
Chemical Shift (ppm)
4.82
0.94
1.90
1.00
1.00
0.95
0.98
1.00

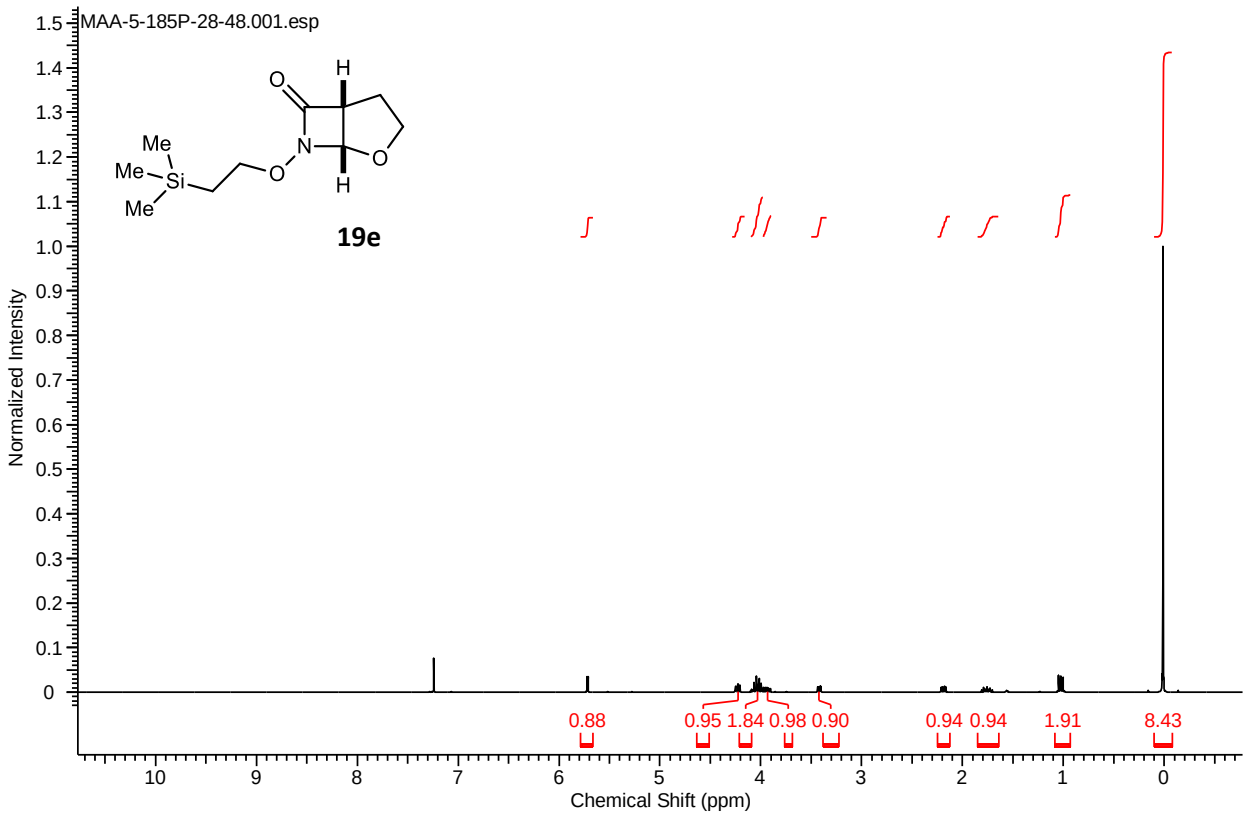

MAA-5-182P-CHARAC2.002.esp
Normalized Intensity
Chemical Shift (ppm)
164.31
135.04
128.98
128.61
91.57
78.41
66.80
51.44
24.88

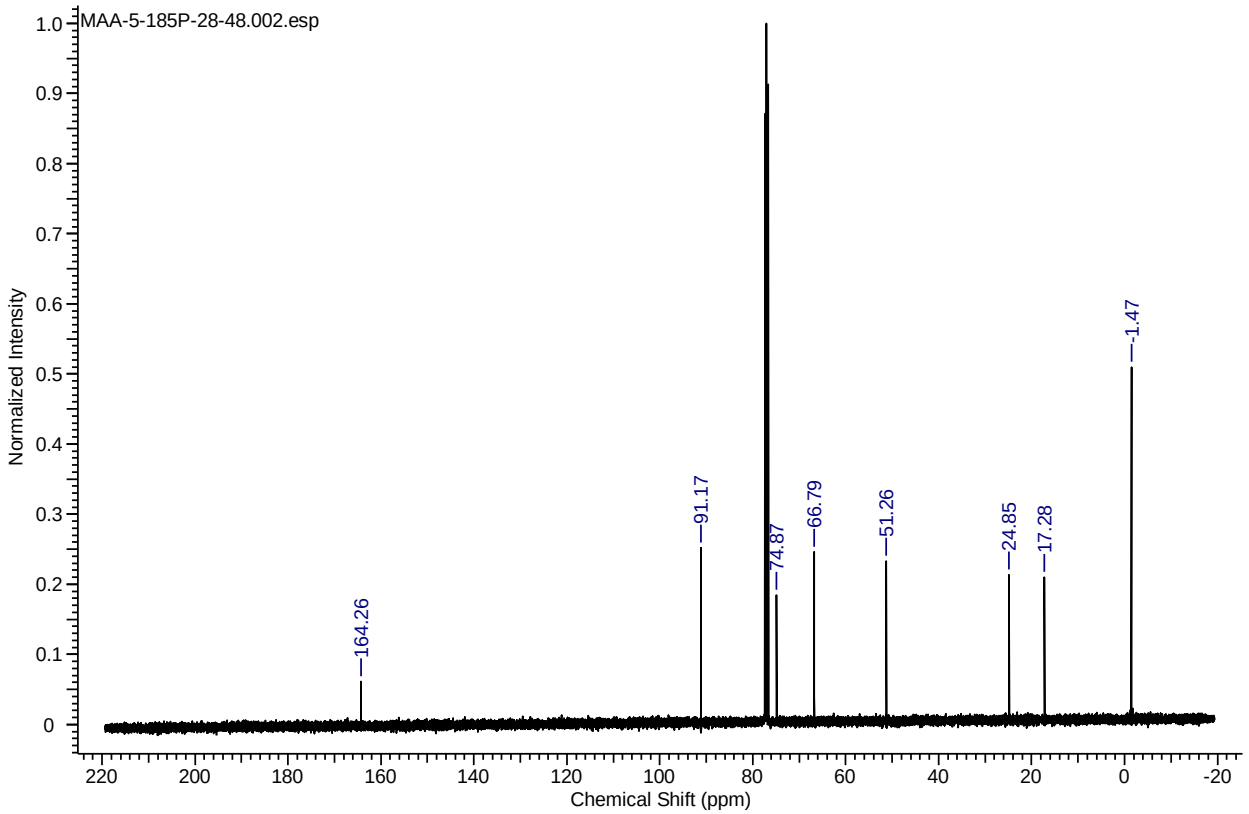

4H MAA-5-188C.001.esp
19d
crude
Normalized Intensity
Chemical Shift (ppm)
1.39 5.26 0.30 1.66 0.68 0.70 1.41 0.80 0.85 0.89 0.73 0.82 0.97

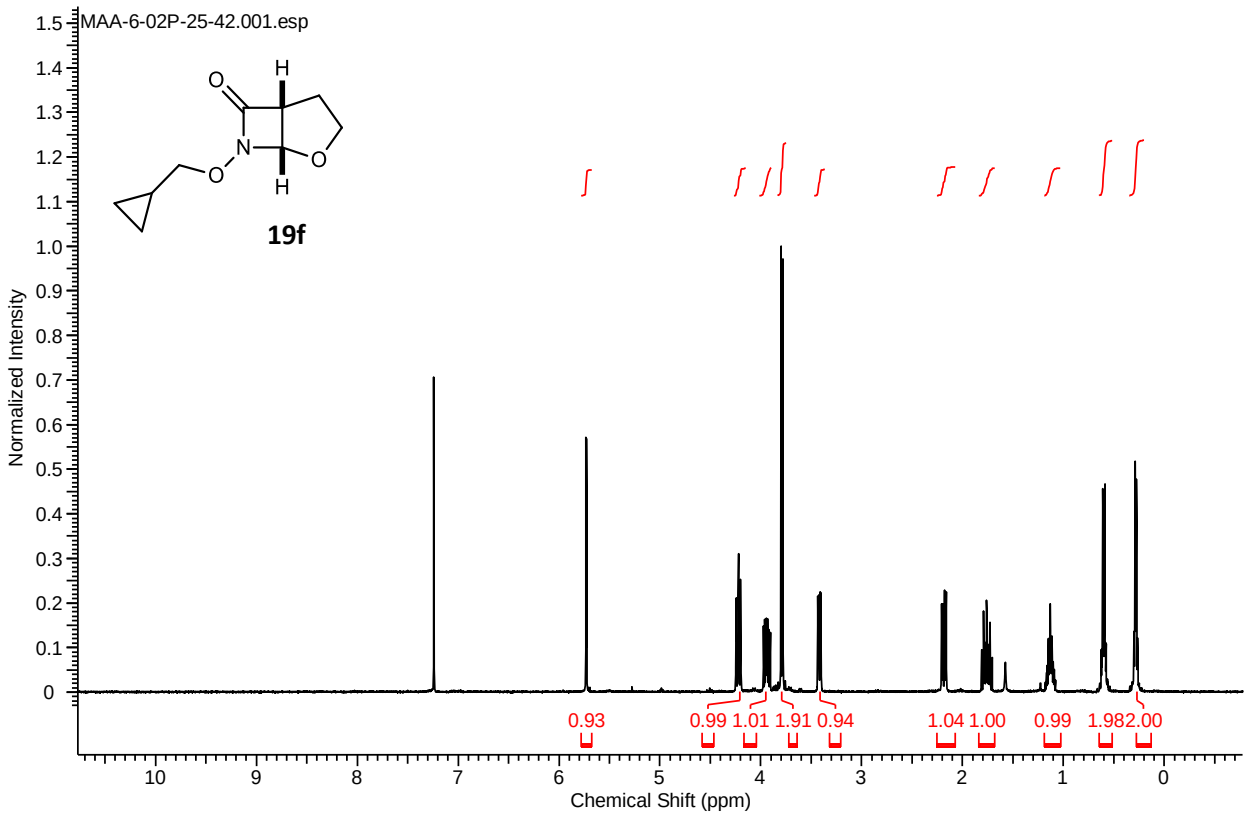

4H MAA-5-188C.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.80
0.85
0.89
0.73

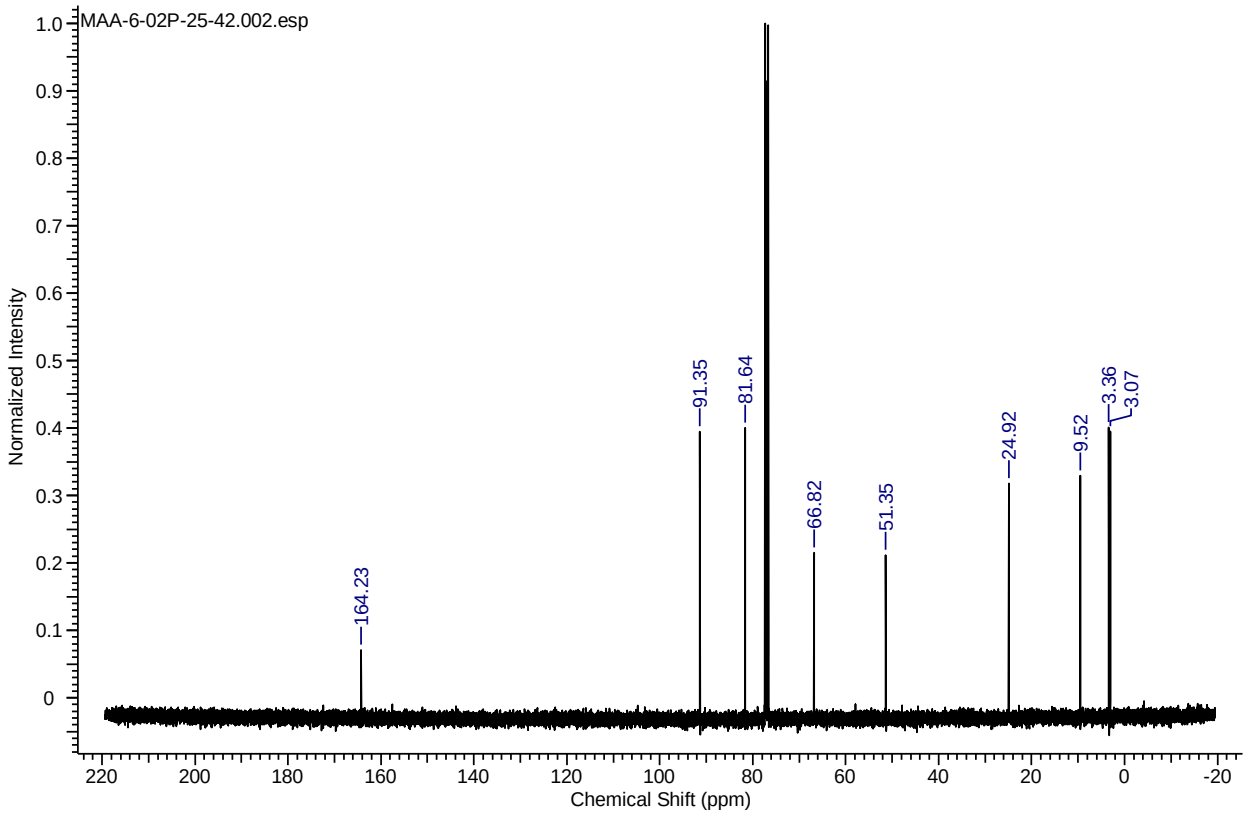

4H MAA-5-188C.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.82
0.97

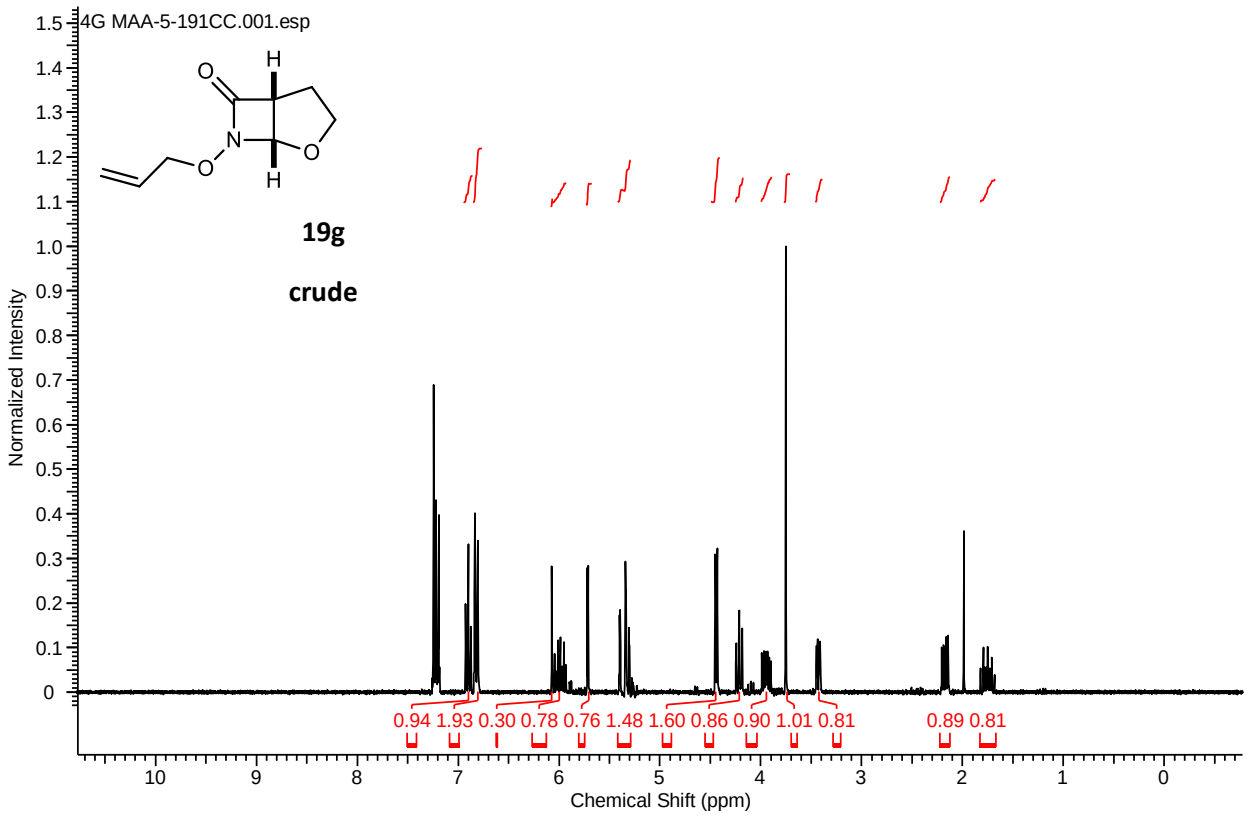

MAA-5-188P CHARAC.002.esp
19d
Normalized Intensity
Chemical Shift (ppm)
164.38
149.63
148.27
143.05
141.09
123.16
108.25
101.29
91.61
78.36
66.85
51.48
24.91

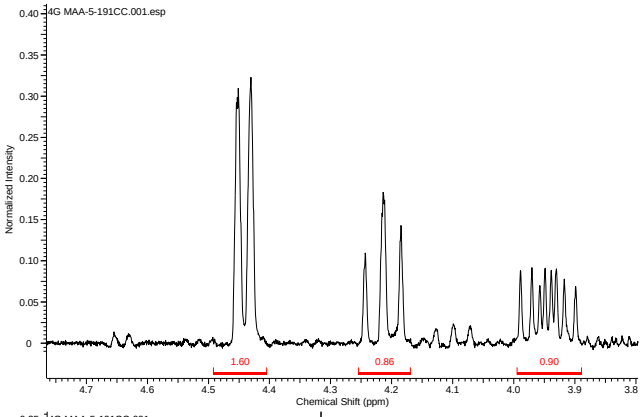

MAA-5-185P-28-48.001.esp
Me
Me
Si
Me
O
N
O
O
H
H
19e
Normalized Intensity
Chemical Shift (ppm)
0.88
0.95
1.84
0.98
0.90
0.94
0.94
1.91
8.43

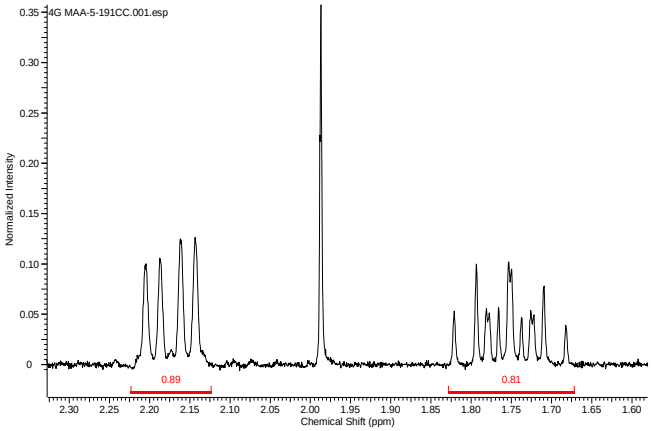

MAA-5-185P-28-48.002.esp
Normalized Intensity
Chemical Shift (ppm)
164.26
91.17
74.87
66.79
51.26
24.85
17.28
-1.47

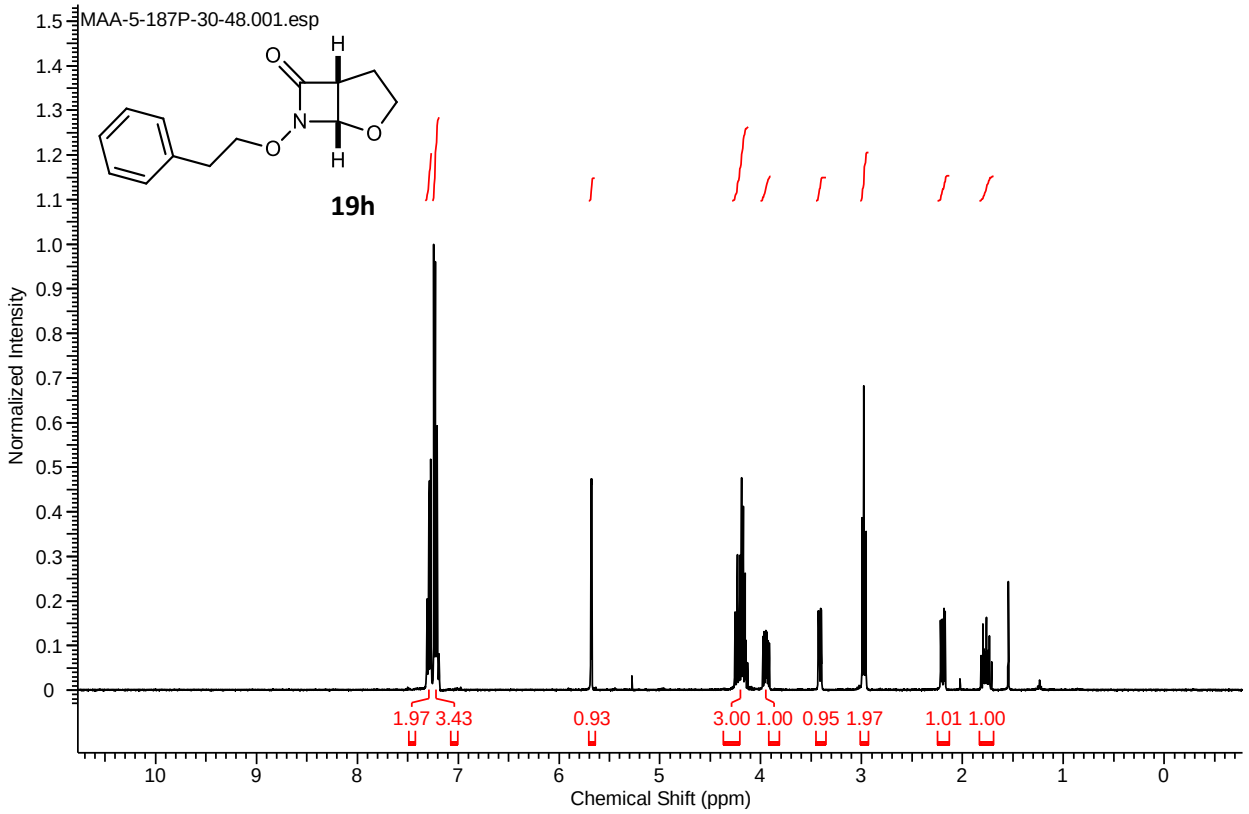

MAA-6-02P-25-42.001.esp
19f
Normalized Intensity
Chemical Shift (ppm)
0.93
0.99 1.01 1.91 0.94
1.04 1.00
0.99
1.98 2.00

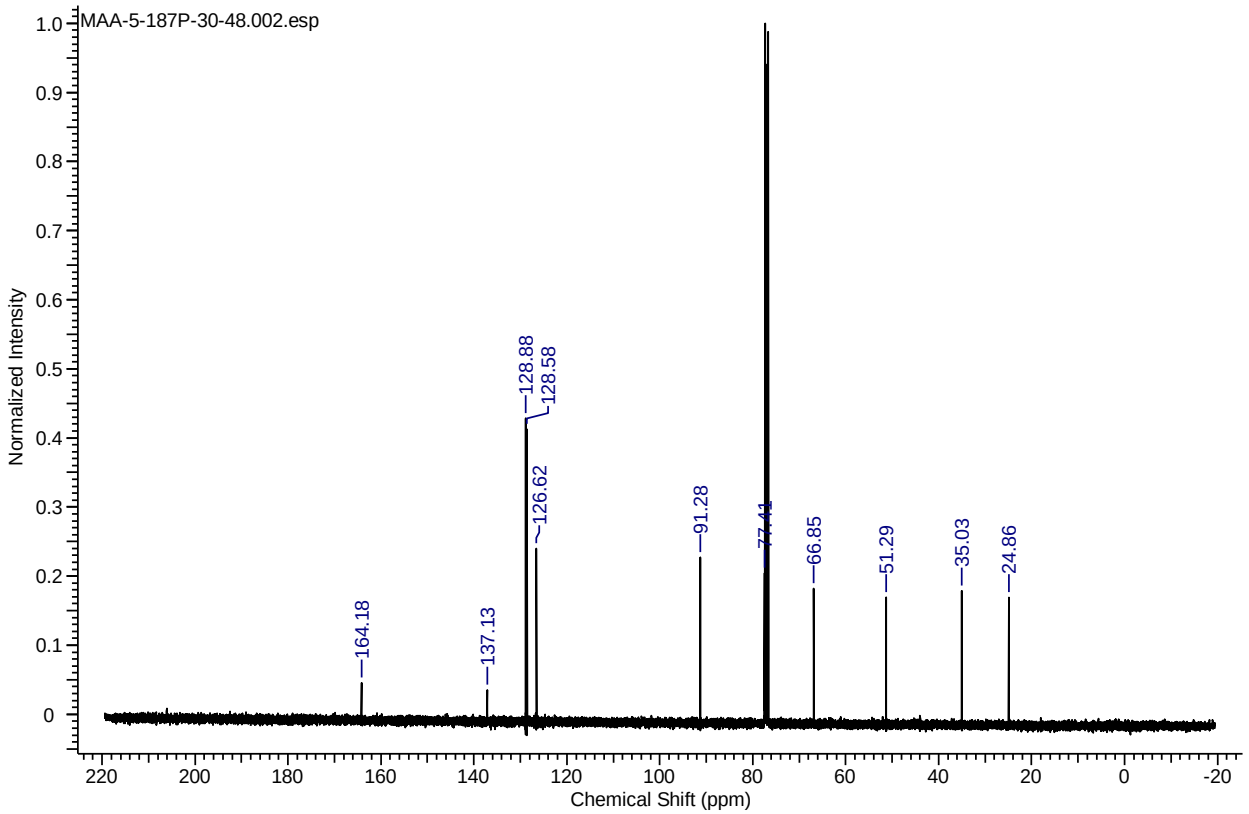

MAA-6-02P-25-42.002.esp
Normalized Intensity
Chemical Shift (ppm)
164.23
91.35
81.64
66.82
51.35
24.92
9.52
3.36
3.07

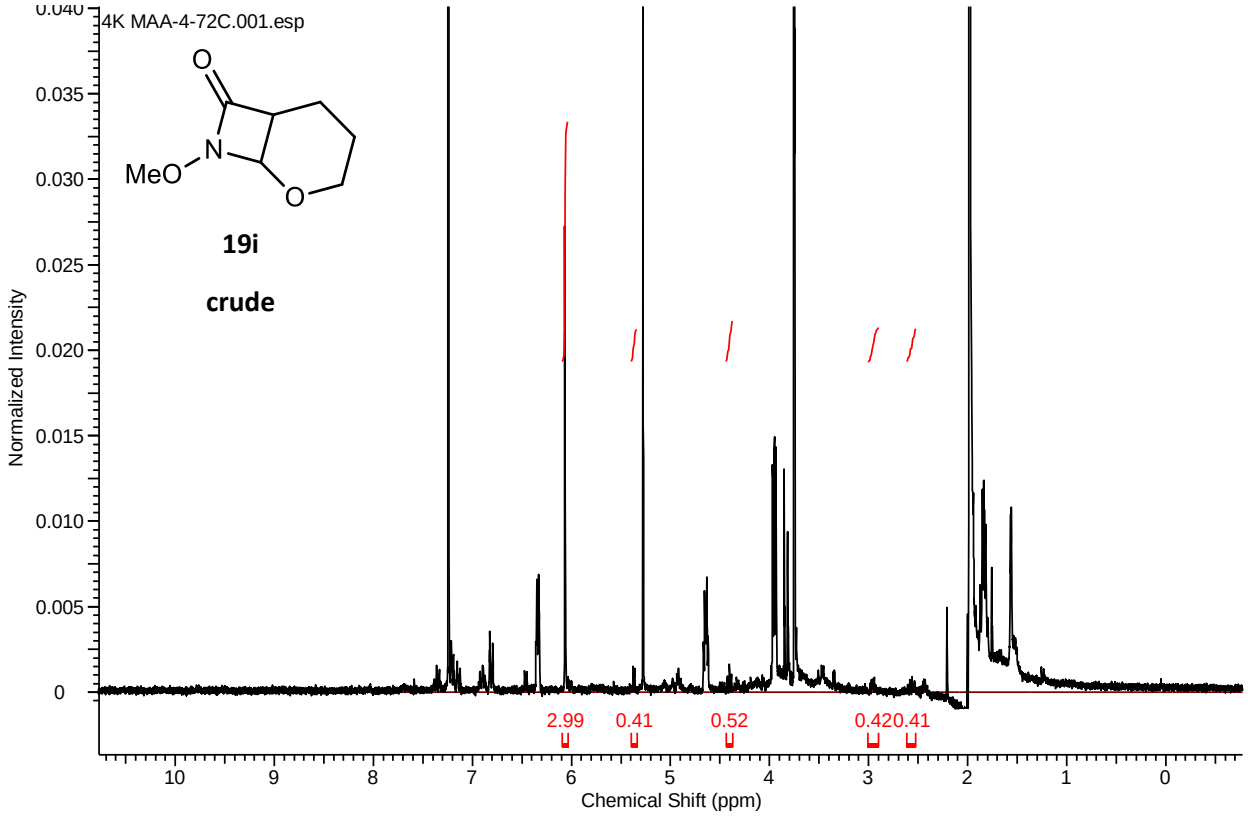

4G MAA-5-191CC.001.esp
19g
crude
Normalized Intensity
Chemical Shift (ppm)
0.94 1.93 0.30 0.78 0.76 1.48 1.60 0.86 0.90 1.01 0.81
0.89 0.81

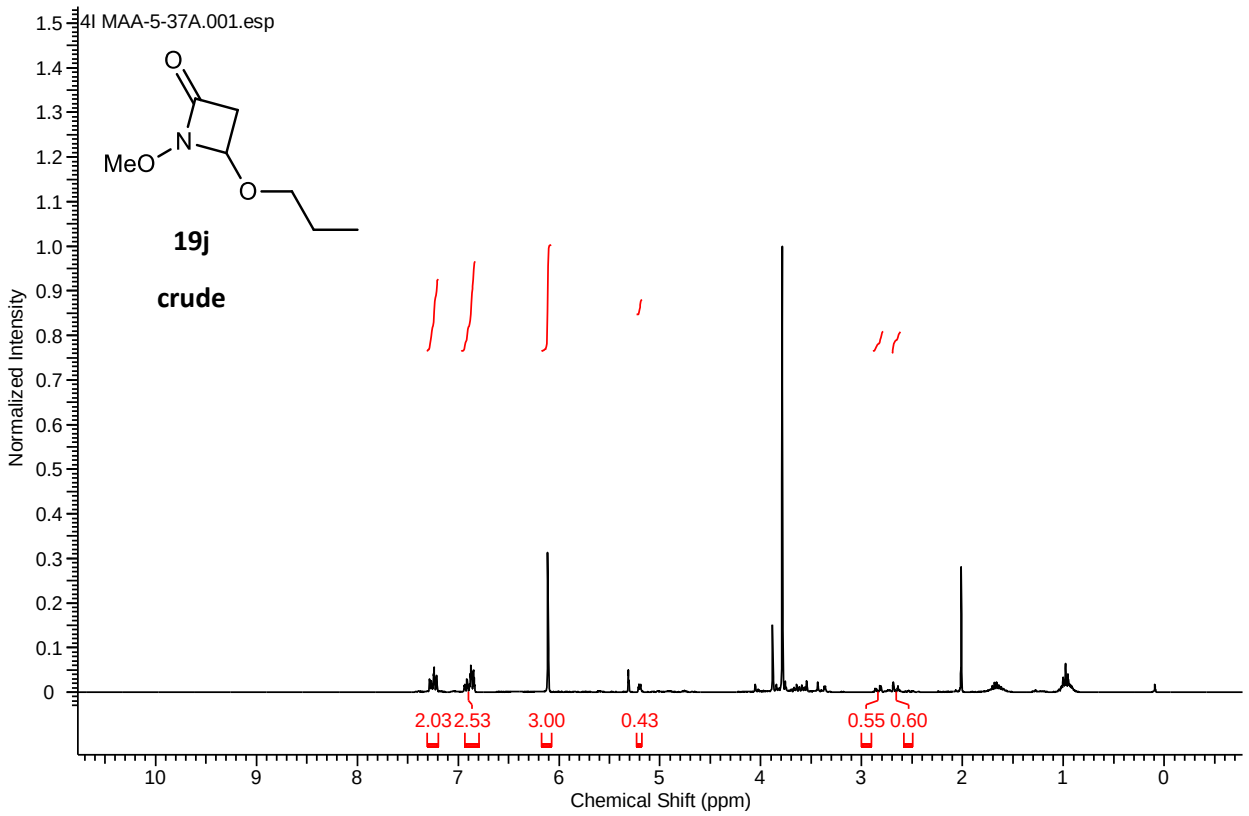

4G MAA-5-191CC.001.esp
Normalized Intensity
Chemical Shift (ppm)
1.60
0.86
0.90

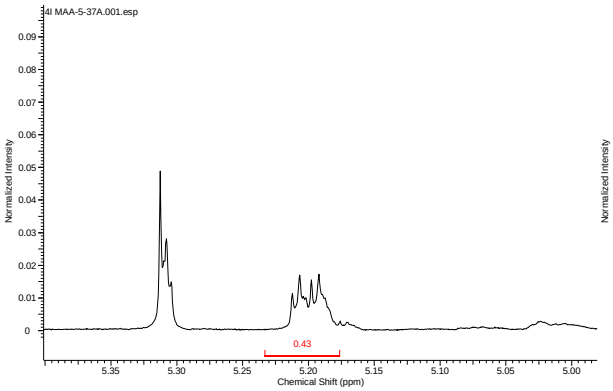

4G MAA-5-191CC.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.89
0.81

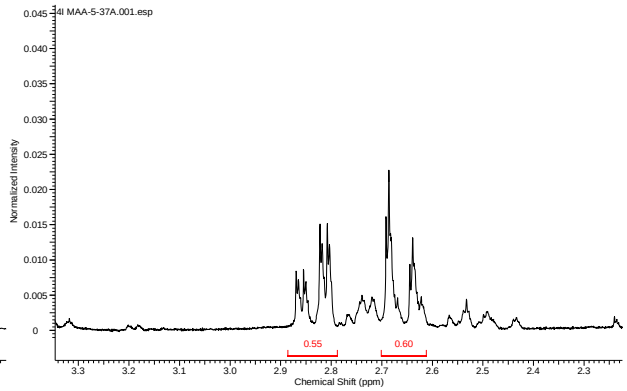

MAA-5-187P-30-48.001.esp
19h
Normalized Intensity
Chemical Shift (ppm)
1.97 3.43
0.93
3.00 1.00 0.95 1.97
1.01 1.00

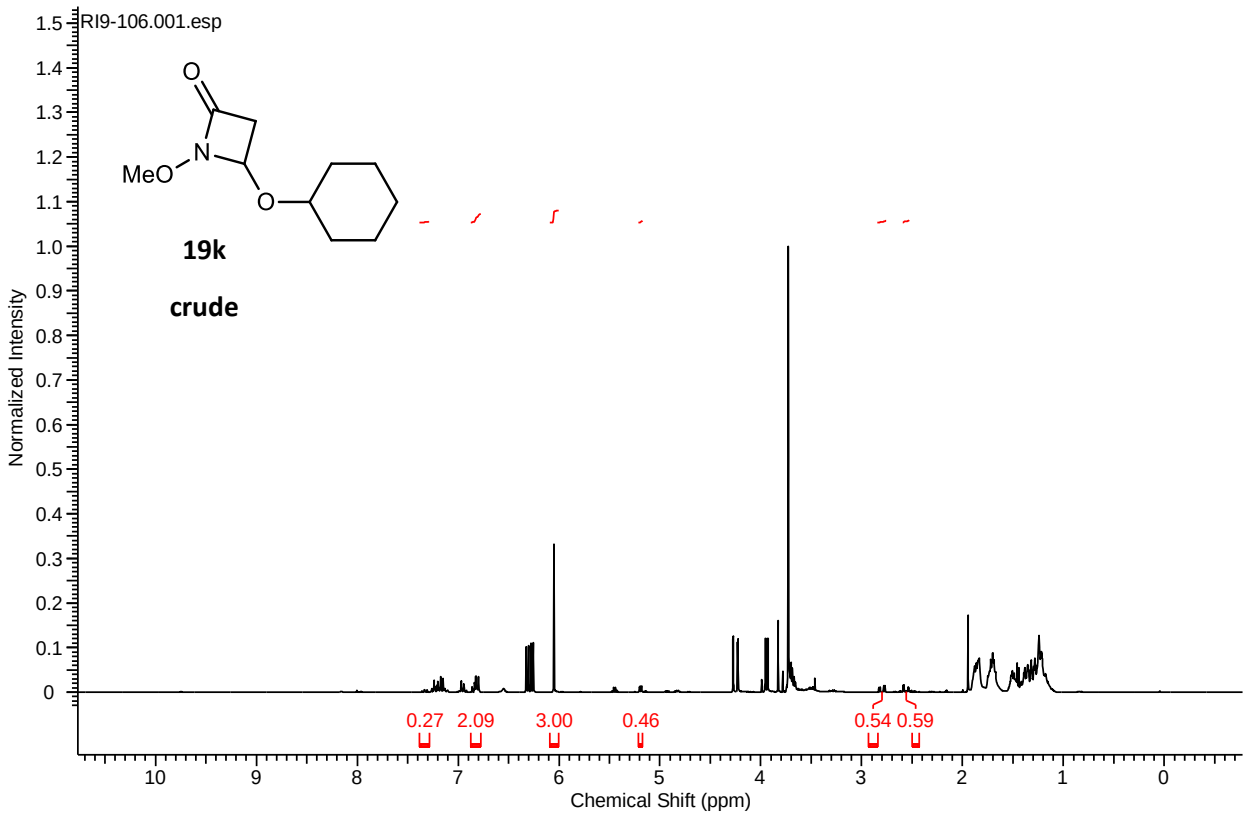

MAA-5-187P-30-48.002.esp
Normalized Intensity
Chemical Shift (ppm)
164.18
137.13
128.88
128.58
126.62
91.28
77.41
66.85
51.29
35.03
24.86

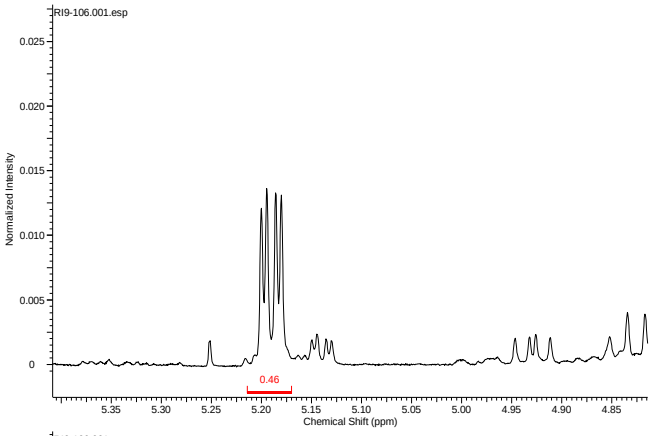

4K MAA-4-72C.001.esp
O
N
MeO
O
19i
crude
Normalized Intensity
0.040
0.035
0.030
0.025
0.020
0.015
0.010
0.005
0
2.99
0.41
0.52
0.42
0.41
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

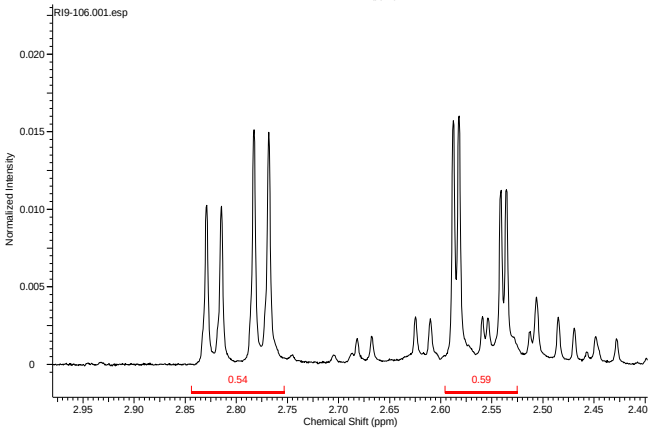

4I MAA-5-37A.001.esp
MeO
N
O
O
19j
crude
Normalized Intensity
Chemical Shift (ppm)
2.03
2.53
3.00
0.43
0.55
0.60

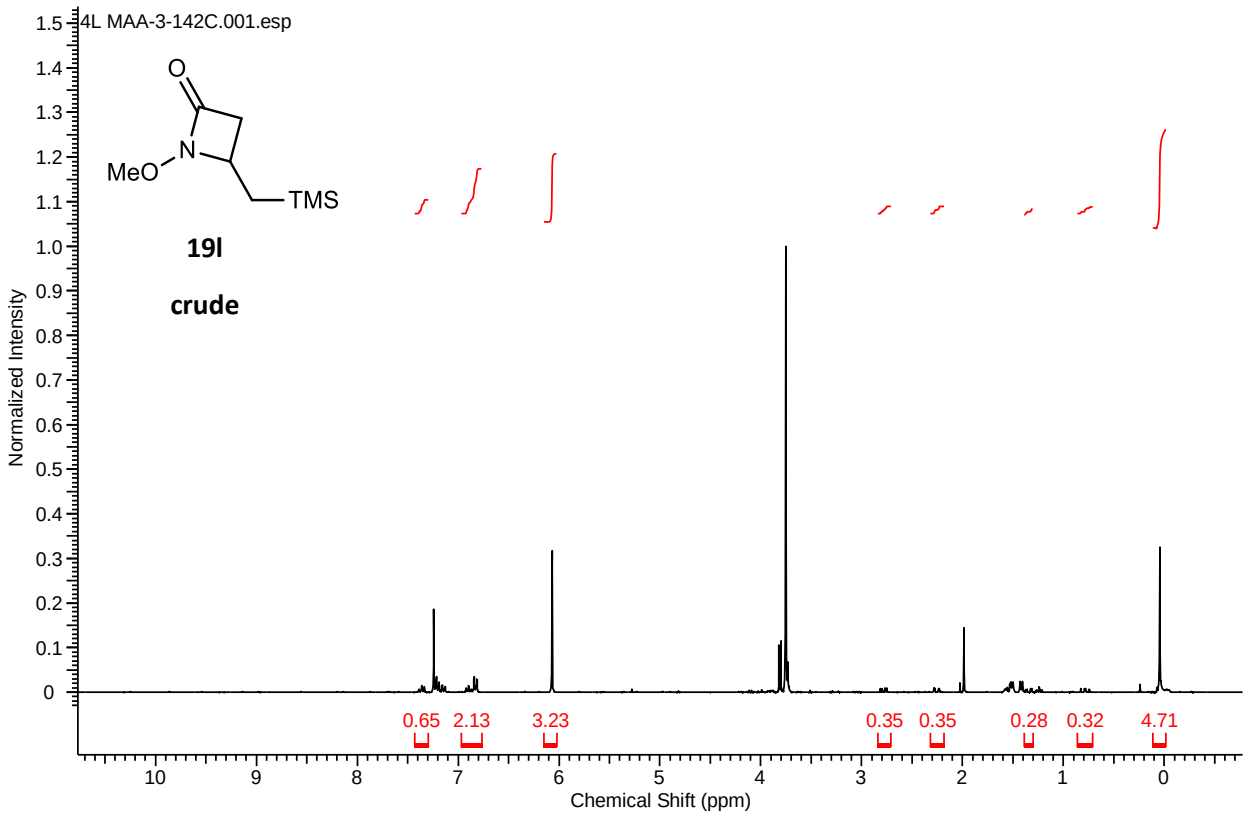

4I MAA-5-37A.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.43

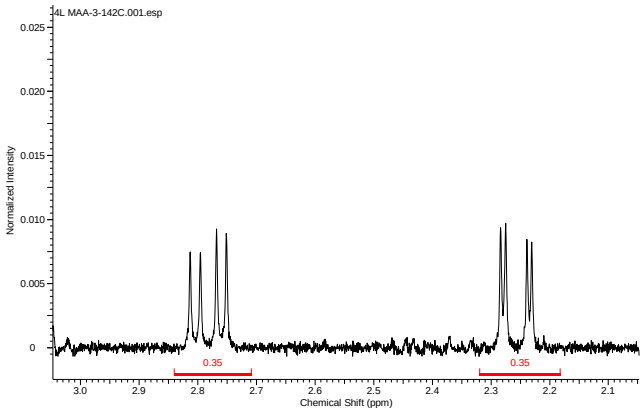

4I MAA-5-37A.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.55
0.60

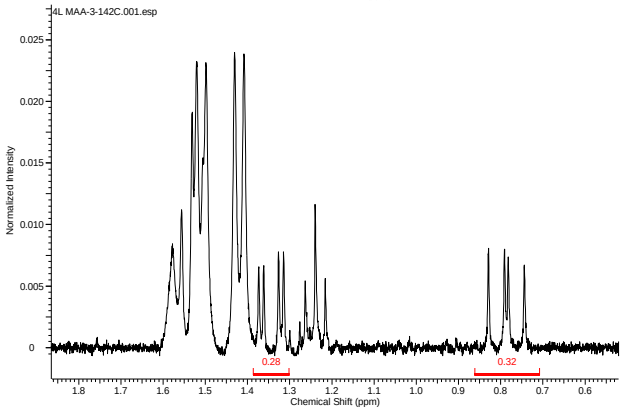

RI9-106.001.esp
O
N
MeO
O
19k
crude
Normalized Intensity
0.27
2.09
3.00
0.46
0.54
0.59
Chemical Shift (ppm)

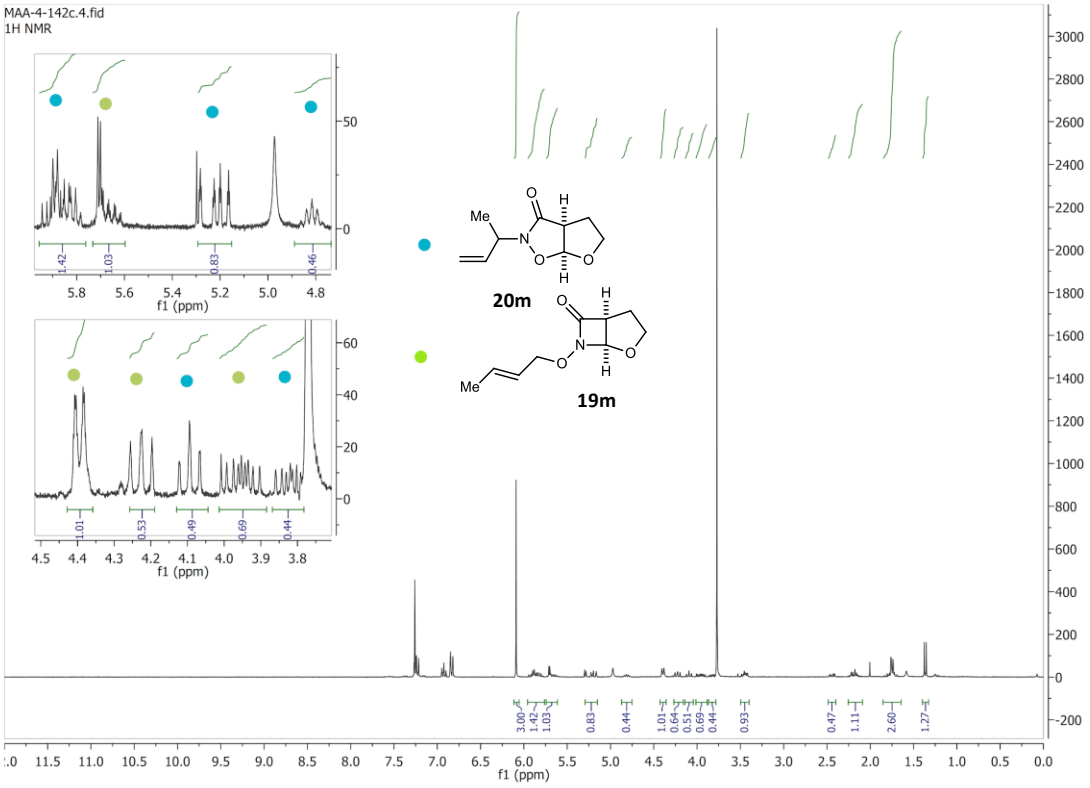

RI9-106.001.esp
Normalized Intensity
0.46
Chemical Shift (ppm)

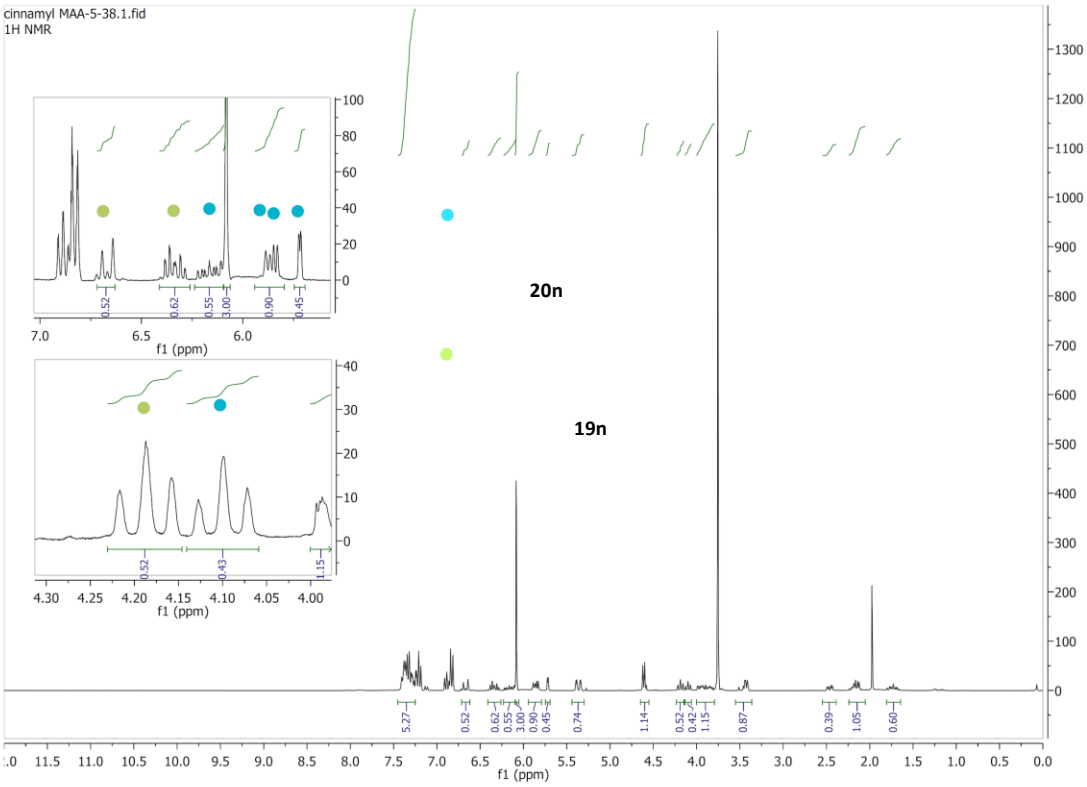

RI9-106.001.esp
Normalized Intensity
0.54
0.59
Chemical Shift (ppm)

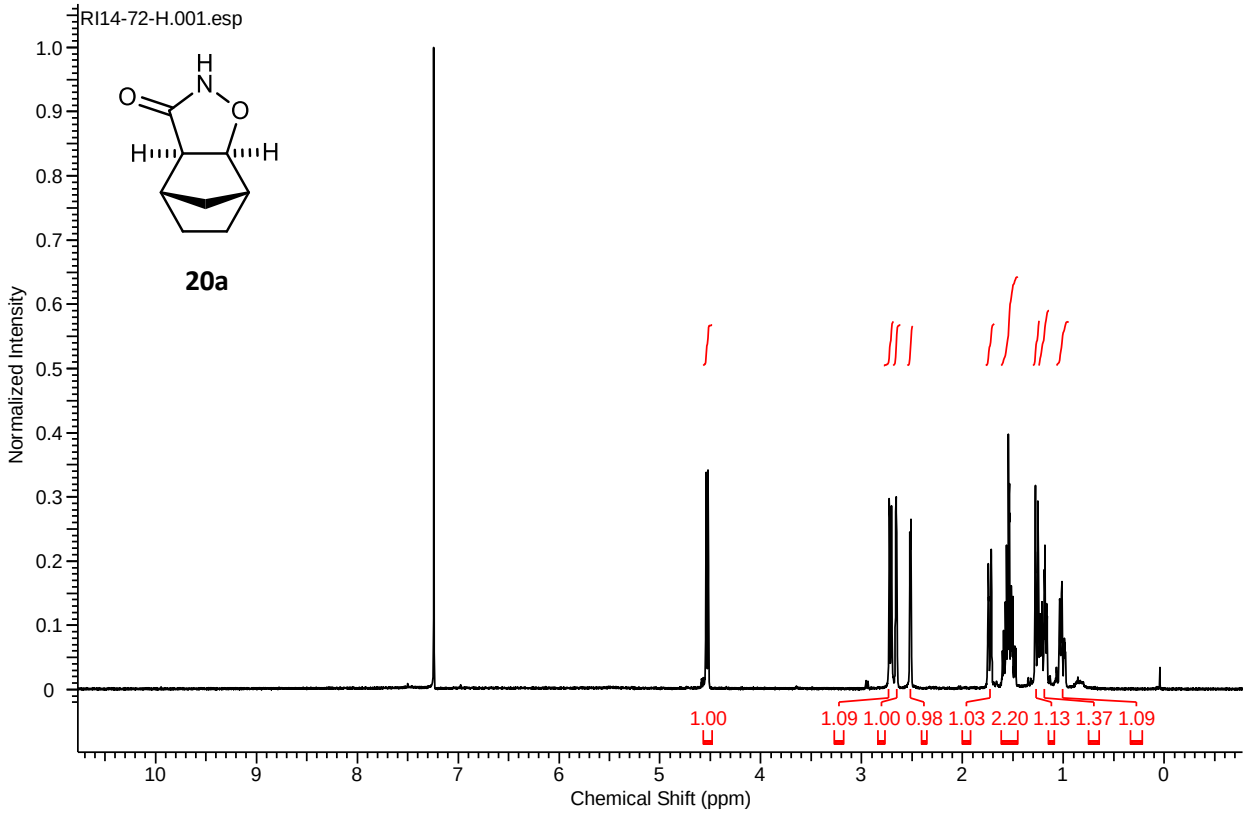

4L MAA-3-142C.001.esp
O
N
MeO
TMS
19l
crude
Normalized Intensity
0.65
2.13
3.23
0.35
0.35
0.28
0.32
4.71
Chemical Shift (ppm)

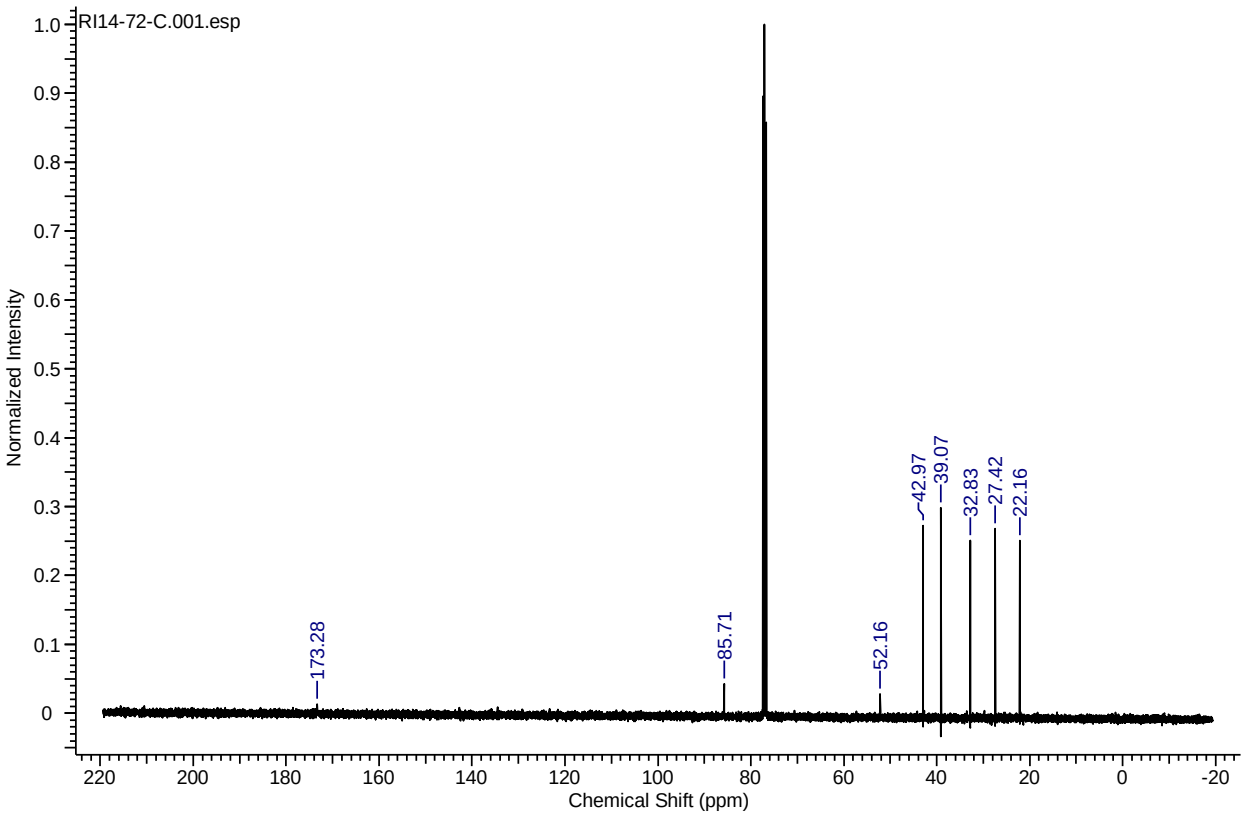

4L MAA-3-142C.001.esp
Normalized Intensity
0.35
0.35
Chemical Shift (ppm)

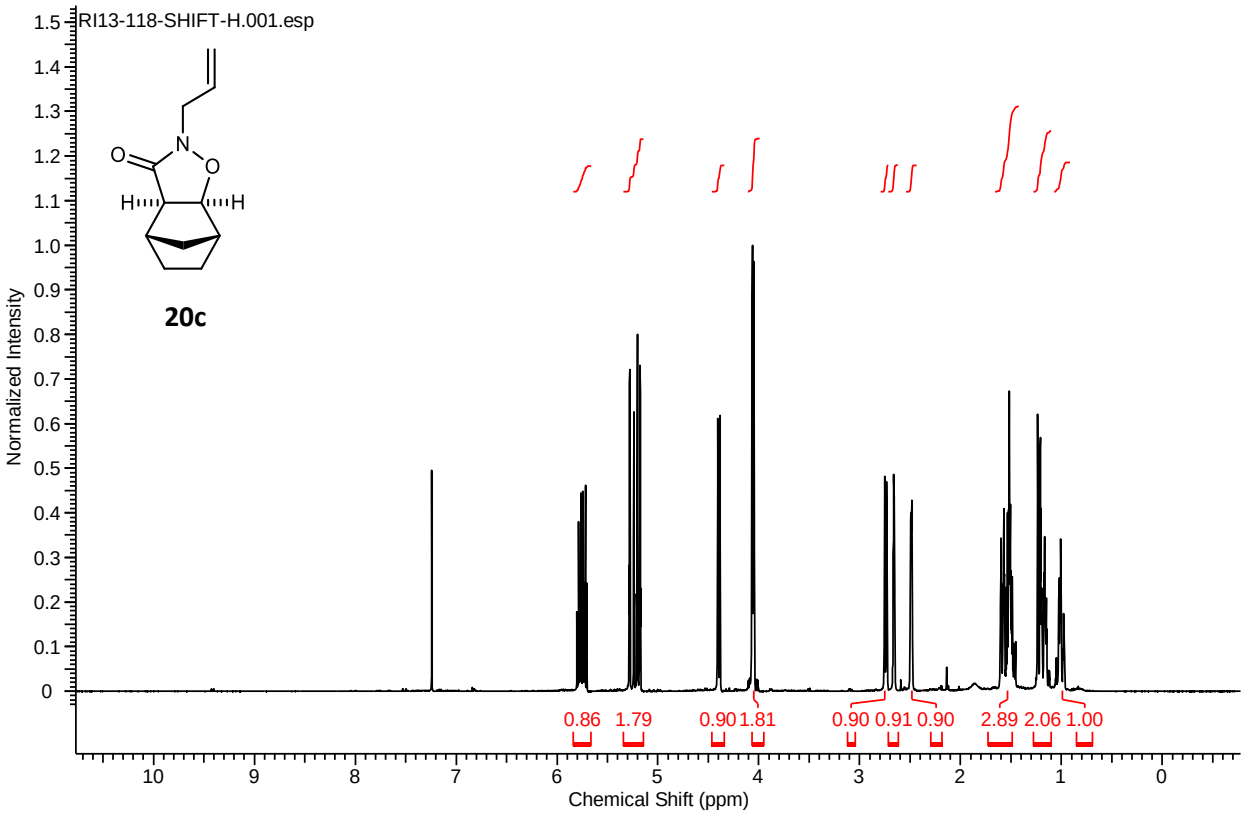

4L MAA-3-142C.001.esp
Normalized Intensity
0.28
0.32
Chemical Shift (ppm)


MAA-4-142c.4.fid
1H NMR
20m
19m
f1 (ppm)

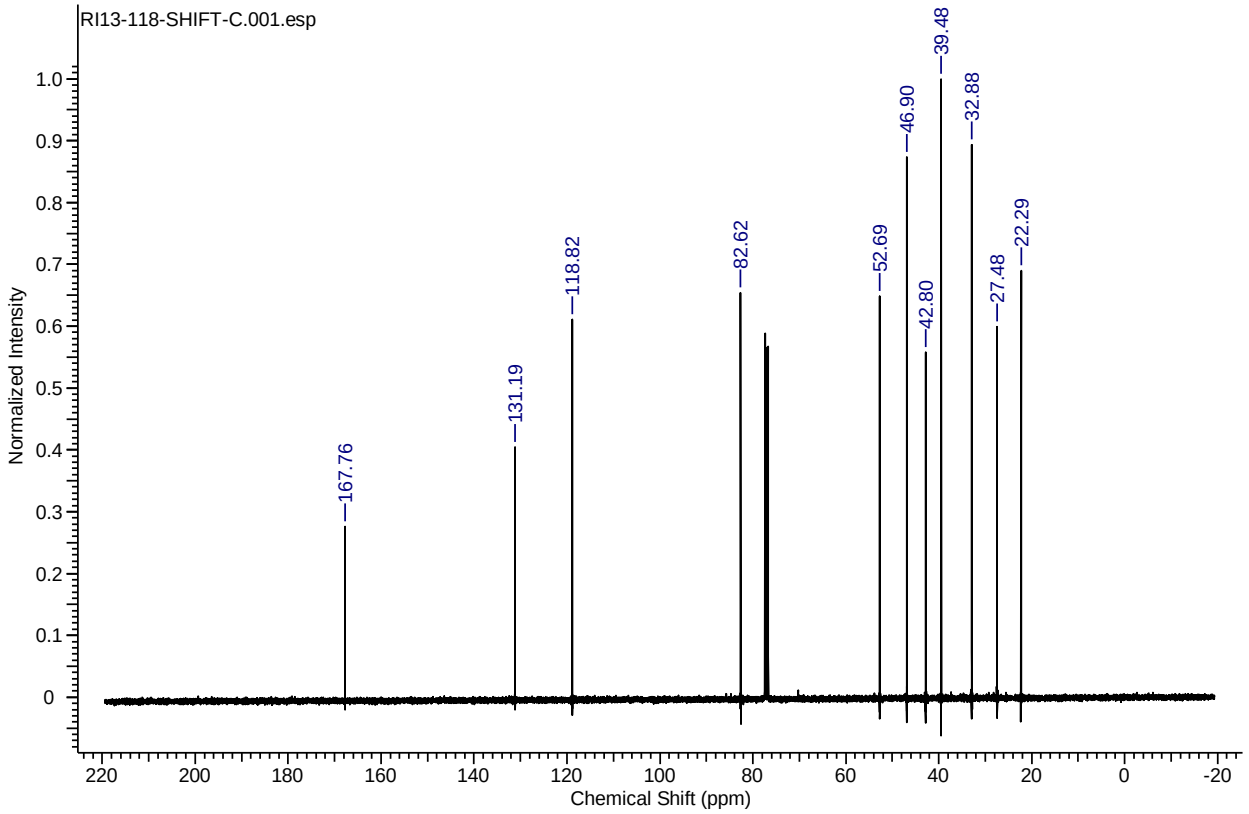

cinnamyl MAA-5-38.1.fid
1H NMR
20n
19n
f1 (ppm)

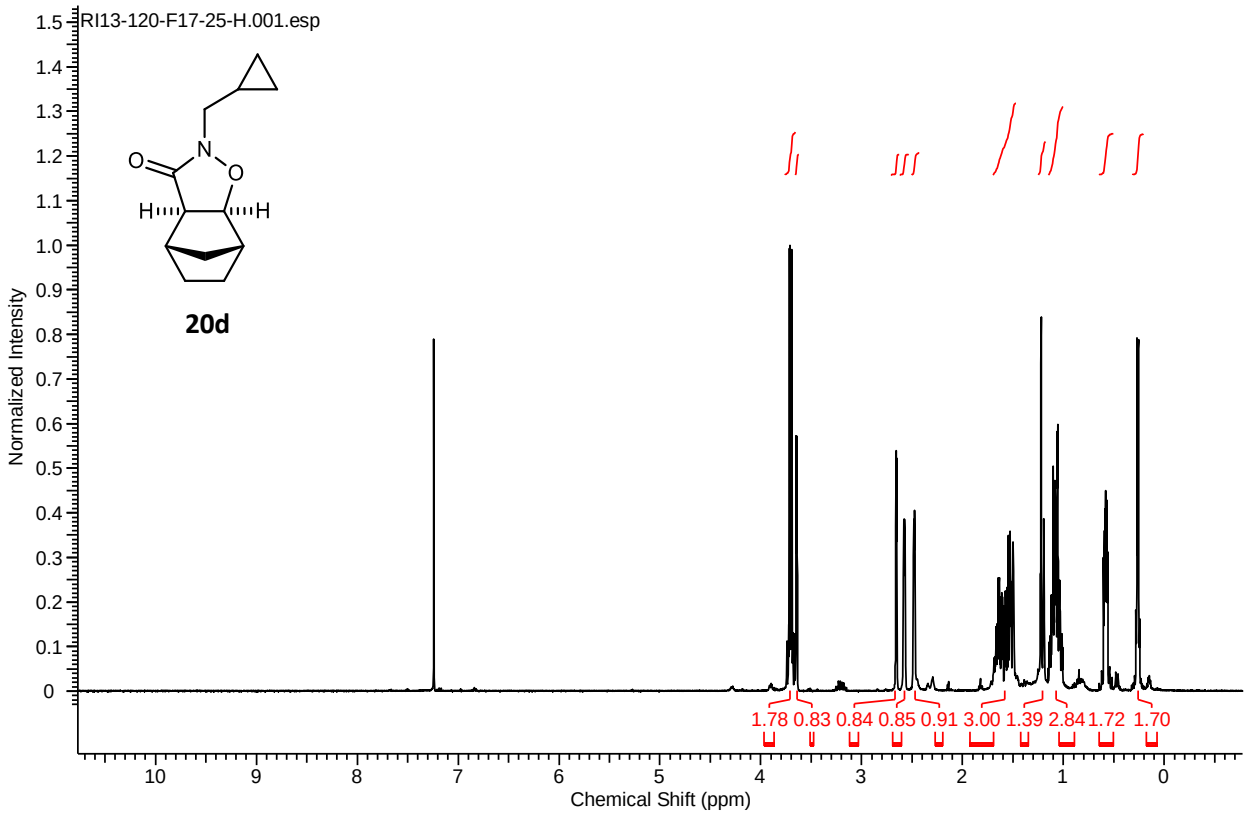

RI14-72-H.001.esp
20a
Normalized Intensity
Chemical Shift (ppm)
1.00
1.09 1.00 0.98 1.03 2.20 1.13 1.37 1.09


RI14-72-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
173.28
85.71
52.16
42.97
39.07
32.83
27.42
22.16

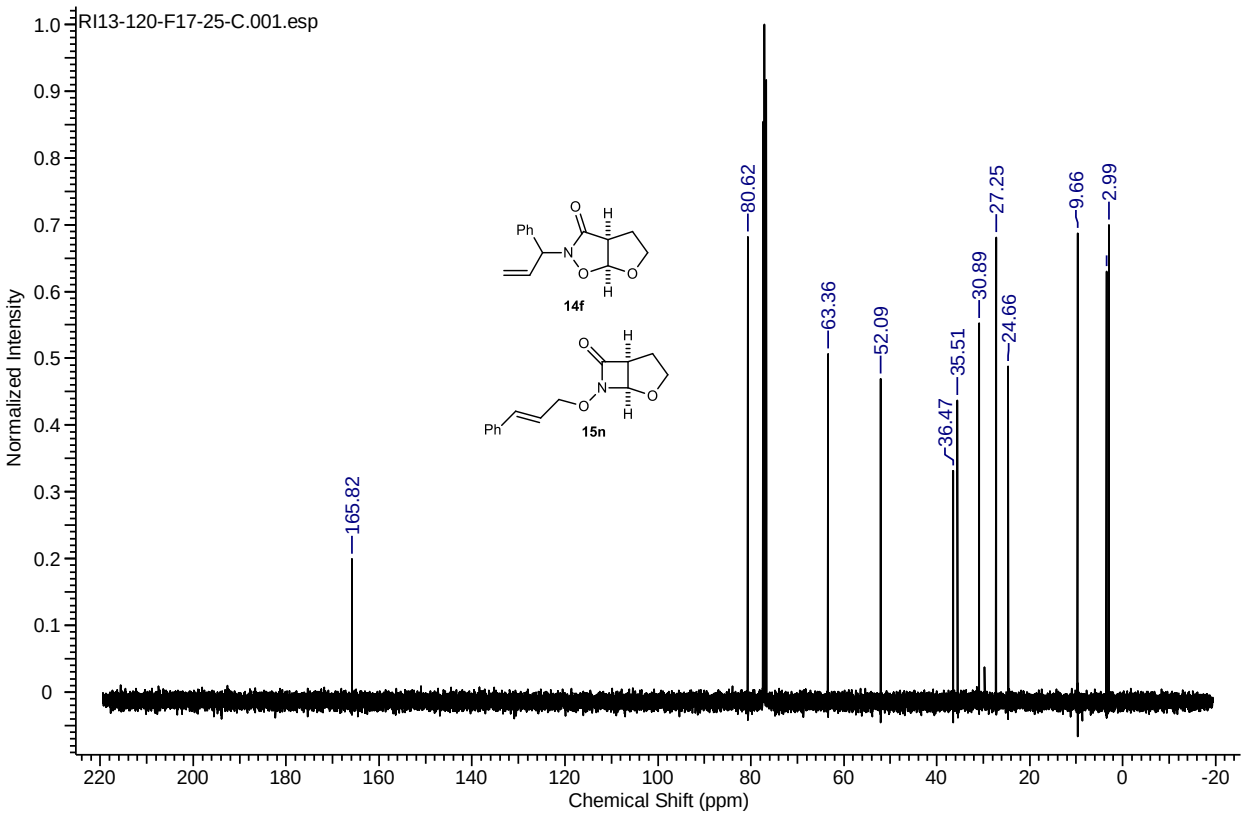

RI13-118-SHIFT-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.86
1.79
0.90
1.81
0.90
0.91
0.90
2.89
2.06
1.00

20c


RI13-118-SHIFT-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
167.76
131.19
118.82
82.62
52.69
46.90
42.80
39.48
32.88
27.48
22.29


RI13-120-F17-25-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
1.78 0.83 0.84 0.85 0.91 3.00 1.39 2.84 1.72 1.70

20d

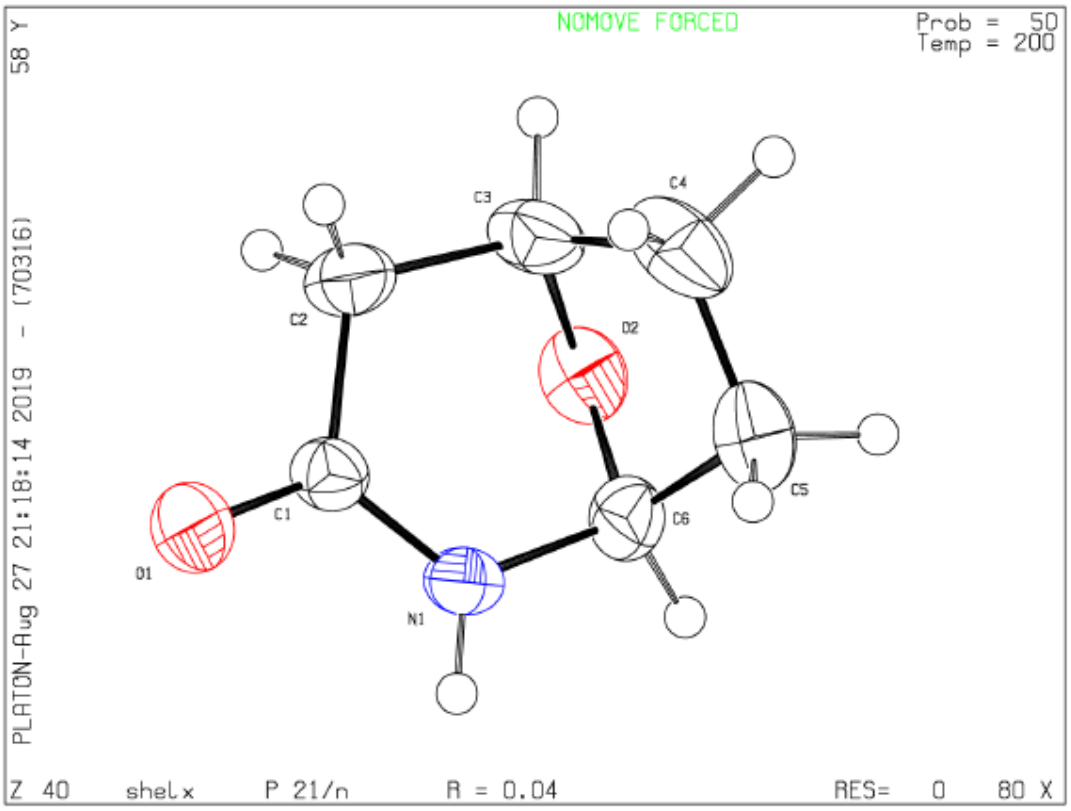

RI13-120-F17-25-C.001.esp
Normalized Intensity
Chemical Shift (ppm)
165.82
80.62
63.36
52.09
36.47
35.51
30.89
27.25
24.66
9.66
2.99
14f
15n

6.2.4 X-Ray Structures

Structure **6a** determination via X-ray analysis (CCDC deposition #: 1949772)

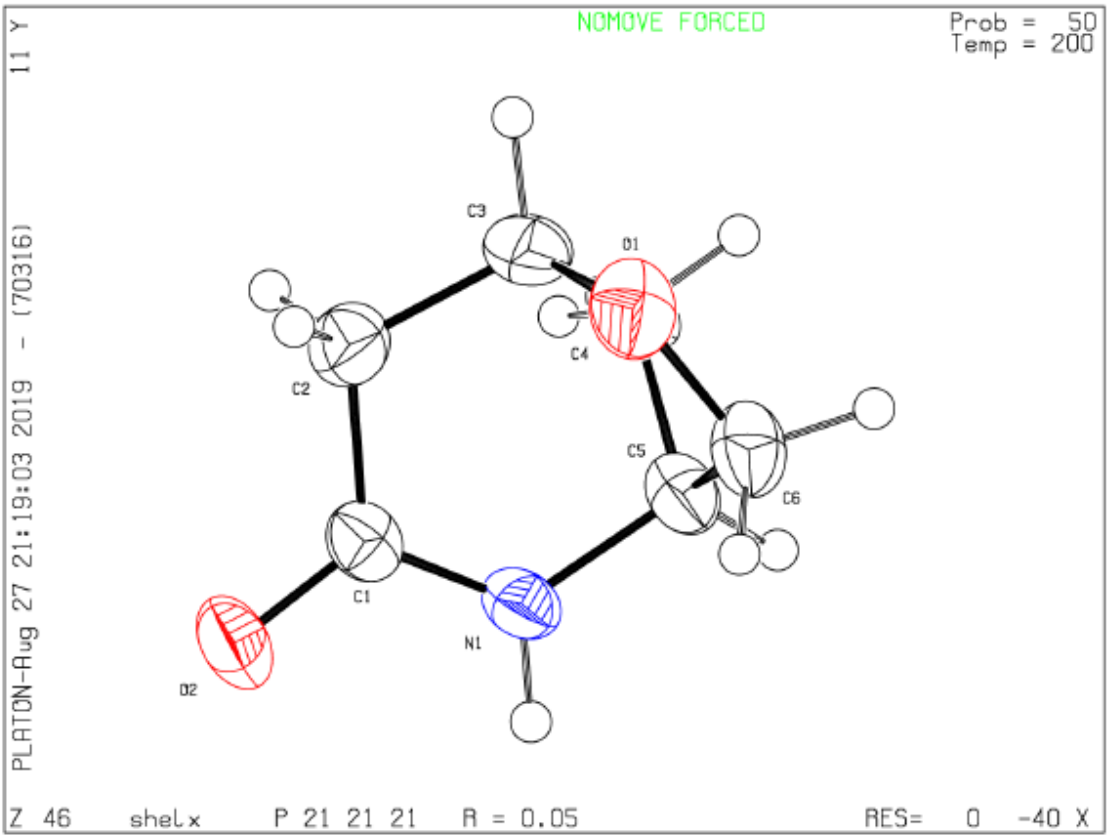
PLATON version of 07/08/2019; check.def file version of 30/07/2019

Datablock shelx - ellipsoid plot



Structure **7a** determination via X-ray analysis (CCDC deposition #: 1949771)

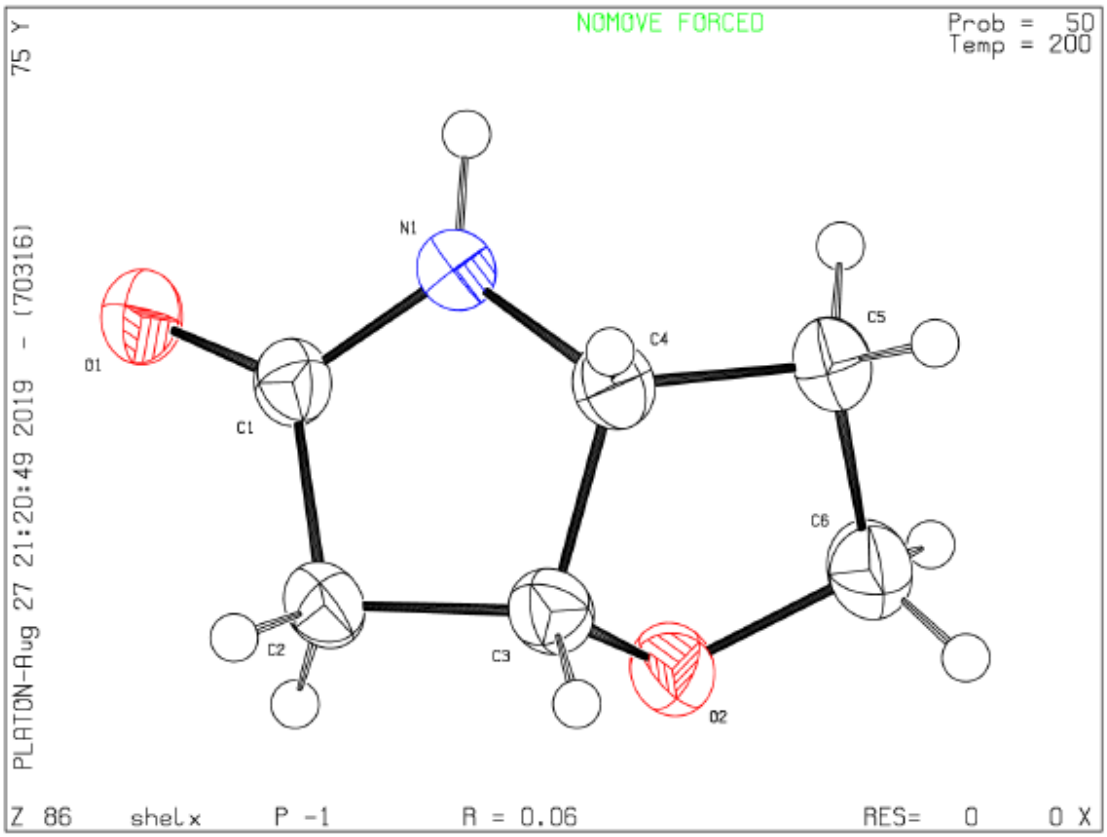
Datablock shelx - ellipsoid plot



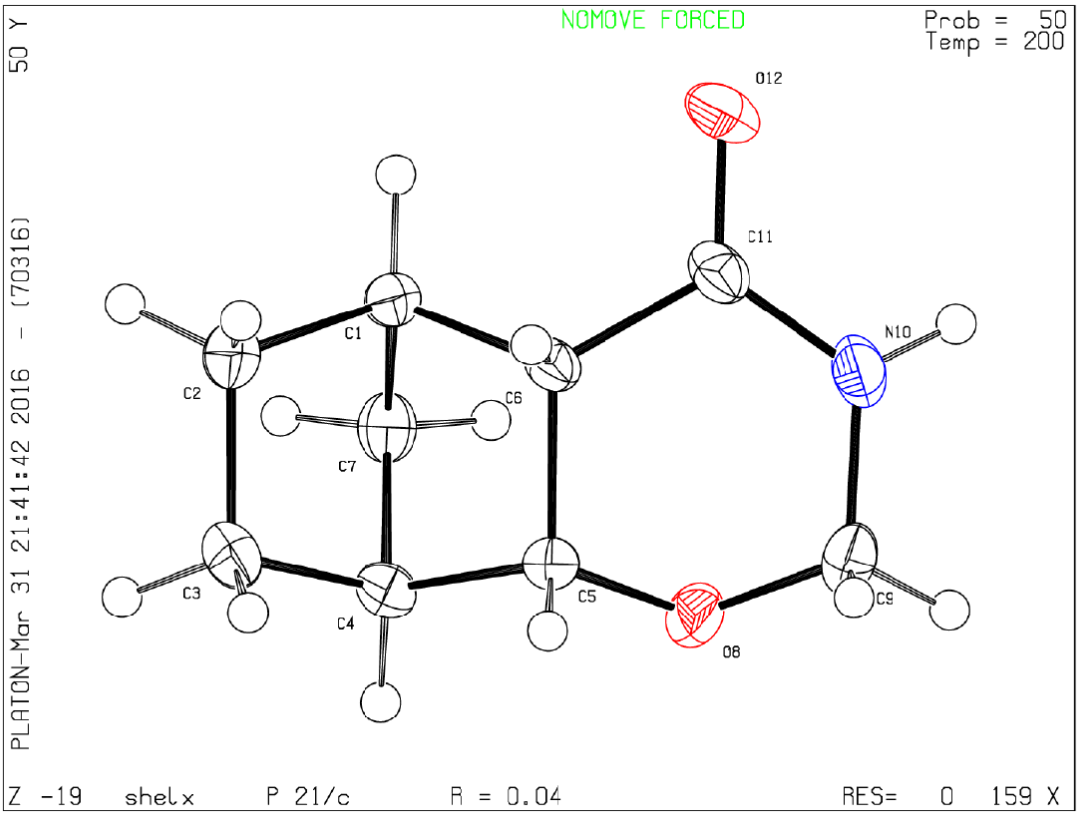
Structure **8a** determination via X-ray analysis (CCDC deposition #: 1949770)

PLATON version of 07/08/2019; check.def file version of 30/07/2019

Datablock shelx - ellipsoid plot

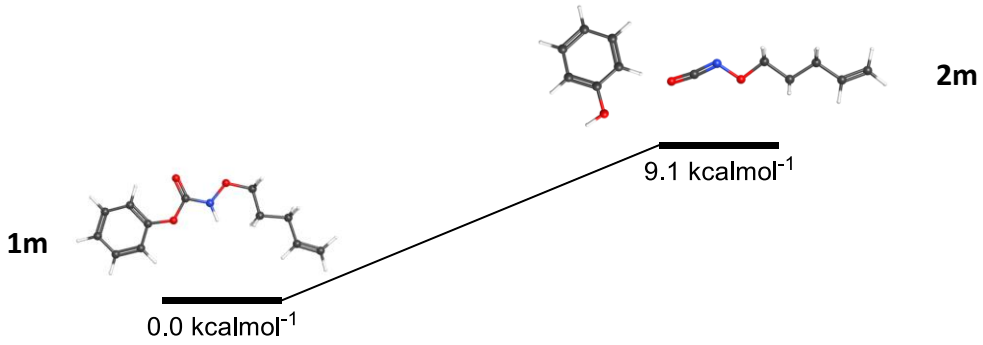


Structure **17a** determination via X-ray analysis (CCDC deposition #: 1949773)

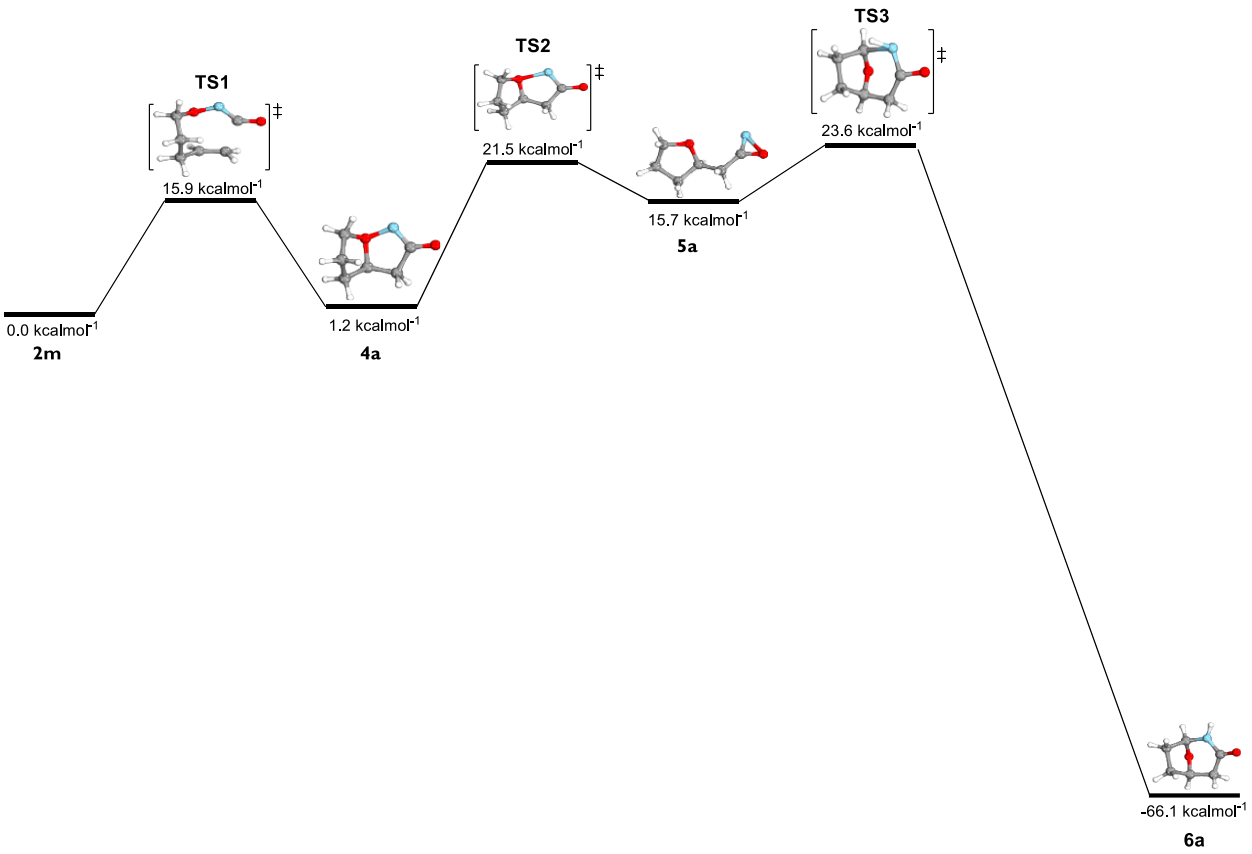


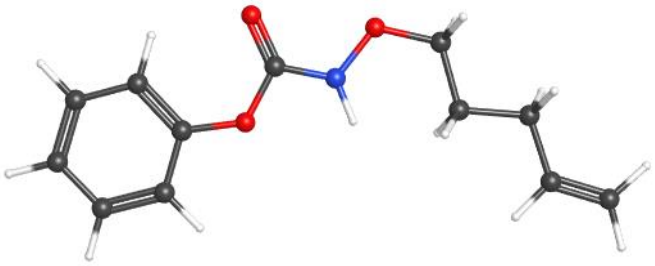
6.2.5 DFT calculations

Density functional theory (DFT) calculations have been performed using WebMO. Optimized molecular geometries were calculated using the B3LYP[219] exchange-correlation functional. The 6-311+G(2d,p) basis set was used for calculations. Vibrational frequency calculations were performed to ensure that the stationary points were true energy minima or transition states (TSs) and to calculate vibrational zero point energy. IRC calculations were used to determine the presence of a transition state. The unscaled frequencies were used for calculating Gibbs free energies of the species (at 298K and 1 atm).



[219] Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.


TS1
TS2
TS3
15.9 kcalmol-1
21.5 kcalmol-1
23.6 kcalmol-1
15.7 kcalmol-1
5a
0.0 kcalmol-1
2m
1.2 kcalmol-1
4a
-66.1 kcalmol-1
6a



Input orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.519800
3	6	0	1.442830	0.000000	2.043423
4	6	0	1.518077	0.000000	3.553568
5	6	0	2.643438	0.000000	4.259699
6	1	0	2.628250	0.000000	5.343094
7	1	0	3.619173	0.000000	3.783264
8	1	0	0.568896	0.000000	4.085048
9	1	0	1.970070	-0.875005	1.650291
10	1	0	1.970070	0.875005	1.650291
11	1	0	-0.512092	0.886473	1.906733
12	1	0	-0.512092	-0.886473	1.906733
13	8	0	-1.289841	0.000000	-0.687176
14	7	0	-2.412575	0.000000	0.137801
15	6	0	-3.615875	0.000000	-0.461466
16	8	0	-4.559811	0.000000	0.533155
17	6	0	-5.936292	0.000000	0.335227
18	6	0	-6.663003	0.000000	1.525250

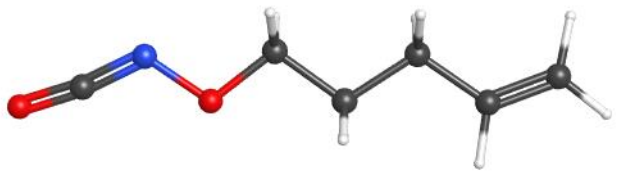
19	6	0	-8.050444	0.000000	1.487534
20	6	0	-8.719390	0.000000	0.265399
21	6	0	-7.982528	0.000000	-0.912845
22	6	0	-6.587899	0.000000	-0.895612
23	1	0	-6.025656	0.000000	-1.813581
24	1	0	-8.491065	0.000000	-1.869673
25	1	0	-9.801875	0.000000	0.234069
26	1	0	-8.607910	0.000000	2.416368
27	1	0	-6.129478	0.000000	2.467404
28	8	0	-3.815775	0.000000	-1.658404
29	1	0	-2.293760	0.000000	1.137794
30	1	0	0.516779	-0.887115	-0.371517
31	1	0	0.516779	0.887115	-0.371517



Input orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.393615

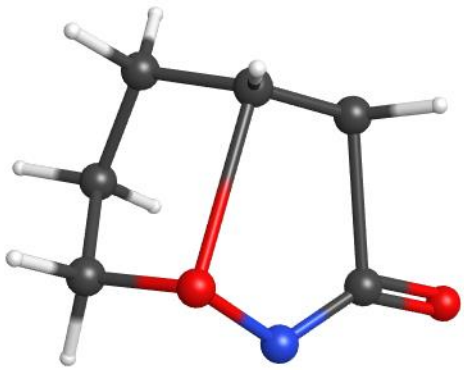
3	6	0	1.214068	0.000000	2.074250
4	6	0	2.417853	0.000000	1.375714
5	6	0	2.406337	0.000000	-0.018321
6	6	0	1.195394	0.000000	-0.709196
7	1	0	1.203151	0.000000	-1.792445
8	8	0	3.557200	0.000000	-0.761735
9	1	0	4.326186	0.000000	-0.177020
10	1	0	3.362293	0.000000	1.909354
11	1	0	1.230816	0.000000	3.157737
12	1	0	-0.934234	0.000000	1.941098
13	1	0	-0.938148	0.000000	-0.542444



Input orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.516415
3	6	0	1.422913	0.000000	2.085365
4	6	0	1.451869	0.000000	3.597291
5	6	0	2.551647	0.000000	4.340235
6	1	0	3.543178	0.000000	3.897894
7	1	0	2.501382	0.000000	5.422158
8	1	0	0.485713	0.000000	4.097286

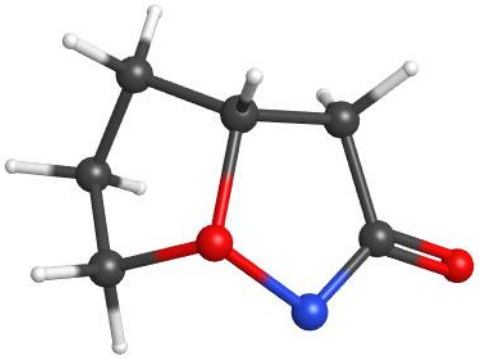
9	1	0	1.965454	-0.875118	1.711269
10	1	0	1.965454	0.875118	1.711269
11	1	0	-0.543339	0.879253	1.875334
12	1	0	-0.543339	-0.879253	1.875334
13	8	0	-1.376863	0.000000	-0.413734
14	7	0	-1.415713	0.000000	-1.824845
15	6	0	-2.492747	0.000000	-2.405468
16	8	0	-3.423352	0.000000	-3.108198
17	1	0	0.493719	-0.889289	-0.403578
18	1	0	0.493719	0.889289	-0.403578



Input orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	8	0	0.000000	0.000000	2.357787
3	6	0	1.445360	0.000000	2.498434
4	6	0	2.086834	0.611686	1.266785
5	6	0	1.500984	-0.051058	0.003803

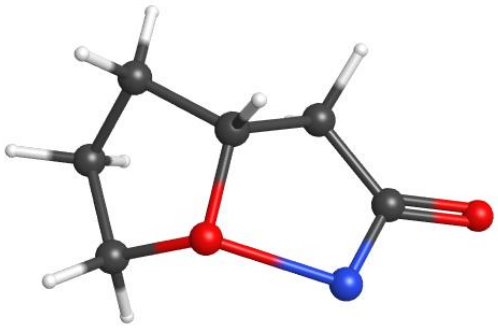
6	1	0	1.833227	-1.089312	-0.049824
7	1	0	1.882802	0.465021	-0.881669
8	1	0	1.906664	1.688628	1.245616
9	1	0	3.169088	0.467163	1.306212
10	1	0	1.712792	0.519538	3.418258
11	1	0	1.692555	-1.058018	2.595598
12	7	0	-0.543156	1.247478	2.627766
13	6	0	-1.060368	1.939949	1.678221
14	6	0	-0.726302	1.151147	-0.157518
15	1	0	-1.779903	1.074937	-0.395720
16	1	0	-0.224815	2.049303	-0.501034
17	8	0	-1.690970	2.945371	1.530932
18	1	0	-0.530999	-0.942056	0.066385



Input orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	8	0	0.000000	0.000000	1.550343
3	6	0	1.417531	0.000000	2.028476

4	6	0	2.223572	0.461317	0.833369
5	6	0	1.471941	-0.167323	-0.349908
6	1	0	1.721547	-1.225382	-0.438696
7	1	0	1.698657	0.316369	-1.299353
8	1	0	2.230789	1.550522	0.768814
9	1	0	3.255285	0.117365	0.896729
10	1	0	1.435492	0.642030	2.901464
11	1	0	1.614017	-1.035488	2.299480
12	7	0	-0.773969	1.198894	2.080771
13	6	0	-1.155844	1.889522	1.007846
14	6	0	-0.669897	1.312691	-0.323789
15	1	0	-1.522382	1.180863	-0.989015
16	1	0	0.009998	2.031885	-0.784384
17	8	0	-1.842508	2.924262	1.084230
18	1	0	-0.611072	-0.863740	-0.243236

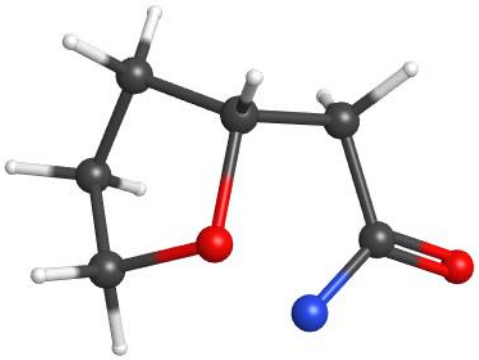


Input orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z

1	6	0	0.000000	0.000000	0.000000
2	8	0	0.000000	0.000000	1.445073

3	6	0	1.359481	0.000000	1.950671
4	6	0	2.266066	0.192973	0.736376
5	6	0	1.421073	-0.388578	-0.406806
6	1	0	1.510428	-1.476148	-0.434366
7	1	0	1.695199	-0.000617	-1.388105
8	1	0	2.468728	1.252929	0.570873
9	1	0	3.222600	-0.315811	0.853045
10	1	0	1.450774	0.794201	2.692147
11	1	0	1.532958	-0.962133	2.439760
12	7	0	-1.390407	1.389060	1.579903
13	6	0	-1.452710	1.956838	0.408086
14	6	0	-0.430902	1.388366	-0.498827
15	1	0	-0.832061	1.349726	-1.513989
16	1	0	0.409826	2.090032	-0.509805
17	8	0	-2.356769	2.874232	0.239780
18	1	0	-0.740000	-0.737351	-0.314518



Input orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000

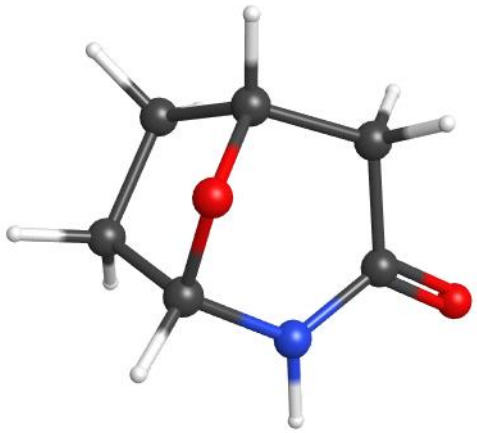
2	8	0	0.000000	0.000000	1.550343
3	6	0	1.417531	0.000000	2.028476
4	6	0	2.223572	0.461317	0.833370
5	6	0	1.471941	-0.167323	-0.349908
6	1	0	1.721547	-1.225382	-0.438696
7	1	0	1.698657	0.316369	-1.299353
8	1	0	2.230789	1.550522	0.768814
9	1	0	3.255285	0.117365	0.896729
10	1	0	1.435492	0.642030	2.901464
11	1	0	1.614017	-1.035488	2.299480
12	7	0	-0.773969	1.198894	2.080771
13	6	0	-1.155844	1.889522	1.007846
14	6	0	-0.669897	1.312690	-0.323789
15	1	0	-1.522382	1.180863	-0.989015
16	1	0	0.009997	2.031886	-0.784384
17	8	0	-1.842508	2.924262	1.084230
18	1	0	-0.611071	-0.863740	-0.243236



Input orientation:

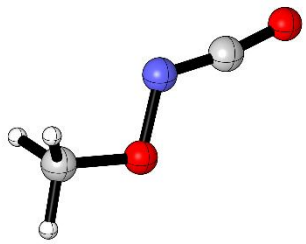
Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z

1	6	0	0.000000	0.000000	0.000000
2	8	0	0.000000	0.000000	1.462777
3	6	0	1.367194	0.000000	1.829689
4	6	0	2.007745	-1.105833	0.891899
5	6	0	1.207409	-0.868729	-0.418980
6	1	0	0.874184	-1.817952	-0.860719
7	1	0	1.825637	-0.353757	-1.185485
8	1	0	1.827528	-2.128414	1.309544
9	1	0	3.103517	-0.990664	0.754262
10	7	0	2.100317	1.774452	1.479583
11	6	0	1.181926	2.169017	0.418955
12	6	0	0.137277	1.462588	-0.402952
13	1	0	0.383787	1.573659	-1.490064
14	1	0	-0.812899	2.025117	-0.266075
15	8	0	1.280879	3.463331	0.553783
16	1	0	2.811919	0.842551	1.432287
17	1	0	1.459402	-0.166042	2.936665
18	1	0	-0.955510	-0.414940	-0.308459



Input orientation:

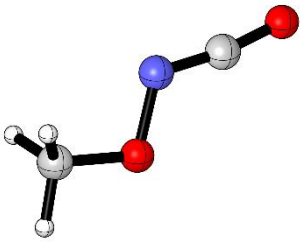
Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	8	0	0.000000	0.000000	1.444724
3	6	0	1.376322	0.000000	1.759556
4	6	0	1.943044	-1.145286	0.905776
5	6	0	1.075150	-1.049111	-0.376140
6	1	0	0.615169	-2.008579	-0.610687
7	1	0	1.652032	-0.737390	-1.247334
8	1	0	1.783235	-2.094454	1.419218
9	1	0	3.010180	-1.030760	0.717343
10	7	0	1.943736	1.300139	1.389828
11	6	0	1.565697	1.988413	0.271808
12	6	0	0.350389	1.418096	-0.456487
13	1	0	0.546984	1.465310	-1.529112
14	1	0	-0.482835	2.095350	-0.250613
15	8	0	2.128297	3.004981	-0.095159
16	1	0	2.760649	1.648412	1.871572
17	1	0	1.489421	-0.138489	2.833825
18	1	0	-1.001656	-0.282855	-0.319934

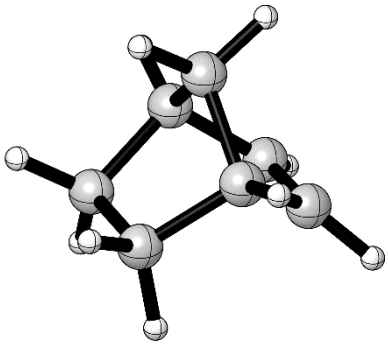


Quantity	Value
Route	#N B3LYP/6-311+G(2d,p) FREQ SCRF=(PCM,Solvent=Acetonitrile) Geom=Conne
Stoichiometry	$C_2H_3NO_2$
Symmetry	CS
Basis	6-311+G(2d,p)
RB3LYP Energy	-283.227246979 Hartree
ZPE	0.053744 Hartree
Conditions	298.150K, 1.00000 atm
Internal Energy	-283.167925 Hartree
Enthalpy	-283.166981 Hartree
Free Energy	-283.202468 Hartree
C_v	16.888 cal/mol-K
Entropy	74.690 cal/mol-K
Dipole Moment	2.8881 Debye
Server	titan.chem.uottawa.ca (4655)
CPU time	273.8 sec

Input orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	8	0	0.000000	0.000000	1.435514
3	7	0	1.338375	0.000000	1.879588
4	6	0	1.598149	0.000000	3.073548
5	8	0	2.019023	0.000000	4.162682
6	1	0	-1.054984	0.000000	-0.267469
7	1	0	0.488155	0.896739	-0.383991
8	1	0	0.488155	-0.896739	-0.383991



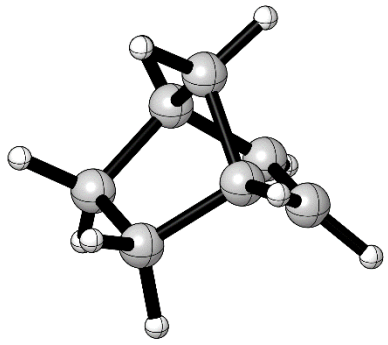


Quantity	Value
Route	#N B3LYP/6-311+G(2d,p) FREQ SCRF=(PCM,Solvent=Acetonitrile) Geom=Conne
Stoichiometry	C_7H_{10}
Symmetry	C1
Basis	6-311+G(2d,p)

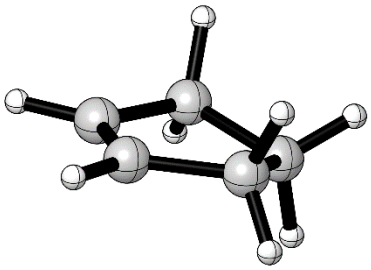
RB3LYP Energy	-272.806569479 Hartree
ZPE	0.152051 Hartree
Conditions	298.150K, 1.00000 atm
Internal Energy	-272.649278 Hartree
Enthalpy	-272.648334 Hartree
Free Energy	-272.683038 Hartree
C_v	22.443 cal/mol-K
Entropy	73.041 cal/mol-K
Dipole Moment	0.5626 Debye
Server	titan.chem.uottawa.ca (22970)
CPU time	2720.1 sec

Input orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.520152
3	6	0	1.273813	0.000000	1.923714
4	6	0	2.149056	0.000164	0.680810
5	6	0	1.988240	-1.419626	0.038819
6	6	0	0.501498	-1.419736	-0.432368
7	1	0	0.430681	-1.532360	-1.516435
8	1	0	-0.088859	-2.214997	0.024034
9	1	0	2.670532	-1.532350	-0.806560
10	1	0	2.208038	-2.214816	0.752024

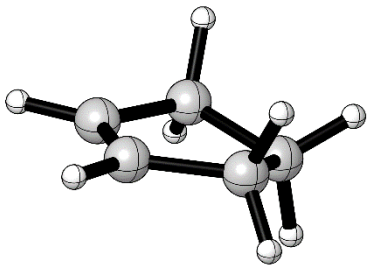


11	6	0	1.269674	0.836175	-0.276009
12	1	0	1.170209	1.876623	0.037657
13	1	0	1.599530	0.793079	-1.317249
14	1	0	3.181564	0.317268	0.817854
15	1	0	1.638844	-0.109763	2.937358
16	1	0	-0.882068	-0.109734	2.138759
17	1	0	-0.923164	0.316834	-0.482491



Quantity	Value
Route	#N B3LYP/6-311+G(2d,p) FREQ SCRF=(PCM,Solvent=Acetonitrile) Geom=Conne
Stoichiometry	C_5H_8
Symmetry	C1
Basis	6-311+G(2d,p)
RB3LYP Energy	-195.387788186 Hartree
ZPE	0.116001 Hartree
Conditions	298.150K, 1.00000 atm
Internal Energy	-195.267113 Hartree
Enthalpy	-195.266169 Hartree
Free Energy	-195.299210 Hartree

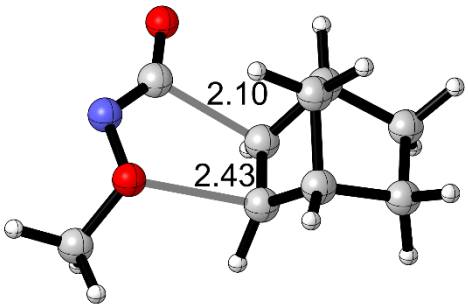
C_v	17.146 cal/mol-K
Entropy	69.541 cal/mol-K
Dipole Moment	0.3413 Debye
Server	10.72.192.49 (31089)
CPU time	544 sec



Input orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.510004
3	6	0	1.232619	0.000000	2.011978
4	6	0	2.287540	0.000032	0.931583
5	6	0	1.477113	0.313272	-0.352756
6	1	0	1.829756	-0.248327	-1.218670
7	1	0	1.574624	1.374573	-0.592234
8	1	0	2.778087	-0.979799	0.876797
9	1	0	3.080742	0.730559	1.113188
10	1	0	1.473316	-0.036470	3.068327
11	1	0	-0.910204	-0.036469	2.097659
12	1	0	-0.312680	-0.979850	-0.381887

13 1 0 -0.694422 0.730498 -0.424228

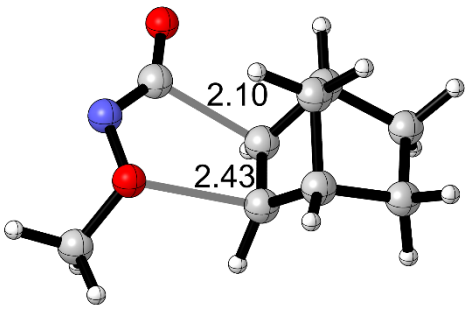


Quantity	Value
Route	#N B3LYP/6-311+G(2d,p) FREQ SCRF=(PCM,Solvent=Acetonitrile) Geom=Conne
Stoichiometry	$C_9H_{13}NO_2$
Symmetry	C1
Basis	6-311+G(2d,p)
RB3LYP Energy	-556.016741749 Hartree
ZPE	0.207661 Hartree
Conditions	298.150K, 1.00000 atm
Internal Energy	-555.798161 Hartree
Enthalpy	-555.797217 Hartree
Free Energy	-555.846134 Hartree
C_v	42.074 cal/mol-K
Entropy	102.955 cal/mol-K
Dipole Moment	6.8140 Debye
Server	titan.chem.uottawa.ca (8221)

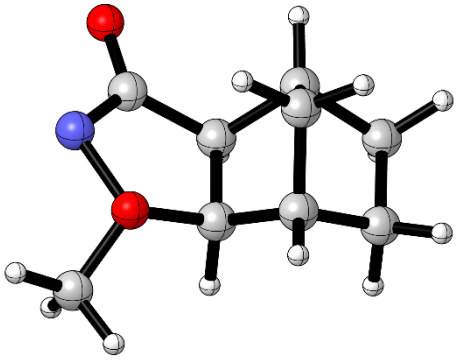
CPU time	12723.4 sec

Input orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.371954
3	6	0	1.421297	0.000000	1.844463
4	6	0	1.898064	-1.474664	1.557500
5	6	0	1.931644	-1.536221	0.001667
6	6	0	1.469525	-0.105783	-0.412819
7	6	0	2.132192	0.741567	0.690362
8	1	0	3.216692	0.628177	0.726151
9	1	0	1.878099	1.801015	0.643924
10	1	0	1.681822	0.163064	-1.444849
11	1	0	2.942820	-1.727265	-0.362473
12	1	0	1.279566	-2.310145	-0.404700
13	1	0	2.890495	-1.614583	1.989373
14	1	0	1.234530	-2.216443	2.002678
15	1	0	1.599411	0.338348	2.862223
16	8	0	-0.753609	2.291994	1.639856
17	7	0	-0.955771	2.681356	0.319622
18	6	0	-0.559080	1.928262	-0.630501
19	8	0	-0.398870	1.934343	-1.814671
20	6	0	-1.989534	2.385932	2.367408
21	1	0	-2.368347	3.407977	2.333427
22	1	0	-2.730598	1.697457	1.956160
23	1	0	-1.741313	2.111787	3.391205
24	1	0	-0.846173	-0.221545	2.006813



25 1 0 -0.808245 -0.425764 -0.582640

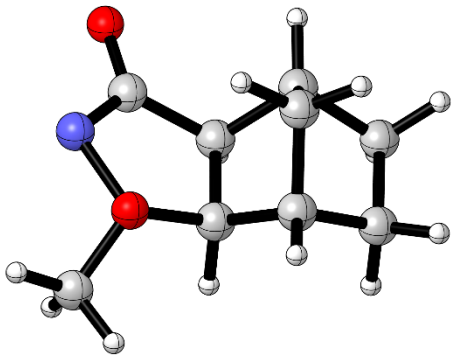


Quantity	Value
Route	#N B3LYP/6-311+G(2d,p) FREQ SCRF=(PCM,Solvent=Acetonitrile) Geom=Conne
Stoichiometry	$C_9H_{13}NO_2$
Symmetry	C1
Basis	6-311+G(2d,p)
RB3LYP Energy	-556.05227638 Hartree
ZPE	0.212701 Hartree
Conditions	298.150K, 1.00000 atm
Internal Energy	-555.829746 Hartree
Enthalpy	-555.828802 Hartree
Free Energy	-555.874492 Hartree
C_v	40.368 cal/mol-K
Entropy	96.163 cal/mol-K
Dipole Moment	11.3900 Debye

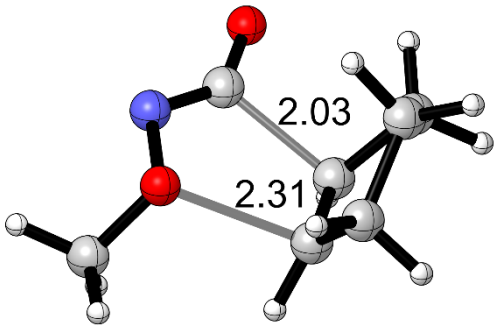
Server	titan.chem.uottawa.ca (5778)
CPU time	13155.6 sec

Input orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.525032
3	6	0	1.470073	0.000000	1.921831
4	6	0	1.993106	-1.417352	1.567153
5	6	0	2.061459	-1.398616	0.007211
6	6	0	1.512488	0.000410	-0.345081
7	6	0	2.093503	0.856314	0.798841
8	1	0	3.183950	0.848391	0.825305
9	1	0	1.748044	1.890815	0.795973
10	1	0	1.719570	0.329534	-1.361243
11	1	0	3.090693	-1.501648	-0.339977
12	1	0	1.477052	-2.198811	-0.449421
13	1	0	2.979518	-1.561885	2.008174
14	1	0	1.345512	-2.206619	1.953583
15	1	0	1.655011	0.303093	2.950768
16	8	0	-0.619740	1.352150	1.860807
17	7	0	-1.156398	2.034953	0.597723
18	6	0	-0.744337	1.272554	-0.412582
19	8	0	-0.957173	1.570024	-1.603335
20	6	0	-1.662708	1.323960	2.881145
21	1	0	-1.960036	2.355496	3.034866
22	1	0	-2.495420	0.718247	2.529642



23	1	0	-1.205874	0.910629	3.776737
24	1	0	-0.625297	-0.741558	2.014765
25	1	0	-0.524401	-0.850161	-0.436789

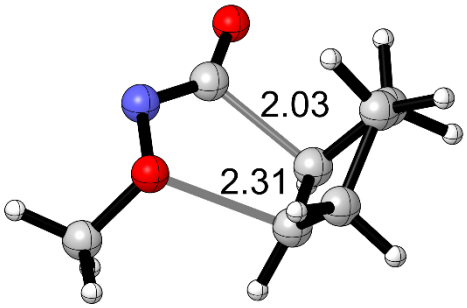


Quantity	Value
Route	#N B3LYP/6-311+G(2d,p) FREQ SCRF=(PCM,Solvent=Acetonitrile) Geom=Conne
Stoichiometry	$C_7H_{11}NO_2$
Symmetry	C1
Basis	6-311+G(2d,p)
RB3LYP Energy	-478.593502355 Hartree
ZPE	0.171874 Hartree
Conditions	298.150K, 1.00000 atm
Internal Energy	-478.412110 Hartree
Enthalpy	-478.411166 Hartree
Free Energy	-478.456322 Hartree
C_v	35.920 cal/mol-K

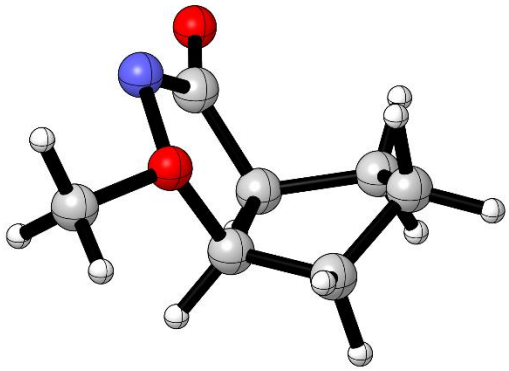
Entropy	95.037 cal/mol-K
Dipole Moment	7.2180 Debye
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CPU time	2843.3 sec

Input orientation:

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3	6	0	1.394570	0.000000	1.936698
4	6	0	2.275797	0.297564	0.700234
5	6	0	1.432522	-0.205478	-0.492607
6	1	0	1.639608	0.322288	-1.427845
7	1	0	1.604358	-1.275628	-0.673333
8	1	0	3.260519	-0.173945	0.759541
9	1	0	2.429211	1.379868	0.614697
10	1	0	1.532606	0.694906	2.771298
11	1	0	1.595688	-1.010069	2.329164
12	8	0	-0.552768	2.224948	1.701170
13	7	0	-0.694284	2.705486	0.400610
14	6	0	-0.371427	1.917040	-0.568659
15	8	0	-0.211632	1.973373	-1.761408
16	6	0	-1.794170	2.375059	2.410597
17	1	0	-2.084337	3.429140	2.437081
18	1	0	-2.585121	1.782693	1.938464
19	1	0	-1.595675	2.014463	3.421770



20	1	0	-0.872457	-0.185896	1.997724
21	1	0	-0.850934	-0.375168	-0.563226

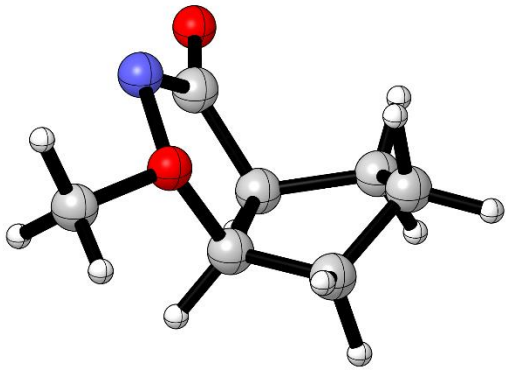


Quantity	Value
Route	#N B3LYP/6-311+G(2d,p) FREQ SCRF=(PCM,Solvent=Acetonitrile) Geom=Conne
Stoichiometry	$C_7H_{11}NO_2$
Symmetry	C1
Basis	6-311+G(2d,p)
RB3LYP Energy	-478.623442032 Hartree
ZPE	0.176706 Hartree
Conditions	298.150K, 1.00000 atm
Internal Energy	-478.437725 Hartree
Enthalpy	-478.436781 Hartree
Free Energy	-478.481042 Hartree
C_v	35.016 cal/mol-K
Entropy	93.154 cal/mol-K

Dipole Moment	11.3953 Debye
Server	10.72.192.49 (11291)
CPU time	3407.8 sec

Input orientation:

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4	6	0	2.210503	0.647399	0.822307
5	6	0	1.488545	0.106344	-0.423328
6	1	0	1.613063	0.734073	-1.305736
7	1	0	1.864389	-0.888563	-0.671601
8	1	0	3.272882	0.403644	0.834549
9	1	0	2.121611	1.735757	0.874539
10	1	0	1.576490	0.492696	2.950974
11	1	0	1.745810	-1.044939	2.108182
12	8	0	-0.605309	1.368833	1.840195
13	7	0	-1.250179	1.980525	0.596231
14	6	0	-0.843690	1.213059	-0.411834
15	8	0	-1.127895	1.460660	-1.598509
16	6	0	-1.560013	1.379936	2.941847
17	1	0	-1.851897	2.415430	3.078402
18	1	0	-2.413645	0.756005	2.684713
19	1	0	-1.029204	1.005335	3.813306
20	1	0	-0.655951	-0.723302	1.996421
21	1	0	-0.481114	-0.884202	-0.416704



6.3 Supporting Information for Chapter 3

6.3.1 General Procedures

General Procedure A: Cascade Substitution/Hydroamination of *N*-Oxyureas

To an oven-dried microwave vial was weighed the allylamine (1.00 equiv.). Phenyl hydroxycarbamate **1a** (1.00 equiv), trifluoromethanesulfonamide (0.50 equiv), EtOAc (0.2 M), and a stir bar were added. The vial was sealed with a microwave cap, purged with argon, and heated to 175 °C via microwave irradiation for 20 min-2.5 h. The reaction mixture was then concentrated under reduced pressure. Purification was performed by flash chromatography.

General procedure B: Synthesis of secondary amines

To a round bottom flask was added 5-bromopent-1-ene (1.0 equiv) followed by dilution in EtOH (2.5 M). A primary amine (5.0 equiv) and NaI (0.05 equiv) were added, and the mixture was heated to reflux for 4 h. Upon completion, the reaction was concentrated via rotary evaporation. The reaction mixture was diluted with DCM and was extracted using 1M KOH (x1), then water (x1), and then brine (x1). The organic phase was dried with Na_2SO_4 and filtered. The filtrate was concentrated via rotary evaporation and the product was isolated using silica-gel flash column chromatography.

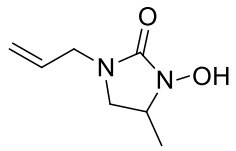
General procedure C: Redox-enabled hydroamination sequence

To a clean dry microwave vial was added the corresponding secondary amine **5** (1.0 equiv) followed by dilution with TFE (0.1 M). UHP was then added (1.2 equiv). The vial was sealed then stirred at 50 °C for 16 h. The reaction vessel was opened and $B_2(OH)_4$ (1.2 equiv for alkyl – substituted amines or 2.2 equiv for Lewis – base – substituted amines) was added. The vial was resealed then stirred at 50 °C for 1 h. The crude reaction mixture was concentrated via rotary evaporation, then diluted with DCM (50 mL) and water (50 mL). 10 mL of 1M HCl was added, and the phases were separated. 15 mL of 1M KOH was added to the aqueous phase, which was then extracted with DCM twice (50 mL each). The combined organic phases were washed with brine, dried over Na_2SO_4, then filtered before concentration via rotary evaporation. The crude product did not require any further purification.

General procedure D: Robustness screen[220]

To a clean dry microwave vial was added additive (0.1 mmol, 1.0 equiv), followed by amine **5a** (17.5 mg, 0.1 mmol) in a solution of TFE (0.1 M). UHP was then added (11.3 mg, 0.12 mmol). The vial was sealed then stirred at 50 °C for 16 h. The reaction vessel was opened and $B_2(OH)_4$ (10.8 mg, 0.12 mmol) was added. The vial was resealed then stirred at 50 °C for 1 h. The crude reaction mixture was concentrated via rotary evaporation, then 1,3,5-trimethoxybenzene (16.8 mg, 0.1 mmol) in a solution of $CDCl_3$ (0.2 M) was added to the crude reaction mixture. ^{1}H NMR spectra were obtained and the integration of diagnostic signals for the additive and for pyrrolidine **10a** were attained to find the amount (%) of both species. When the additive was volatile and no signals for this species could be observed, no amount remaining is reported. However, when the additive was somewhat volatile and signals for this species could be observed, likely in reduced quantities due to evaporation, the amount remaining is reported.

6.3.2 Characterization



1-Allyl-3-hydroxy-4-methylimidazolidin-2-one (2a)

The title compound was synthesized according to general procedure **A** using phenyl *N*-hydroxycarbamate **1a** (0.061 g, 0.400 mmol), diallylamine (0.039 g, 0.400 mmol), and trifluoromethanesulfonamide (0.030 g, 0.200 mmol) in EtOAc (2.0 mL, 0.20 M). The vial was sealed with a microwave cap, purged, then heated for 1 h at 175 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (50% EtOAc/Hexane then 100% EtOAc). The title compound was obtained as an amorphous white solid (0.039 g, 62%).

TLC R*f:* 0.57 in 100% EtOAc.

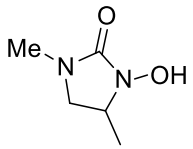
[220] Collins, K. D.; Glorius, F. *Nat. Chem.* **2013**, *5*, 597.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (br s, 1H), 5.72 (ddt, *J* = 17.6, 9.8, 6.1 Hz, 1H), 5.23-5.18 (m, 2H), 3.91 (ddt, *J* = 15.4, 5.9, 1.5 Hz, 1H), 3.72 (ddt, *J* = 15.4, 6.3, 1.3 Hz, 1H), 3.59 (ddt, *J* = 9.5, 7.7, 6.1 Hz, 1H), 3.35 (dd, *J* = 8.7, 7.7 Hz, 1H), 2.82 (dd, *J* = 9.5, 8.7 Hz, 1H), 1.33 (d, *J* = 6.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2 (C), 132.2 (CH), 118.4 (CH_2), 55.4 (CH), 47.8 (CH_2), 46.7 (CH_2), 16.7 (CH_3).

IR (FTIR): 3198, 2973, 2898, 1690, 1490, 1449, 1258, 977 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_7H_{12}N_2O_2$ $[M]^+$: 156.0899. Found: 156.0918.



3-Hydroxy-1,4-dimethylimidazolidin-2-one (2b)

The title compound was synthesized according to general procedure **A** using phenyl *N*-hydroxycarbamate **1a** (0.061 g, 0.400 mmol), *N*-methylallylamine (0.028 g, 0.400 mmol), and trifluoromethanesulfonamide (0.030 g, 0.200 mmol) in EtOAc (2.0 mL, 0.20 M). The vial was sealed with a microwave cap, purged, then heated for 2.5 h at 175 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (65% EtOAc/Hexane then 100% EtOAc). The title compound was obtained as an amorphous white solid (0.020 g, 38%).

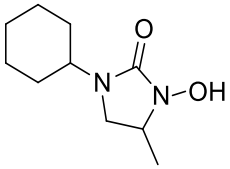
TLC R*f:* 0.12 in 100% EtOAc.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (br s, 1H), 3.58 (ddq, *J* = 9.5, 7.7, 6.1 Hz, 1H), 3.38 (dd, *J* = 8.5, 7.7 Hz, 1H), 2.85 (dd, *J* = 9.5, 8.5 Hz, 1H), 2.82 (s, 3H), 1.30 (d, *J* = 6.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7 (C), 55.3 (CH), 50.5 (CH), 31.1 (CH_3), 16.7 (CH_3).

IR (FTIR): 3196, 2906, 1694, 1497, 1404, 1261, 1015 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_5H_{10}N_2O_2$ $[M]^+$: 130.0742. Found: 130.0758.



1-Cyclohexyl-3-hydroxy-4-methylimidazolidin-2-one (2c)

The title compound was synthesized according to general procedure **A** using phenyl *N*-hydroxycarbamate **1a** (0.061 g, 0.400 mmol), *N*-cyclohexylallylamine (0.056 g, 0.400 mmol), and trifluoromethanesulfonamide (0.030 g, 0.200 mmol) in EtOAc (2.0 mL, 0.20 M). The vial was sealed with a microwave cap, purged, then heated for 20 min at 175 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (65% EtOAc/Hexane then 75% EtOAc/Hexane). The title compound was obtained as an amorphous white solid (0.039 g, 49%).

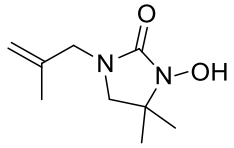
TLC R*f*: 0.34 in 75% EtOAc/Hexane.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (br s, 1H), 3.72 (tt, *J* = 11.6, 3.8 Hz, 1H), 3.51 (ddq, *J* = 9.5, 7.7, 6.1 Hz, 1H), 3.33 (dd, *J* = 8.5, 7.7 Hz, 1H), 2.81 (dd, *J* = 9.5, 8.5 Hz, 1H), 1.81-1.64 (m, 5H), 1.39-1.24 (m, 7H), 1.12-1.01 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 163.8 (C), 55.9 (CH), 51.6 (CH), 44.0 (CH_2), 30.2 (CH_2), 29.8 (CH_2), 25.4 (CH_2), 25.4 (CH_2), 25.3 (CH_2), 16.7 (CH_3).

IR (FTIR): 3189, 2924, 2853, 1690, 1484, 1436, 1254 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{10}H_{18}N_2O_2$ $[M]^+$: 198.1368. Found: 198.1348.



3-Hydroxy-4,4-dimethyl-1-(2-methylallyl)imidazolidin-2-one (2d)

The title compound was synthesized according to general procedure **A** using phenyl *N*-hydroxycarbamate **1a** (0.061 g, 0.400 mmol), bis(2-methyl)allylamine (0.050 g, 0.400 mmol), and trifluoromethanesulfonamide (0.030 g, 0.200 mmol) in EtOAc (2.0 mL, 0.20 M). The vial was sealed with a microwave cap, purged, then heated for 1 h at 175 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (60% EtOAc/Hexane). The title compound was obtained as an amorphous white solid (0.054 g, 72%).

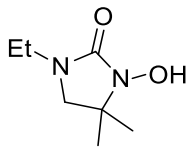
TLC R*f*: 0.62 in 100% EtOAc.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 (br s, 1H), 4.90-4.84 (m, 2H), 3.75 (s, 2H), 2.95 (s, 2H), 1.69 (s, 3H), 1.30 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 163.0 (C), 140.2 (C), 113.4 (CH_2), 59.4 (C), 53.9 (CH_2), 50.1 (CH_2), 22.7 (CH_3), 19.9 (CH_3).

IR (FTIR): 3199, 2988, 2969, 2916, 2854, 1686, 1482, 1317, 948 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_9H_{16}N_2O_2$ $[M]^+$: 184.1212. Found: 184.1187.



1-Ethyl-3-hydroxy-4,4-dimethylimidazolidin-2-one (2e)

The title compound was synthesized according to general procedure **A** using phenyl *N*-hydroxycarbamate **1a** (0.061 g, 0.400 mmol), *N*-ethyl(2-methyl)allylamine (0.040 g, 0.400 mmol), and trifluoromethanesulfonamide (0.030 g, 0.200 mmol) in EtOAc (2.0 mL, 0.20 M). The vial was sealed with a microwave cap, purged, then heated for 1 h at 175 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (60% EtOAc/Hexane then 100% EtOAc). The title compound was obtained as an amorphous white solid (0.039 g, 62%).

TLC R*f:* 0.43 in 100% EtOAc.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (br s, 1H), 3.27 (q, *J* = 7.3 Hz, 2H), 3.03 (t, *J* = 7.3 Hz, 2H), 1.30 (s, 1H), 1.10 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.7 (C), 59.5 (C), 53.6 (CH_2), 38.4 (CH_2), 22.4 (CH_3), 12.3 (CH_3).

IR (FTIR): 3178, 2970, 2930, 2856, 1694, 1451, 1441, 1236, 1089, 796 cm^{-1}.

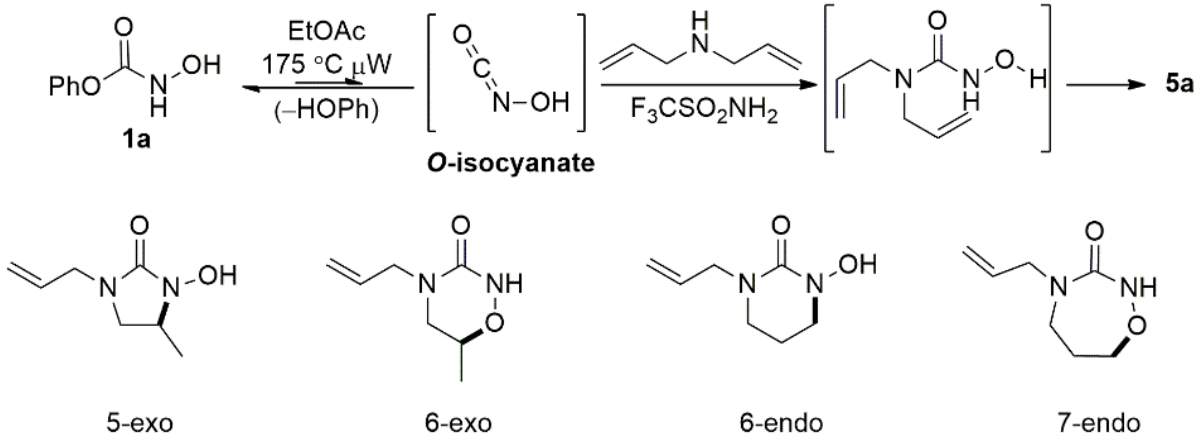
HRMS (EI): Exact mass calcd for $C_7H_{14}N_2O_2$ $[M]^+$: 158.1055. Found: 158.1076.

Structural Assignment of Cyclic *N*-Hydroxyureas

The structural assignment of the cyclic products obtained from the cascade substitution and hydroamination of hydroxy-carbamate *O*-isocyanate precursors was completed as follows.

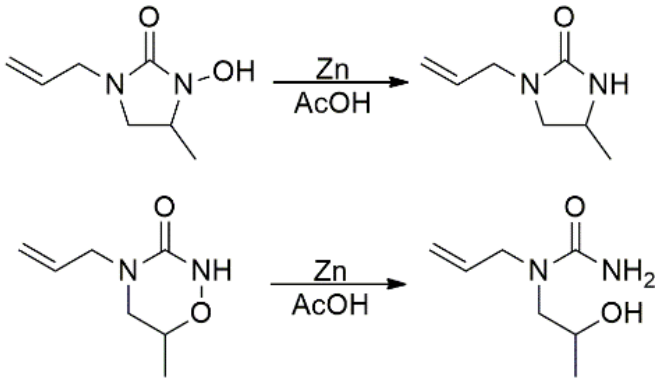
From the given reaction of hydroxy-carbamate 1a, there are 4 possible cyclic urea products that correspond the to found accurate mass of 5a (Found: 156.0918); 5-exo, 6-exo, 6-endo, and 7-endo (Scheme S3).

Scheme S3: Possible Cyclic Urea Products



The ^{1}H NMR of **5a** definitively removes the 6-endo and 7-endo cyclizations as possible products. The 5-exo and 6-exo are more structurally similar, so further derivatization was required. The cleavage of the N-O bond using zinc dust and AcOH was used to conclusively determine the product (**Scheme S4**).

Scheme S4. Reduction of **2a**



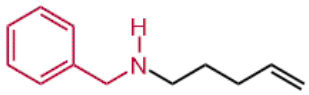
The ^{1}H NMR, ^{13}C NMR, and HRMS all suggest that the cyclic urea is the product of the reduction of **2a** rather than the acyclic urea, allowing the conclusion that the 5-exo cyclic hydroxyurea is the product of the cascade substitution and hydroamination of **1a**.

1-allyl-4-methylimidazolidin-2-one

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.76 (ddt, *J* = 17.1, 10.1, 6.1, 1H), 5.23-5.15 (m, 2H), 4.66 (br s, 1H), 3.86-3.71 (m, 3H), 3.50 (dd, *J* = 8.5, 8.5 Hz, 1H), 2.82 (dd, *J* = 8.7, 6.5 Hz, 1H), 1.24 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 161.7 (C), 133.3 (CH), 117.6 (CH_2), 51.9 (CH), 46.2 (CH_2), 45.6 (CH_2), 21.4 (CH_3).

HRMS (EI): Exact mass calcd for $C_7H_{12}N_2O$ $[M]^+$: 140.0950. Found: 140.0975.

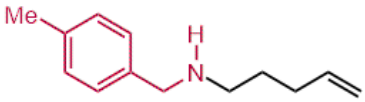


***N*-Benzylpent-4-en-1-amine (5a)**

The title compound was synthesized according to general procedure **B** using 5-bromopent-1-ene (1.49 g, 10.0 mmol), benzylamine (5.50 mL, 50.0 mmol), sodium iodide (0.075 g, 0.05 mmol) in EtOH (2.5 M). The product was purified using silica-gel flash column chromatography (20% EtOAc/Hexanes to 40% EtOAc/Hexanes) to yield the title compound as a yellow oil (1.28 g, 73%). Characterization data is in good agreement with previously reported data.[221]

TLC R*f*: 0.52 in 10% MeOH/DCM

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 – 7.18 (m, 5H), 5.82 (ddt, *J* = 16.9, 10.1, 6.6 Hz, 1H), 4.84 – 5.11 (m, 2H), 3.80 (s, 2H), 2.73 – 2.58 (m, 2H), 2.11 (dtt, *J* = 8.0, 6.6, 1.4 Hz, 2H), 1.63 (p, *J* = 7.4 Hz, 2H).



***N*-(4-Methylbenzyl)pent-4-en-1-amine (5d)**

The title compound was synthesized according to general procedure **B** using 5-bromopent-1-ene (1.01 g, 6.80 mmol), *p*-tolylmethanamine (4.33 mL, 34.0 mmol), sodium iodide (0.102 g, 0.680 mmol) in EtOH (2.5 M). The product was purified using silica-gel flash column chromatography (20% EtOAc/Hexanes + 1% Et_3N) to yield the title compound as a yellow oil (1.09 g, 85%).

TLC R*f*: 0.28 in 30% EtOAc/Hexanes

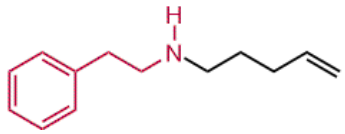
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.12 (m, 2H), 7.05 (m, 2H), 5.73 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 4.93 (dq, *J* = 17.1, 1.7 Hz, 1H), 4.87 (ddt, *J* = 10.1, 2.2, 1.3 Hz, 1H), 3.66 (s, 2H), 2.60 – 2.52 (m, 2H), 2.25 (s, 3H), 2.06 – 1.97 (m, 2H), 1.52 (p, *J* = 7.3 Hz, 2H) , 1.21 (br s, 1H).

[221] Y. -H. Wang, J. -L. Ye, A. -E. Wang and P. -Q. Huang, *Org. Biomol. Chem.* 2012, **10**, 6504.

^{13}C NMR (125 MHz, $CDCl_3$): δ 138.6 (CH), 137.6 (C), 136.4 (C), 129.1 (CH), 128.1 (CH), 114.6 (CH_2), 53.8 (CH_2), 48.9 (CH_2), 31.6 (CH_2), 29.4 (CH_2), 21.1 (CH_3).

IR (FTIR): 3316, 3001, 2922, 1639, 1513, 1448, 1113, 908, 802 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{13}H_{19}N$ [M]+ 189.1517. Found: 189.1515.



***N*-Phenethylpent-4-en-1-amine (5e)**

The title compound was synthesized according to general procedure **B** using 5-bromopent-1-ene (2.51 g, 16.8 mmol), 2-phenylethane-1-amine (10.6 mL, 84.2 mmol), sodium iodide (0.252 g, 1.68 mmol) in EtOH (2.5 M). The product was purified using silica-gel flash column chromatography (20% EtOAc/Hexanes + 1% Et_3N) to yield the title compound as a yellow oil (0.59 g, 61%).

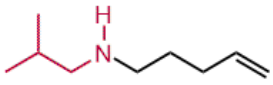
TLC R*f*: 0.43 in 10% MeOH/DCM

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29 – 7.15 (m, 2H), 7.18 – 7.09 (m, 3H), 5.72 (ddt, *J* = 16.9, 10.1, 6.7 Hz, 1H), 4.95 – 4.88 (m, 1H), 4.86 (ddt, *J* = 10.2, 2.2, 1.2 Hz, 1H), 2.85 – 2.68 (m, 4H), 2.62 – 2.50 (m, 2H), 2.04 – 1.91 (m, 2H), 1.49 (p, *J* = 7.4 Hz, 2H), 1.26 (s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 140.1 (C), 138.4 (CH), 128.7 (CH), 128.5 (CH), 126.2 (CH), 114.67 (CH_2), 51.2 (CH_2), 49.3 (CH_2), 36.4 (CH_2), 31.6 (CH_2), 29.2 (CH_2).

IR (FTIR): 3030, 3021, 2917, 2801, 1636, 1464, 1451, 1126, 906, 742, 696 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{13}H_{19}N$ [M]+ 189.1517. Found: 189.1535.



***N*-Isobutylpent-4-en-1-amine (5f)**

The title compound was synthesized according to general procedure **B** using 5-bromopent-1-ene (1.01 g, 6.80 mmol), isobutylamine (3.38 mL, 34.0 mmol), sodium iodide (0.102 g, 0.680 mmol) in EtOH (2.5 M). The product was purified using silica-gel flash column chromatography (20% EtOAc/Hexanes + 1% Et_3N) to yield the title compound as a yellow oil (0.59 g, 61%).

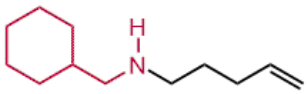
TLC R*f*: 0.30 in 30% EtOAc/Hexanes

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.82 – 5.70 (m, 1H), 4.95 (dq, *J* = 17.1, 1.6 Hz, 1H), 4.88 (ddt, *J* = 10.1, 2.3, 1.3 Hz, 1H), 2.53 (td, *J* = 7.3, 1.9 Hz, 2H), 2.34 (dt, *J* = 6.8, 1.3 Hz, 2H), 2.07 – 1.98 (m, 2H), 1.68 (dpd, *J* = 13.4, 6.7, 1.7 Hz, 1H), 1.52 (pd, *J* = 7.4, 1.8 Hz, 2H), 1.31 (br s, 1H), 0.83 (dt, *J* = 6.5, 1.3 Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 138.6 (CH), 114.6 (CH_2), 58.1 (CH_2), 49.6 (CH_2), 31.6 (CH_2), 29.3 (CH_2), 28.3 (CH), 20.7 (CH_3).

IR (FTIR): 3325, 3074, 2952, 2869, 1640, 1465, 1126, 990, 908, 734 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_9H_{18}N$ [M – H]+ 140.1439. Found: 140.1432.



***N*-(Cyclohexylmethyl)pent-4-en-1-amine (5g)**

The title compound was synthesized according to general procedure **B** using 5-bromopent-1-ene (1.49 g, 10.0 mmol), cyclohexylmethanamine (6.51 mL, 50.0 mmol), sodium iodide (0.150 g, 1.00 mmol) in EtOH (2.5 M). The product was purified using silica-gel flash column chromatography (80% EtOAc/Hexanes) to yield the title compound as a yellow oil (1.75 g, 96%).

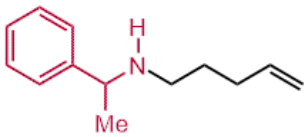
TLC R*f*: 0.33 in 30% EtOAc/Hexanes

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.75 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 4.95 (dq, *J* = 17.1, 1.7 Hz, 1H), 4.88 (ddt, *J* = 10.2, 2.3, 1.3 Hz, 1H), 2.56 – 2.49 (m, 2H), 2.36 (d, *J* = 6.7 Hz, 2H), 2.06 – 1.98 (m, 2H), 1.71 – 1.55 (m, 5H), 1.52 (p, *J* = 7.4 Hz, 2H), 1.44 – 1.32 (m, 1H), 1.25 – 1.01 (m, 4H), 0.83 (qd, *J* = 12.5, 3.8 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 138.6 (CH), 114.6 (CH_2), 56.9 (CH_2), 49.7 (CH_2), 38.0 (CH), 31.7 (CH_2), 31.5 (CH_2), 29.3 (CH_2), 26.7 (CH_2), 26.1 (CH_2).

IR (FTIR): 3081, 2919, 2848, 1639, 1445, 1127, 909 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{12}H_{24}N$ [M+H]+ 182.1909. Found: 182.1903.



***N*-(1-Phenylethyl)pent-4-en-1-amine (5h)**

The title compound was synthesized according to general procedure **B** using 5-bromopent-1-ene (1.49 g, 10.0 mmol), 1-phenylethanamine (6.40 mL, 50.0 mmol), sodium iodide (0.075 g, 0.50 mmol) in EtOH (2.5 M). The product was purified using silica-gel flash column chromatography (60% EtOAc/Hexanes) to yield the title compound as a yellow oil (1.76 g, 93%).

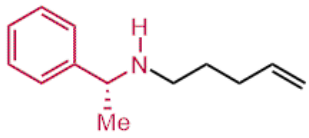
TLC R*f*: 0.37 in 60% EtOAc/Hexanes

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 – 7.28 (m, 4H), 7.26 – 7.20 (m, 1H), 5.78 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 4.98 (ap dq, *J* = 17.2, 1.7 Hz, 1H), 4.92 (ddt, *J* = 10.2, 2.2, 1.3 Hz, 1H), 3.75 (q, *J* = 6.6 Hz, 1H), 2.52 (ddd, *J* = 11.4, 7.9, 6.3 Hz, 1H), 2.43 (ddd, *J* = 11.4, 7.9, 6.8 Hz, 1H), 2.05 (dddt, *J* = 10.8, 5.6, 2.8, 1.4 Hz, 2H), 1.64 – 1.47 (m, 2H), 1.35 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 145.8 (C), 138.5 (CH), 128.4 (CH), 126.8 (CH), 126.5 (CH), 114.5 (CH_2), 58.3 (CH), 47.3 (CH_2), 31.6 (CH_2), 29.4 (CH_2), 24.4 (CH_3).

IR (FTIR): 3027, 3017, 2956, 2931, 2805, 1637, 1456, 1447, 1132, 910, 761, 697 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{13}H_{18}N$ [M-H]+ 188.1439. Found: 188.1449.



(*R*)-*N*-(1-Phenylethyl)pent-4-en-1-amine (5i)

The title compound was synthesized according to general procedure **B** using 5-bromopent-1-ene (0.745 g, 5.00 mmol), (*R*)-1-phenylethanamine (3.22 mL, 25.0 mmol), sodium iodide (0.038 g, 0.25 mmol) in EtOH (2.5 M). The product was purified using silica-gel flash column chromatography (25% EtOAc/Hexanes + 1% NEt_3) to yield the title compound as a yellow oil (0.830 g, 88%).

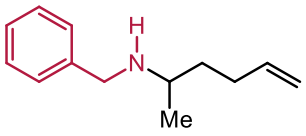
TLC R*f*: 0.30 in 20% EtOAc/Hexanes + 1% NEt_3

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 – 7.29 (m, 4H), 7.25 – 7.20 (m, 1H), 5.78 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 4.99 (ap dq, *J* = 17.1, 1.7 Hz, 1H), 4.93 (ddt, *J* = 10.2, 2.3, 1.3 Hz, 1H), 3.75 (q, *J* = 6.6 Hz, 1H), 2.52 (ddd, *J* = 11.4, 7.9, 6.3 Hz, 1H), 2.43 (ddd, *J* = 11.4, 7.9, 6.8 Hz, 1H), 2.14 – 1.98 (m, 2H), 1.62 – 1.50 (m, 2H), 1.35 (d, *J* = 6.6 Hz, 3H).

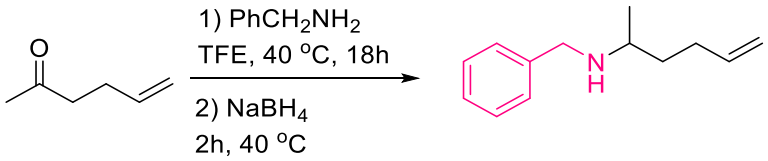
^{13}C NMR (100 MHz, $CDCl_3$): δ 145.8 (C), 138.5 (CH), 128.4 (CH), 126.8 (CH), 126.5 (CH), 114.5 (CH_2), 58.3 (CH), 47.3 (CH_2), 31.5 (CH_2), 29.5 (CH_2), 24.4 (CH_3).

IR (FTIR): 3028, 2956, 2915, 2810, 1637, 1447, 1124, 906, 761, 697 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{13}H_{18}N$ [M – H]+ 188.1439. Found: 188.1418.



***N*-Benzylhex-5-en-2-amine (5j)**



To a vial was added a solution of hex-5-en-2-one (1.0 mL, 8.6 mmol) and TFE (17 mL), which was stirred at rt for 18 h. Then, benzylamine (1.0 mL, 9.5 mmol) was added and the mixture vigorously stirred overnight. Then, $NaBH_4$ (0.39 g, 10 mmol) was added. After completion of the reaction, as monitored by TLC, the reaction mixture was filtered, washing with TFE (17 mL). The filtrate was concentrated via rotary evaporation, and the crude product was purified using silica-gel flash column chromatography (20% EtOAc/petroleum ether + 1% NEt_3). Characterization data is in good agreement with previously reported data.[222]

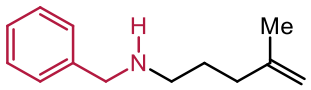
TLC R*f*: 0.34 in 20% EtOAc/Petroleum ether + 1% NEt_3

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 – 7.21 (m, 4H), 7.21 – 7.12 (m, 1H), 5.74 (ddt, *J* = 16.9, 10.1, 6.6 Hz, 1H), 5.06 – 4.74 (m, 2H), 3.76 (d, *J* = 12.9 Hz, 1H), 3.67 (d, *J* = 13.0 Hz, 1H), 2.64 (h, *J* = 6.3 Hz, 1H), 2.03 (ddddd, *J* = 15.7, 13.2, 8.0, 6.6, 1.4 Hz, 2H), 1.57 – 1.46 (m, 1H), 1.36 (m, 2H), 1.03 (d, *J* = 6.3 Hz, 3H).

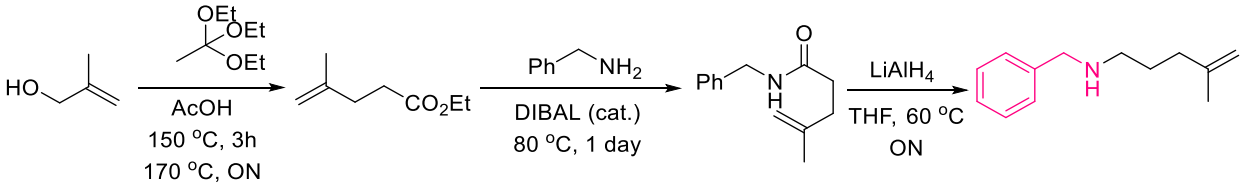
^{13}C NMR (125 MHz, $CDCl_3$): δ 140.8 (C), 138.8 (CH), 128.4 (CH), 128.2 (CH), 126.9 (CH), 114.5 (CH_2), 52.1 (CH), 51.4 (CH_2), 36.2 (CH_2), 30.3 (CH_2), 20.3 (CH_3).

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[222] C. Quinet, P. Jourdain, C. Hermans, A. Ates, I. Lucas, I. E. Markó, *Tetrahedron,* **2008**, *64*, 1077-1087.



_N_-Benzyl-4-methylpent-4-en-1-amine (5k)



Ethyl 4-methylpent-4-enoate was prepared using a literature procedure. The obtained crude product (2.10 g, 98%) was used next step without further purification.[223] To a vial was added benzylamine (0.60 mL, 5.50 mmol) and 1M DIBAL in THF solution (1.0 mL, 1.0 mmol), which was stirred at rt. After 5 minutes, ethyl 4-methylpent-4-enoate (711 mg, 5 mmol) was added and the mixture was vigorously stirred at 80 °C for 24 h. Upon completion by TLC, the mixture was transferred to a 100 mL round bottomed flask and the vial was rinsed with additional THF (15 mL) and cooled to 0 °C. $LiAlH_4$ was added slowly to the flask. The reaction mixture was allowed to warm to room temperature, then was and stirred overnight at 60 °C. The reaction was quenched by cooling to 0 °C and adding sequentially water (1 mL per g $LiAlH_4$), then 15% aqueous NaOH (1 mL per g $LiAlH_4$), then water (3 mL per g $LiAlH_4$), then saturated Rochelle's solution (50 mL). The solution was allowed to stir for 1 h then filtered, washing with EtOAc. The filtrate was added into an extraction funnel and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine, then dried over Na_2SO_4, and concentrated via rotary evaporation. The crude product was purified by alumina column chromatography (20% EtOAc/hexanes + 1% NEt_3) to yield the title compound as a yellow oil (0.53 g, 56% over 3 steps). Characterization data is in good agreement with previously reported data.[224]

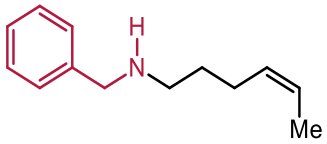
TLC R*f*: 0.20 in 20% EtOAc/Petroleum ether + 1% NEt_3

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30 – 7.22 (m, 4H), 7.22 – 7.12 (m, 1H), 4.67 – 4.56 (m, 2H), 3.71 (s, 2H), 2.62 – 2.48 (m, 2H), 2.04 – 1.92 (m, 2H), 1.64 (s, 3H), 1.64 – 1.52 (m, 2H).

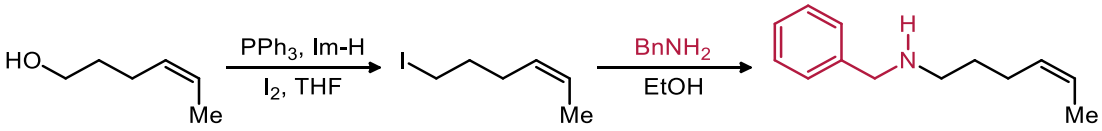
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[223] Adrio, L. A.; Quek, L. S.; Taylor, J. G.; Hii, K. K. *Tetrahedron* **2009**, *65*, 10334-10338.
[224] A. J. Musacchio, B. C. Lainhart, X. Zhang, S. G. Naugib, T. C. Sherwood, R. R. Knowles, *Science* **2017**, *355*, 727.

^{13}C NMR (75 MHz, $CDCl_3$): δ 145.6 (C), 140.4 (C), 128.4 (CH), 128.1 (CH), 126.9 (CH), 110.0 (CH_2), 54.0 (CH_2), 49.1 (CH_2), 35.5 (CH_2), 28.0 (CH_2), 22.4 (CH_3).



(*Z*)-*N*-Benzylhex-4-en-1-amine (5l')



The title compound was synthesized according to a two-step procedure. To a round bottom flask was added (*Z*)-hex-4-en-1-ol (1.002 g, 10.00 mmol) followed by dilution in THF (0.2 M). PPh_3 (3.147 g, 12.00 mmol), then imidazole (2.042 g, 30.00 mmol) were added, and the mixture was cooled to 0 °C. Iodine (2.785 g, 11.00 mmol) was then added. The reaction mixture was stirred at 0 °C for 30 min then rt for 30 min. Upon completion, the reaction was concentrated via rotary evaporation. The reaction mixture was diluted with EtOAc and was extracted using water (x1) and then brine (x1). The organic phase was dried with Na_2SO_4 and filtered. The filtrate was concentrated via rotary evaporation and $OPPh_3$ was removed from the mixture via recrystallization using Et_2O/hexanes. The filtrate was concentrated, and this product was used without further purification. Then, the amine was alkylated according to a modified general procedure **B** using the crude 6-iodohex-2-ene, *N*-benzylamine (5.50 mL, 50.0 mmol) in EtOH (2.5 M). The product was purified using silica-gel flash column chromatography (20% EtOAc/Hexanes + 1% NEt_3) to yield the title compound as a yellow oil (0.397 g, 21% over two steps).

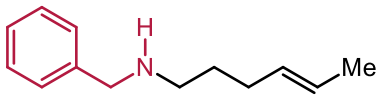
TLC R*f*: 0.38 in 20% EtOAc/Hexanes + 1% NEt_3

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 – 7.30 (m, 4H), 7.29 – 7.20 (m, 1H), 5.52 – 5.32 (m, 2H), 3.79 (s, 2H), 2.65 (dd, *J* = 7.2 Hz, 2H), 2.14 – 2.04 (m, 2H), 1.64-1.53 (m, 5H).

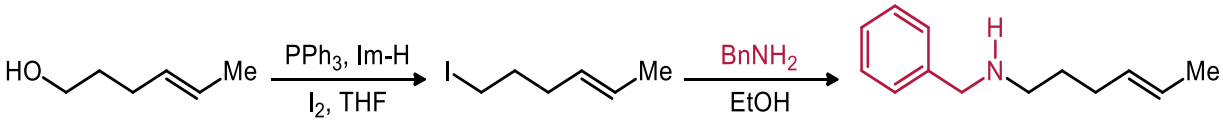
^{13}C NMR (125 MHz, $CDCl_3$): δ 140.5 (C), 130.1 (CH), 128.4 (CH), 128.1 (CH), 126.8 (CH), 124.2 (CH), 54.1 (CH_2), 49.1 (CH_2), 29.9 (CH_2), 24.6 (CH_2), 12.7 (CH_3).

IR (FTIR): 3012, 2923, 2807, 1653, 1494, 1452, 1117, 1028 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{13}H_{19}N$ [M]+ 189.1517. Found: 189.1503.



(*E*)-*N*-Benzylhex-4-en-1-amine (5l'')



The title compound was synthesized according to a two-step procedure. To a round bottom flask was added (*E*)-hex-4-en-1-ol (1.502 g, 15.00 mmol) followed by dilution in THF (0.2 M). PPh_3 (4.721 g, 18.00 mmol), then imidazole (3.064 g, 45.00 mmol) were added, and the mixture was cooled to 0 °C. Iodine (4.177 g, 16.50 mmol) was then added. The reaction mixture was stirred at 0 °C for 30 min then rt for 30 min. Upon completion, the reaction was concentrated via rotary evaporation. The reaction mixture was diluted with EtOAc and was extracted using water (x1) and then brine (x1). The organic phase was dried with Na_2SO_4 and filtered. The filtrate was concentrated via rotary evaporation and $OPPh_3$ was removed from the mixture via recrystallization using Et_2O/hexanes. The filtrate was concentrated, and this product was used without further purification. Then, the amine was alkylated according to a modified general procedure **B** using the crude 6-iodohex-2-ene, *N*-benzylamine (8.20 mL, 75.0 mmol) in EtOH (2.5 M). The product was purified using silica-gel flash column chromatography (20% EtOAc/Hexanes + 1% NEt_3) to yield the title compound as a yellow oil (1.174 g, 41% over two steps).

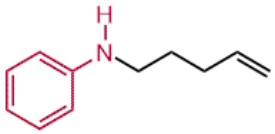
TLC R*f*: 0.75 in 10% MeOH/DCM

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 – 7.30 (m, 4H), 7.27 – 7.21 (m, 1H), 5.49 – 5.32 (m, 2H), 3.78 (s, 2H), 2.63 (t, *J* = 7.1 Hz, 2H), 2.05 – 1.99 (m, 2H), 1.63 (dt, *J* = 4.8, 1.2 Hz, 3H), 1.57 (p, J = 7.4 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 140.5 (C), 130.9 (CH), 128.4 (CH), 128.1 (CH), 126.9 (CH), 125.1 (CH), 54.0 (CH_2), 48.9 (CH_2), 30.3 (CH_2), 29.8 (CH_2), 17.0 (CH_3).

IR (FTIR): 3022, 2916, 2851, 2810, 1602, 1494, 1452, 1116, 1028, 963 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{13}H_{19}N$ [M]+ 189.1517. Found: 189.1508.



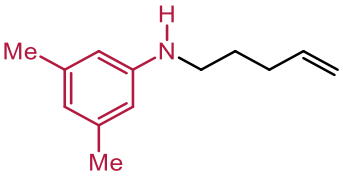
_N_-(Pent-4-en-1-yl)aniline (5m)

The title compound was synthesized according to general procedure **B** using 5-bromopent-1-ene (0.745 g, 5.0 mmol), aniline (2.3 mL, 25.0 mmol), sodium iodide (0.38 g, 0.25 mmol) in EtOH (2.5 M). The product was purified using silica gel flash column chromatography (5% EtOAc/Hexanes) to yield the title compound as a yellow oil (0.667 g, 83%). Characterization data is in good agreement with previously reported data.[225]

TLC R*f*: 0.39 in 5% EtOAc/Hexanes

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22 – 7.11 (m, 2H), 6.72 – 6.68 (m, 1H), 6.63 – 6.58 (m, 2H), 5.85 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 4.98 – 5.14 (m, 2H), 3.64 (br s, 1H), 3.15 (t, *J* = 7.1 Hz, 2H), 2.31 – 2.08 (m, 2H), 1.73 (p, *J* = 7.2 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ148.4 (C), 138.1 (CH), 129.3 (CH), 117.2 (CH), 115.1 (CH_2), 112.8 (CH), 43.4 (CH_2), 31.3 (CH_2), 28.7 (CH_2).



3,5-Dimethyl-*N*-(pent-4-en-1-yl)aniline (5n)

The title compound was synthesized according to general procedure **B** using 5-bromopent-1-ene (1.193 g, 8.0 mmol), 3,5-dimethylaniline (5.00 mL, 40.0 mmol), sodium iodide (0.600 g, 0.400 mmol) in EtOH (2.5 M). The product was purified using silica gel flash column chromatography (5% EtOAc/Hexanes) to yield the title compound as an orange-brown oil (1.134 g, 75%).

TLC R*f*: 0.37 in 5% EtOAc/Hexanes

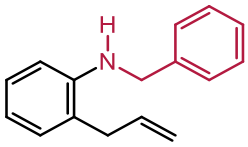
[225] T. Brown, M. Cumbes, L. J. Diorazio, G. J. Clarkson and M. Wills, *J. Org. Chem.* **2017**, *82*, 10489.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.37 (s, 1H), 6.26 (s, 1H), 5.85 (ddt, J = 16.9, 10.2, 6.6 Hz, 1H), 5.13 – 4.94 (m, 2H), 3.12 (t, J = 7.1 Hz, 2H), 2.25 (s, 6H), 2.21 – 2.15 (m, 2H), 1.72 (p, J = 7.2 Hz, 2H).

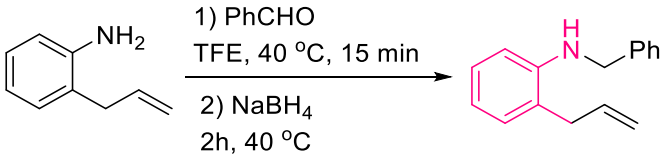
^{13}C NMR (100 MHz, $CDCl_3$): δ 148.4 (C), 138.9 (C), 138.1 (CH), 119.3 (CH), 115.0 (CH_2), 110.8 (CH), 43.5 (CH_2), 31.3 (CH_2), 28.7 (CH_2), 21.5 (CH_3).

IR (FTIR): 3396, 3014, 2917, 2854, 1599, 1513, 1472, 1337, 1185, 990, 908, 818 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{13}H_{19}N$ [M]+ 189.1517. Found:189.1488.



2-Allyl-*N*-benzylaniline (5o)



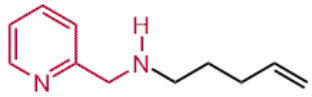
To a clean dry microwave vial was added a solution of benzaldehyde (0.3 mL, 3 mmol) and TFE (6 mL) and was magnetically stirred at RT. After 5 minutes, the respective *o*-allylanline (3 mmol) was added and the mixture vigorously stirred. After stirring for overnight, $NaBH_4$ (0.14 g, 3.6 mmol) was added. After completion of the reaction, as monitored by TLC, the mixture was filtered, washing with TFE (6 mL). The filtrate was concentrated via rotary evaporation and the crude product was purified using silica-gel flash column chromatography (30% toluene/petroleum ether). Characterization data is in good agreement with previously reported data.[226]

TLC R*f*: 0.38 in 30% Toluene/Petroleum ether

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 – 7.24 (m, 4H), 7.20 (tdd, *J* = 10.0, 4.2, 2.7 Hz, 1H), 7.11 – 6.95 (m, 2H), 6.64 (td, *J* = 7.4, 1.2 Hz, 1H), 6.59 – 6.49 (m, 1H), 5.88 (ddt, *J* = 16.6, 10.3, 6.2 Hz, 1H), 5.10 – 4.94 (m, 2H), 4.27 (s, 2H), 4.07 (br s, 1H), 3.24 (dt, *J* = 6.2, 1.7 Hz, 2H).

[226] H. Shen, Q. Deng, R. Liu, Y. Feng, C. Zheng, Y. Xiong, *Org. Chem. Front.,* 2017, **4**, 1806-1811.

^{13}C NMR (75 MHz, $CDCl_3$): δ 146.1 (C), 139.4 (C), 136.0 (CH), 129.8 (CH), 128.6 (CH), 127.7 (CH), 127.4 (CH), 127.2 (CH), 123.6 (C), 117.4 (CH), 116.4 (CH_2), 110.8 (CH), 48.2 (CH_2), 36.6 (CH_2).



***N*-(Pyridin-2-ylmethyl)pent-4-en-1-amine (5p)**

The title compound was synthesized according to general procedure **B** using 5-bromopent-1-ene (1.49 g, 10.0 mmol), pyridine-2-ylmethanamine (5.20 mL, 50.0 mmol), sodium iodide (0.075 g, 0.50 mmol) in EtOH (2.5 M). The product was purified using silica-gel flash column chromatography (8% MeOH/DCM to 12% MeOH/DCM) to yield the title compound as an orange oil (1.39 g, 79%).

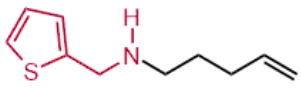
TLC R*f*: 0.40 in 10% MeOH/DCM

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1H), 7.63 (td, *J* = 7.6, 1.8 Hz, 1H), 7.30 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.15 (ddd, *J* = 7.6, 4.9, 1.2 Hz, 1H), 5.80 (ddt, *J* = 16.9, 10.1, 6.6 Hz, 1H), 5.01 (ap dq, *J* = 17.1, 1.7 Hz, 1H), 4.94 (ddt, *J* = 10.2, 2.2, 1.3 Hz, 1H), 3.90 (s, 2H), 2.67 (t, *J* = 7.3 Hz, 2H), 2.14 (br s, 1H), 2.11 (dtt, *J* = 8.0, 6.6, 1.5 Hz, 3H), 1.64 (p, *J* = 7.4 Hz, 2H).

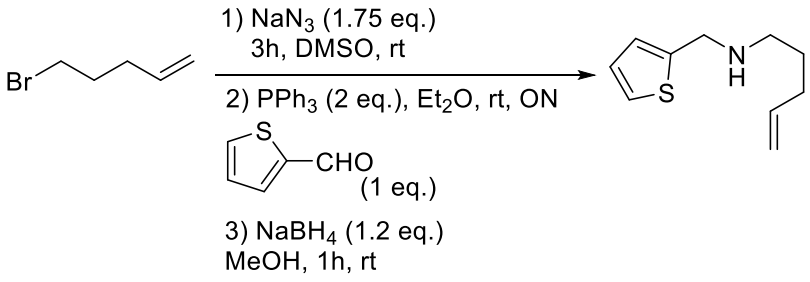
^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7 (C), 149.3 (CH), 138.4 (CH), 136.4 (CH), 122.2 (CH), 121.9 (CH), 114.6 (CH_2), 55.2 (CH_2), 49.1 (CH_2), 31.5 (CH_2), 29.2 (CH_2).

IR (FTIR): 3083, 2912, 1636, 1588, 1470, 1434, 1129, 991, 911, 747 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{11}H_{15}N_2$ [M – H]+ 175.1235. Found: 175.1232.



***N*-(Thiophen-2-ylmethyl)pent-4-en-1-amine (5q)**



To a round bottom flask was added 5-bromopent-1-ene (1.01 g, 6.8 mmol) followed by dilution in DMSO (1 M). NaN_3 (0.771 g, 11.9 mmol) was added and the mixture was stirred at room temperature for 3 h until the solution gets cloudy. Upon completion, the reaction mixture was poured into water (50 mL) and extracted with Et_2O (50 mL x 2), then the organic layer was dried through Na_2SO_4. PPh_3 (3.56 g, 13.6 mmol) and thiophene – 2 – carbaldehyde (0.76 g, 6.8 mmol) were added to the ether solution and the mixture was stirred over night at room temperature. The reaction mixture was concentrated via rotary evaporation and added MeOH (20 mL) followed by $NaBH_4$ (0.308 g, 8.13 mmol). The mixture was stirred at room temperature for 1h. Upon completion, HCl 1 M (20 mL) and H_2O (30 mL) were added, the slurry mixture was filtered to remove phosphine-based by-products. The acidic solution was extracted with Et_2O (50 mL) to remove other impurities and then basified by NaOH 1M (25 mL). The basic solution was extracted by DCM (50 mL x 2), then the DCM layer was rinsed with water (x1), and then brine (x1). The organic phase was dried with Na_2SO_4 and filtered. The filtrate was concentrated via rotary evaporation. The product was purified using silica-gel flash column chromatography (20% EtOAc/Hexanes + 1% Et_3N) to yield the title compound as a yellow oil (0.43 g, 37%).

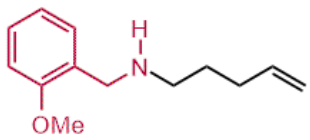
TLC R*f*: 0.44 in 30% EtOAc/Hexanes

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.13 (dd, *J* = 5.0, 1.3 Hz, 1H), 6.95 – 6.78 (m, 2H), 5.74 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 4.94 (ddt, *J* = 17.1, 2.0, 1.6 Hz, 1H), 4.88 (ddt, *J* = 10.1, 2.0, 1.2 Hz, 1H), 3.91 (d, *J* = 0.8 Hz, 2H), 2.72 – 2.50 (m, 2H), 2.03 (dtt, *J* = 7.9, 6.6, 1.4 Hz, 2H), 1.63 – 1.46 (m, 2H), 1.31 (br s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 144.3 (C), 138.4 (CH), 126.5 (CH), 124.6 (CH), 124.2 (CH), 114.6 (CH_2), 48.5 (CH_2), 48.3 (CH_2), 31.4 (CH_2), 29.1 (CH_2).

IR (FTIR): 3309, 3070, 2919, 2812, 1639, 1437, 1108, 908, 691 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{10}H_{15}NS$ [M]+ 181.0925. Found: 181.0940.



***N*-(2-Methoxybenzyl)pent-4-en-1-amine (5r)**

The title compound was synthesized according to general procedure **B** using 5-bromopent-1-ene (1.013 g, 6.80 mmol), (2-methoxyphenyl)methanamine (4.44 mL, 34.0 mmol), sodium iodide (0.102 g, 0.680

mmol) in EtOH (2.5 M). The product was purified using silica-gel flash column chromatography (20% EtOAc/Hexanes + 1% Et_3N) to yield the title compound as a yellow oil (0.904 g, 65%).

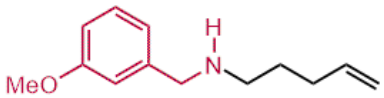
TLC R*f*: 0.25 in 30% EtOAc/Hexanes

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20 – 7.12 (m, 2H), 6.84 (td, *J* = 7.4, 1.1 Hz, 1H), 6.79 (dd, *J* = 8.6, 1.1 Hz, 1H), 5.74 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 4.93 (dq, *J* = 17.1, 1.7 Hz, 1H), 4.87 (ddt, *J* = 10.2, 2.3, 1.3 Hz, 1H), 3.76 (s, 3H), 3.71 (s, 2H), 2.54 (t, *J* = 7.2 Hz, 2H), 2.06 – 1.98 (m, 2H), 1.54 (m, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 157.7 (C), 138.7 (CH), 129.8 (CH), 128.6 (C), 128.1 (CH), 120.4 (CH), 114.5 (CH_2), 110.2 (CH), 55.2 (CH_3), 49.4 (CH_2), 48.8 (CH_2), 31.6 (CH_2), 29.3 (CH_2).

IR (FTIR): 3332, 3074, 2926, 2835, 1639, 1600, 1490, 1237, 1029, 908, 749 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{13}H_{19}NO$ [M]+ 205.1467. Found: 205.1459.



***N*-(3-Methoxybenzyl)pent-4-en-1-amine (5s)**

The title compound was synthesized according to general procedure **B** using 5-bromopent-1-ene (1.01 g, 6.80 mmol), (3-methoxyphenyl)methanamine (4.35 mL, 34.0 mmol), sodium iodide (0.102 g, 0.680 mmol) in EtOH (2.5 M). The product was purified using silica-gel flash column chromatography (20% EtOAc/Hexanes + 1% Et_3N) to yield the title compound as a yellow oil (0.97 g, 69%).

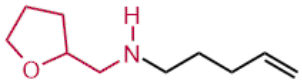
TLC R*f*: 0.3 in 30% EtOAc/Hexanes

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.19 – 7.12 (m, 1H), 6.85 – 6.79 (m, 2H), 6.71 (ddd, *J* = 8.2, 2.6, 1.0 Hz, 1H), 5.74 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 4.94 (dq, *J* = 17.1, 1.7 Hz, 1H), 4.87 (ddt, *J* = 10.2, 2.3, 1.3 Hz, 1H), 3.73 (s, 3H), 3.69 (s, 2H), 2.60 – 2.53 (m, 2H), 2.07 – 1.99 (m, 2H), 1.54 (p, *J* = 7.4 Hz, 2H), 1.20 (s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 159.8 (C), 142.3 (C), 138.6 (CH), 129.4 (CH), 120.4 (CH), 114.6 (CH_2), 113.6 (CH), 112.4 (CH), 55.2 (CH_3), 54.0 (CH_2), 49.0 (CH_2), 31.6 (CH_2), 29.3 (CH_2).

IR (FTIR): 3310, 3075, 2925, 2831, 1584, 1451, 1260, 1152, 1042, 908, 775, 691 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{13}H_{19}NO$ [M]+ 205.1467. Found: 205.1489.



***N*-((Tetrahydrofuran-2-yl)methyl)pent-4-en-1-amine (5t)**

The title compound was synthesized according to general procedure **B** using 5-bromopent-1-ene (1.49 g, 10.0 mmol), (tetrahydrofuran-2-yl)methanamine (5.20 mL, 50.0 mmol), sodium iodide (0.075 g, 0.50 mmol) in EtOH (2.5 M). The product was purified using silica-gel flash column chromatography (12% MeOH/DCM) to yield the title compound as a pale yellow oil (1.03 g, 61%).

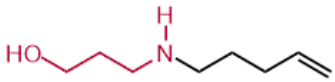
TLC R*f*: 0.31 in 10% MeOH/DCM

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.80 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.00 (ap dq, *J* = 17.1, 1.7 Hz, 1H), 4.94 (ddt, *J* = 10.2, 2.2, 1.3 Hz, 1H), 4.00 (qd, *J* = 7.3, 3.9 Hz, 1H), 3.84 (dt, *J* = 8.4, 6.7 Hz, 1H), 3.73 (dt, *J* = 8.3, 6.8 Hz, 1H), 2.72 – 2.56 (m, 4H), 2.13 – 2.03 (m, 2H), 1.96 (dddd, *J* = 11.5, 8.5, 6.7, 5.1 Hz, 1H), 1.91 – 1.82 (m, 2H), 1.65 – 1.43 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.5 (CH), 114.5 (CH_2), 78.2 (CH), 67.8 (CH_2), 54.4 (CH_2), 49.6 (CH_2), 31.5 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 25.7 (CH_2).

IR (FTIR): 3054, 2959, 2912, 2847, 1637, 1462, 1129, 1056, 996, 905, 737 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{10}H_{18}NO$ [M – H]+ 168.1388. Found: 168.1387.



3-(Pent-4-en-1-ylamino)propan-1-ol (5u)

The title compound was synthesized according to general procedure **B** using 5-bromopent-1-ene (1.01 g, 6.80 mmol), (3-methoxyphenyl)methanamine (2.59 mL, 34.0 mmol), sodium iodide (0.102 g, 0.680 mmol) in EtOH (2.5 M). The product was purified using silica-gel flash column chromatography (40% MeOH/DCM + 1% NH_4OH) to yield the title compound as a yellow oil (0.45 g, 46%).

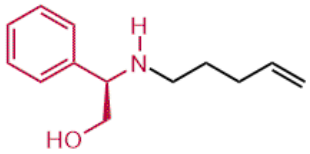
TLC R*f*: 0.32 in 40% MeOH/DCM + 1% NH_4OH

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.79 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.01 (dq, *J* = 17.1, 1.7 Hz, 1H), 4.96 (dq, *J* = 10.1, 1.4 Hz, 1H), 3.83 – 3.77 (m, 2H), 3.07 (br s, 2H), 2.90 – 2.84 (m, 2H), 2.62 (t, *J* = 7.1 Hz, 2H), 2.13 – 2.04 (m, 2H), 1.69 (p, *J* = 5.5 Hz, 2H), 1.57 (p, *J* = 7.3 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 138.2 (CH), 114.9 (CH_2), 64.6 (CH_2), 50.2 (CH_2), 49.2 (CH_2), 31.4 (CH_2), 30.6 (CH_2), 29.0 (CH_2).

IR (FTIR): 3268, 3071, 2924, 2833, 1639, 1437, 1114, 1060, 907 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_8H_{18}NO$ [M+H]+ 144.1388. Found: 144.1360.



(*R*)-2-(Pent-4-en-1-ylamino)-2-phenylethanol (5v)

The title compound was synthesized according to general procedure **B** using 5-bromopent-1-ene (0.745 g, 5.00 mmol), (*R*)-2-amino-2-phenylethanol (3.43 g, 25.0 mmol), sodium iodide (0.038 g, 0.025 mmol) in EtOH (2.5 M). The product was purified using silica-gel flash column chromatography (70% EtOAc/Hexanes) to yield the title compound as a pale yellow oil (0.615 g, 60%).

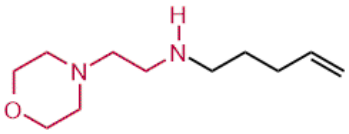
TLC R*f*: 0.35 in 70% EtOAc/Hexanes

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 – 7.30 (m, 2H), 7.30 – 7.24 (m, 3H), 5.78 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 4.99 (ap dq, *J* = 17.1, 1.7 Hz, 1H), 4.94 (ddt, *J* = 10.2, 2.3, 1.4 Hz, 1H), 3.75 (dd, *J* = 8.5, 4.5 Hz, 1H), 3.70 (dd, *J* = 10.5, 4.5 Hz, 1H), 3.52 (dd, *J* = 10.5, 8.5 Hz, 1H), 2.59 (dt, *J* = 11.5, 7.1 Hz, 1H), 2.49 (ddd, *J* = 11.5, 7.6, 6.5 Hz, 1H), 2.19 – 1.99 (m, 2H), 1.58 (dddd, *J* = 12.8, 11.2, 9.3, 6.5 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 140.9 (C), 138.4 (CH), 128.6 (CH), 127.6 (CH), 127.0 (CH), 114.7 (CH_2), 66.5 (CH_2), 64.5 (CH), 46.8 (CH_2), 31.4 (CH_2), 29.4 (CH_2).

IR (FTIR): 3336, 3053, 2908, 2823, 1643, 1472, 1449, 1041, 916, 753, 699 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{13}H_{20}NO$ [M+H]+ 206.1545. Found: 206.1555.



***N*-(2-Morpholinoethyl)pent-4-en-1-amine (5w)**

The title compound was synthesized according to general procedure **B** using 5-bromopent-1-ene (1.49 g, 10.0 mmol), 2-morpholinoethanamine (6.60 mL, 50.0 mmol), sodium iodide (0.075 g, 0.50 mmol) in EtOH (2.5 M). The product was adequately pure with further purification yielding the title compound as a yellow oil (1.62 g, 82%).

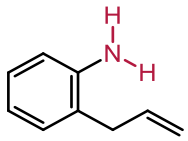
TLC R*f*: 0.50 in 10% MeOH/DCM

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.81 (ddt, *J* = 16.9, 10.1, 6.7 Hz, 1H), 5.01 (ap dq, *J* = 17.1, 1.7 Hz, 1H), 4.94 (ddt, *J* = 10.1, 2.3, 1.2 Hz, 1H), 3.77 – 3.62 (m, 4H), 2.69 (dd, *J* = 6.6, 5.6 Hz, 2H), 2.65 – 2.58 (m, 2H), 2.48 (dd, *J* = 6.6, 5.7 Hz, 2H), 2.45 – 2.35 (m, 4H), 2.15 – 2.03 (m, 2H), 1.65 – 1.49 m, 2H).

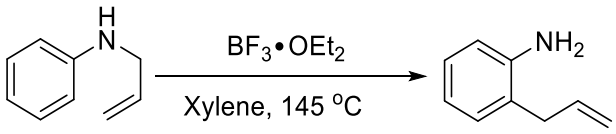
^{13}C NMR (100 MHz, $CDCl_3$): δ 138.4 (CH), 114.6 (CH_2), 67.0 (CH_2), 58.3 (CH_2), 53.7 (CH_2), 49.4 (CH_2), 46.0 (CH_2), 31.5 (CH_2), 29.1 (CH_2).

IR (FTIR): 3085, 2915, 2846, 2813, 1636, 1450, 1270, 1118, 907, 758 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{11}H_{23}N_2O$ [M+H]+ 199.1810. Found: 199.1818.



2-Allylaniline (5x)

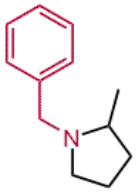


The title compound was prepared using a modified literature procedure to yield the title compound as a yellow oil (0.57 g, 57%). Characterization data is in good agreement with previously reported data.[227]

TLC R*f*: 0.38 in 10% EtOAc/Petroleum ether

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.05 – 6.91 (m, 2H), 6.67 (tt, *J* = 7.4, 1.3 Hz, 1H), 6.59 (d, *J* = 7.8 Hz, 1H), 5.97 – 5.77 (m, 1H), 5.10 – 4.94 (m, 2H), 3.62 – 3.53 (m, 2H), 3.22 (dd, *J* = 6.0, 1.6 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 144.8 (C), 136.0 (CH), 130.2 (CH), 127.6 (CH), 124.0 (C), 118.9 (CH), 116.1 (CH_2), 115.8 (CH), 36.5 (CH_2).



1-Benzyl-2-methylpyrrolidine (10a)

The title compound was synthesized according to general procedure **C** using urea hydrogen peroxide (0.068 g, 0.72 mmol), amine **5a** (0.105 g, 0.60 mmol), $B_2(OH)_4$ (0.064 g, 0.72 mmol) in TFE (0.1 M). The product was isolated after aqueous extraction to yield the title compound as a pale yellow oil (0.090 g, 85%). Characterization data is in good agreement with previously reported data.[228]

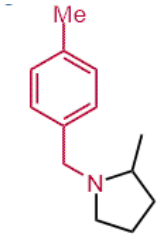
TLC R*f*: 0.45 in 10% MeOH/DCM

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 – 7.29 (m, 4H), 7.25 – 7.22 (m, 1H), 4.02 (d, *J* = 12.8 Hz, 1H), 3.14 (d, *J* = 12.8 Hz, 1H), 2.91 (td, *J* = 10.8, 2.6 Hz, 1H), 2.39 (dq, *J* = 13.5, 6.2 Hz, 1H), 2.10 (q, *J* = 9.0 Hz, 1H), 1.94 (dddd, *J* = 12.5, 9.7, 7.3, 5.3 Hz, 1H), 1.76 – 1.67 (m, 1H), 1.64 (dddd, *J* = 13.8, 8.7, 6.3, 3.3 Hz, 1H), 1.46 (dddd, *J* = 12.5, 10.8, 8.6, 5.8 Hz, 1H), 1.18 (d, *J* = 6.0 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 139.6 (C), 129.1 (CH), 128.2 (CH), 126.8 (CH), 59.6 (CH), 58.4 (CH_2), 54.1 (CH_2), 32.8 (CH_2), 21.5 (CH_2), 19.2 (CH_3).

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[227] S. Fu, S.; H. Yang, G. Li, Y. Deng, H. Jiang, W. Zeng, *Org. Lett.* 2015, **17**, 1018–1021.
[228] J. Zhang and S. Chang, *J. Am. Chem. Soc.* 2020, **142**, 12585.



2-Methyl-1-(4-methylbenzyl)pyrrolidine (10d)

The title compound was synthesized according to general procedure **C** using urea hydrogen peroxide (0.0677 g, 0.72 mmol), amine **5d** (0.114 g, 0.60 mmol), $B_2(OH)_4$ (0.118 g, 1.32 mmol) in TFE (0.1 M). The crude reaction mixture was concentrated via rotary evaporation, then diluted with DCM (50 mL) and water (50 mL). 10 mL of 1 M HCl was added, and the phases were separated. Additional 20 mL of water was added into DCM layer, the aqueous phases were separated and combined. The product was isolated after basic extraction to yield the title compound as a yellow oil (0.076 g, 67%).

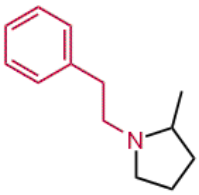
TLC R*f*: 0.39 in 5% MeOH/DCM + 0.5% NH_4OH

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15 – 7.10 (m, 2H), 7.09 – 6.99 (m, 2H), 3.90 (d, *J* = 12.7 Hz, 1H), 3.05 (d, *J* = 12.8 Hz, 1H), 2.82 (ddd, *J* = 9.4, 8.1, 2.6 Hz, 1H), 2.35 – 2.26 (m, 1H), 2.25 (s, 3H), 2.02 (q, *J* = 9.0 Hz, 1H), 1.85 (dddd, *J* = 12.5, 9.7, 7.4, 5.3 Hz, 1H), 1.69 – 1.57 (m, 1H), 1.57 – 1.48 (m, 1H), 1.38 (dddd, *J* = 12.3, 10.8, 8.6, 5.8 Hz, 1H), 1.09 (d, *J* = 6.0 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 136.4 (C), 136.2 (C), 129.1 (CH), 128.9 (CH), 59.6 (CH_3), 57.9 (CH_2), 53.9 (CH_2), 32.8 (CH_2), 21.5 (CH_2), 21.1 (CH), 19.1 (CH_3).

IR (FTIR): 3004, 2960, 2779, 1513, 1373, 1138, 1100, 804 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{13}H_{19}N$ [M]+ 189.1517. Found: 189.1515.



2-Methyl-1-phenethylpyrrolidine (10e)

The title compound was synthesized according to a modified general procedure **C** using urea hydrogen peroxide (0.085 g, 0.90 mmol), amine **5e** (0.114 g, 0.60 mmol), $B_2(OH)_4$ (0.081 g, 0.90 mmol) in TFE (0.1 M). The product was isolated after aqueous extraction to yield the title compound as a pale yellow oil (0.078 g, 68%).

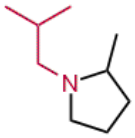
TLC R*f*: 0.45 in 10% MeOH/DCM

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 – 7.25 (m, 2H), 7.22 – 7.15 (m, 3H), 3.26 (td, *J* = 8.7, 2.7 Hz, 1H), 3.03 (td, *J* = 11.5, 5.8 Hz, 1H), 2.83 (pd, *J* = 13.0, 5.6 Hz, 2H), 2.37 – 2.26 (m, 2H), 2.20 (q, *J* = 8.8 Hz, 1H), 1.93 (dddd, *J* = 12.3, 9.7, 7.2, 5.2 Hz, 1H), 1.82 (dddd, *J* = 17.3, 10.8, 8.5, 5.2 Hz, 1H), 1.71 (dddd, *J* = 12.5, 11.4, 6.0, 2.7 Hz, 1H), 1.45 (dddd, *J* = 12.3, 10.6, 8.7, 6.0 Hz, 1H), 1.12 (d, *J* = 6.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 140.7 (C), 128.6 (CH), 128.3 (CH), 126.0 (CH), 60.0 (CH), 56.1 (CH_2), 54.0 (CH_2), 35.5 (CH_2), 32.7 (CH_2), 21.7 (CH_2), 18.93 (CH_3).

IR (FTIR): 3029, 2953, 2775, 1600, 1457, 1451, 1373, 1134, 743, 695 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{13}H_{19}N$ [M]+189.1517. Found: 189.1495.



1-Isobutyl-2-methylpyrrolidine hydrochloride (10f)

The title compound was synthesized according to general procedure **C** using urea hydrogen peroxide (0.0677 g, 0.72 mmol), amine **5f** (0.114 g, 0.60 mmol), $B_2(OH)_4$ (0.118 g, 1.32 mmol) in TFE (0.1 M). The crude reaction mixture was concentrated via rotary evaporation, then diluted with DCM (50 mL) and water (50 mL). 10 mL of 1M HCl was added, and the phases were separated. Additional 20 mL of water was added into DCM layer, the aqueous phases were separated and combined. The product was isolated after basic extraction and direct salt formation in DCM by HCl/dioxane 4 M solution (0.2 mL, 0,8 mmol) to yield the title compound as a white solid (0.079 g, 74%).

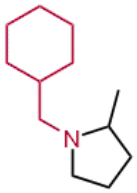
TLC R*f*: 0.18 in 5% MeOH/DCM + 0.5% NH_4OH

^{1}H NMR (500 MHz, CD_3OD): δ 3.75 (ddd, *J* = 11.6, 7.9, 5.5 Hz, 1H), 3.48 (dt, *J* = 9.9, 6.5 Hz, 1H), 3.24 – 3.11 (m, 2H), 2.93 (dd, *J* = 12.8, 5.2 Hz, 1H), 2.31 (dtd, *J* = 13.0, 7.5, 5.0 Hz, 1H), 2.10 (dqt, *J* = 12.0, 8.6, 3.6 Hz, 4H), 1.82 (dq, *J* = 13.1, 9.2 Hz, 1H), 1.49 (d, *J* = 6.5 Hz, 3H), 1.10 (d, *J* = 6.6 Hz, 3H), 1.06 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (125 MHz, CD_3OD): δ 65.8 (CH), 61.1 (CH_2), 53.9 (CH_2), 30.8 (CH_2), 25.5 (CH), 21.0 (CH_2), 19.8 (CH_3), 19.2 (CH_3), 14.6 (CH_3).

IR (FTIR): 3388, 2964, 2873, 2592, 1420, 1047 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_9H_{19}N$ [M]+ 141.1517. Found: 141.1533.



1-(Cyclohexylmethyl)-2-methylpyrrolidine (10g)

The title compound was synthesized according to general procedure **C** using urea hydrogen peroxide (0.0677 g, 0.72 mmol), amine **5g** (0.109 g, 0.60 mmol), $B_2(OH)_4$ (0.118 g, 1.32 mmol) in TFE (0.1 M). The crude reaction mixture was concentrated via rotary evaporation, then diluted with DCM (50 mL) and water (50 mL). 10 mL of 1M HCl was added, and the phases were separated. Additional 20 mL of water was added into DCM layer, the aqueous phases were separated and combined. The product was isolated after basic extraction to yield the title compound as a yellow oil (0.070 g, 64%).

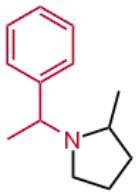
TLC R*f*: 0.38 in 5% MeOH/DCM + 0.5% NH_4OH

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.07 (td, *J* = 8.7, 2.8 Hz, 1H), 2.44 (dd, *J* = 11.9, 9.4 Hz, 1H), 2.22 – 2.10 (m, 1H), 1.97 (q, *J* = 8.9 Hz, 1H), 1.92 – 1.75 (m, 3H), 1.75 – 1.53 (m, 6H), 1.43 – 1.29 (m, 2H), 1.24 – 1.01 (m, 3H), 1.00 (d, *J* = 6.1 Hz, 3H), 0.89 – 0.72 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 61.8 (CH_2), 60.8 (CH), 54.6 (CH_2), 37.1 (CH), 32.6 (CH_2), 32.5 (CH_2), 32.0 (CH_2), 26.8 (CH_2), 26.3 (CH_2), 26.1 (CH_2), 21.8 (CH_2), 19.0 (CH_3).

IR (FTIR): 2958, 2918, 2849, 2779, 1447, 1374, 1170, 1118 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{12}H_{23}N$ [M]+ 181.1830. Found: 181.1821.



2-Methyl-1-(1-phenylethyl)pyrrolidine (10h)

The title compound was synthesized according to general procedure **C** using urea hydrogen peroxide (0.068 g, 0.72 mmol), amine **5h** (0.114 g, 0.60 mmol), $B_2(OH)_4$ (0.065 g, 0.72 mmol) in TFE (0.1 M). The product was isolated after aqueous extraction to yield the title compound as a 2.2:1 diastereomeric mixture and a pale yellow oil (0.098 g, 86%).

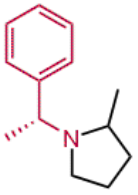
TLC R*f*: 0.40 in 10% MeOH/DCM

^{1}H NMR (500 MHz, $CDCl_3$): δ (*major*) 7.38 – 7.20 (m, 5H), 3.86 (q, *J* = 6.9 Hz, 1H), 2.87 (td, *J* = 8.5, 3.3 Hz, 1H), 2.55 (ap h, *J* = 6.3 Hz, 1H), 2.41 (q, *J* = 8.2 Hz, 1H), 1.82 (ddt, *J* = 11.8, 9.0, 7.3 Hz, 1H), 1.74 (tdd, *J* = 9.3, 7.4, 4.4 Hz, 1H), 1.61 – 1.54 (m, 1H), 1.47 (d, *J* = 6.9 Hz, 3H), 1.43 – 1.39 (m, 1H), 1.11 (d, *J* = 6.1 Hz, 3H). δ (*minor*) 7.38 – 7.20 (m, 5H), 3.68 (q, *J* = 6.7 Hz, 1H), 2.95 – 2.89 (m, 1H), 2.77 (dt, *J* = 9.1, 3.7 Hz, 1H), 2.46 (q, *J* = 8.8 Hz, 1H), 1.92 (ddt, *J* = 12.3, 9.2, 7.7 Hz, 1H), 1.78 – 1.71 (m, 1H), 1.66 (ddd, *J* = 16.0, 7.8, 3.7 Hz, 1H),1.43 – 1.39 (m, 1H), 1.36 (d, *J* = 6.6 Hz, 3H), 0.86 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ (*major*) 140.2 (C), 128.1 (CH), 127.9 (CH), 126.8 (CH), 58.7 (CH), 54.9 (CH), 48.2 (CH_2), 32.6 (CH_2), 21.8 (CH_2), 19.4 (CH_3), 18.4 (CH_3). δ (minor) 141.9 (C), 128.0 (CH), 127.7 (CH), 126.6 (CH), 60.4 (CH), 56.2 (CH), 49.8 (CH_2), 32.9 (CH_2), 22.3 (CH_2), 21.8 (CH_3), 19.0 (CH_3).

IR (FTIR): 3019, 2965, 2875, 2777, 1456, 1449, 1367, 1153, 757, 698 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{13}H_{19}N$ [M]+ 189.1517. Found: 189.1532.



2-Methyl-1-((*R*)-1-phenylethyl)pyrrolidine (10i)

The title compound was synthesized according to a modified general procedure **C** using urea hydrogen peroxide (0.068 g, 0.72 mmol), amine **5i** (0.114 g, 0.60 mmol), $B_2(OH)_4$ (0.118 g, 1.32 mmol) in TFE (0.1 M). The product was isolated after aqueous extraction to yield the title compound as a yellow oil (0.067 g, 59%).

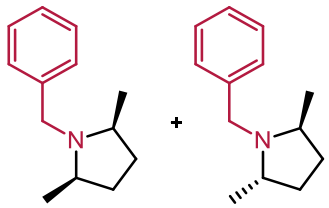
TLC R*f*: 0.40 in 10% MeOH/DCM

^{1}H NMR (500 MHz, $CDCl_3$): δ (*major*) 7.38 – 7.20 (m, 5H), 3.86 (q, *J* = 6.9 Hz, 1H), 2.86 (td, *J* = 8.3, 3.4 Hz, 1H), 2.54 (ap h, *J* = 6.3 Hz, 1H), 2.40 (q, *J* = 8.1 Hz, 1H), 1.82 (ddt, *J* = 11.8, 9.0, 7.3 Hz, 1H), 1.74 (tdd, *J* = 9.3, 7.4, 4.4 Hz, 1H), 1.61 – 1.54 (m, 1H), 1.46 (d, *J* = 6.9 Hz, 3H), 1.43 – 1.39 (m, 1H), 1.10 (d, *J* = 6.1 Hz, 3H). δ (*minor*) 7.38 – 7.20 (m, 5H), 3.67 (q, *J* = 6.6 Hz, 1H), 2.95 – 2.89 (m, 1H), 2.77 (dt, *J* = 8.7, 3.7 Hz, 1H), 2.45 (q, *J* = 8.8 Hz, 1H), 1.92 (ddt, *J* = 12.2, 9.2, 7.7 Hz, 1H), 1.78 – 1.71 (m, 1H), 1.66 (ddd, *J* = 16.0, 7.8, 3.7 Hz, 1H),1.43 – 1.39 (m, 1H), 1.36 (d, *J* = 6.6 Hz, 3H), 0.85 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ (*major*) 140.9 (C), 128.1 (CH), 127.9 (CH), 126.8 (CH), 58.7 (CH), 54.9 (CH), 48.2 (CH_2), 32.5 (CH_2), 21.8 (CH_2), 19.4 (CH_3), 18.4 (CH_3). δ (minor) 141.9 (C), 128.0 (CH), 127.7 (CH), 126.6 (CH), 60.4 (CH), 56.2 (CH), 49.9 (CH_2), 32.9 (CH_2), 22.3 (CH_2), 21.7 (CH_3), 19.0 (CH_3).

IR (FTIR): 3018, 2957, 2865, 2779, 1456, 1450, 1367, 1155, 763, 699 cm^{-1}.

HRMS (ESI): Exact mass calcd for $C_{13}H_{20}N$ [M+H]+ 190.1596. Found: 190.1591.



1-Benzyl-2,5-dimethylpyrrolidine (10j)

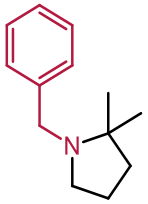
The title compound was synthesized according to general procedure **C** using urea hydrogen peroxide (0.068 g, 0.72 mmol), amine **5j** (0.134 g, 0.60 mmol), $B_2(OH)_4$ (0.118 g, 1.32 mmol) in TFE (0.1 M). The crude reaction mixture was concentrated via rotary evaporation, then diluted with DCM (50 mL) and water (50 mL). 10 mL of 1M HCl was added, and the phases were separated. 15 mL of 1M KOH and 100 mL of brine were added. The product was isolated after 3 x 50 mL DCM extractions to yield the title

compound as a 6.8:1 diastereomeric mixture as a pail yellow oil (0.089 g, 78%). Characterization data is in good agreement with previously reported data.[229]

TLC R*f*: 0.48 in 5% MeOH/DCM + 1% NEt_3

^{1}H NMR (500 MHz, $CDCl_3$): δ (*cis*) 7.25 – 7.09 (m, 5H), 3.65 (s, 2H), 2.55 – 2.44 (m, 2H), 1.74 – 1.64 (m, 2H), 1.34 – 1.23 (m, 2H), 0.97 (d, *J* = 6.1 Hz, 6H). δ (*trans*) 7.41 – 7.00 (m, 5H), 3.75 (d, *J* = 13.8 Hz, 1H), 3.43 (d, *J* = 13.8 Hz, 1H), 2.99 – 2.86 (m, 2H), 1.97 – 1.84 (m, 2H), 1.34 – 1.23 (m, 2H), 0.89 (d, *J* = 6.3 Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ (*cis*) 139.3 (C), 129.3 (CH), 128.0 (CH), 126.7 (CH), 59.7 (CH), 55.2 (CH_2), 31.3 (CH_2), 20.7 (CH_3). δ (*trans*) 140.4 (C), 128.6 (CH), 128.1 (CH), 126.5 (CH), 55.1 (CH), 51.7 (CH_2), 31.0 (CH_2), 17.1 (CH_3).



1-Benzyl-2,2-dimethylpyrrolidine (10k)

The title compound was synthesized according to general procedure **C** using urea hydrogen peroxide (0.068 g, 0.72 mmol), amine **5k** (0.114 g, 0.60 mmol), $B_2(OH)_4$ (0.065 g, 0.72 mmol) in TFE (0.1 M). The crude reaction mixture was concentrated via rotary evaporation, then diluted with DCM (50 mL) and water (50 mL). 10 mL of 1 M HCl was added, and the phases were separated. The product was isolated after basic extraction to yield the title compound as a yellow oil (0.077 g, 68%). Characterization data is in good agreement with previously reported data.[230]

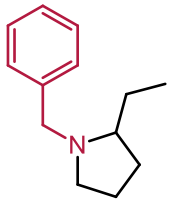
TLC R*f*: 0.34 in 5% MeOH/DCM + 1% NEt_3

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30 – 7.06 (m, 5H), 3.42 (s, 2H), 2.60 – 2.45 (m, 2H), 1.73 – 1.52 (m, 4H), 1.01 (s, 6H).

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[229] C. Quinet, P. Jourdain, C. Hermans, A. Ates, I. Lucas, I. E. Markó,*Tetrahedron,* 2008, **64**, 1077-1087.
[230] A. Agosti, S. Britto, P. Renaud, *Org. Lett.,* 2008, **10**, 1417-1420.

^{13}C NMR (75 MHz, $CDCl_3$): δ 141.0 (C), 128.6 (CH), 128.2 (CH), 126.6 (CH), 60.2 (C), 53.2 (CH_2), 50.9 (CH_2), 40.0 (CH_2), 23.1 (CH_3), 20.5 (CH_2).



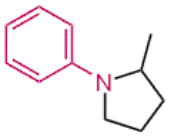
1-Benzyl-2-ethylpyrrolidine (10l)

The title compound was synthesized according to a modified general procedure **C** using urea hydrogen peroxide (0.068 g, 0.72 mmol), amine **5l'** (0.114 g, 0.60 mmol), $B_2(OH)_4$ (0.118 g, 1.32 mmol) in TFE (0.1 M). The product was isolated after aqueous extraction to yield the title compound as a yellow oil (0.053 g, 47%). Characterization data is in good agreement with previously reported data.[231]

TLC R*f*: 0.34 in 10% MeOH/DCM

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 – 7.25 (m, 5H), 4.05 (d, J = 12.9 Hz, 1H), 3.17 (d, J = 12.9 Hz, 1H), 2.93 (ddd, J = 9.1, 7.3, 2.4 Hz, 1H), 2.29 (qd, J = 8.1, 3.1 Hz, 1H), 2.12 (q, J = 9.0 Hz, 1H), 1.93 (dddd, J = 12.3, 9.5, 7.8, 6.0 Hz, 1H), 1.79 (dqd, J = 13.2, 7.5, 3.3 Hz, 1H), 1.72 – 1.59 (m, 2H), 1.51 (dddd, J = 13.2, 10.2, 8.0, 5.3 Hz, 1H), 1.43 – 1.27 (m, 1H), 0.93 (t, J = 7.4 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 139.1 (C), 129.1 (CH), 128.2 (CH), 126.8 (CH), 65.8 (CH), 58.5 (CH_2), 54.2 (CH_2), 29.8 (CH_2), 26.5 (CH_2), 21.8 (CH_2), 10.5 (CH_3).



2-Methyl-1-phenylpyrrolidine (10m)

The title compound was synthesized according to a modified general procedure **C** using urea hydrogen peroxide (0.068 g, 0.72 mmol), amine **5m** (0.097 g, 0.60 mmol), $B_2(OH)_4$ (0.645 g, 0.72 mmol) in TFE (0.1

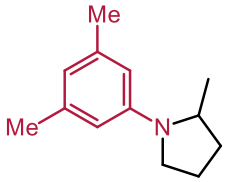
[231] Musacchio, A. J.; Lainhart, B. C.; Zhang, X.; Naguib, S. G.; Sherwood, T. C.; Knowles, R. R. *Science* **2017**, *355*, 727-730.

M). The product was isolated after aqueous extraction to yield the title compound as a brown oil (0.049 g, 51%). Characterization data is in good agreement with previously reported data.[232]

TLC R*f*: 0.91 in 40% EtOAc/Hexanes

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 – 7.19 (m, 2H), 6.67 – 6.59 (m, 1H), 6.61 – 6.52 (m, 2H), 3.88 (pd, *J* = 6.2, 1.6 Hz, 1H), 3.42 (ddd, *J* = 9.2, 7.6, 2.6 Hz, 1H), 3.16 (td, *J* = 8.9, 6.8 Hz, 1H), 2.13 – 2.01 (m, 2H), 1.97 (dddd, *J* = 10.0, 7.4, 5.1, 3.0 Hz, 1H), 1.71 (dddd, *J* = 10.3, 7.8, 6.5, 2.3 Hz, 1H), 1.17 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 147.2 (C), 129.1 (CH), 115.1 (CH), 111.7 (CH), 53.6 (CH), 48.1 (CH_2), 33.1 (CH_2), 23.3 (CH_2), 19.4 (CH_3).



1-(3,5-Dimethylphenyl)-2-methylpyrrolidine (10n)

The title compound was synthesized according to a modified general procedure **C** using urea hydrogen peroxide (0.068 g, 0.72 mmol), amine **5n** (0.114 g, 0.60 mmol), $B_2(OH)_4$ (0.118 g, 1.32 mmol) in TFE (0.1 M). The crude reaction mixture was concentrated via rotary evaporation, then diluted with DCM (50 mL) and brine (50 mL), and the phases were separated. The aqueous phase was then extracted with DCM (50 mL). The combined organic phases were dried over Na_2SO_4, then filtered before concentration via rotary evaporation. The crude reaction mixture was purified by silica plug (100% DCM) to yield the title compound a viscous orange oil (0.054 g, 47%). Characterization data is in good agreement with previously reported data.[233]

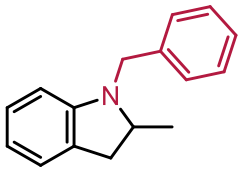
TLC R*f*: 0.84 in 20% EtOAc/Hexanes

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.32 (s, 1H), 6.23 (s, 2H), 3.92 – 3.79 (m, 1H), 3.41 (t, J = 7.7 Hz, 1H), 3.19 – 3.09 (m, 1H), 2.27 (s, 6H), 2.10 – 1.90 (m, 3H), 1.73 – 1.63 (m, 1H), 1.17 (d, J = 6.3 Hz, 3H).

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[232] La, M. T.; Kang, S.; Kim, H. -K. *J. Org. Chem.* 2019, **84**, 6689.
[233] V. H. Tran, M. T. La, S. Kang and H. -K. Kim, *Org. Biomol. Chem.* **2020**,*18*, 5008-5016.

^{13}C NMR (100 MHz, $CDCl_3$): δ 147.4 (C), 138.7 (C), 117.2 (CH), 109.7 (CH), 53.5 (CH), 48.2 (CH_2), 33.0 (CH_2), 23.2 (CH_2), 21.7 (CH_3), 19.5 (CH_3).



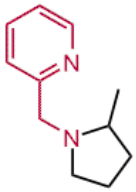
1-Benzyl-2-methylindoline (10o)

The title compound was synthesized according to a modified general procedure **C** using urea hydrogen peroxide (0.068 g, 0.72 mmol), amine **5o** (0.134 g, 0.60 mmol), $B_2(OH)_4$ (0.065 g, 0.72 mmol) in TFE (0.1 M). The crude reaction mixture was concentrated via rotary evaporation, and it was purified by column chromatography (20% toluene/petroleum ether) to yield the title compound as a yellow oil (0.043 g, 32%). Characterization data is in good agreement with previously reported data.[234]

TLC R*f*: 0.3 in 20% Toluene/Petroleum ether

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 – 7.25 (m, 2H), 7.22 (dd, *J* = 8.5, 6.8 Hz, 2H), 7.18 – 7.12 (m, 1H), 6.96 (dd, *J* = 7.1, 1.3 Hz, 1H), 6.93 – 6.86 (m, 1H), 6.54 (td, *J* = 7.3, 1.0 Hz, 1H), 6.23 (d, *J* = 7.8 Hz, 1H), 4.27 (d, *J* = 16.1 Hz, 1H), 4.11 (d, *J* = 16.1 Hz, 1H), 3.64 (ddq, *J* = 9.5, 8.6, 6.1 Hz, 1H), 3.08 (dd, *J* = 15.5, 8.6 Hz, 1H), 2.59 (ddt, *J* = 15.5, 9.5, 1.1 Hz, 1H), 1.21 (d, *J* = 6.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 152.8 (C), 139.3 (C), 128.9 (C), 128.5 (CH), 127.4 (CH), 127.4 (CH), 126.9 (CH), 124.2 (CH), 117.4 (CH), 106.9 (CH), 60.6 (CH), 51.2 (CH_2), 37.5 (CH_2), 19.7 (CH_3).



2-((2-Methylpyrrolidin-1-yl)methyl)pyridine (10p)

[234] A. F. G. Maier, S. Tussing, T. Schneider, U. Flörke, Z.-W. Qu, S. Grimme and J. Paradies, *Angew. Chem. Int. Ed.,* 2016, **10**, 12219–12223.

The title compound was synthesized according to a modified general procedure **C** using urea hydrogen peroxide (0.068 g, 0.72 mmol), amine **5p** (0.106 g, 0.60 mmol), $B_2(OH)_4$ (0.118 g, 1.32 mmol) in TFE (0.1 M). The product was isolated after aqueous extraction to yield the title compound as an orange oil (0.070 g, 66%).

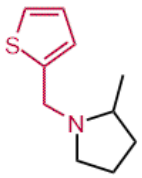
TLC R*f*: 0.29 in 10% MeOH/DCM

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.53 (ddd, *J* = 5.0, 1.9, 0.9 Hz, 1H), 7.63 (td, *J* = 7.6, 1.8 Hz, 1H), 7.14 (dd, *J* = 7.9, 4.6 Hz, 1H), 7.41 (d, *J* = 7.8 Hz, 1H), 4.11 (d, *J* = 13.6 Hz, 1H), 3.38 (d, *J* = 13.6 Hz, 1H), 2.97 (ddd, *J* = 10.6, 8.4, 2.8 Hz, 1H), 2.50 (td, *J* = 12.3, 4.9 Hz, 1H), 2.22 (q, *J* = 8.9 Hz, 1H), 1.95 (dddd, *J* = 12.5, 9.6, 7.3, 5.3 Hz, 1H), 1.80 – 1.71 (m, 1H), 1.71 – 1.58 (m, 1H), 1.47 (dddd, *J* = 12.1, 10.5, 8.5, 6.0 Hz, 1H), 1.15 (d, *J* = 6.1 Hz, 3H),

^{13}C NMR (125 MHz, $CDCl_3$): δ159.7 (C), 149.0 (CH), 136.3 (CH), 123.2 (CH), 121.8 (CH), 60.1 (CH), 60.0 (CH_2), 54.3 (CH_2), 32.6 (CH_2), 21.7 (CH_2), 19.0 (CH_3).

IR (FTIR): 3079, 2954, 2782, 1586, 1569, 1433, 1376, 1134, 991, 757 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{11}H_{16}N_2$ [M]+ 176.1313. Found: 176.1296.



2-Methyl-1-(thiophen-2-ylmethyl)pyrrolidine (10q)

The title compound was synthesized according to general procedure **C** using urea hydrogen peroxide (0.0677 g, 0.72 mmol), amine **5q** (0.109 g, 0.60 mmol), $B_2(OH)_4$ (0.118 g, 1.32 mmol) in TFE (0.1 M). The product was isolated after aqueous extraction to yield the title compound as a yellow oil (0.071 g, 65%).

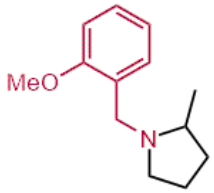
TLC R*f*: 0.46 in 5% MeOH/DCM + 0.5% NH_4OH

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.11 (dd, *J* = 5.1, 1.3 Hz, 1H), 6.85 (dd, *J* = 5.1, 3.4 Hz, 1H), 6.84 – 6.80 (m, 1H), 4.04 (dd, *J* = 14.0, 1.0 Hz, 1H), 3.48 (d, *J* = 14.0 Hz, 1H), 2.95 (td, *J* = 8.7, 2.7 Hz, 1H), 2.40 – 2.28 (m, 1H), 2.16 (q, *J* = 8.9 Hz, 1H), 1.84 (dddd, *J* = 12.5, 9.6, 7.3, 5.2 Hz, 1H), 1.67 (ddtd, *J* = 17.3, 10.8, 8.5, 5.2 Hz, 1H), 1.61 – 1.46 (m, 1H), 1.38 (dddd, *J* = 12.4, 10.8, 8.6, 6.0 Hz, 1H), 1.08 (d, *J* = 6.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 142.1 (C), 126.4 (CH), 125.8 (CH), 124.6 (CH), 58.7 (CH), 53.7 (CH_2), 51.6 (CH_2), 32.8 (CH_2), 21.5 (CH_2), 19.0 (CH_3).

IR (FTIR): 3064, 2959, 2780, 1457, 1374, 1172, 852, 690 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{10}H_{15}NS$ [M]+ 181.0925. Found: 181.0908.



1-(2-Methoxybenzyl)-2-methylpyrrolidine (10r)

The title compound was synthesized according to general procedure **C** using urea hydrogen peroxide (0.0677 g, 0.72 mmol), amine **5r** (0.123 g, 0.60 mmol), $B_2(OH)_4$ (0.118 g, 1.32 mmol) in TFE (0.1 M). The product was isolated after aqueous extraction to yield the title compound as a yellow oil (0.077 g, 63%).

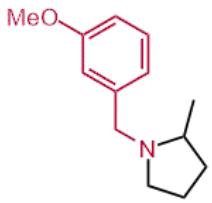
TLC R*f*: 0.29 in 5% MeOH/DCM + 0.5% NH_4OH

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 (dd, *J* = 7.4, 1.8 Hz, 1H), 7.13 (td, *J* = 7.8, 1.8 Hz, 1H), 6.83 (td, *J* = 7.4, 1.1 Hz, 1H), 6.77 (dd, *J* = 8.2, 1.1 Hz, 1H), 3.91 (d, *J* = 13.5 Hz, 1H), 3.73 (s, 3H), 3.24 (d, *J* = 13.4 Hz, 1H), 2.94 (ddd, *J* = 9.3, 8.1, 2.5 Hz, 1H), 2.41 – 2.30 (m, 1H), 2.09 (q, *J* = 9.0 Hz, 1H), 1.84 (dddd, *J* = 12.5, 9.7, 7.3, 5.2 Hz, 1H), 1.73 – 1.58 (m, 1H), 1.60 – 1.46 (m, 1H), 1.37 (dddd, *J* = 12.3, 10.8, 8.7, 5.9 Hz, 1H), 1.11 (d, *J* = 6.0 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 157.7 (C), 130.8 (CH), 127.9 (CH), 127.5 (C), 120.2 (CH), 110.4 (CH), 59.6 (CH), 55.4 (CH), 54.2 (CH_2), 51.5 (CH_2), 32.8 (CH_2), 21.7 (CH_2), 19.2 (CH_3).

IR (FTIR): 3033, 2960, 2873, 1589, 1490, 1237, 1030, 750 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{13}H_{19}NO$ [M]+ 205.1467. Found: 205.1450.



1-(3-Methoxybenzyl)-2-methylpyrrolidine (10s)

The title compound was synthesized according to general procedure **C** using urea hydrogen peroxide (0.0677 g, 0.72 mmol), amine **5s** (0.123 g, 0.60 mmol), $B_2(OH)_4$ (0.118 g, 1.32 mmol) in TFE (0.1 M). The product was isolated after aqueous extraction to yield the title compound as a yellow oil (0.083 g, 67%).

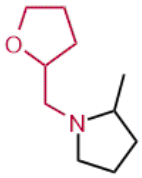
TLC R*f*: 0.32 in 5% MeOH/DCM + 0.5% NH_4OH

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.12 (t, *J* = 7.8 Hz, 1H), 6.85 – 6.79 (m, 2H), 6.69 (ddd, *J* = 8.2, 2.7, 1.0 Hz, 1H), 3.90 (d, *J* = 12.9 Hz, 1H), 3.71 (s, 3H), 3.04 (d, *J* = 12.9 Hz, 1H), 2.84 (ddd, *J* = 9.1, 8.0, 2.6 Hz, 1H), 2.36 – 2.25 (m, 1H), 2.02 (q, *J* = 9.0 Hz, 1H), 1.84 (dddd, *J* = 12.5, 9.7, 7.3, 5.3 Hz, 1H), 1.68 – 1.58 (m, 1H), 1.58 – 1.49 (m, 1H), 1.37 (dddd, *J* = 12.4, 10.8, 8.6, 5.9 Hz, 1H), 1.08 (d, *J* = 6.0 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 159.6 (C), 141.3 (C), 129.1 (CH), 121.5 (CH), 114.6 (CH), 112.2 (CH), 59.7 (CH), 58.4 (CH_2), 55.2 (CH_3), 54.1 (CH_2), 32.8 (CH_2), 21.6 (CH_2), 19.2 (CH_3).

IR (FTIR): 3009, 2957, 2779, 1585, 1486, 1260, 1148, 1042, 770, 692 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{13}H_{19}NO$ [M]+ 205.1467. Found: 205.1439.



2-Methyl-1-((tetrahydrofuran-2-yl)methyl)pyrrolidine (10t)

The title compound was synthesized according to a modified general procedure **C** using urea hydrogen peroxide (0.068 g, 0.72 mmol), amine **5t** (0.102 g, 0.60 mmol), $B_2(OH)_4$ (0.118 g, 1.32 mmol) in TFE (0.1 M). The product was isolated after aqueous extraction to yield the title compound as a 1.1:1 diastereomeric mixture and a yellow oil (0.081 g, 80%).

Note: No common NMR solvents tested gave adequately resolved ^{1}H NMR signals for unambiguous structural determination of the major and minor diastereomers. In $CDCl_3$, one signal was well – resolved: (*minor*) 2.91 (dd, *J* = 12.6, 8.1 Hz, 1H) and (*major*) 2.81 (dd, *J* = 12.4, 5.7 Hz, 1H). In benzene-d_6, three signals were well – resolved: (major) 4.05 (p, *J* = 6.5 Hz, 1H) and (minor) 3.96 (p, *J* = 4.8 Hz, 1H), (major) 3.30 (ddd, *J* = 9.8, 7.9, 2.8 Hz, 1H) and (minor) 3.22 (ddd, *J* = 8.9, 7.7, 3.0 Hz, 1H), (major) 2.76 (dd, *J* = 12.1, 6.5 Hz, 1H) and (minor) 2.85 (dd, *J* = 12.9, 5.8 Hz, 1H).

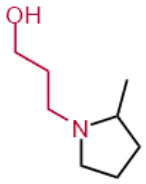
TLC R*f*: 0.26 in 10% MeOH/DCM

^{1}H NMR (500 MHz, benzene-d_6): δ (*major*) 4.05 (p, *J* = 6.5 Hz, 1H), 3.77 – 3.72 (m, 1H), 3.63 – 3.53 (m, 1H), 3.30 (ddd, *J* = 9.8, 7.9, 2.8 Hz, 1H), 2.76 (dd, *J* = 12.1, 6.5 Hz, 1H), 2.38 – 2.27 (m, 1H), 2.27 – 2.18 (m, 1H), 2.15 (q, *J* = 8.8 Hz, 1H), 1.79 – 1.42 (m, 7H), 1.35 – 1.27 (m, 1H), 1.06 (dd, *J* = 6.0 Hz, 3H). δ (*minor*) 3.96 (p, *J* = 4.8 Hz, 1H), 3.77 – 3.72 (m, 1H), 3.63 – 3.53 (m, 1H), 3.22 (ddd, *J* = 8.9, 7.7, 3.0 Hz, 1H), 2.85 (dd, *J* = 12.9, 5.8 Hz, 1H), 2.38 – 2.27 (m, 2H), 2.27 – 2.18 (m, 1H), 1.79 – 1.42 (m, 7H), 1.35 – 1.27 (m, 1H), 1.05 (dd, *J* = 6.0 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ (*1:1 mix of two diastereomers)* 78.5 (CH), 77.5 (CH), 68.0 (CH_2), 67.8 (CH_2), 60.5 (CH, two overlapping signals), 58.9 (CH_2), 58.7 (CH_2), 54.9 (CH_2), 54.6 (CH_2), 32.4 (CH_2), 32.3 (CH_2), 30.5 (CH_2), 30.3 (CH_2), 25.5 (CH_2), 25.3 (CH_2), 21.9 (CH_2), 21.8 (CH_2), 19.0 (CH_3), 18.9 (CH_3).

IR (FTIR): 2953, 2859, 2777, 1545, 1376, 1168, 1056 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{10}H_{19}NO$ [M]+ 169.1467. Found: 169.1477.



3-(2-Methylpyrrolidin-1-yl)propan-1-ol (10u)

The title compound was synthesized according to general procedure **C** using urea hydrogen peroxide (0.0677 g, 0.72 mmol), amine **5u** (0.086 g, 0.60 mmol), $B_2(OH)_4$ (0.118 g, 1.32 mmol) in TFE (0.1 M). The crude reaction mixture was concentrated via rotary evaporation, then diluted with DCM (50 mL) and water (50 mL). 10 mL of 1M HCl was added, and the phases were separated. 15 mL of 1M KOH and

excessive amount of NaCl were added to saturate the acidic solution. The product was isolated after aqueous extraction to yield the title compound as a yellow oil (0.053 g, 62%).

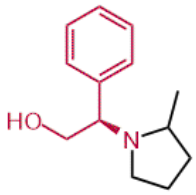
TLC R*f*: 0.46 in 40% MeOH/DCM + 1% NH_4OH

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.69 (s, 1H), 3.78 – 3.68 (m, 2H), 3.26 (ddd, *J* = 9.4, 7.9, 3.2 Hz, 1H), 2.93 (td, *J* = 11.7, 4.1 Hz, 1H), 2.37 – 2.30 (m, 1H), 2.30 – 2.20 (m, 1H), 2.04 (q, *J* = 8.8 Hz, 1H), 1.91 – 1.77 (m, 2H), 1.74 – 1.54 (m, 2H), 1.49 (dp, *J* = 14.7, 3.8 Hz, 1H), 1.33 (dddd, *J* = 12.5, 10.3, 8.5, 6.2 Hz, 1H), 1.08 (d, *J* = 6.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 64.6 (CH_2), 60.4 (CH), 54.2 (CH_2), 54.0 (CH_2), 32.6 (CH_2), 29.1 (CH_2), 21.6 (CH_2), 18.9 (CH_3).

IR (FTIR): 3335, 2955, 2868, 2796, 1374, 1061 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_8H_{17}NO$ [M]+ 143.1310. Found: 143.1330.



(2*R*)-2-(2-methylpyrrolidin-1-yl)-2-phenylethanol (10v)

The title compound was synthesized according to a modified general procedure **C** using urea hydrogen peroxide (0.055 g, 0.60 mmol), amine **5v** (0.102 g, 0.50 mmol), $B_2(OH)_4$ (0.099 g, 1.10 mmol) in TFE (0.1 M). The product was isolated after aqueous extraction to yield the title compound as a 2.6:1 diastereomeric mixture as a yellow oil (0.081 g, 79%). Characterization data is in good agreement with previously reported data for the major diastereomer.[235]

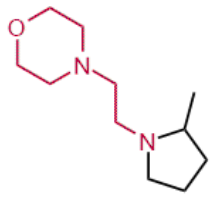
TLC R*f*: 0.31 and 0.53 in 10% MeOH/DCM

^{1}H NMR (500 MHz, benzene-*d*$_6$): δ (*major*) 7.15 – 7.10 (m, 3H), 6.95 – 6.88 (m, 2H), 3.98 – 3.84 (m, 2H), 3.68 (dd, *J* = 9.7, 4.5 Hz, 1H), 2.71 – 2.64 (m, 1H), 2.43 (ap h, *J* = 6.0 Hz, 1H), 2.02 (q, *J* = 8.5 Hz, 1H), 1.48 –

[235] J. M. Andres, I. Herraiz-Sierra, R. Pedrosa and A. Perez-Encabo, *Eur. J. Org. Chem.* 2000, **9**, 1719.

1.39 (m, 2H), 1.20 – 1.07 (m, 2H), 1.00 (d, *J* = 6.0 Hz, 3H). δ (*minor*) 7.31 – 7.20 (m, 2H), 7.15 – 7.10 (m, 3H), 3.98 – 3.84 (m, 1H), 3.75 (dd, *J* = 10.8, 5.7 Hz, 1H), 3.59 (t, *J* = 6.0 Hz, 1H), 2.89 – 2.80 (m, 1H), 2.78 – 2.73 (m, 1H), 2.50 (dt, *J* = 9.1, 7.6 Hz, 1H), 1.63 – 1.48 (m, 2H), 1.37 – 1.27 (m, 1H), 1.20 – 1.07 (m, 1H), 0.83 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ (*major*) 134.9 (C), 129.2 (CH), 128.1 (CH), 127.8 (CH), 67.5 (CH), 62.0 (CH), 60.9 (CH_2), 54.5 (CH_2), 45.3 (CH_2), 32.0 (CH_2), 21.5 (CH_2), 19.1 (CH_3). δ (*minor*) 138.4 (C), 129.0 (CH), 128.4 (CH), 127.8 (CH), 77.2 (CH), 63.4 (CH_2), 55.3 (CH), 52.5 (CH_2), 33.0 (CH_2), 22.4 (CH_2), 20.2 (CH_3).



4-(2-(2-Methylpyrrolidin-1-yl)ethyl)morpholine (10w)

The title compound was synthesized according to a modified general procedure **C** using urea hydrogen peroxide (0.124 g, 1.32 mmol), amine **5w** (0.119 g, 0.60 mmol), $B_2(OH)_4$ (0.172 g, 1.92 mmol) in TFE (0.1 M). The product was isolated after aqueous extraction to yield the title compound as a yellow oil (0.055 g, 46%).

TLC R*f*: 0.25 in 10% MeOH/DCM

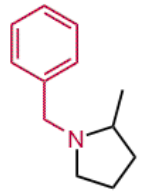
^{1}H NMR (500 MHz, $CDCl_3$): δ 3.71 (t, *J* = 4.7 Hz, 4H), 3.17 (td, *J* = 8.7, 2.8 Hz, 1H), 2.97 (ddd, *J* = 11.7, 8.9, 6.5 Hz, 1H), 2.56 – 2.45 (m, 6H), 2.29 (dt, *J* = 8.5, 6.3 Hz, 1H), 2.19 (ddd, *J* = 11.7, 8.5, 6.4 Hz, 1H), 2.11 (q, *J* = 8.9 Hz, 1H), 1.90 (dddd, *J* = 12.4, 9.7, 7.2, 5.2 Hz, 1H), 1.77 (dddd, *J* = 17.3, 10.8, 8.5, 5.1 Hz, 1H), 1.69 (dddd, *J* = 12.5, 9.6, 6.3, 3.2 Hz, 1H), 1.41 (dddd, *J* = 12.4, 10.6, 8.7, 6.1 Hz, 1H), 1.10 (d, *J* = 6.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 66.9 (CH_2), 60.5 (CH), 58.1 (CH_2), 54.4 (CH_2), 54.2 (CH_2), 51.2 (CH_2), 32.4 (CH_2), 21.7 (CH_2), 18.9 (CH_3).

IR (FTIR): 2936, 2915, 2863, 1637, 1452, 1124, 994, 906, 763, 697 cm^{-1}.

HRMS (EI): Exact mass calcd for $C_{11}H_{22}N_2O$ [M]+ 198.1732. Found: 198.1760.

Gram – scale reaction



1-Benzyl-2-methylpyrrolidine 10a

The title compound was synthesized according to a modified general procedure **C** using urea hydrogen peroxide (0.678 g, 7.20 mmol), amine **5a** (1.05 g, 6.00 mmol), $B_2(OH)_4$ (0.646 g, 7.20 mmol) in TFE (55 mL, 0.11 M). The reaction was stirred in a 55 mL volume screw cap vial (no headspace). The product was isolated after aqueous extraction to yield the title compound as a pale yellow oil (0.904 g, 86%). Characterization data is in good agreement with previously reported data.[236]

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 – 7.29 (m, 4H), 7.25 – 7.22 (m, 1H), 3.96 (d, *J* = 12.8 Hz, 1H), 3.08 (d, *J* = 12.8 Hz, 1H), 2.85 (td, *J* = 10.8, 2.6 Hz, 1H), 2.32 (dq, *J* = 13.5, 6.2 Hz, 1H), 2.04 (q, *J* = 9.0 Hz, 1H), 1.88 (dddd, *J* = 12.5, 9.7, 7.3, 5.3 Hz, 1H), 1.71 – 1.62 (m, 1H), 1.64 (dddd, *J* = 13.8, 8.7, 6.3, 3.3 Hz, 1H), 1.40 (dddd, *J* = 12.5, 10.8, 8.6, 5.8 Hz, 1H), 1.11 (d, *J* = 6.0 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 139.7 (C), 129.1 (CH), 128.1 (CH), 126.7 (CH), 59.6 (CH), 58.3 (CH2), 54.0 (CH2), 32.7 (CH2), 21.5 (CH2), 19.1 (CH3).

1-Benzyl-2-methylpyrrolidine 10a·HCl

To a stirred solution of pyrrolidine **5a** in 10 mL ether was added 1.4 mL of 4M HCl in dioxane dropwise and solids precipitated immediately. The product was isolated after filtration, washing with hexanes, to yield the title compound as a 9.5:1 diastereomeric mixture as a white solid (0.931 g, 73%).

TLC R*f*: 0.31 in 10% MeOH/DCM

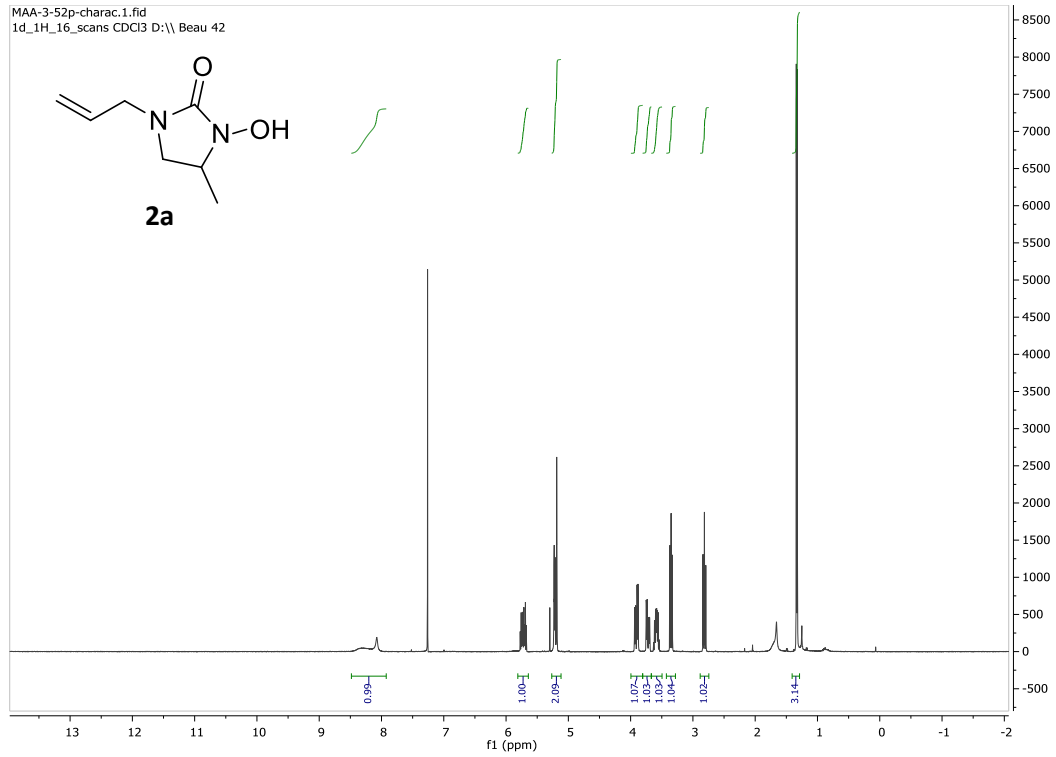
^{1}H NMR (500 MHz, $CDCl_3$): δ (*major*) 12.45 (br s, 1H), 7.61 – 7.57 (m, 2H), 7.47 – 7.41 (m, 3H), 4.33 (dd, *J* = 13.2, 4.5 Hz, 1H), 4.06 (dd, *J* = 13.3, 5.4 Hz, 1H), 3.62 (dq, *J* = 11.7, 6.8, 5.1 Hz, 1H), 3.23 (p, *J* = 7.4 Hz, 1H), 2.83 (p, *J* = 8.5 Hz, 1H), 2.26 – 2.14 (m, 2H), 2.11 – 2.03 (m, 1H), 1.86 (tt, *J* = 13.8, 8.7 Hz, 1H), 1.86 (tt, *J* = 13.8, 8.7 Hz, 1H).

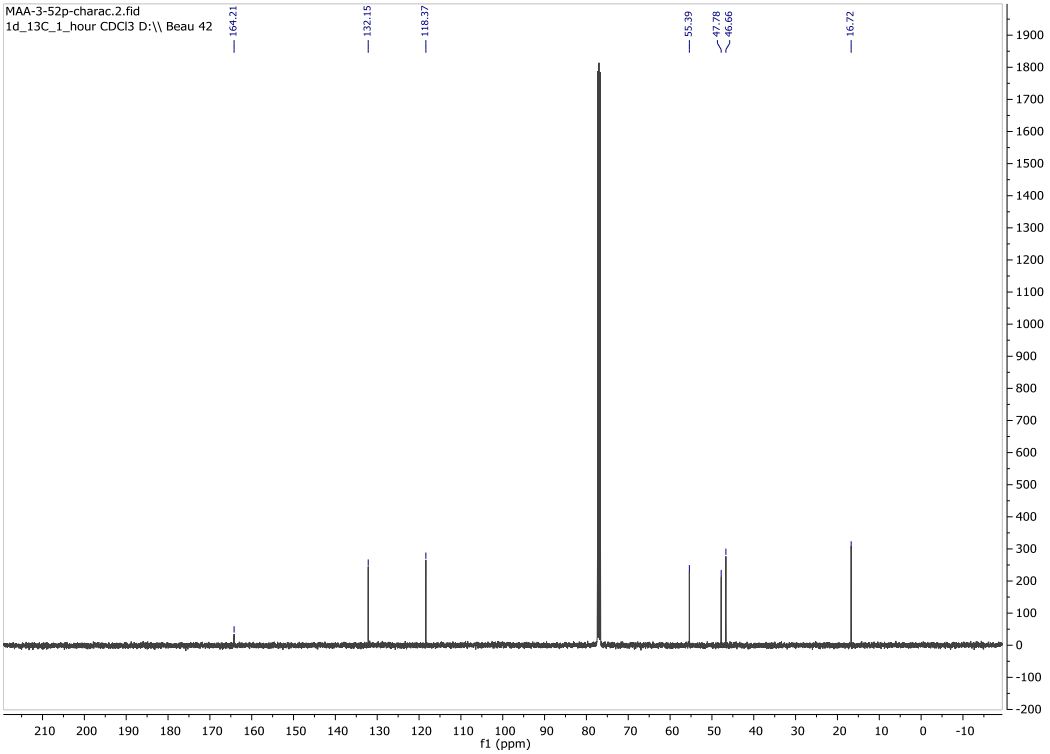
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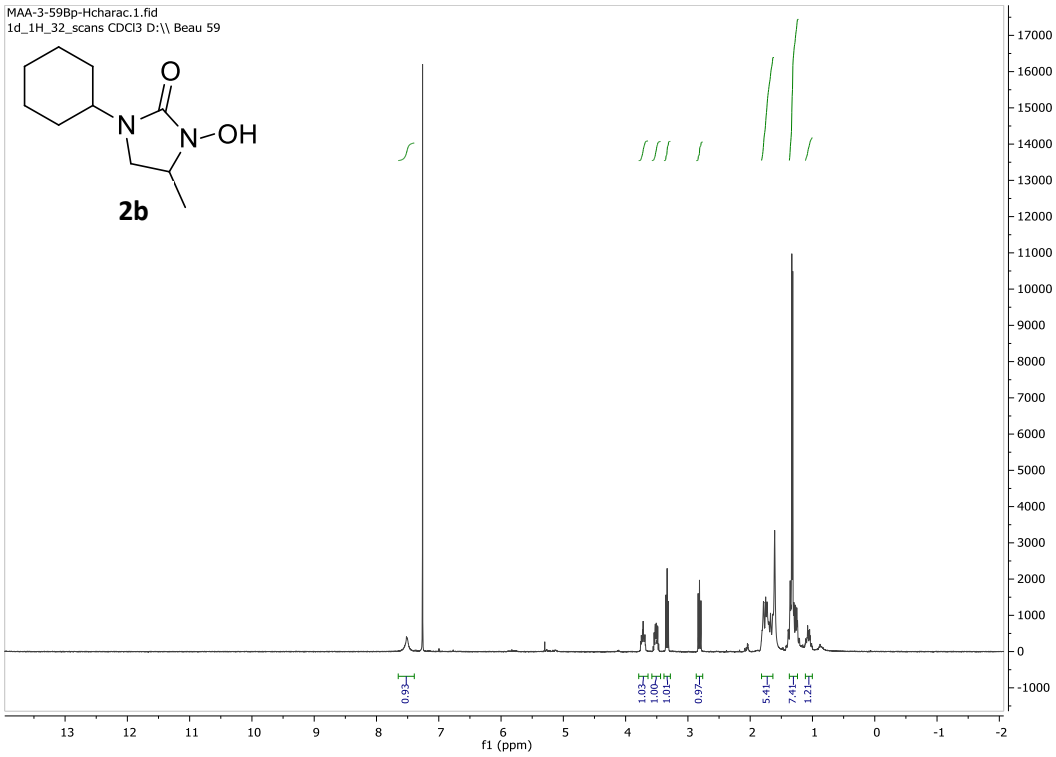
[236] J. Zhang and S. Chang, *J. Am. Chem. Soc.* 2020, **142**, 12585.

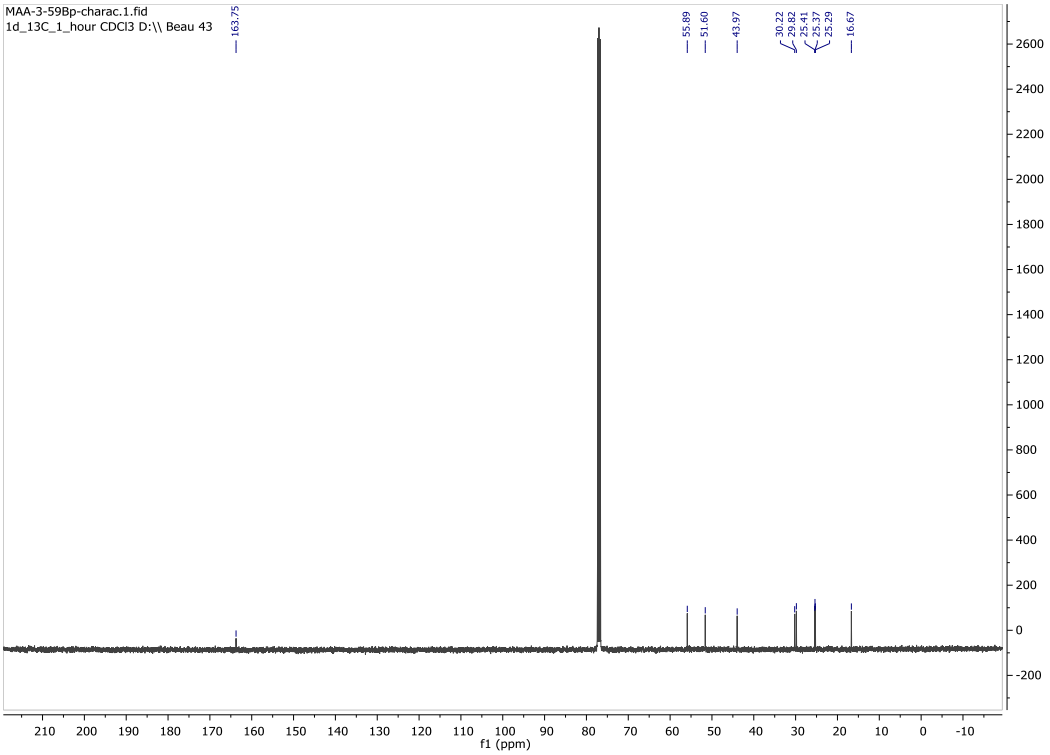
^{13}C NMR (125 MHz, $CDCl_3$): δ (*major*) 131.2 (CH), 130.0 (C), 129.29 (CH), 128.9 (CH), 62.6 (CH), 55.6 (CH_2), 52.4 (CH_2), 31.3 (CH_2), 20.9 (CH_2), 15.8 (CH_3).

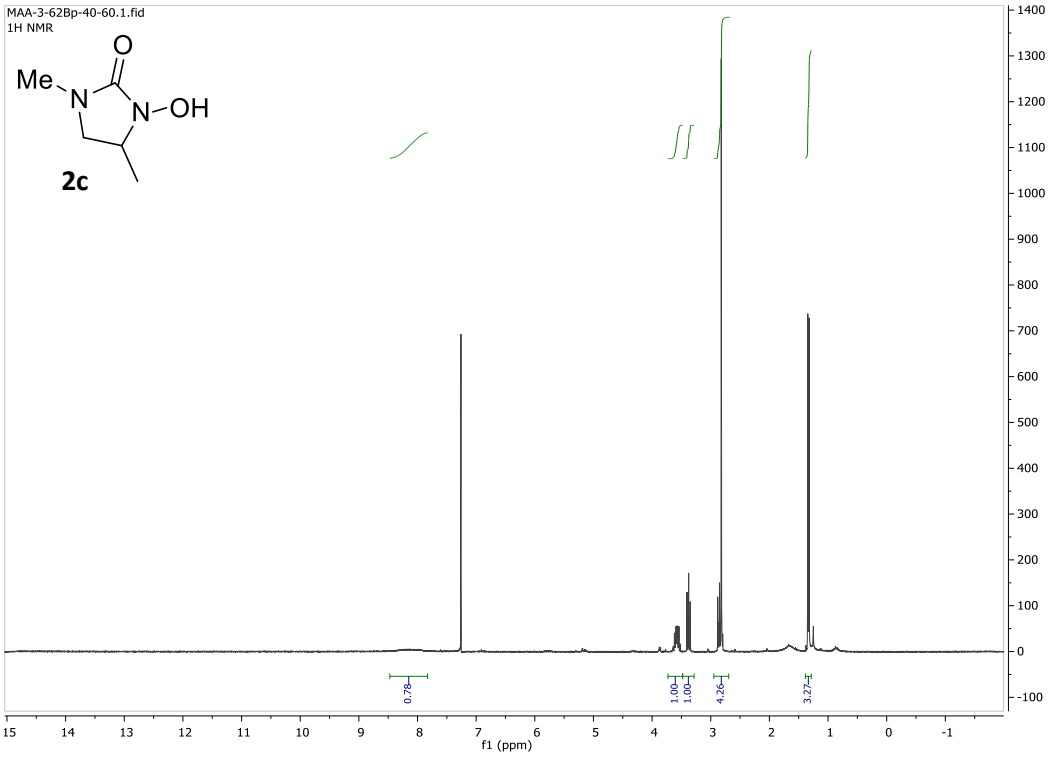
6.3.3 NMR spectra

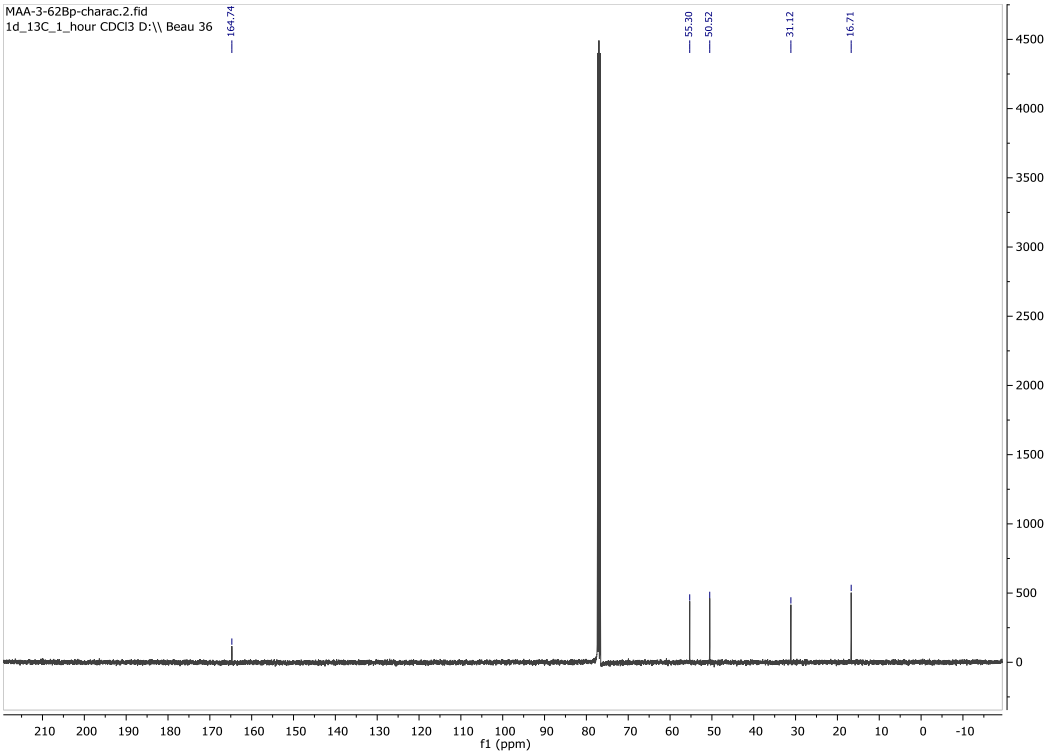


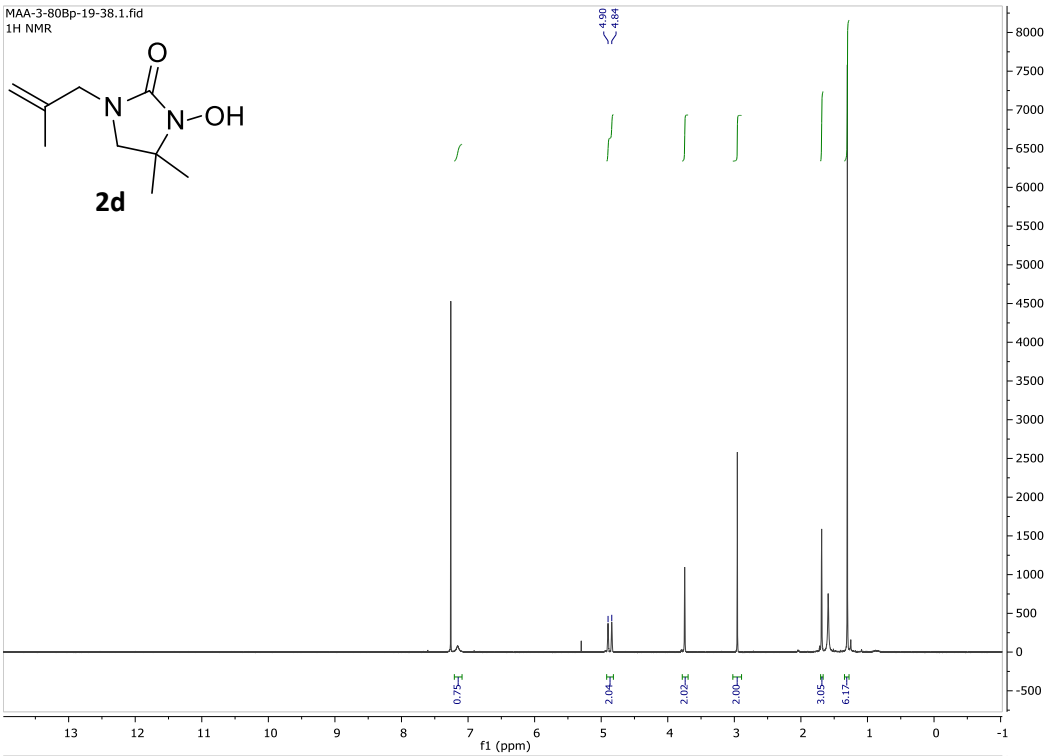


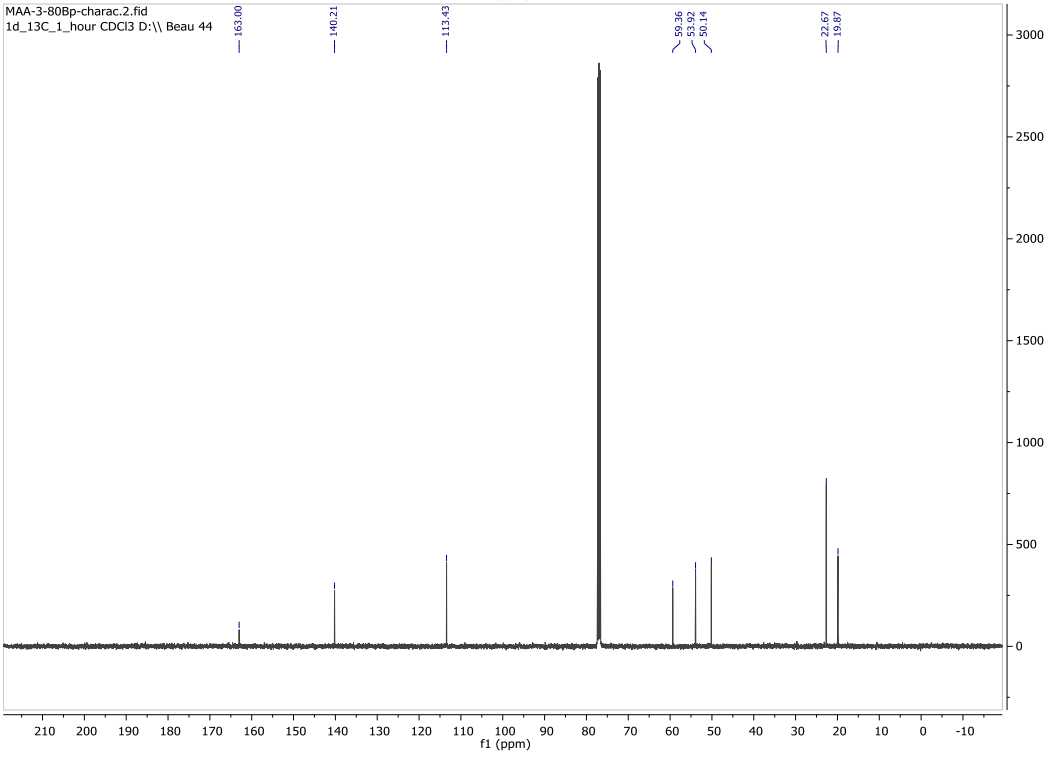

MAA-3-59Bp-Hcharac.1.fid
1d_1H_32_scans CDCl3 D:\\ Beau 59
O
N
N–OH
2b
0.93
1.03
1.00
1.01
0.97
5.41
7.41
1.21
f1 (ppm)

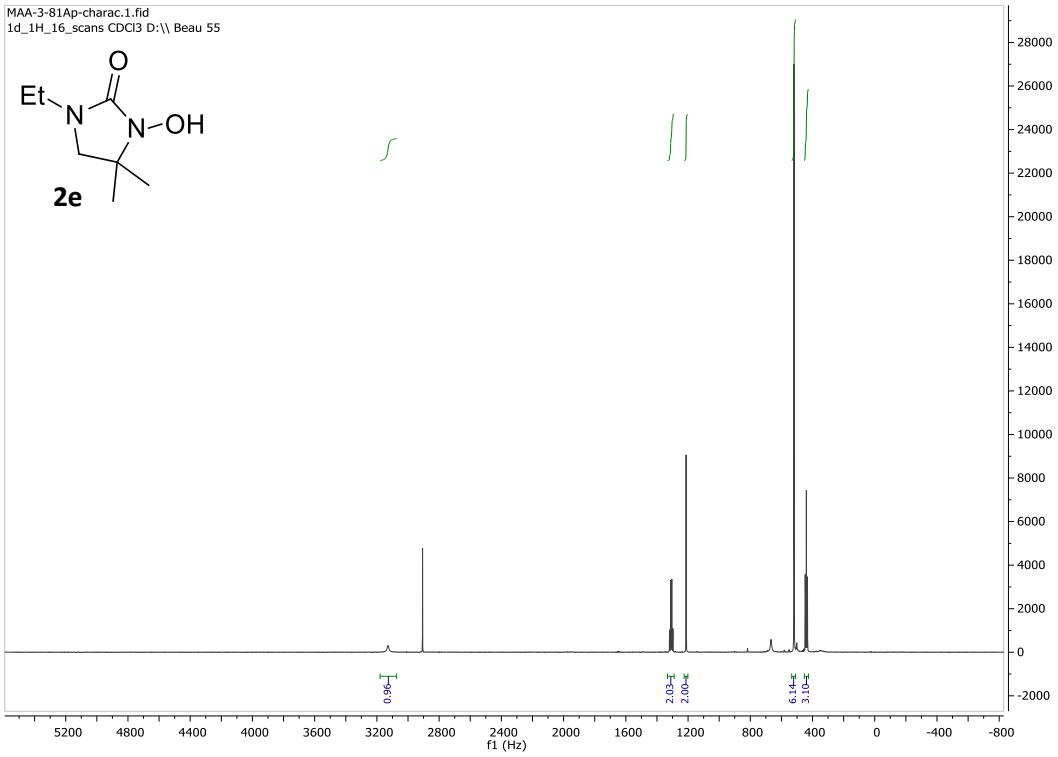

MAA-3-59Bp-charac.1.fid
1d_13C_1_hour CDCl3 D:\\ Beau 43
163.75
55.89
51.60
43.97
30.22
29.82
25.41
25.37
25.29
16.67
f1 (ppm)

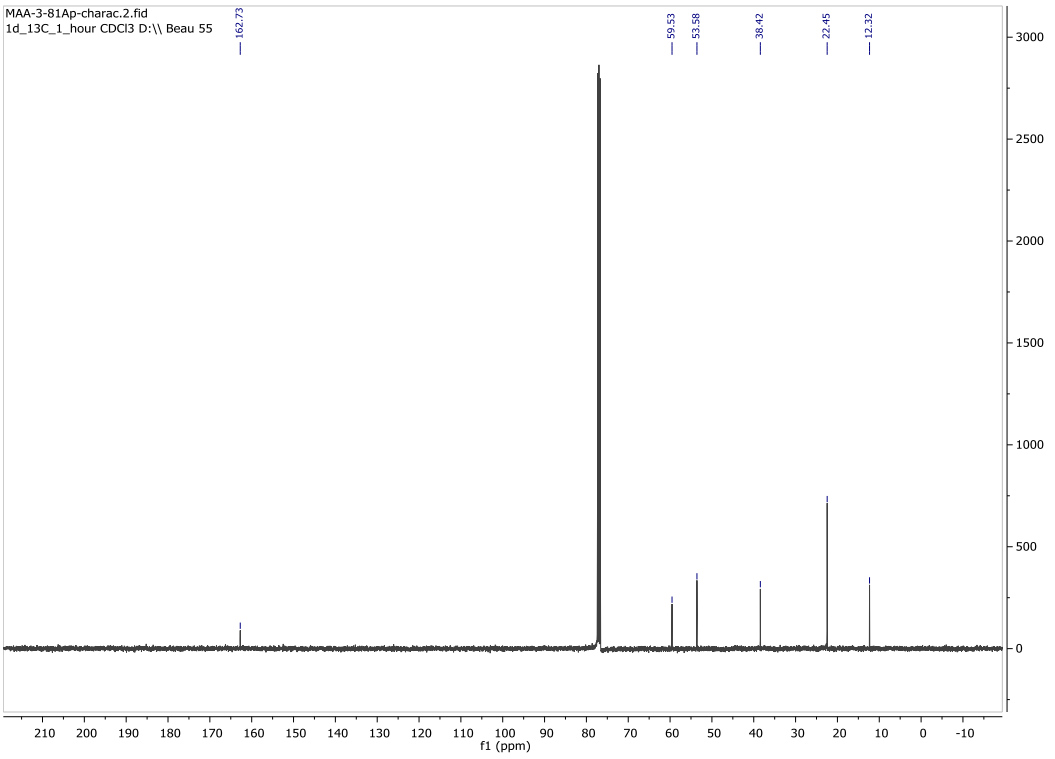

MAA-3-62Bp-40-60.1.fid
1H NMR
Me
N
O
N
OH
2c
0.78
1.00
1.00
4.26
3.27
f1 (ppm)

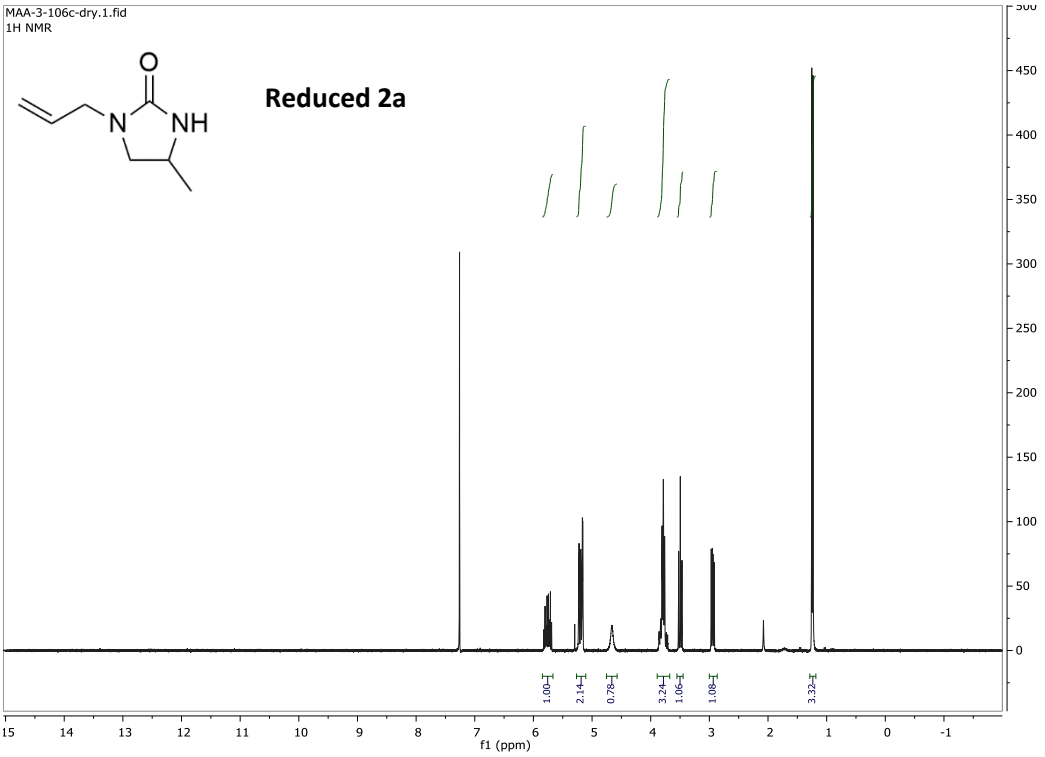

MAA-3-62Bp-charac.2.fid
1d_13C_1_hour CDCl3 D:\\ Beau 36
164.74
55.30
50.52
31.12
16.71
f1 (ppm)

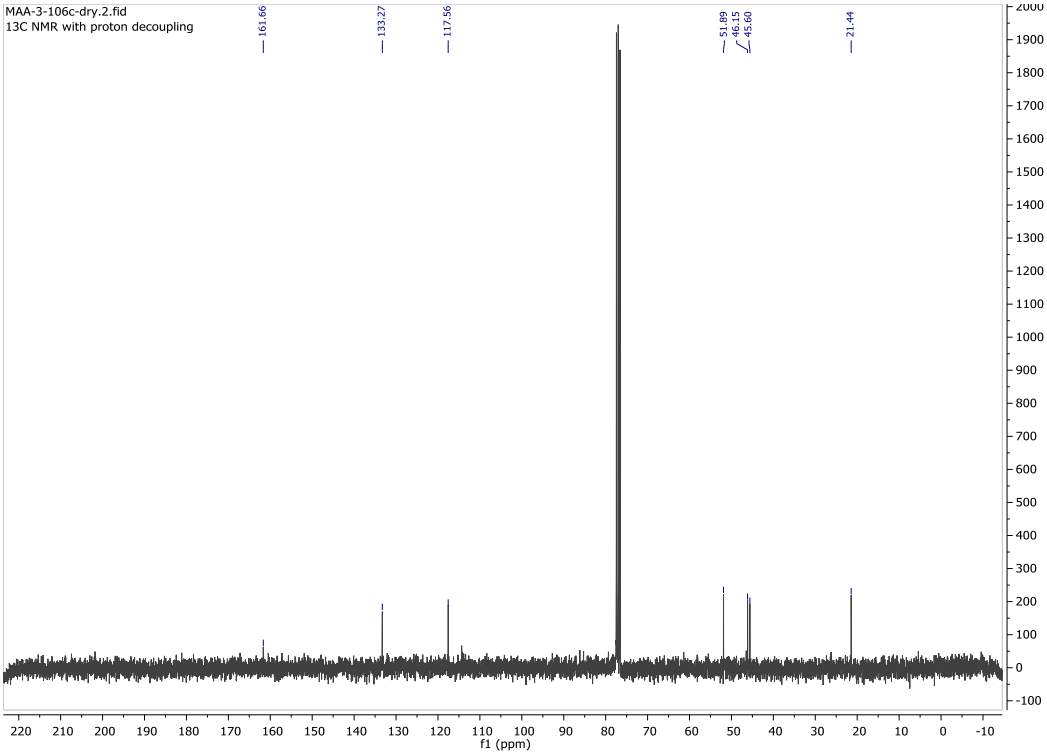

MAA-3-80Bp-19-38.1.fid
1H NMR
O
N
N
OH
2d
4.90
4.84
0.75
2.04
2.02
2.00
3.05
6.17
f1 (ppm)

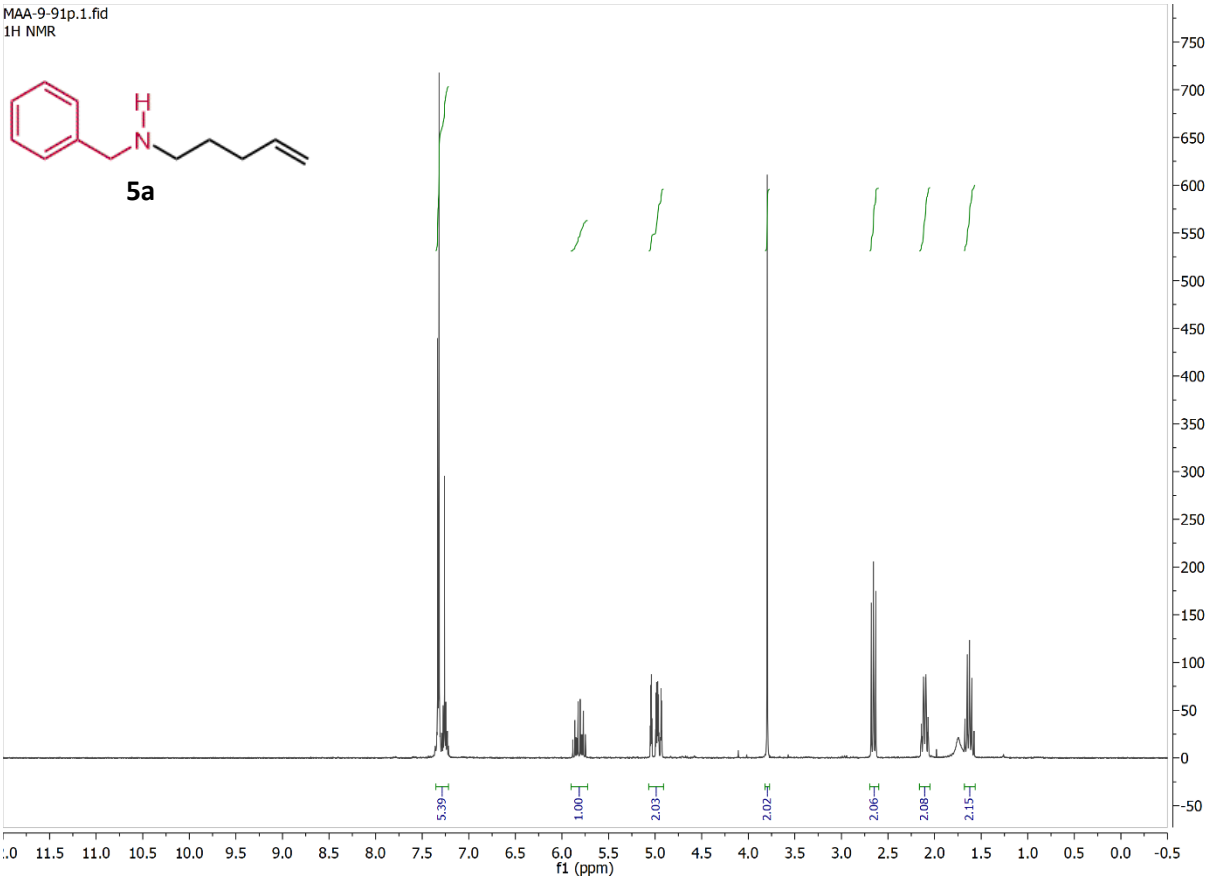

MAA-3-80Bp-charac.2.fid
1d_13C_1_hour CDCl3 D:\\ Beau 44
163.00
140.21
113.43
59.26
53.92
50.14
22.67
19.87
f1 (ppm)

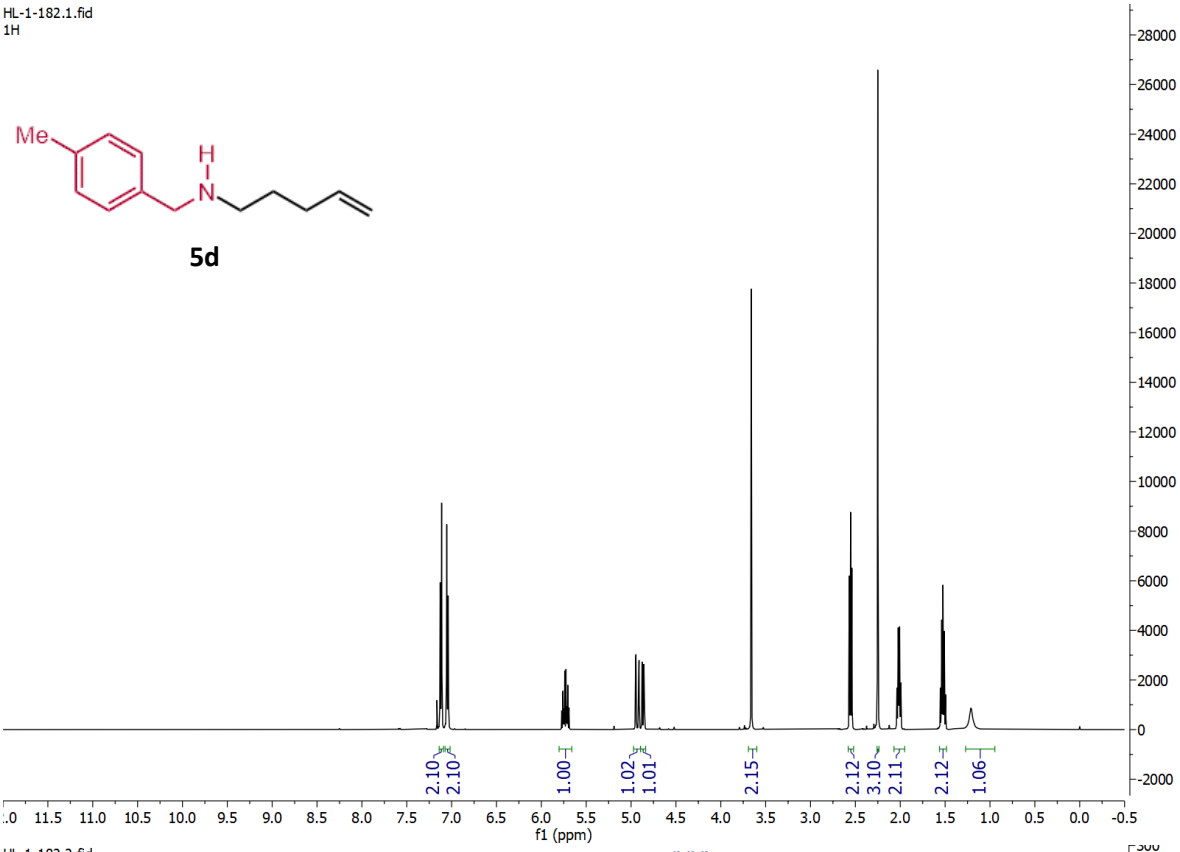

MAA-3-81Ap-charac.1.fid
1d_1H_16_scans CDCl3 D:\\ Beau 55
Et
N
O
N
OH
2e
0.96
2.03
2.00
6.14
3.10
f1 (Hz)

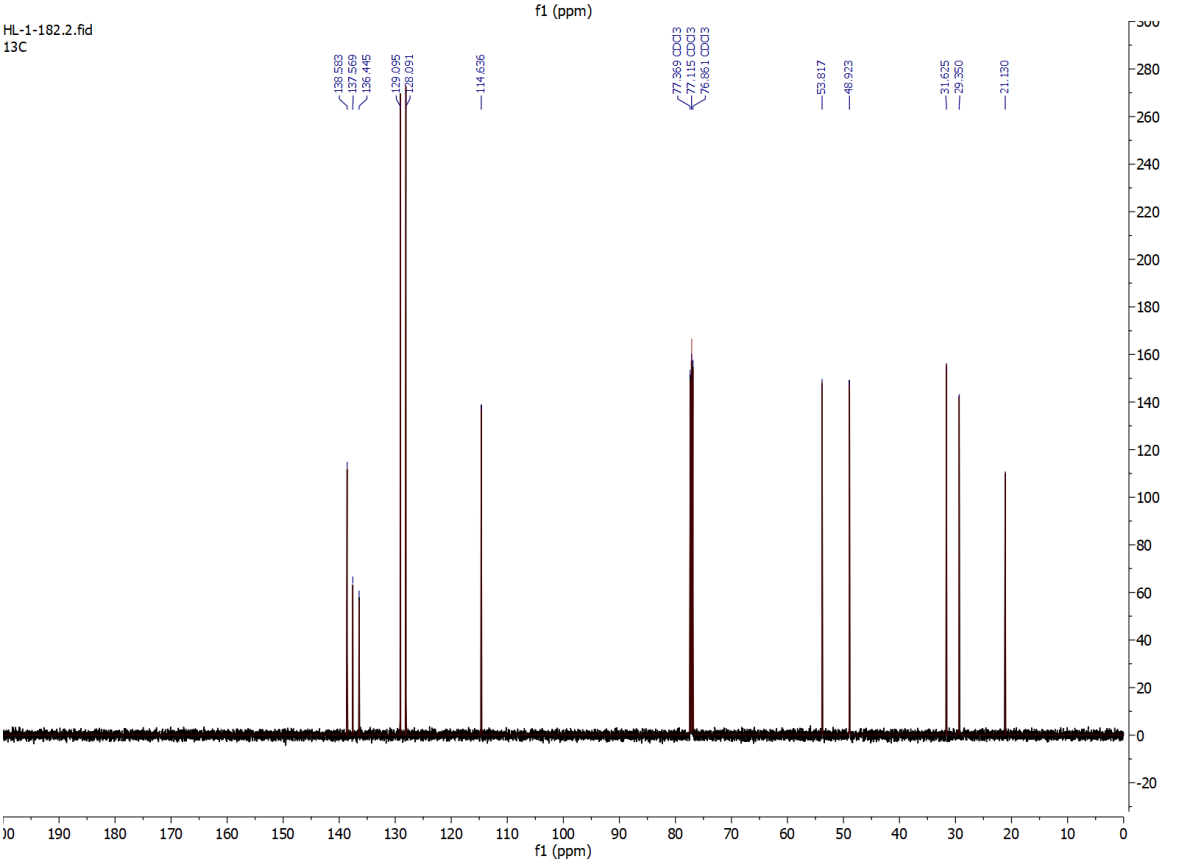

MAA-3-81Ap-charac.2.fid
1d_13C_1_hour CDCl3 D:\\ Beau 55
162.73
59.53
53.58
38.42
22.45
12.32
f1 (ppm)

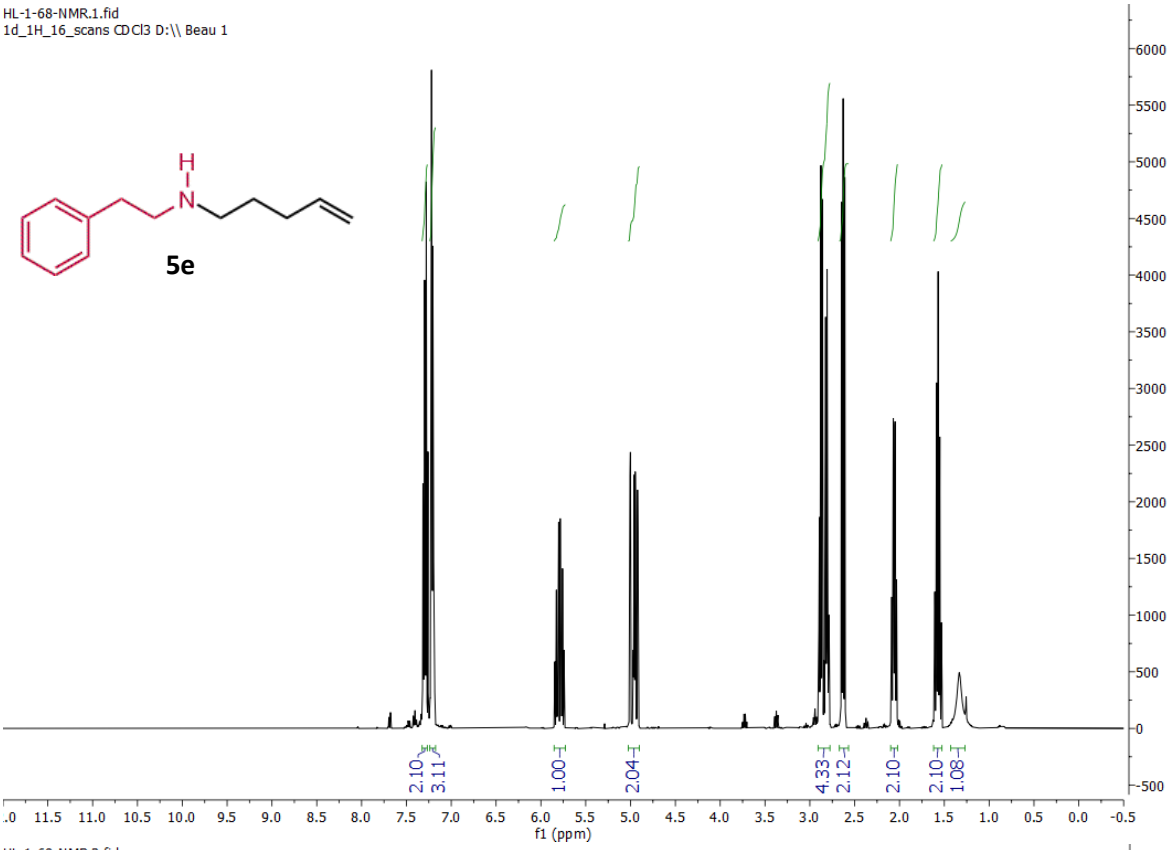

MAA-3-106c-dry.1.fid
1H NMR
Reduced 2a
O
N
NH
1.00
2.14
0.78
3.24
1.06
1.08
3.32
f1 (ppm)

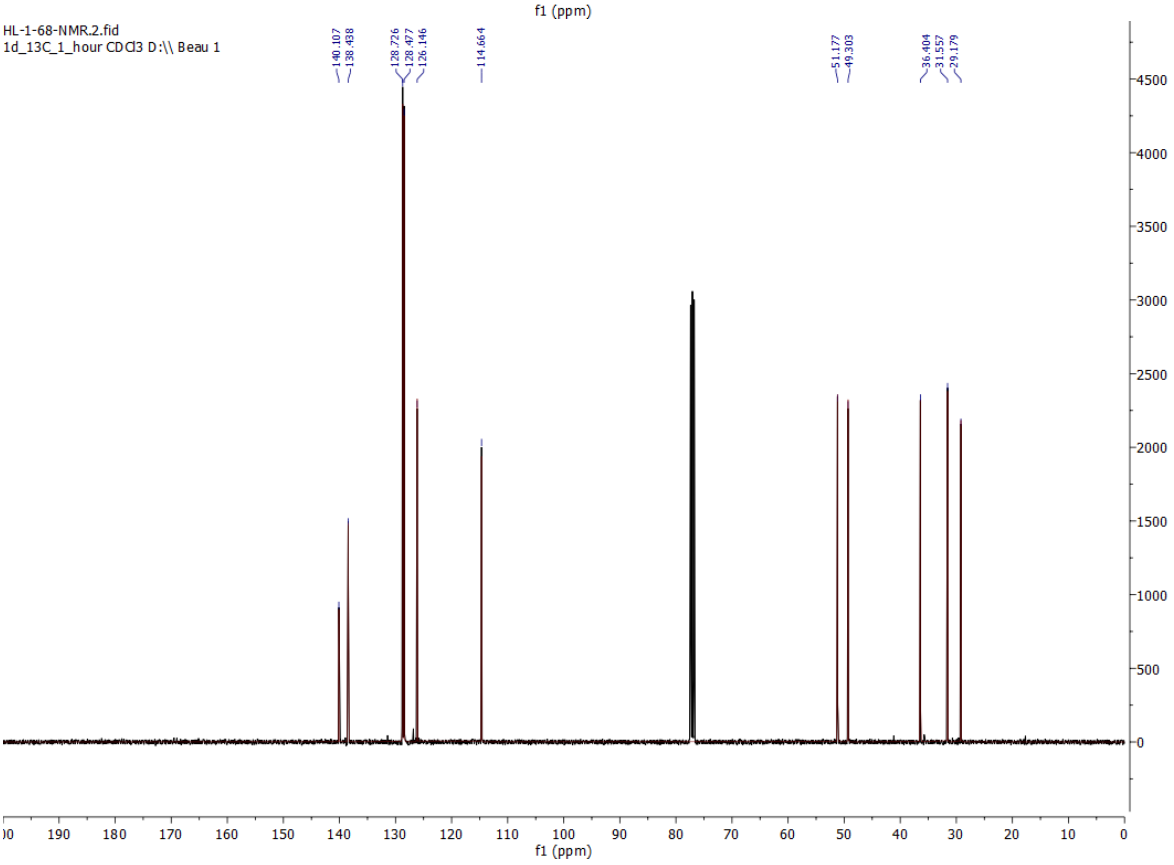

MAA-3-106c-dry.2.fid
13C NMR with proton decoupling
161.66
133.27
117.56
51.89
46.15
45.60
21.44
f1 (ppm)

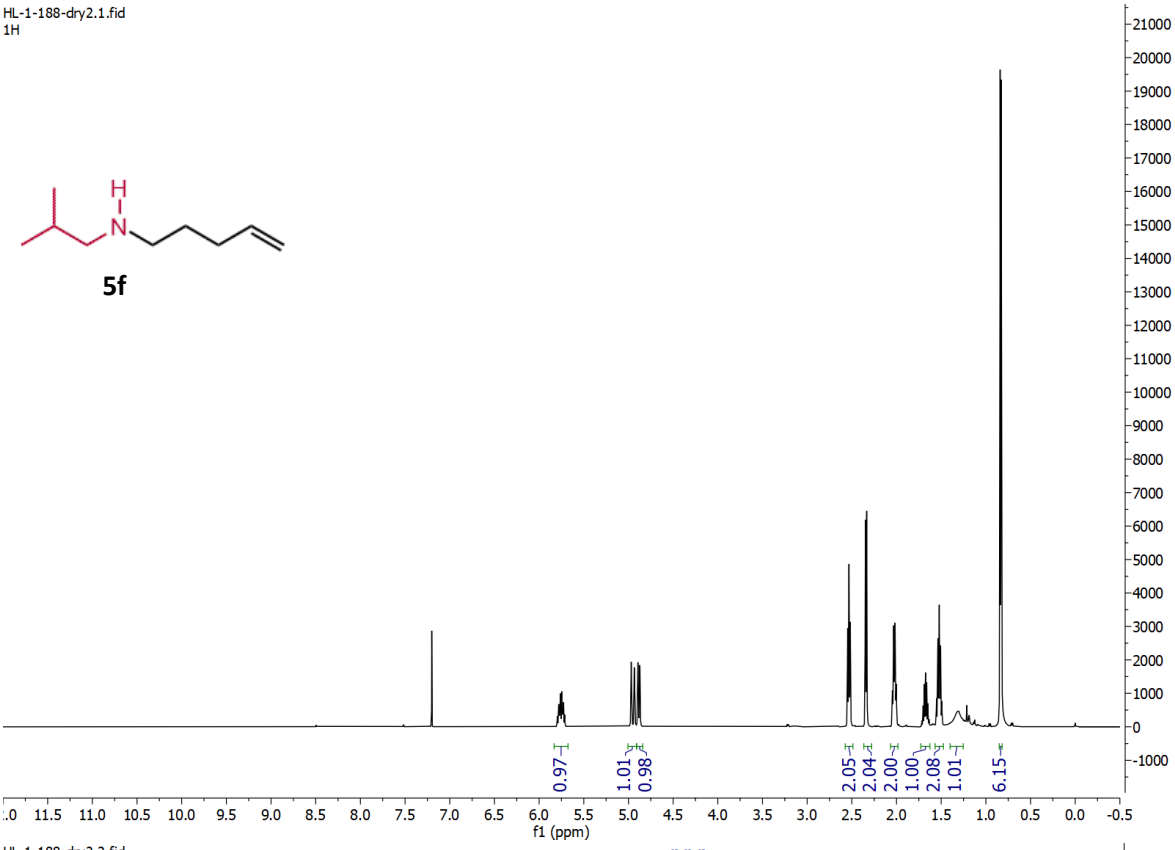

MAA-9-91p.1.fid
1H NMR
H
N
5a
5.39
1.00
2.03
2.02
2.06
2.08
2.15
f1 (ppm)


HL-1-182.1.fid
1H
Me
H
N
5d
2.10
2.10
1.00
1.02
1.01
2.15
2.12
3.10
2.11
2.12
1.06
f1 (ppm)

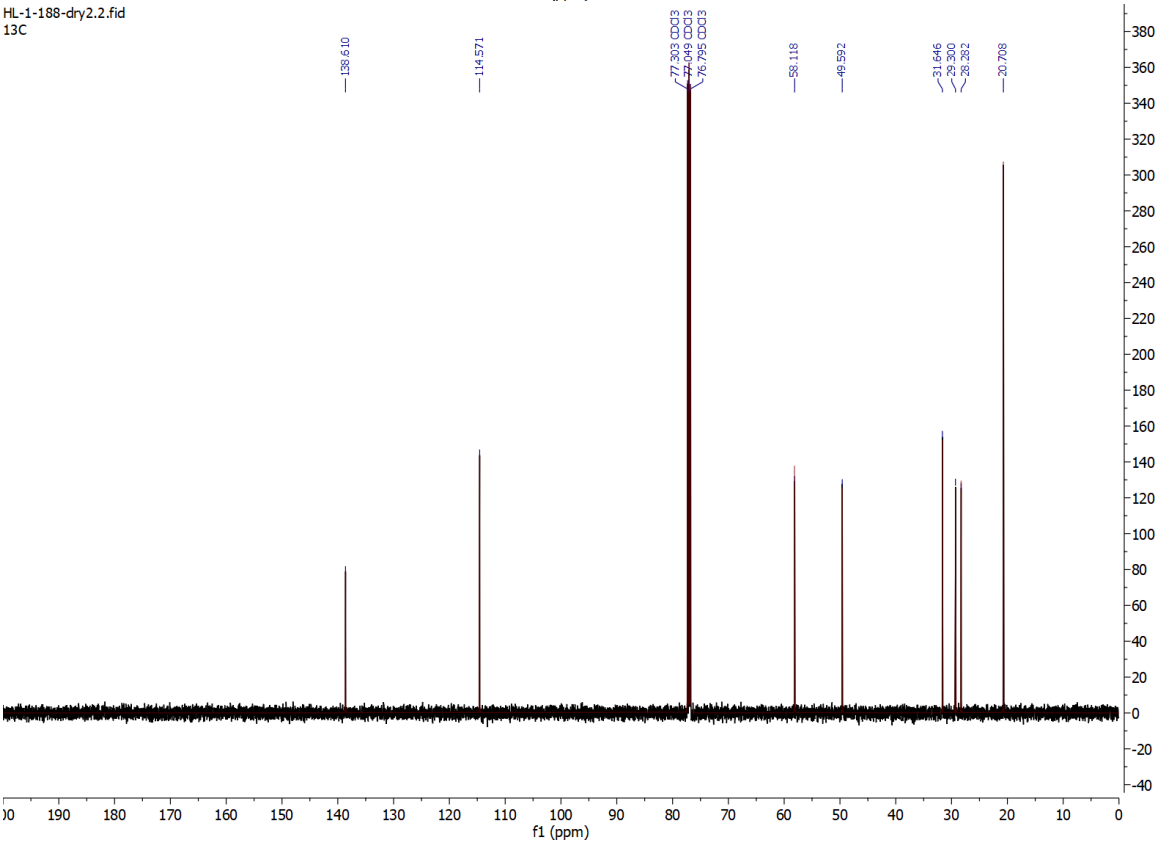

HL-1-182.2.fid
13C
138.583
137.569
136.445
129.095
128.091
114.636
77.369 CDCl3
77.115 CDCl3
76.861 CDCl3
53.817
48.923
31.625
29.350
21.130
f1 (ppm)

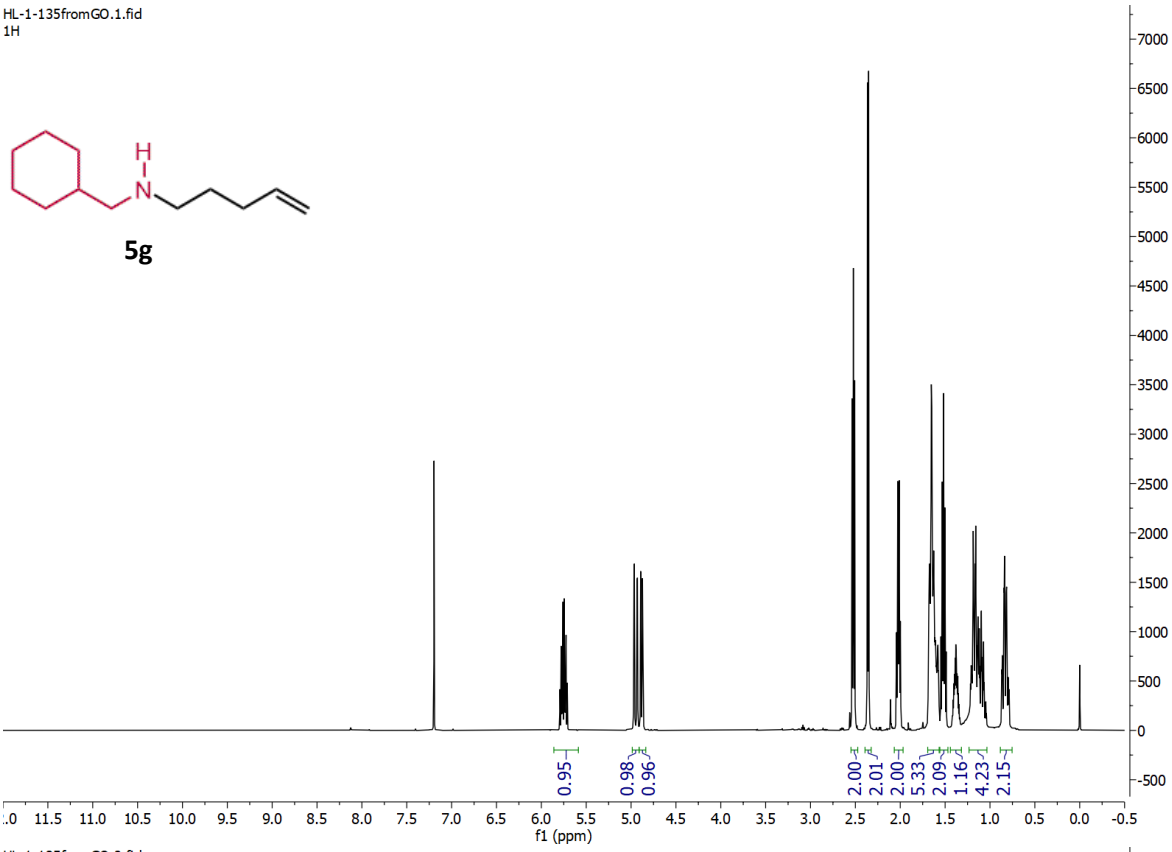

HL-1-68-NMR.1.fid
1d_1H_16_scans CDCl3 D:\\ Beau 1
5e
2.10
3.11
1.00
2.04
4.33
2.12
2.10
2.10
1.08
f1 (ppm)

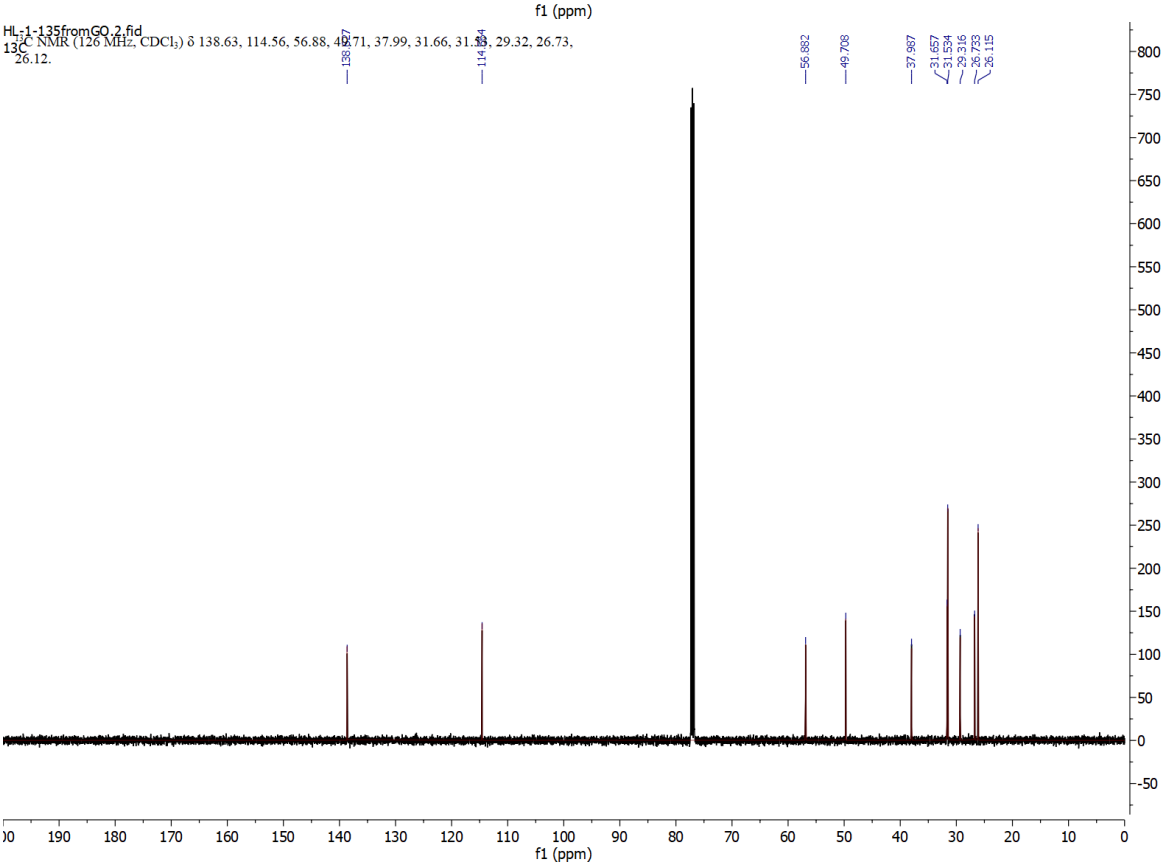

HL-1-68-NMR.2.fid
1d_13C_1_hour CDCl3 D:\\ Beau 1
140.107
138.438
128.726
128.477
126.146
114.664
51.177
49.303
36.404
31.557
29.179
f1 (ppm)

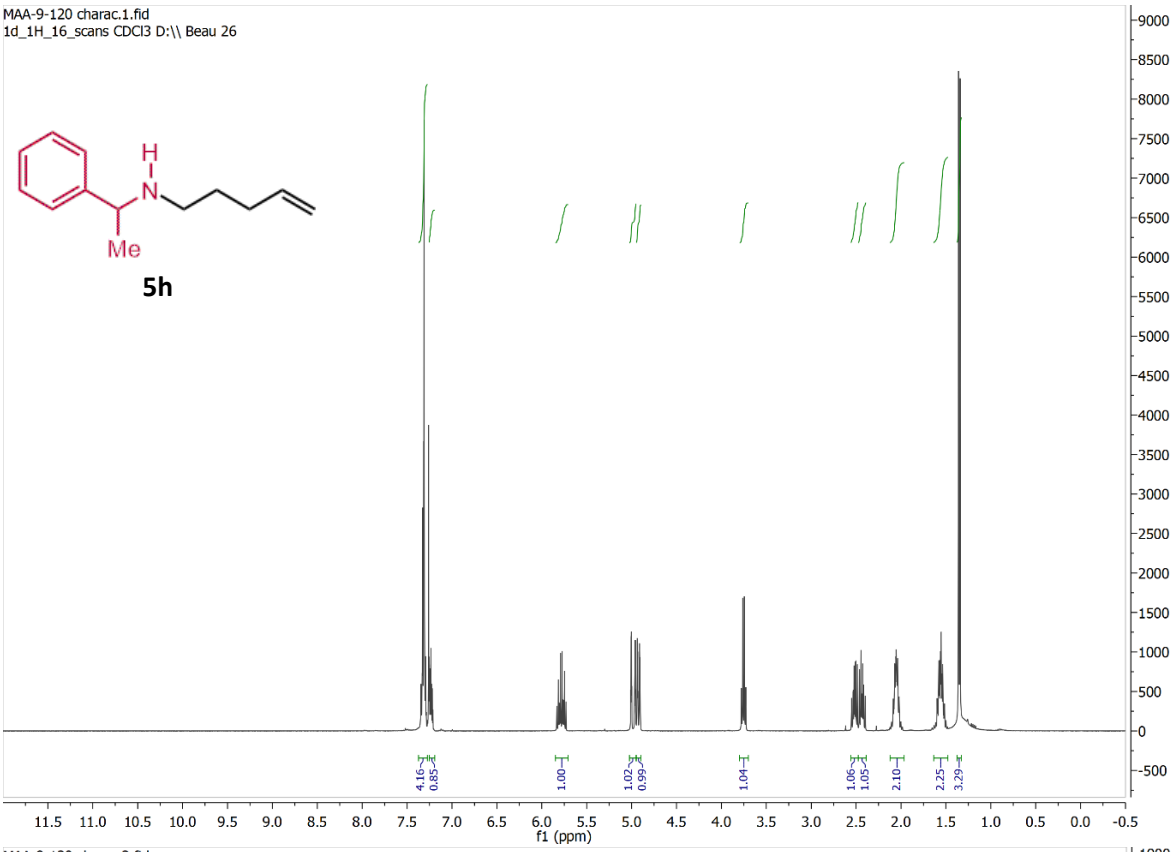

HL-1-188-dry2.1.fid
1H
H
N
0.97
1.01
0.98
2.05
2.04
2.00
1.00
2.08
1.01
6.15
f1 (ppm)

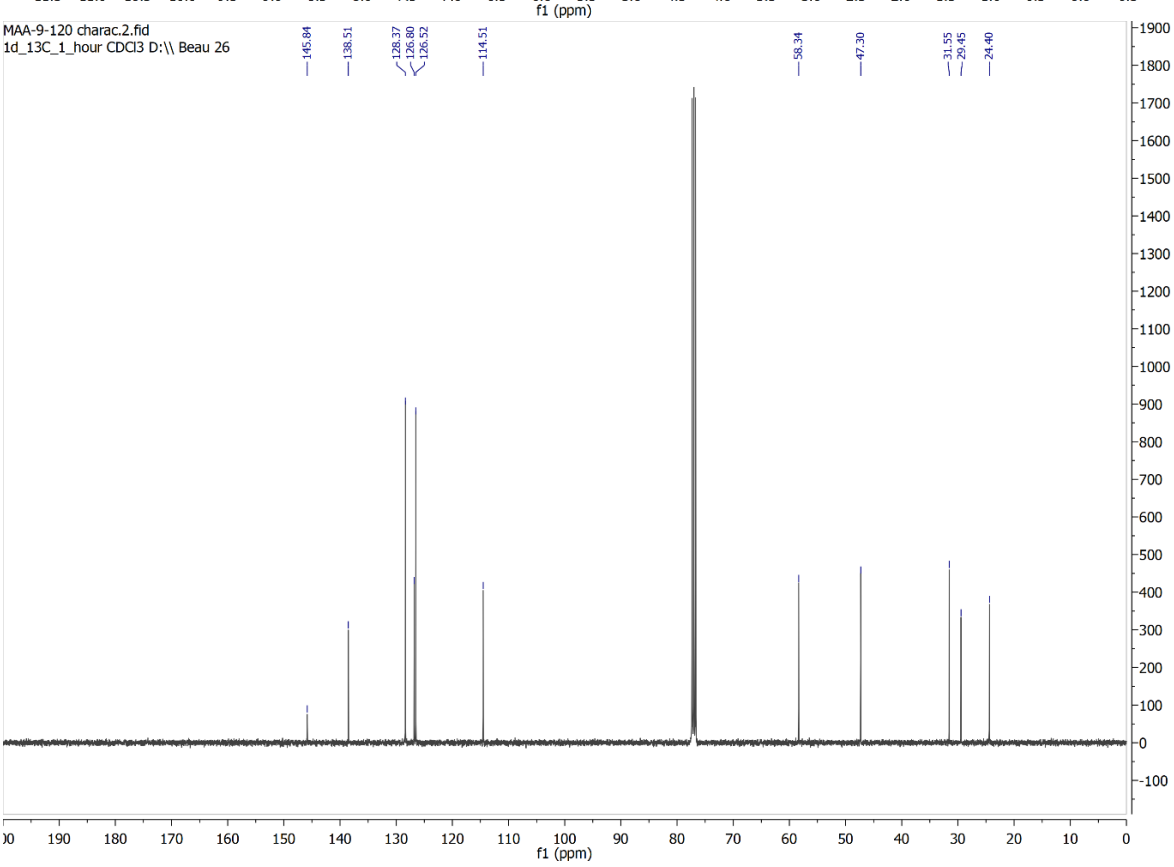
5f

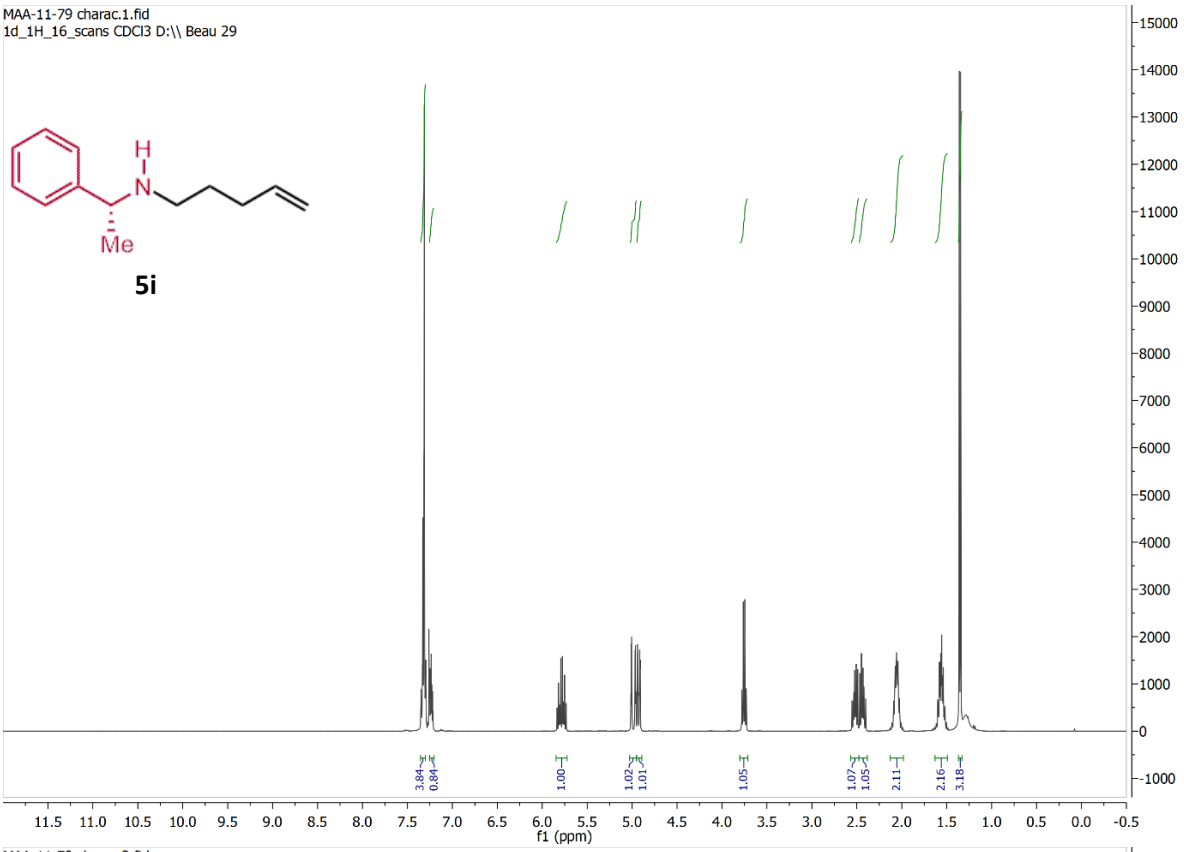

HL-1-188-dry2.2.fid
13C
138.610
114.571
77.303 CDCl3
77.049 CDCl3
76.795 CDCl3
58.118
49.592
31.646
29.300
28.282
20.708
f1 (ppm)


HL-1-135fromGO.1.fid
1H
H
N
5g
0.95
0.98
0.96
2.00
2.01
2.00
5.33
2.09
1.16
4.23
2.15
f1 (ppm)

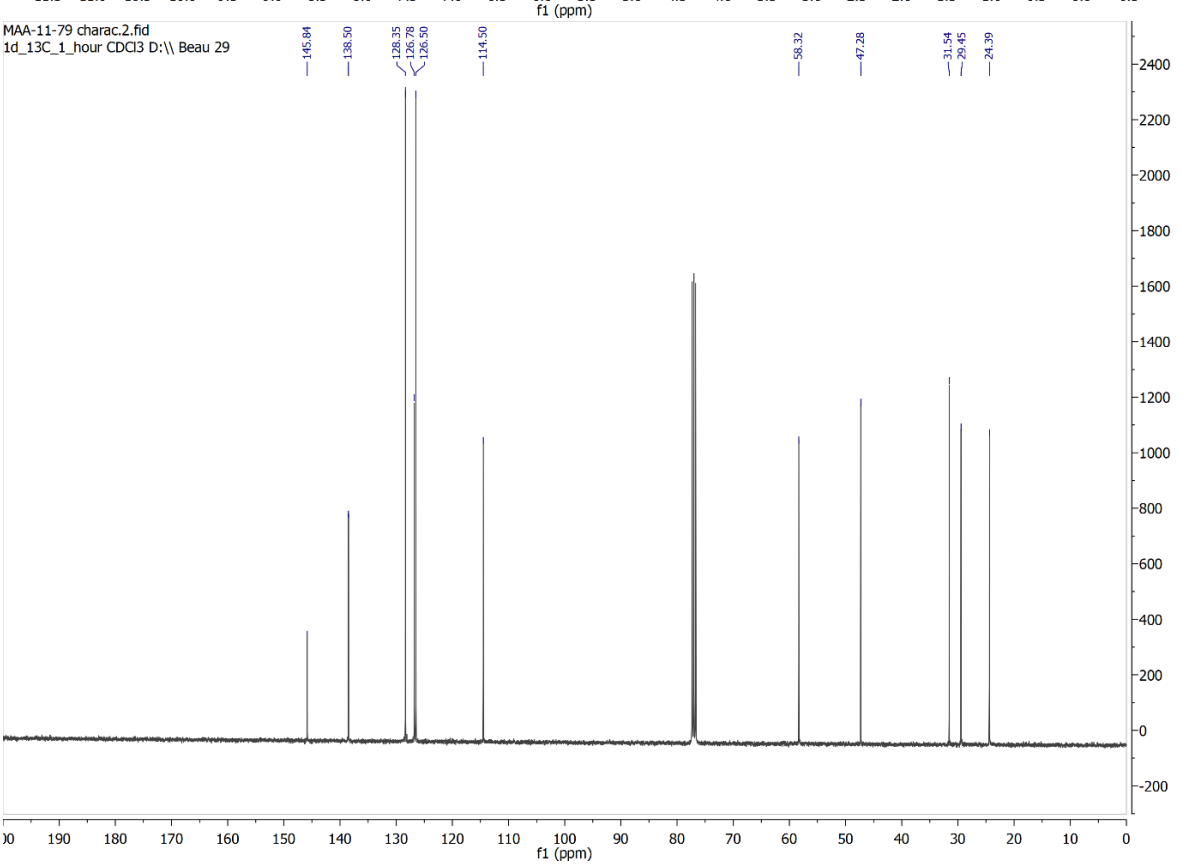

HL-1-135fromGO.2.fid
13C NMR (126 MHz, CDCl3) δ 138.63, 114.56, 56.88, 49.71, 37.99, 31.66, 31.53, 29.32, 26.73, 26.12.
138.627
114.564
56.882
49.708
37.987
31.657
31.534
29.316
26.733
26.115
f1 (ppm)

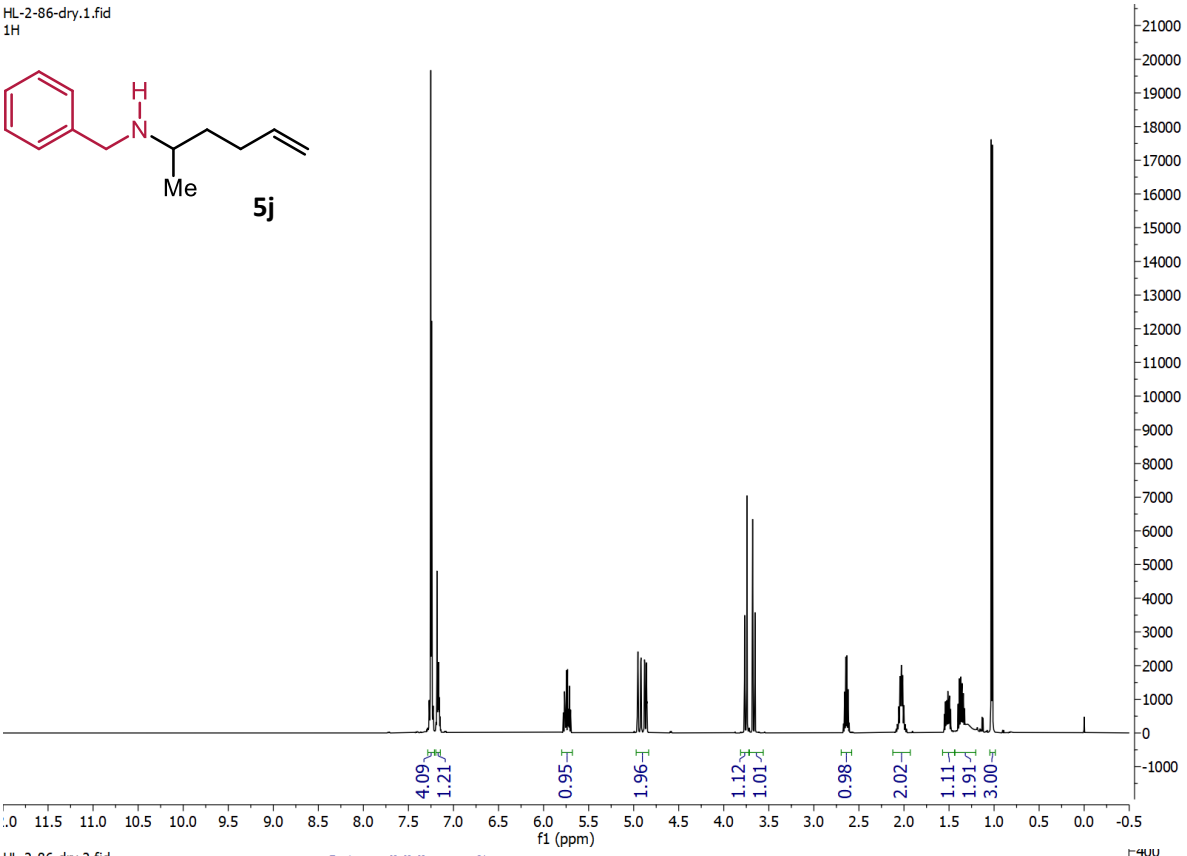

MAA-9-120 charac.1.fid
1d_1H_16_scans CDCl3 D:\\ Beau 26
H
N
Me
5h
4.16
0.85
1.00
1.02
0.99
1.04
1.06
1.05
2.10
2.25
3.29
f1 (ppm)

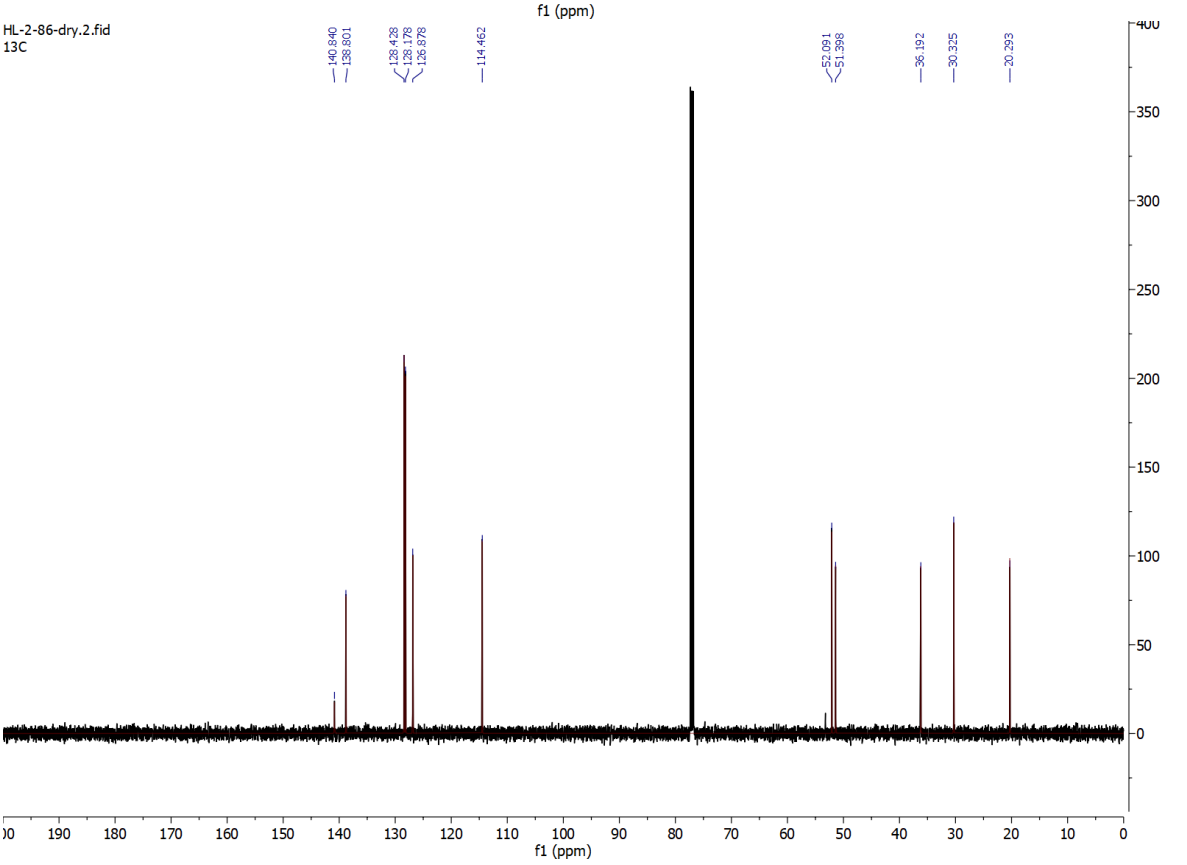

MAA-9-120 charac.2.fid
1d_13C_1_hour CDCl3 D:\\ Beau 26
145.84
138.51
128.37
126.80
126.52
114.51
58.34
47.30
31.55
29.45
24.40
f1 (ppm)

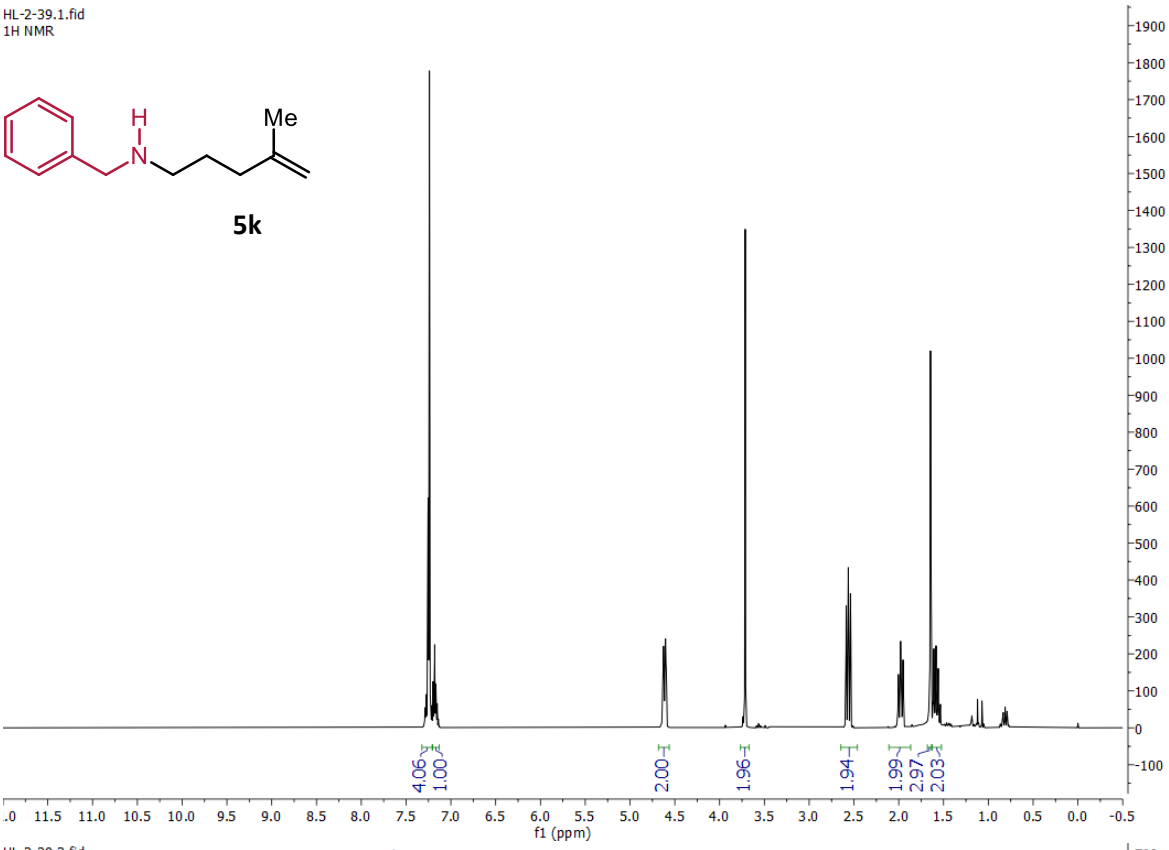

MAA-11-79 charac.1.fid
1d_1H_16_scans CDCl3 D:\\ Beau 29
H
N
Me
3.84
0.84
1.00
1.02
1.01
1.05
1.07
1.05
2.11
2.16
3.18
f1 (ppm)

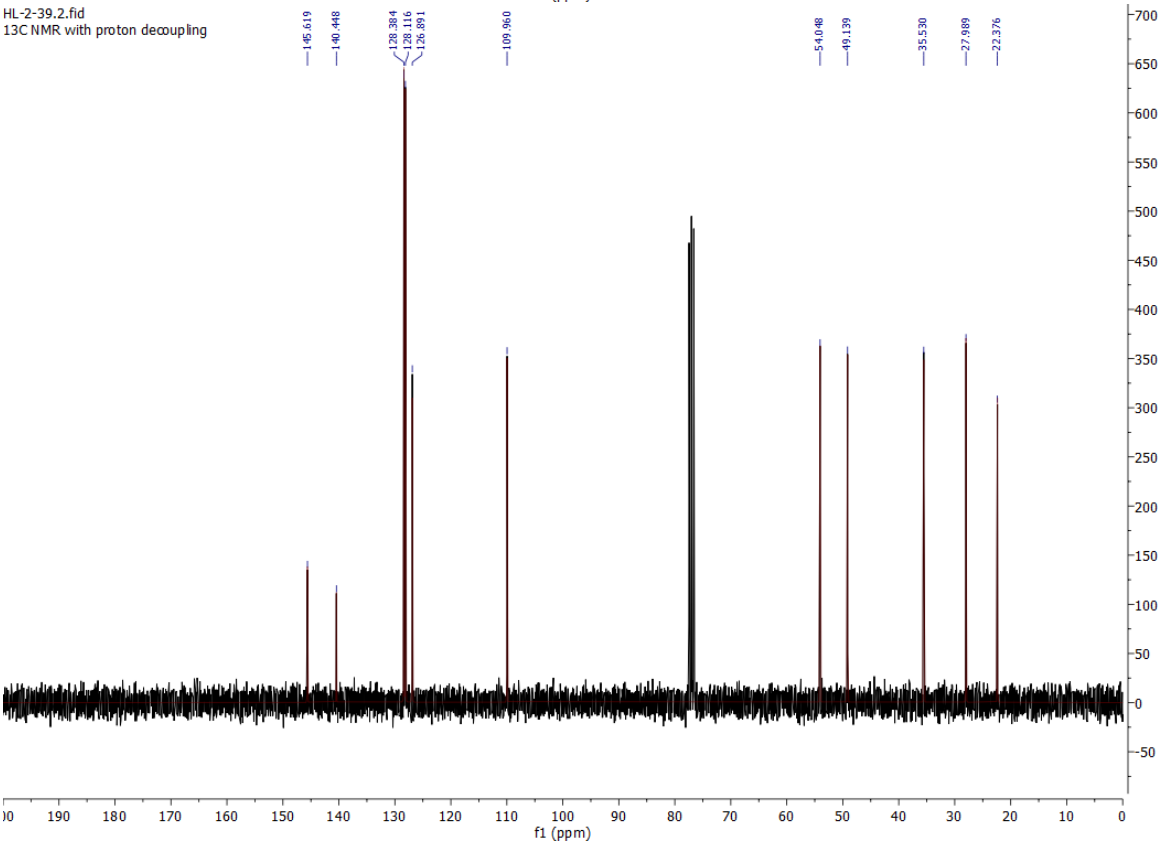
5i

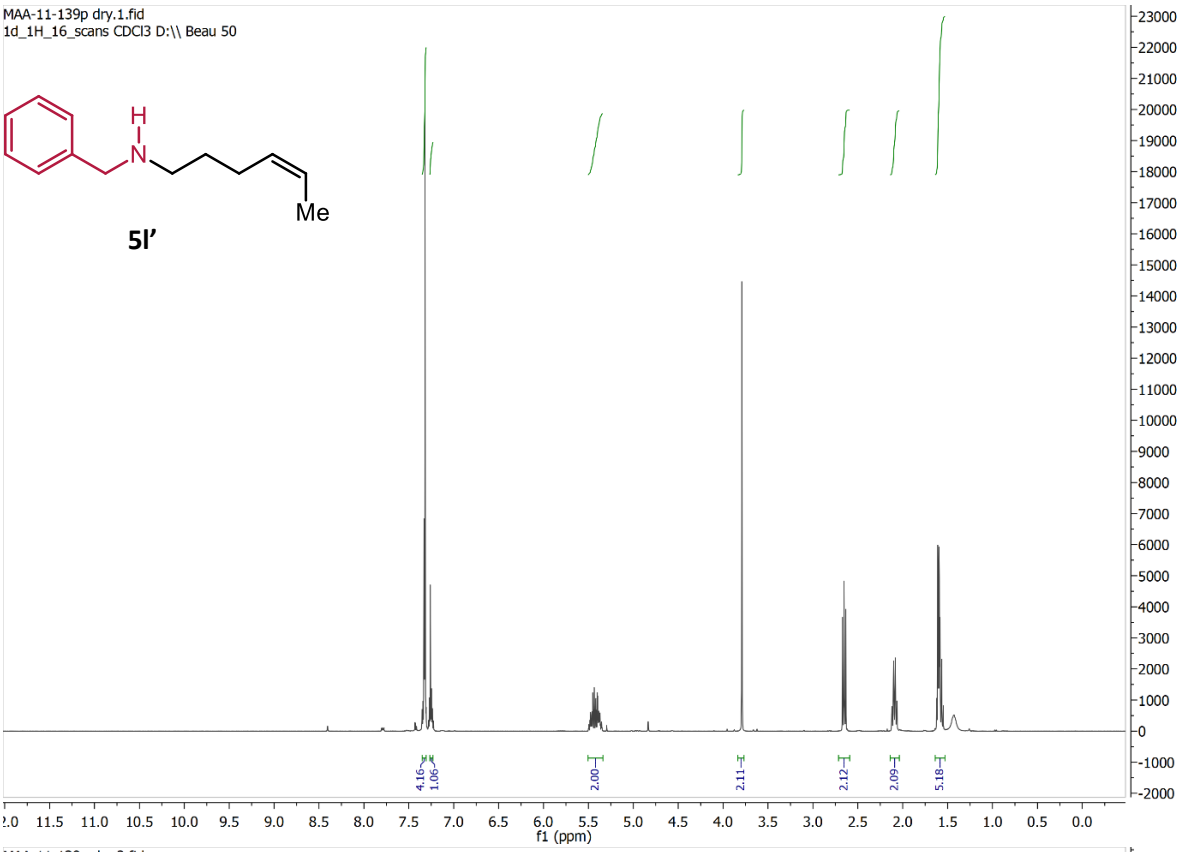

MAA-11-79 charac.2.fid
1d_13C_1_hour CDCl3 D:\\ Beau 29
145.84
138.50
128.35
126.78
126.50
114.50
58.32
47.28
31.54
29.45
24.39
f1 (ppm)

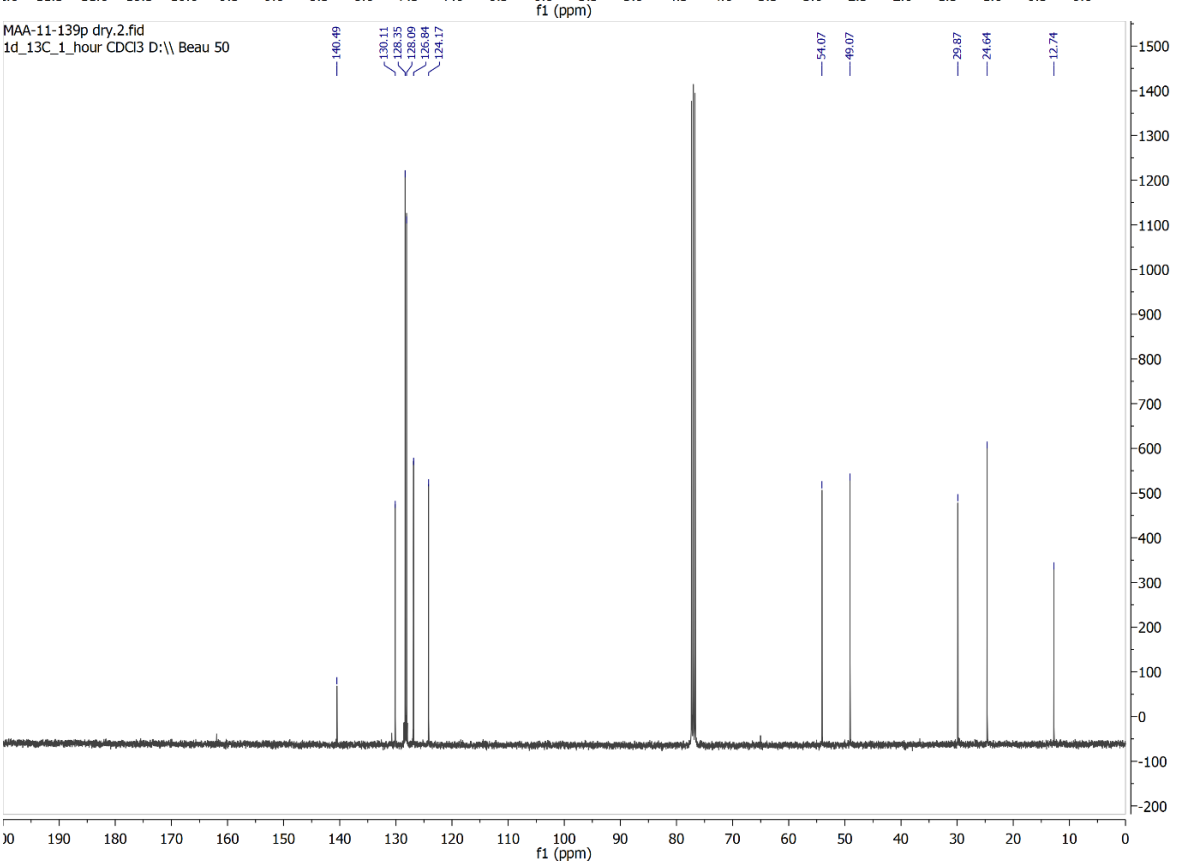

HL-2-86-dry.1.fid
1H
H
N
Me
5j
4.09
1.21
0.95
1.96
1.12
1.01
0.98
2.02
1.11
1.91
3.00
f1 (ppm)

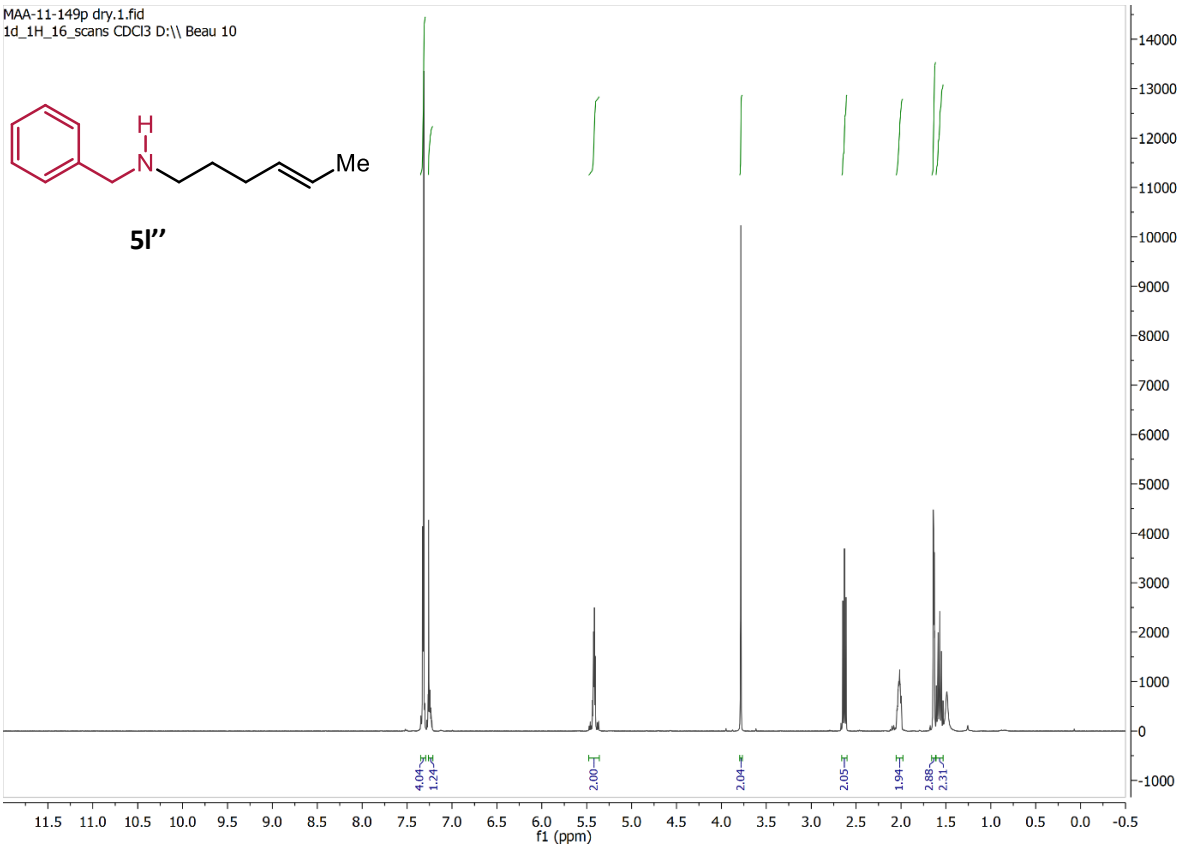

HL-2-86-dry.2.fid
13C
140.840
138.801
128.428
128.178
126.878
114.462
52.091
51.398
36.192
30.325
20.293
f1 (ppm)

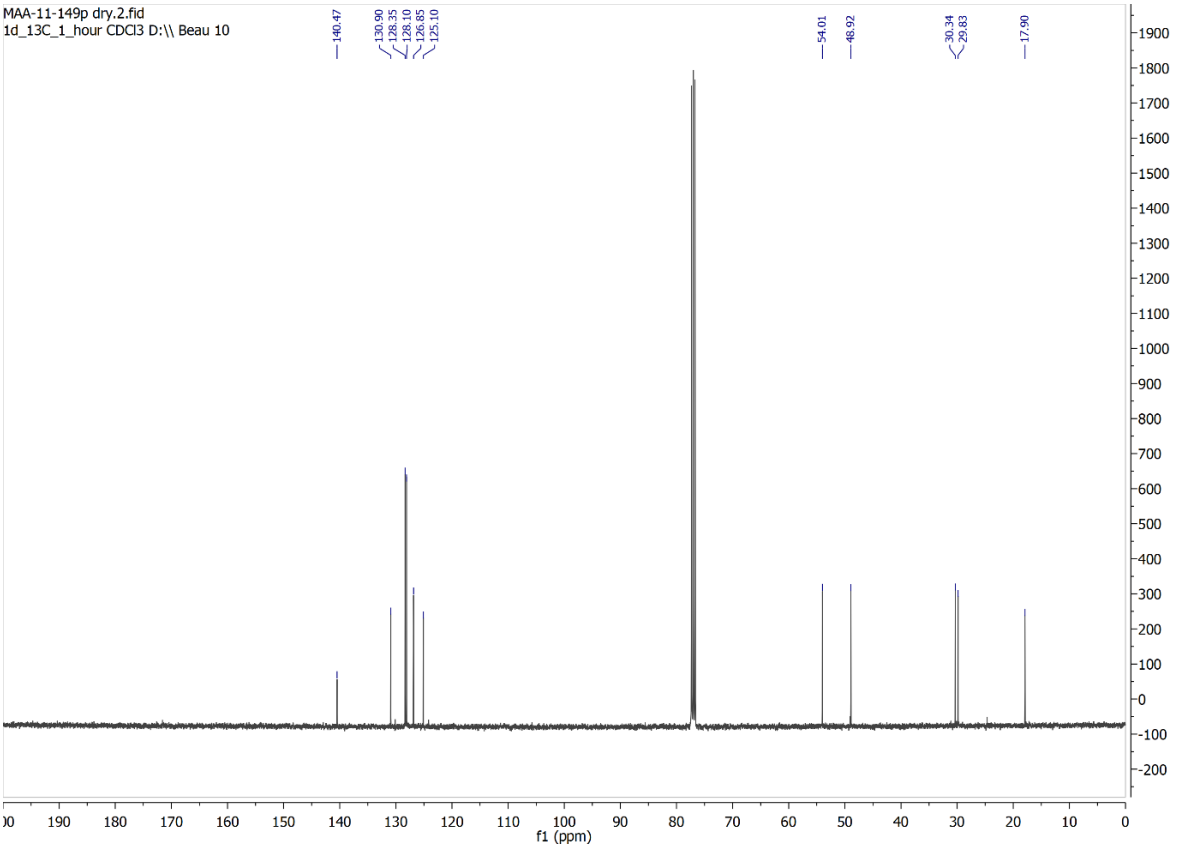

HL-2-39.1.fid
1H NMR
H
N
Me
5k
4.06
1.00
2.00
1.96
1.94
1.99
2.97
2.03
f1 (ppm)

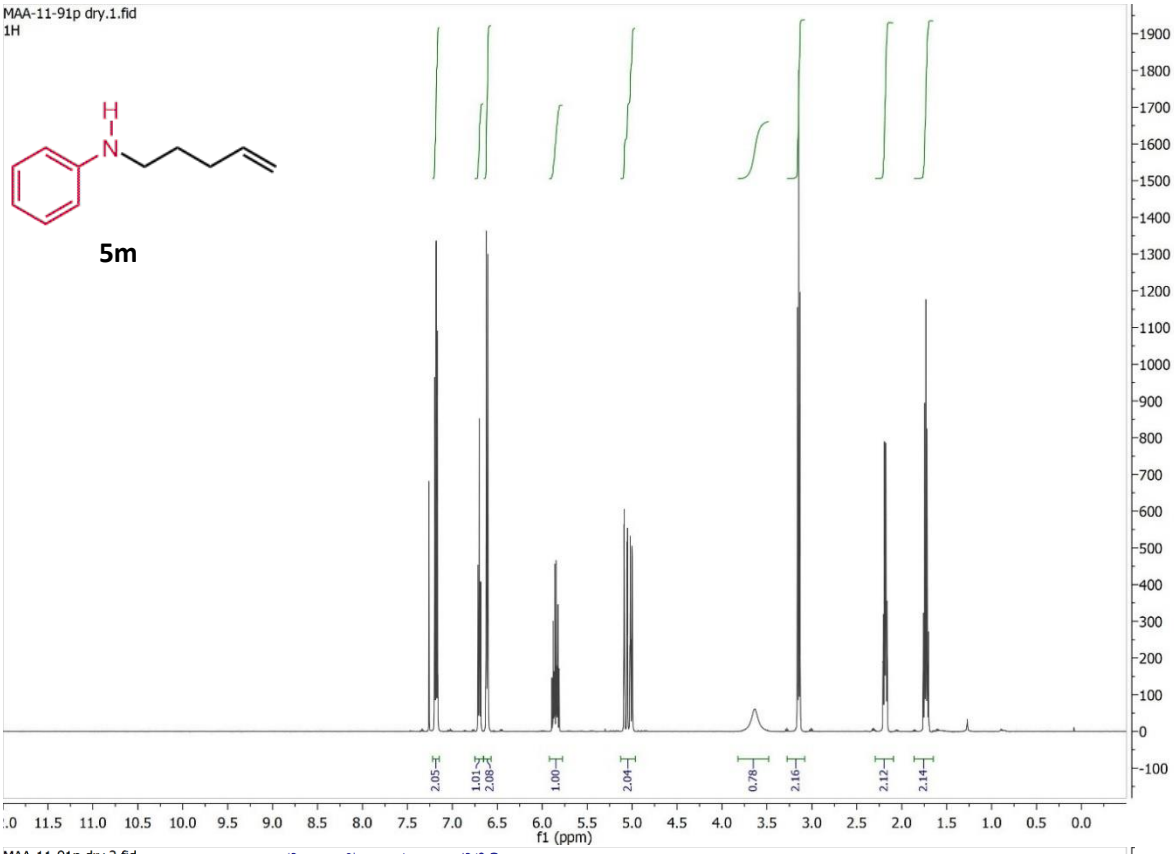

HL-2-39.2.fid
13C NMR with proton decoupling
145.619
140.448
128.384
128.116
126.891
109.960
54.048
49.139
35.530
27.989
22.376
f1 (ppm)

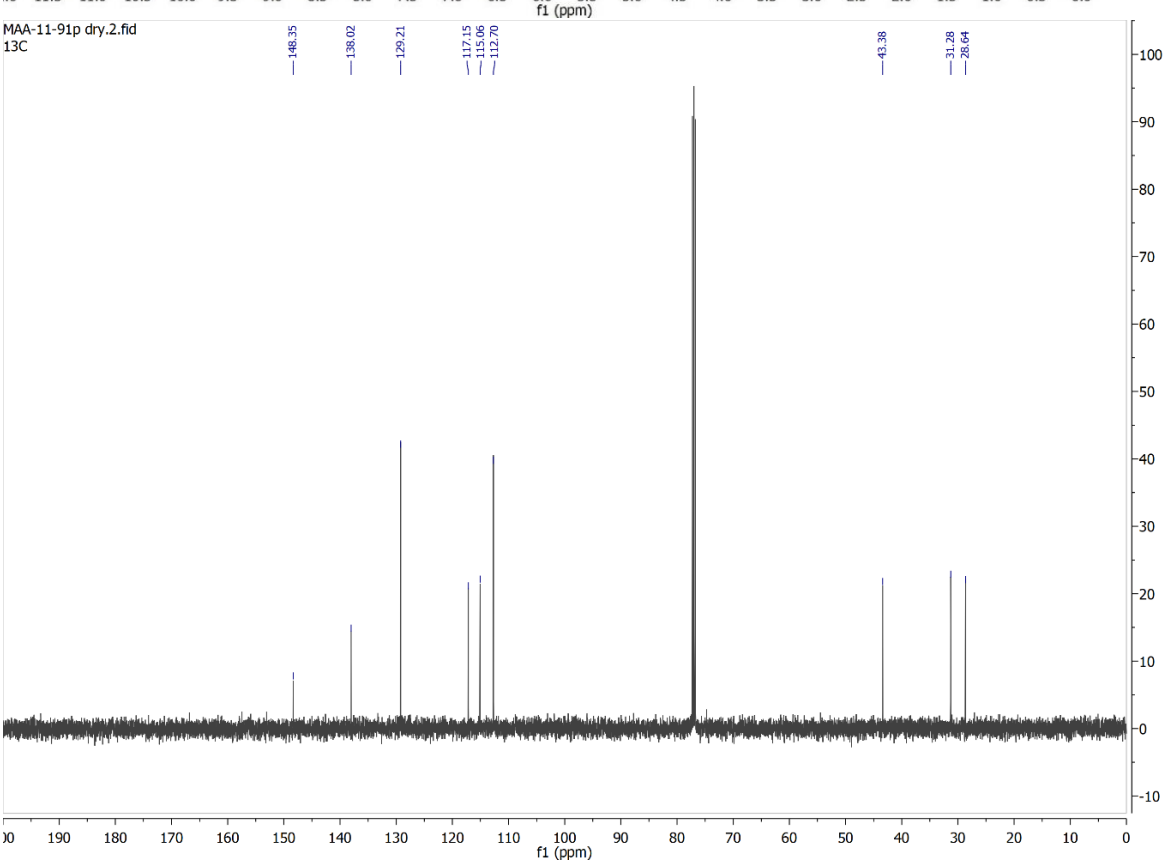

MAA-11-139p dry.1.fid
1d_1H_16_scans CDCl3 D:\\ Beau 50
H
N
Me
5l'
4.16
1.06
2.00
2.11
2.12
2.09
5.18
f1 (ppm)

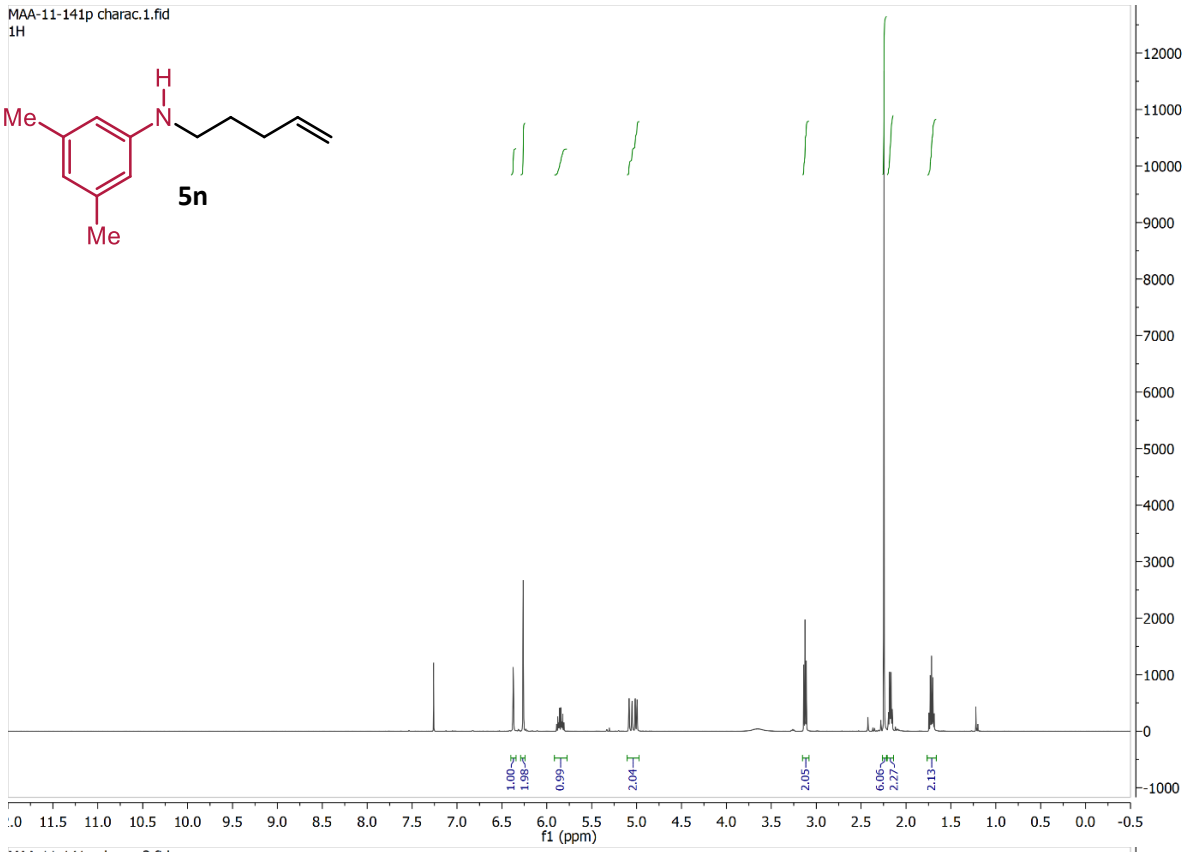

MAA-11-139p dry.2.fid
1d_13C_1_hour CDCl3 D:\\ Beau 50
140.49
130.11
128.35
128.09
126.84
124.17
54.07
49.07
29.87
24.64
12.74
f1 (ppm)

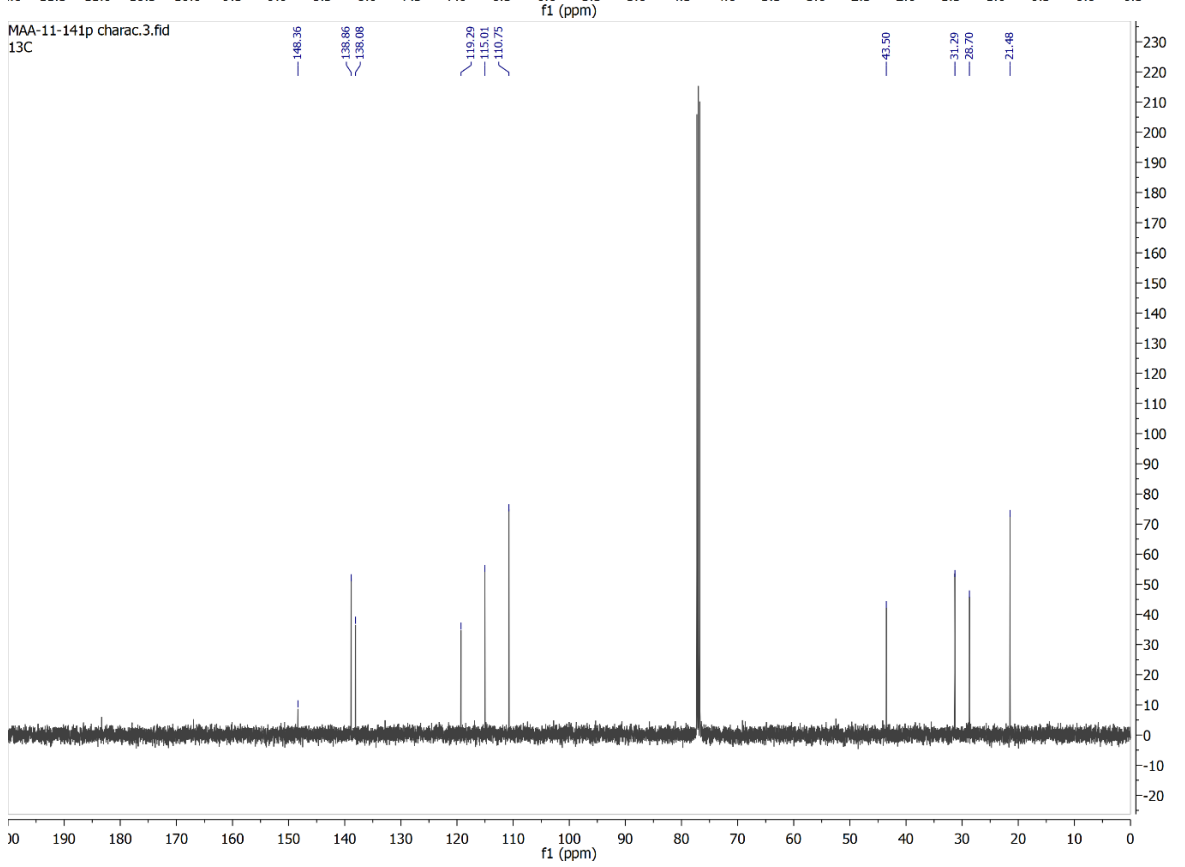

MAA-11-149p dry.1.fid
1d_1H_16_scans CDCl3 D:\\ Beau 10
H
N
Me
5l''
4.04
1.24
2.00
2.04
2.05
1.94
2.88
2.31
f1 (ppm)

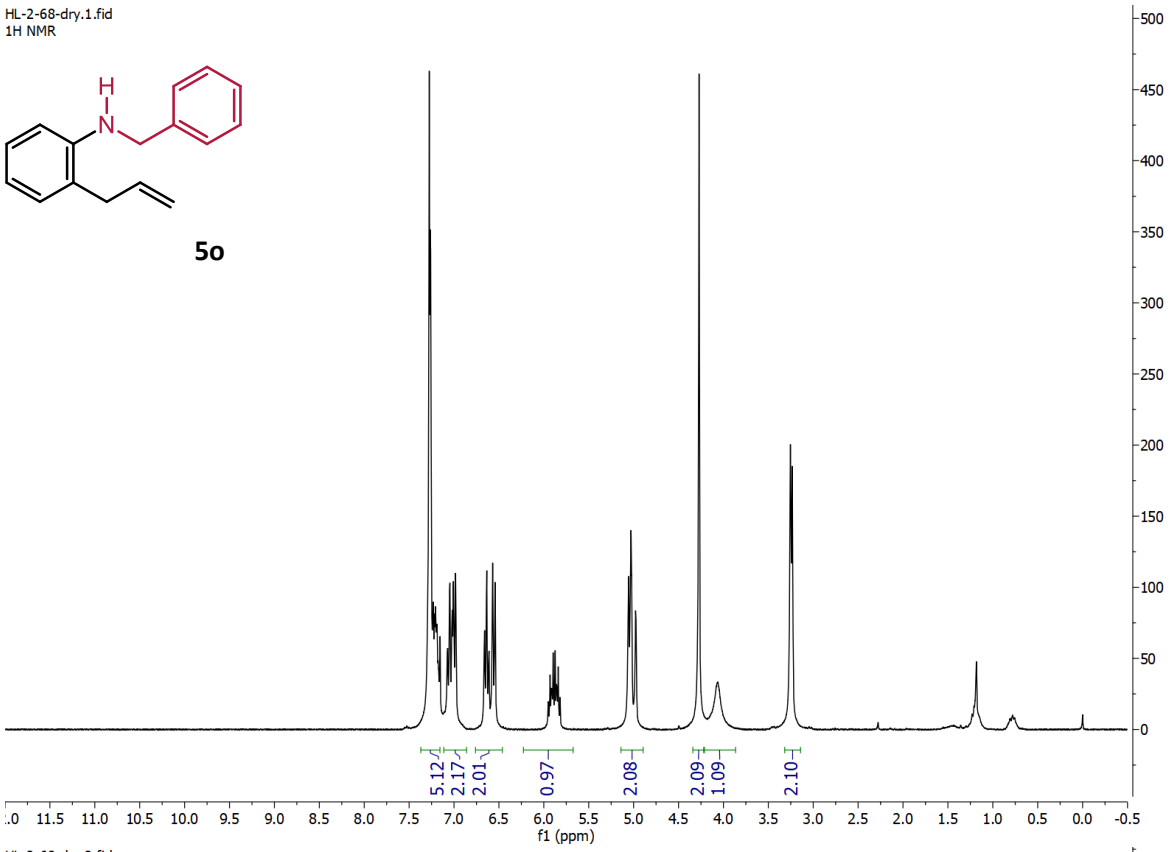

MAA-11-149p dry.2.fid
1d_13C_1_hour CDCl3 D:\\ Beau 10
140.47
130.90
128.35
128.10
126.85
125.10
54.01
48.92
30.34
29.83
17.90
f1 (ppm)


MAA-11-91p dry.1.fid
1H
5m
2.05
1.01
2.08
1.00
2.04
0.78
2.16
2.12
2.14
f1 (ppm)

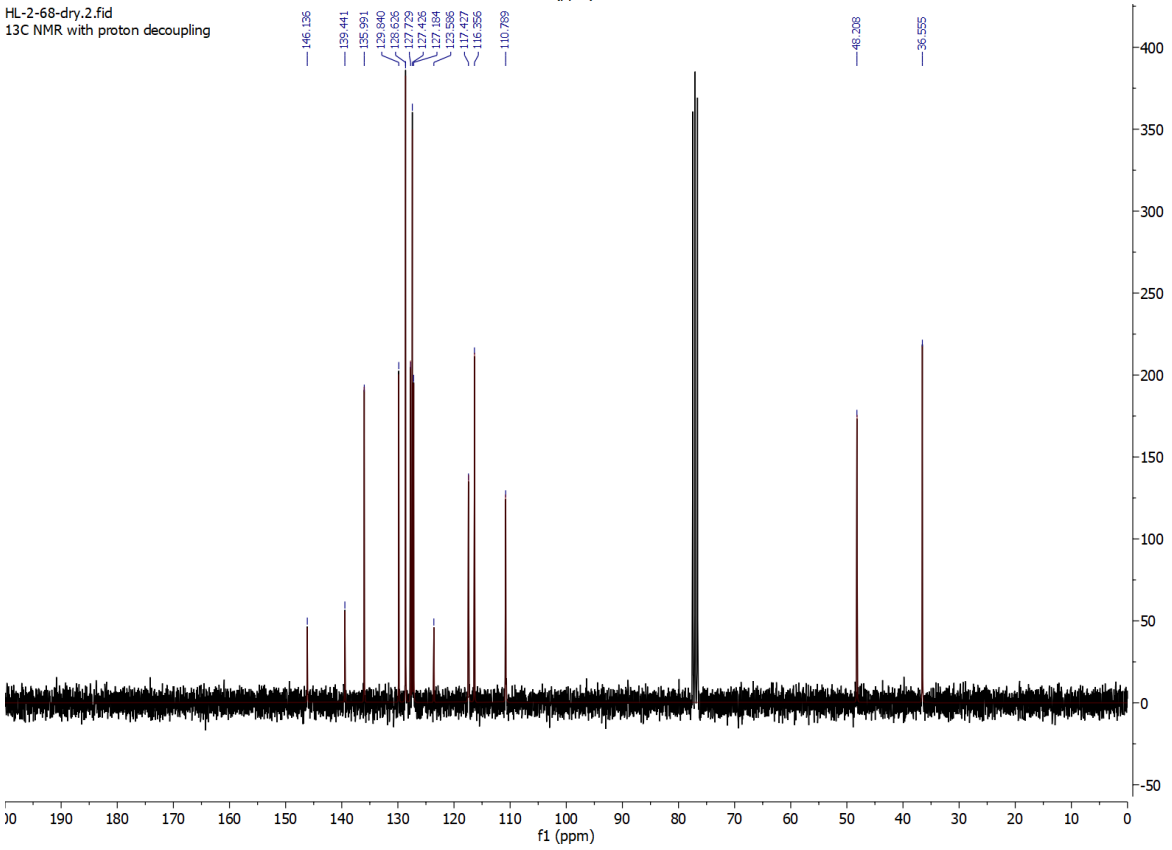

MAA-11-91p dry.2.fid
13C
148.35
138.02
129.21
117.15
115.06
112.70
43.38
31.28
28.64
f1 (ppm)

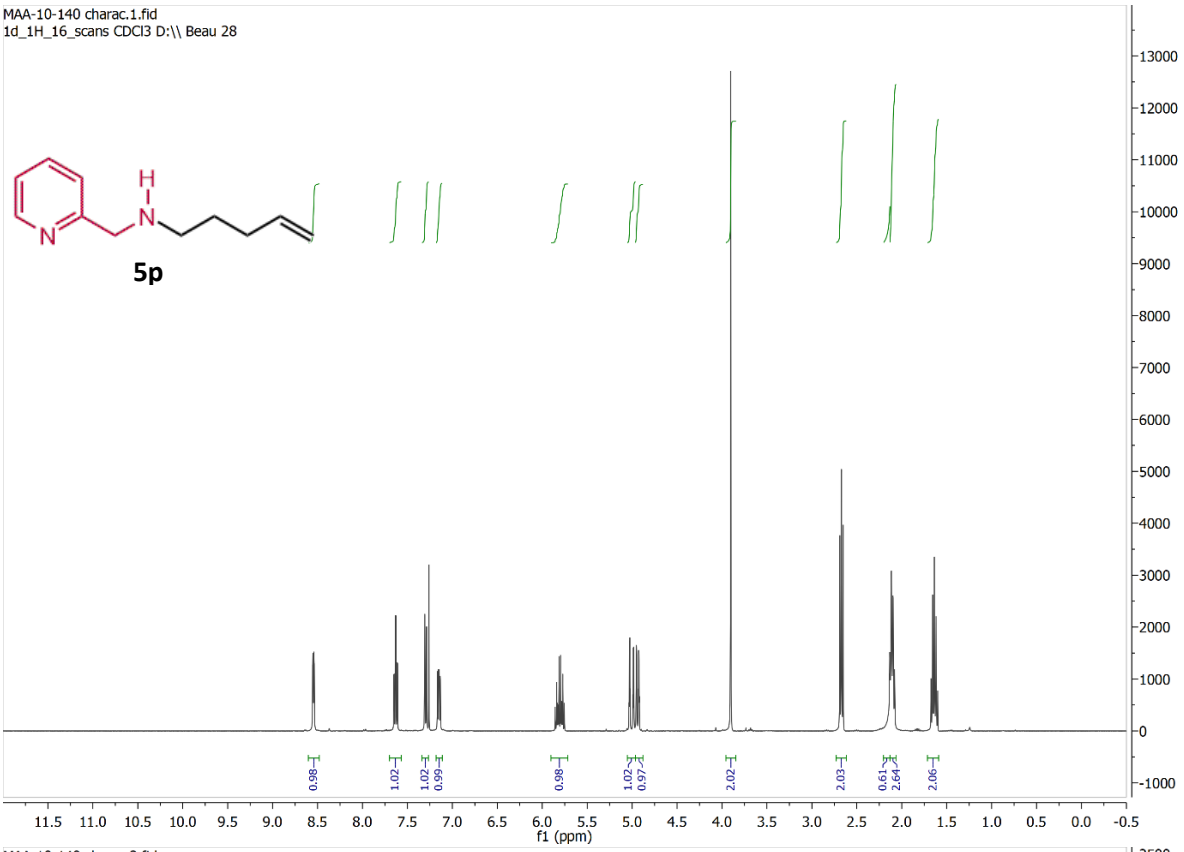

MAA-11-141p charac.1.fid
1H
Me
H
N
Me
5n
1.00
1.98
0.99
2.04
2.05
6.06
2.27
2.13
f1 (ppm)

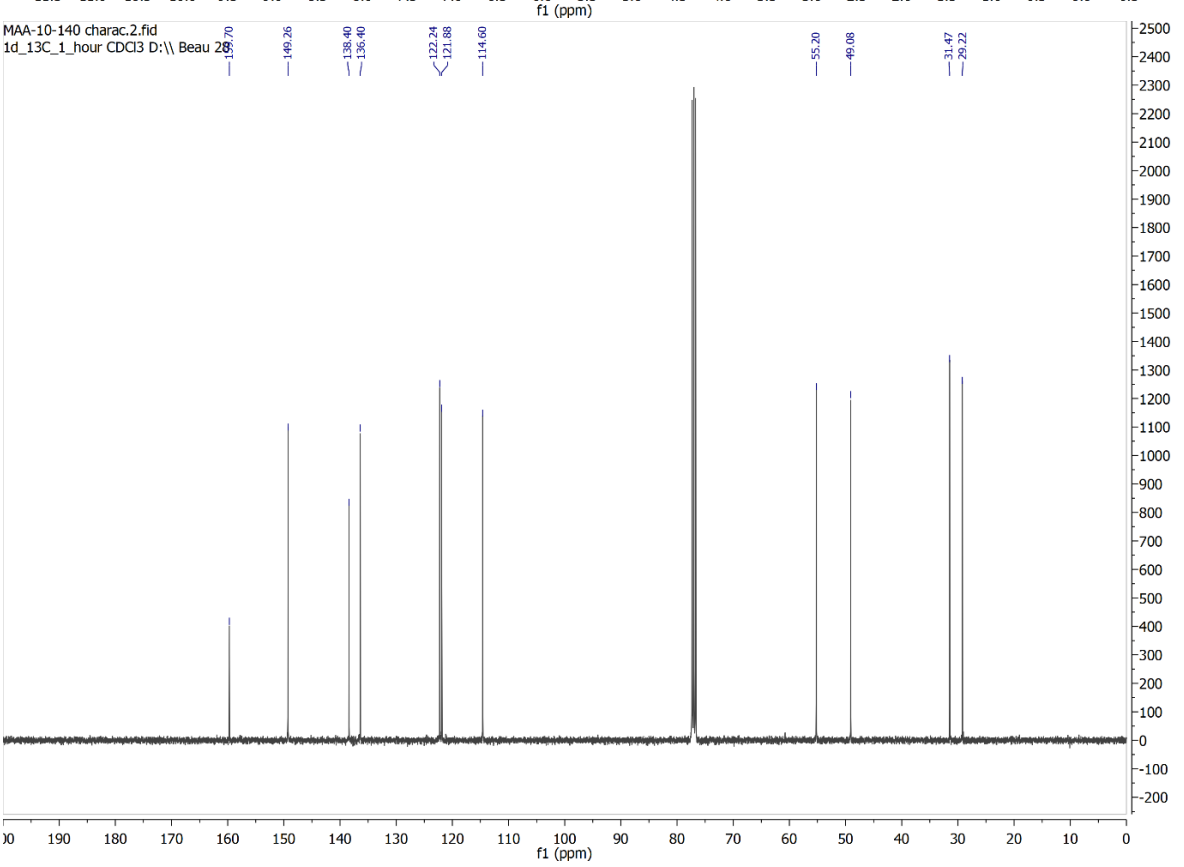

MAA-11-141p charac.3.fid
13C
148.36
138.86
138.08
119.29
115.01
110.75
43.50
31.29
28.70
21.48
f1 (ppm)

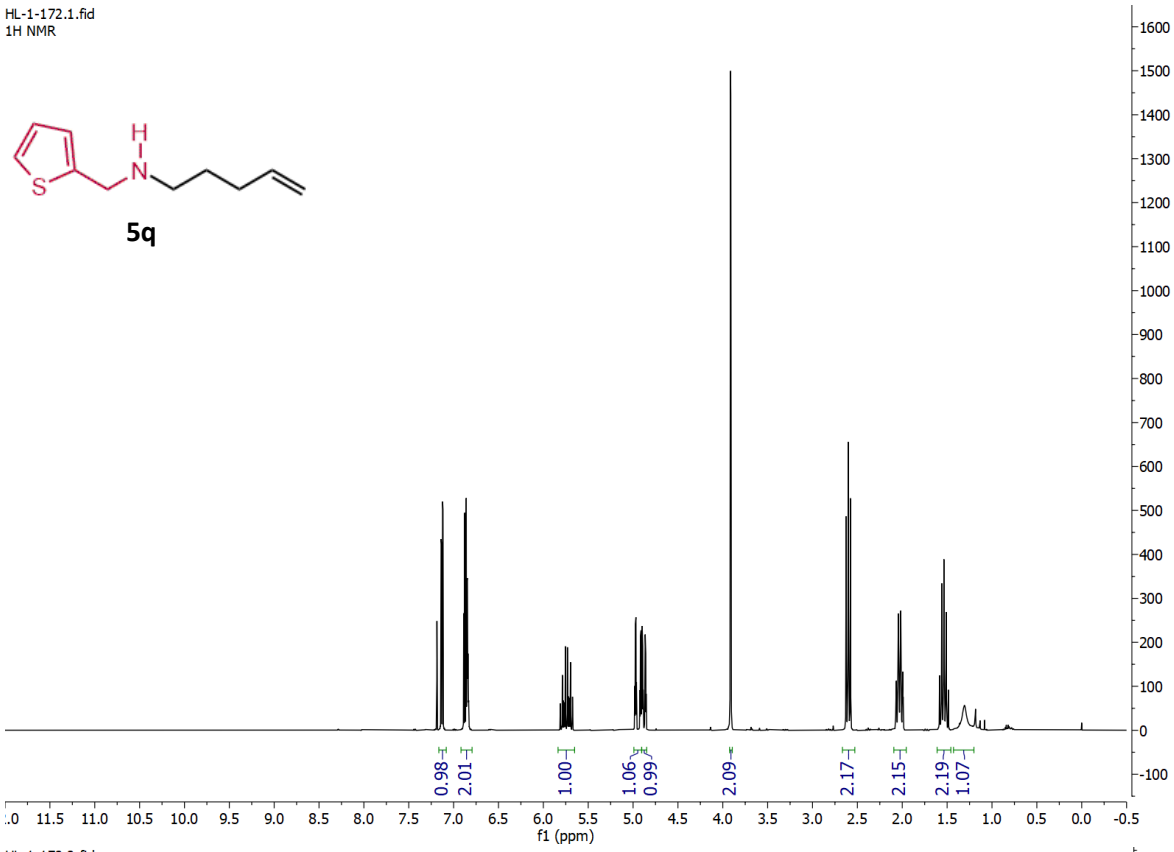

HL-2-68-dry.1.fid
1H NMR
5.12
2.17
2.01
0.97
2.08
2.09
1.09
2.10
f1 (ppm)

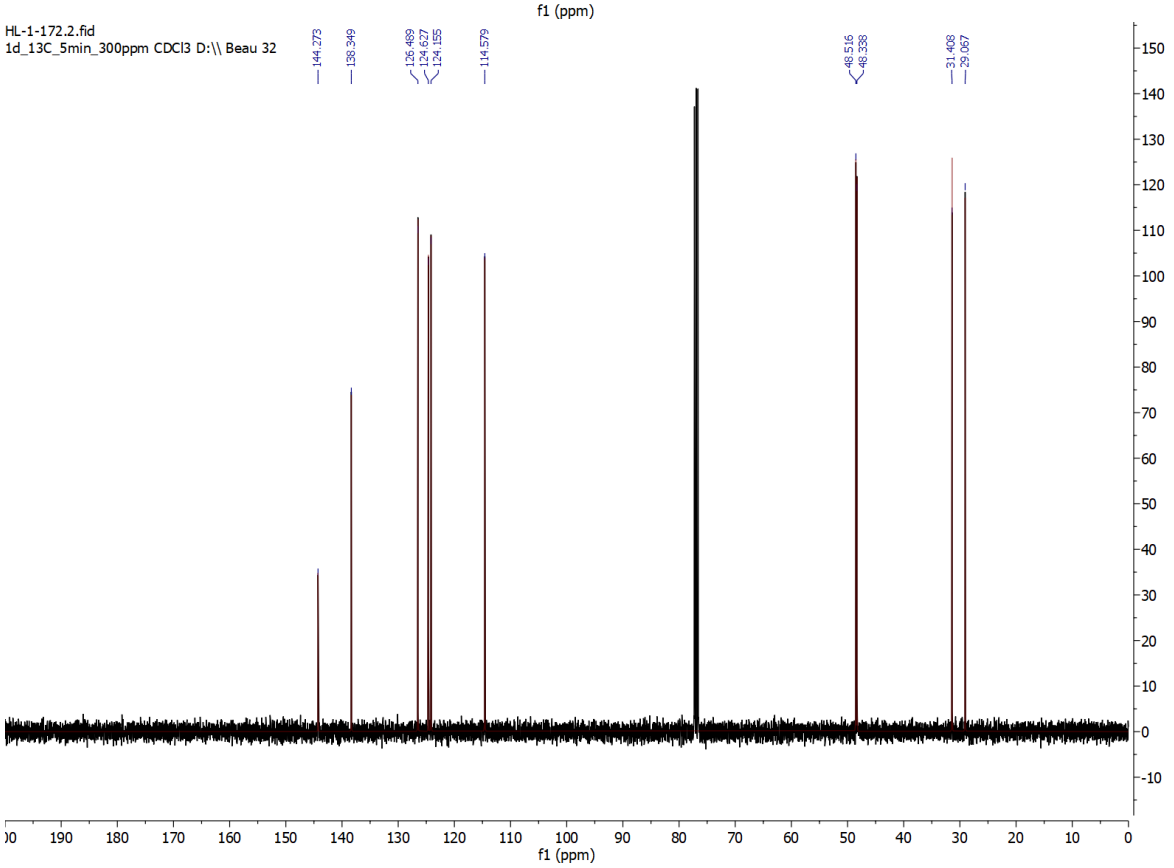
5o

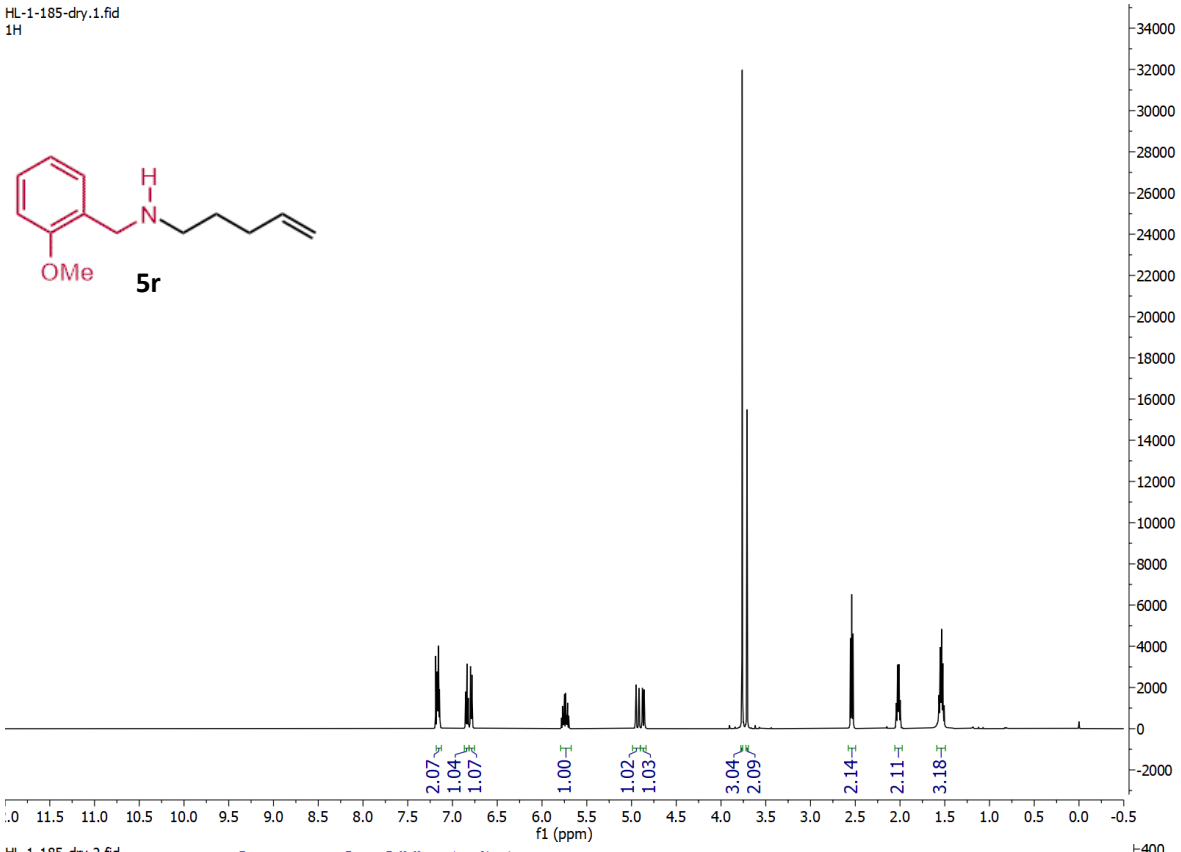

HL-2-68-dry.2.fid
13C NMR with proton decoupling
146.136
139.441
135.991
129.840
128.626
127.729
127.426
127.184
123.586
117.427
116.356
110.789
48.208
36.555
f1 (ppm)

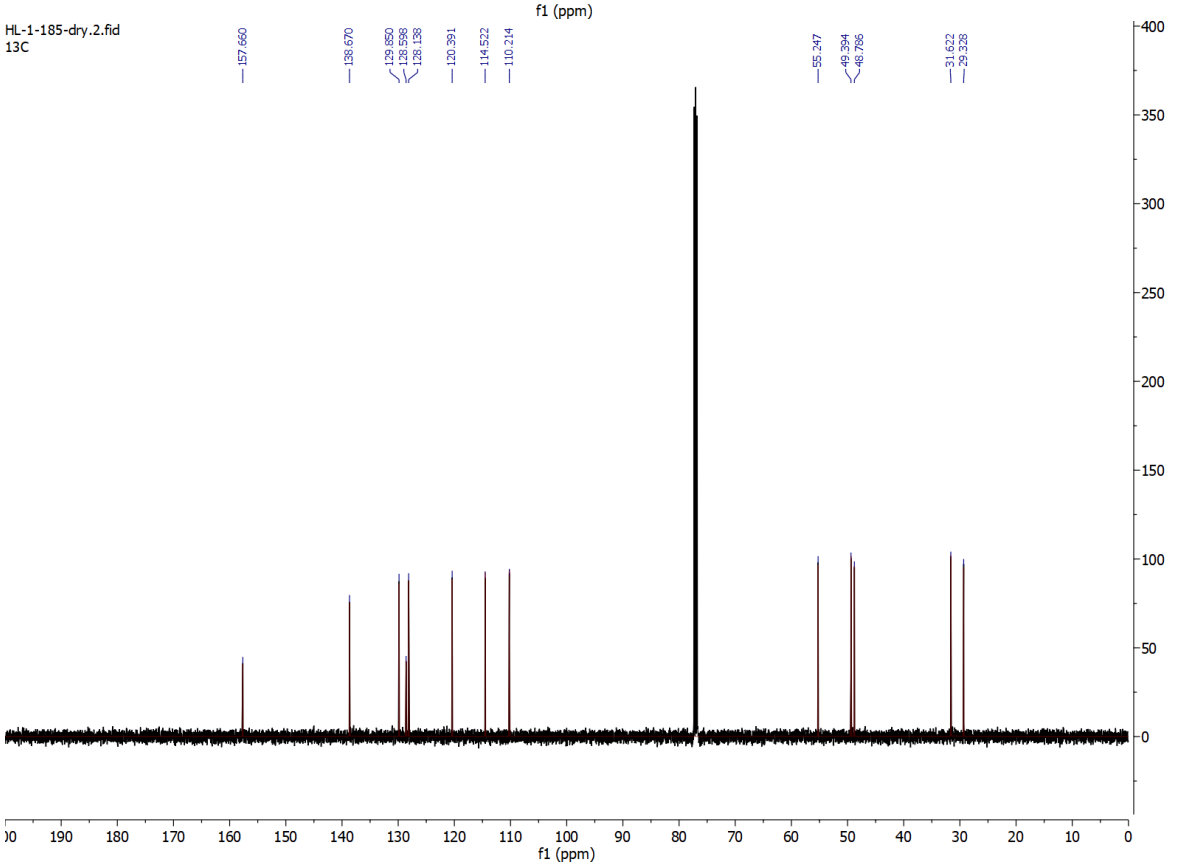

MAA-10-140 charac.1.fid
1d_1H_16_scans CDCl3 D:\\ Beau 28
5p
f1 (ppm)


MAA-10-140 charac.2.fid
1d_13C_1_hour CDCl3 D:\\ Beau 28
159.70
149.26
138.40
136.40
122.24
121.88
114.60
55.20
49.08
31.47
29.22
f1 (ppm)


HL-1-172.1.fid
1H NMR
5q
0.98
2.01
1.00
1.06
0.99
2.09
2.17
2.15
2.19
1.07
f1 (ppm)

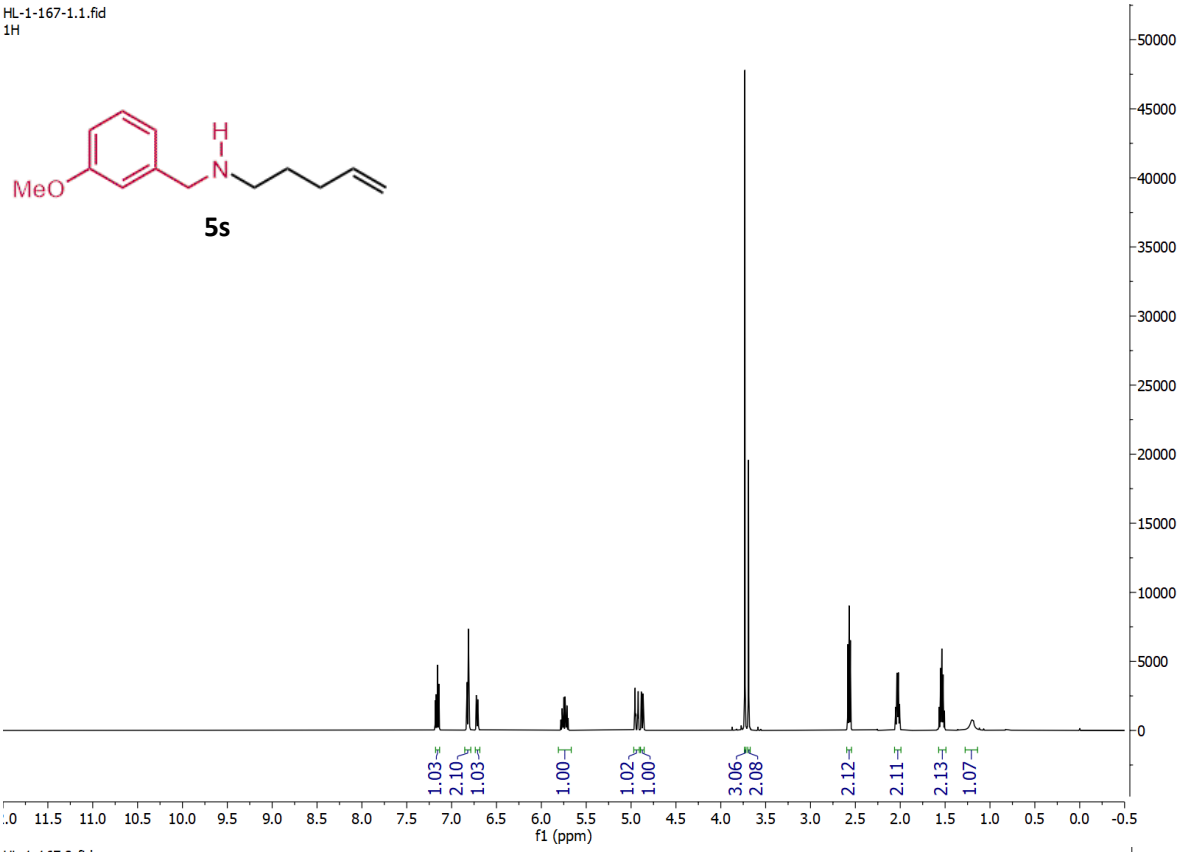

HL-1-172.2.fid
1d_13C_5min_300ppm CDCl3 D:\\ Beau 32
144.273
138.349
126.489
124.627
124.155
114.579
48.516
48.338
31.408
29.067
f1 (ppm)


HL-1-185-dry.1.fid
1H
H
N
OMe
5r
2.07
1.04
1.07
1.00
1.02
1.03
3.04
2.09
2.14
2.11
3.18
f1 (ppm)

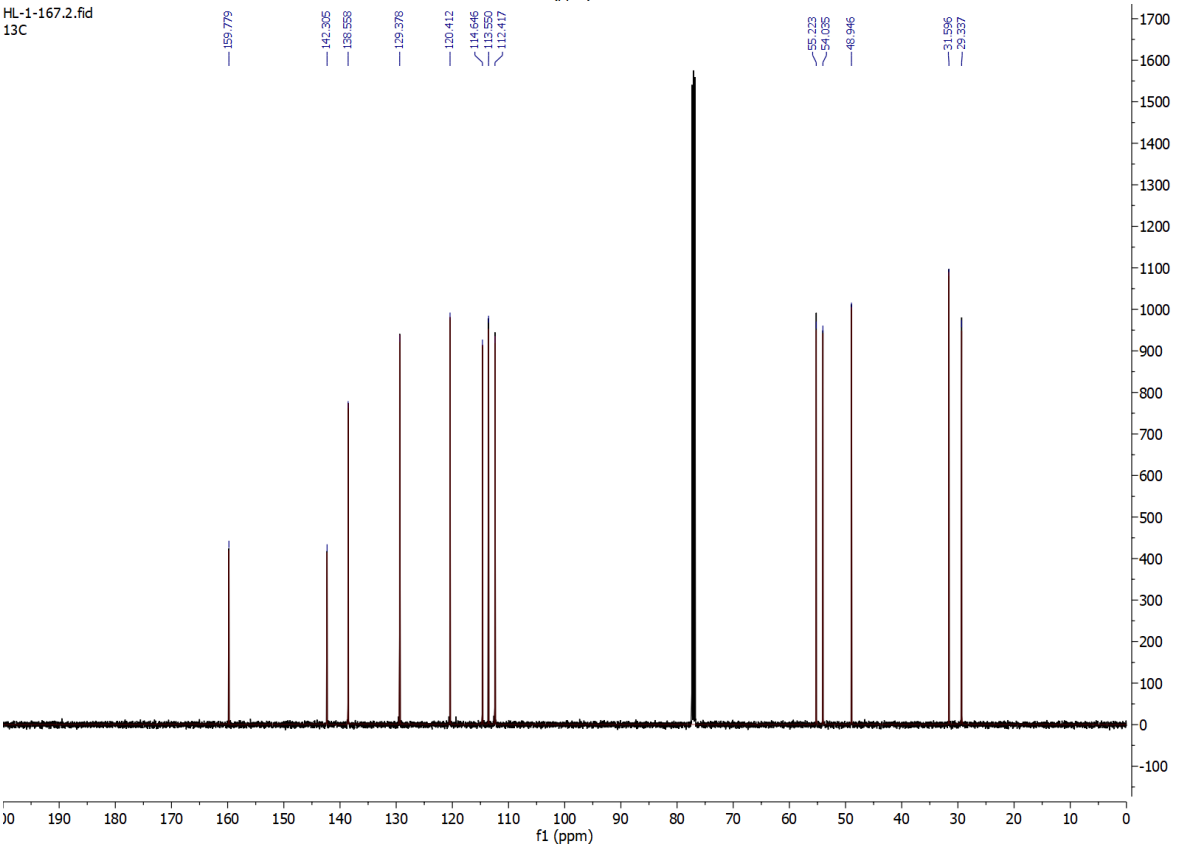

HL-1-185-dry.2.fid
13C
157.660
138.670
129.850
128.598
128.138
120.391
114.522
110.214
55.247
49.394
48.786
31.622
29.328
f1 (ppm)

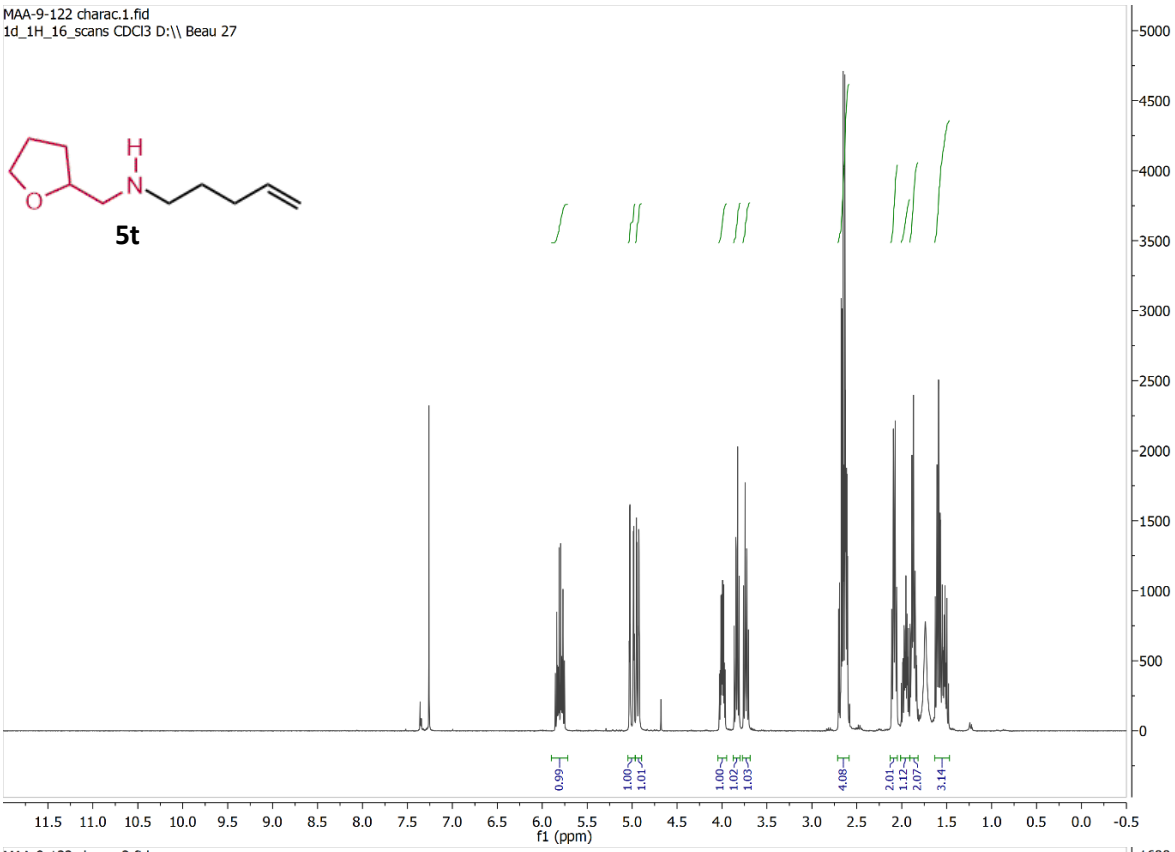
HL-1-167-1.1.fid
1H

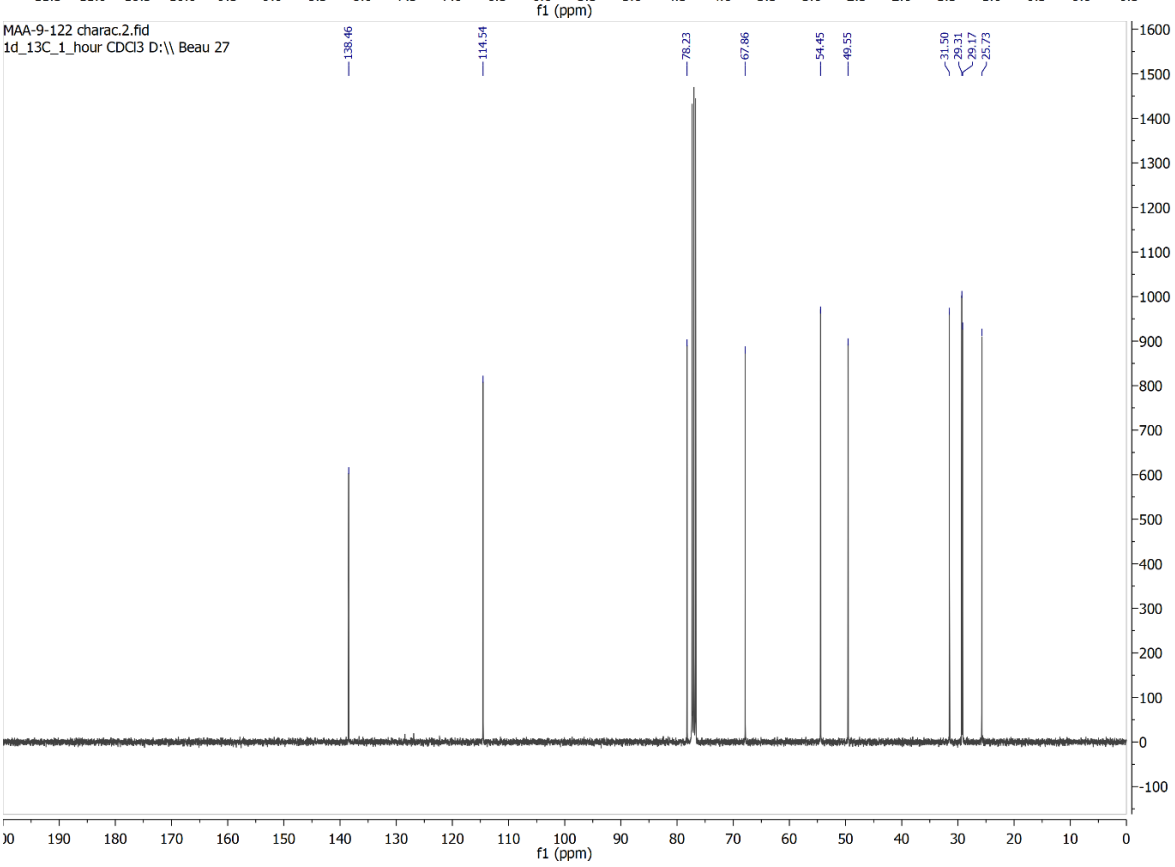
5s

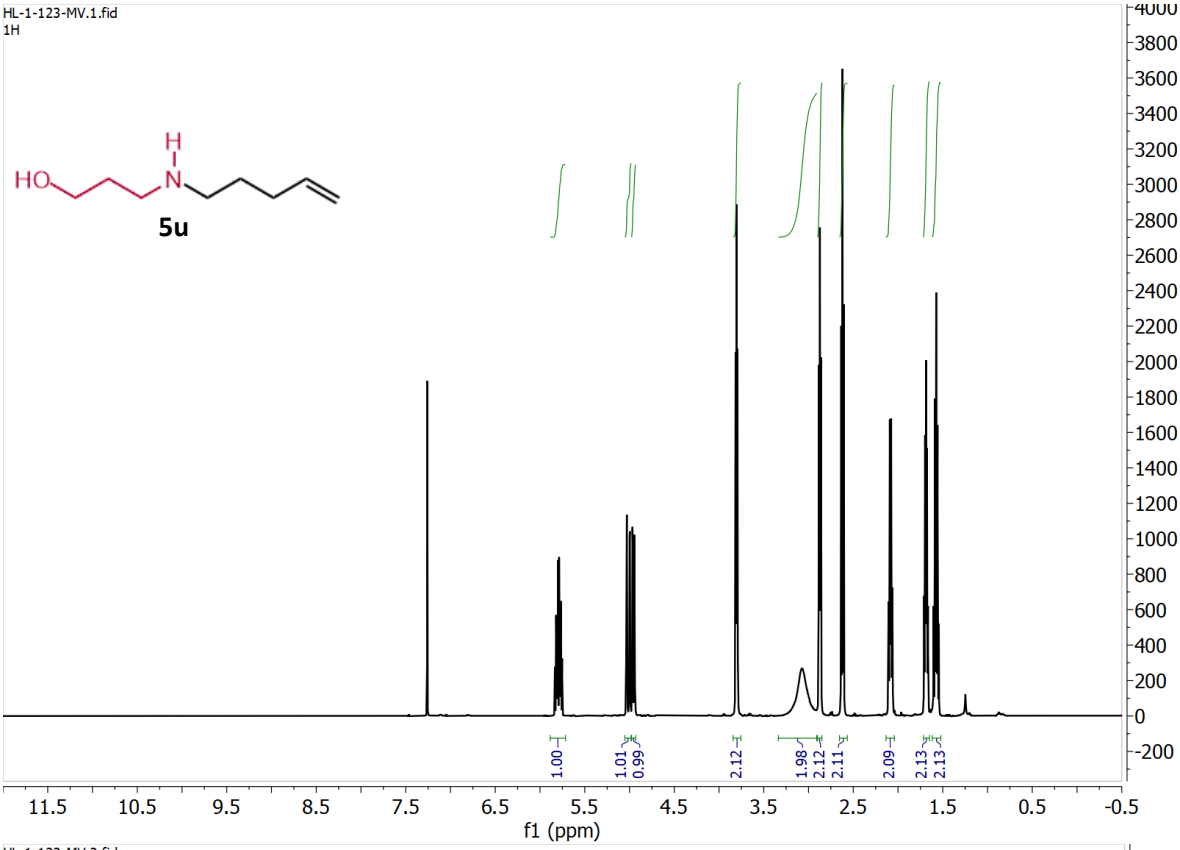


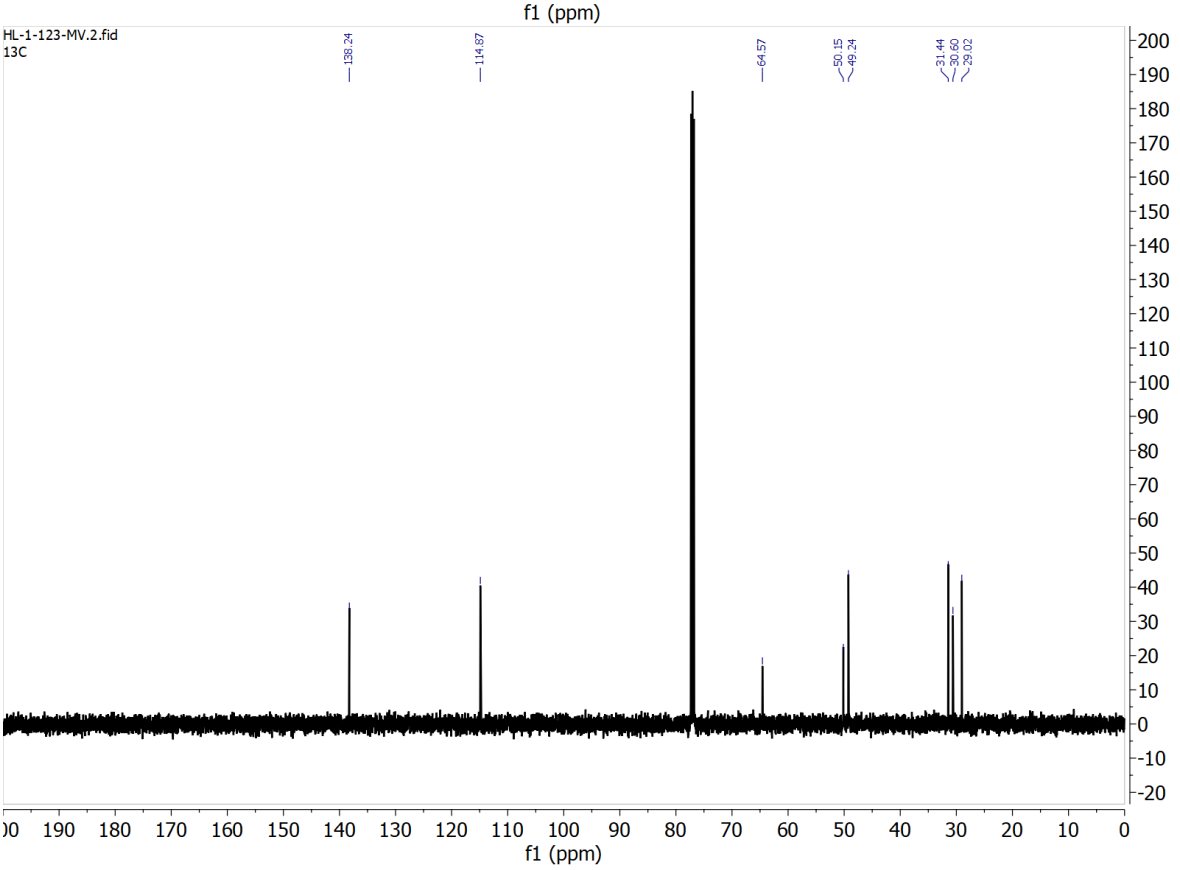
HL-1-167.2.fid
13C

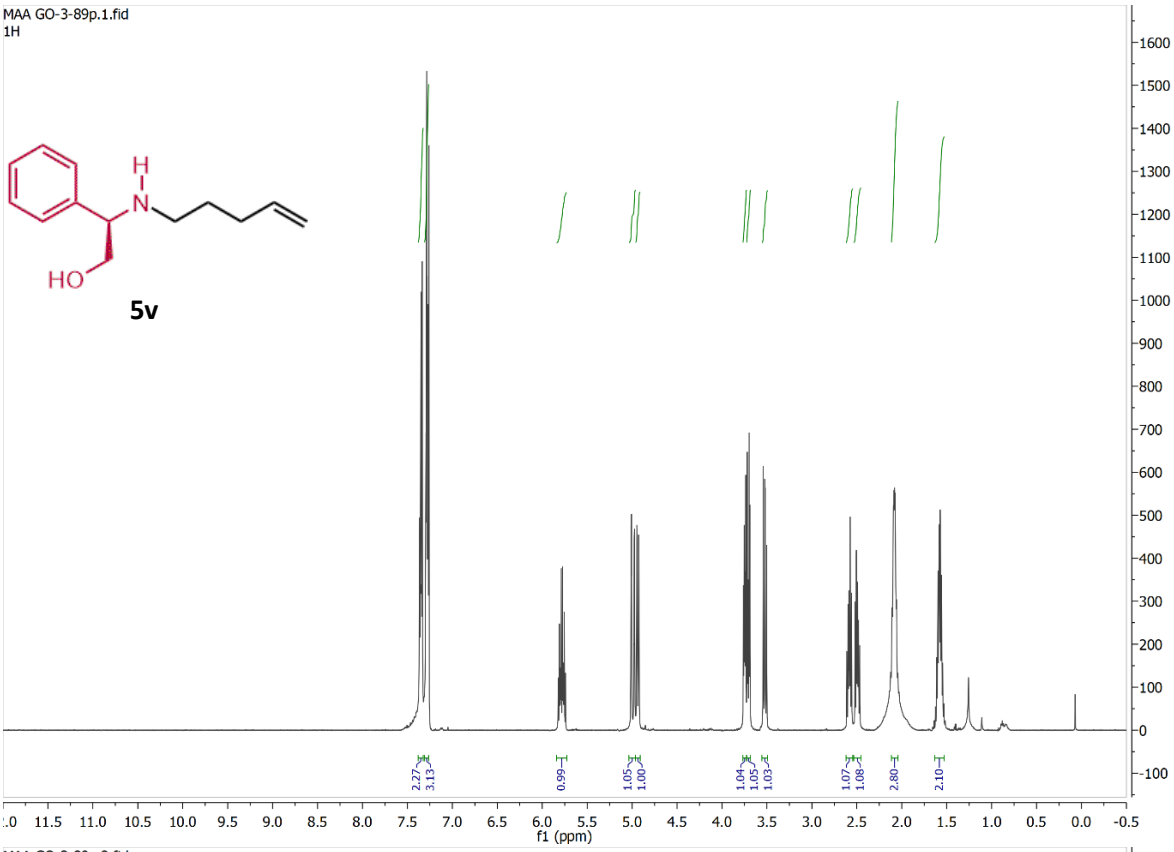


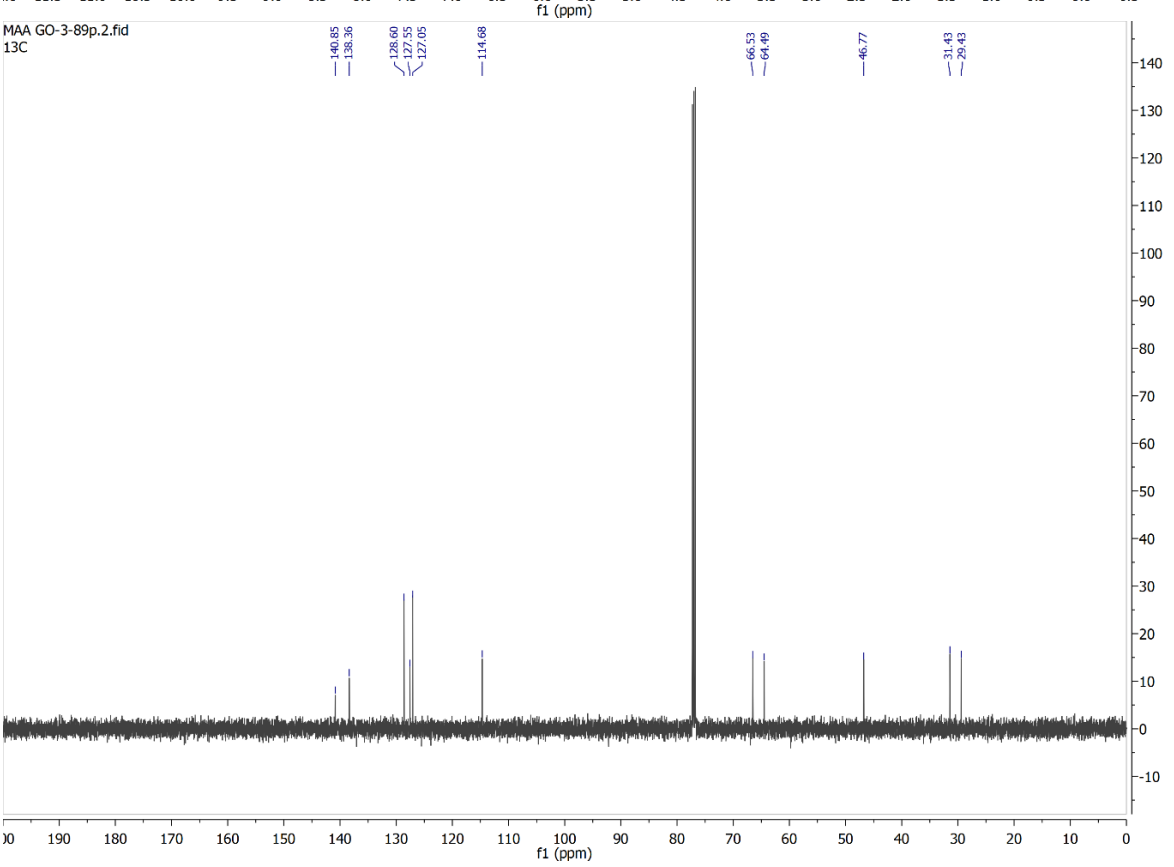

MAA-9-122 charac.1.fid
1d_1H_16_scans CDCl3 D:\\ Beau 27
H
N
O
5t
0.99
1.00
1.01
1.00
1.02
1.03
4.08
2.01
1.12
2.07
3.14
f1 (ppm)

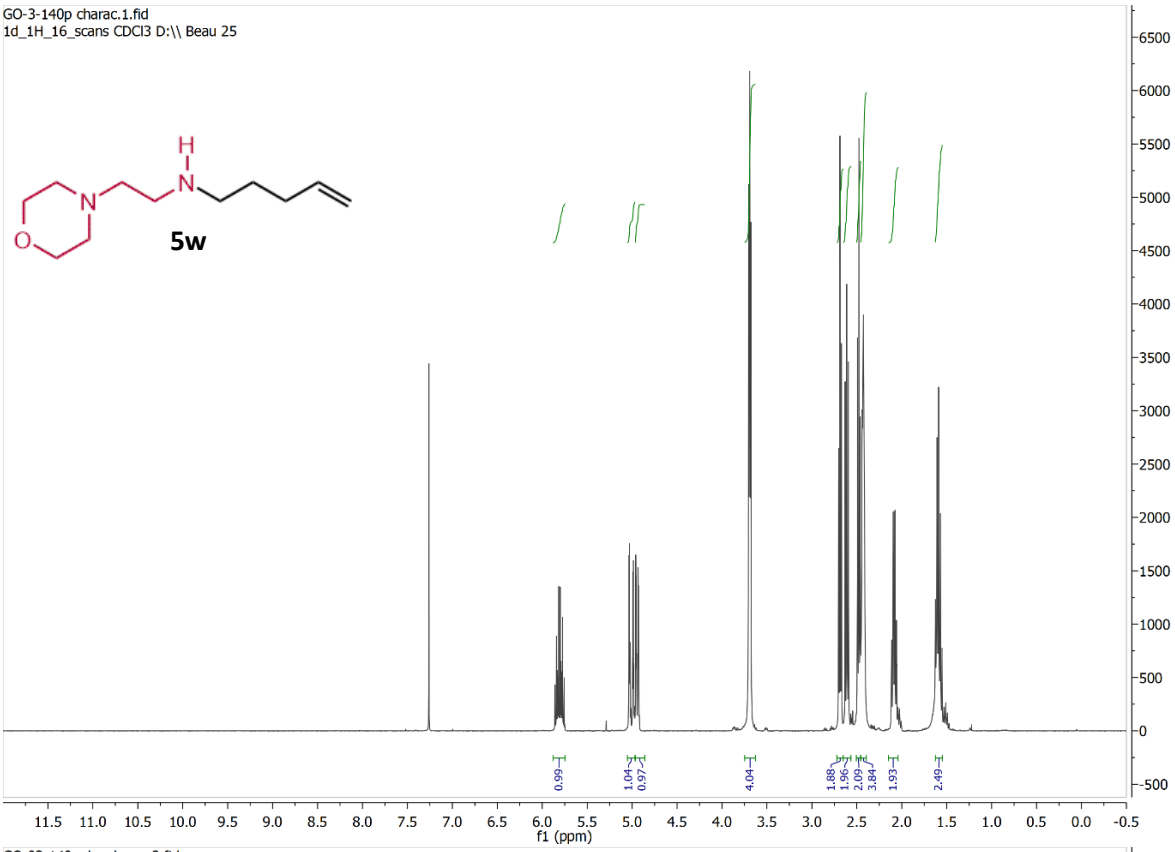

MAA-9-122 charac.2.fid
1d_13C_1_hour CDCl3 D:\\ Beau 27
138.46
114.54
78.23
67.86
54.45
49.55
31.50
29.31
29.17
25.73
f1 (ppm)

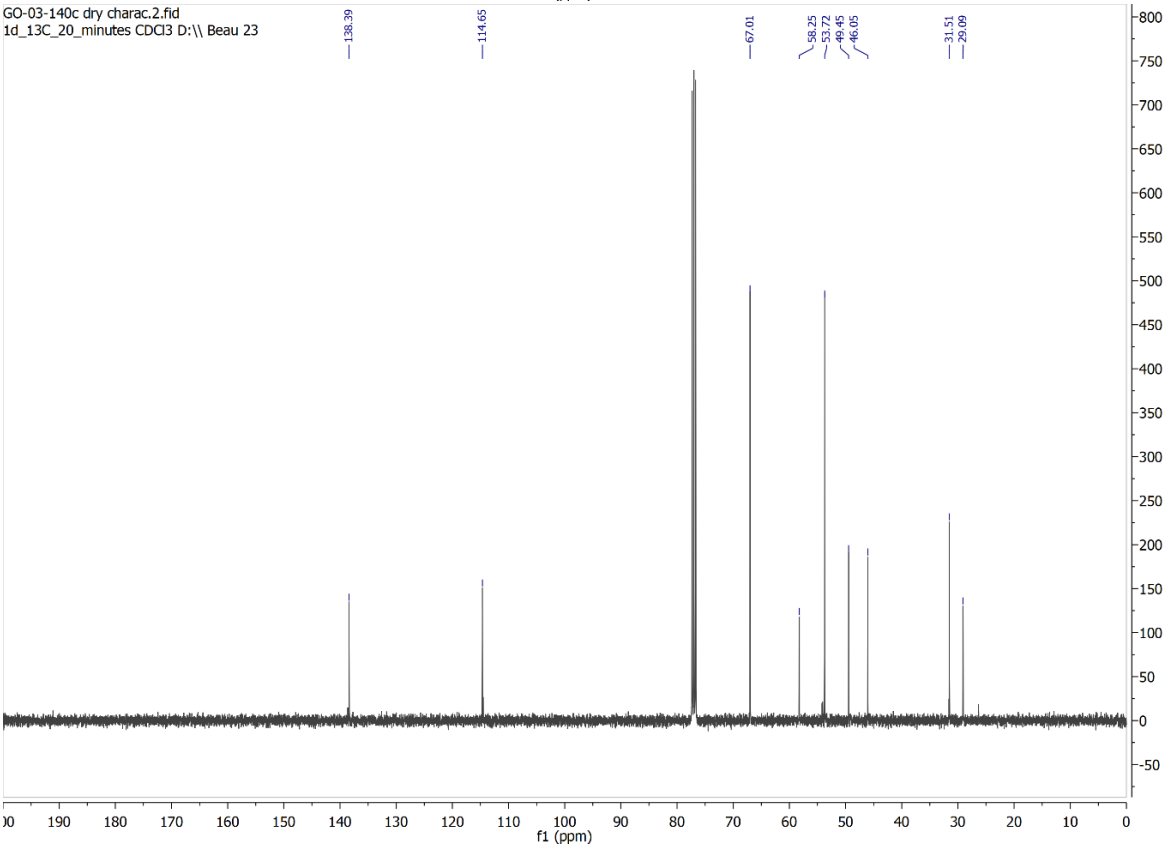

HL-1-123-MV.1.fid
1H
HO
H
N
5u
1.00
1.01
0.99
2.12
1.98
2.12
2.11
2.09
2.13
2.13
f1 (ppm)

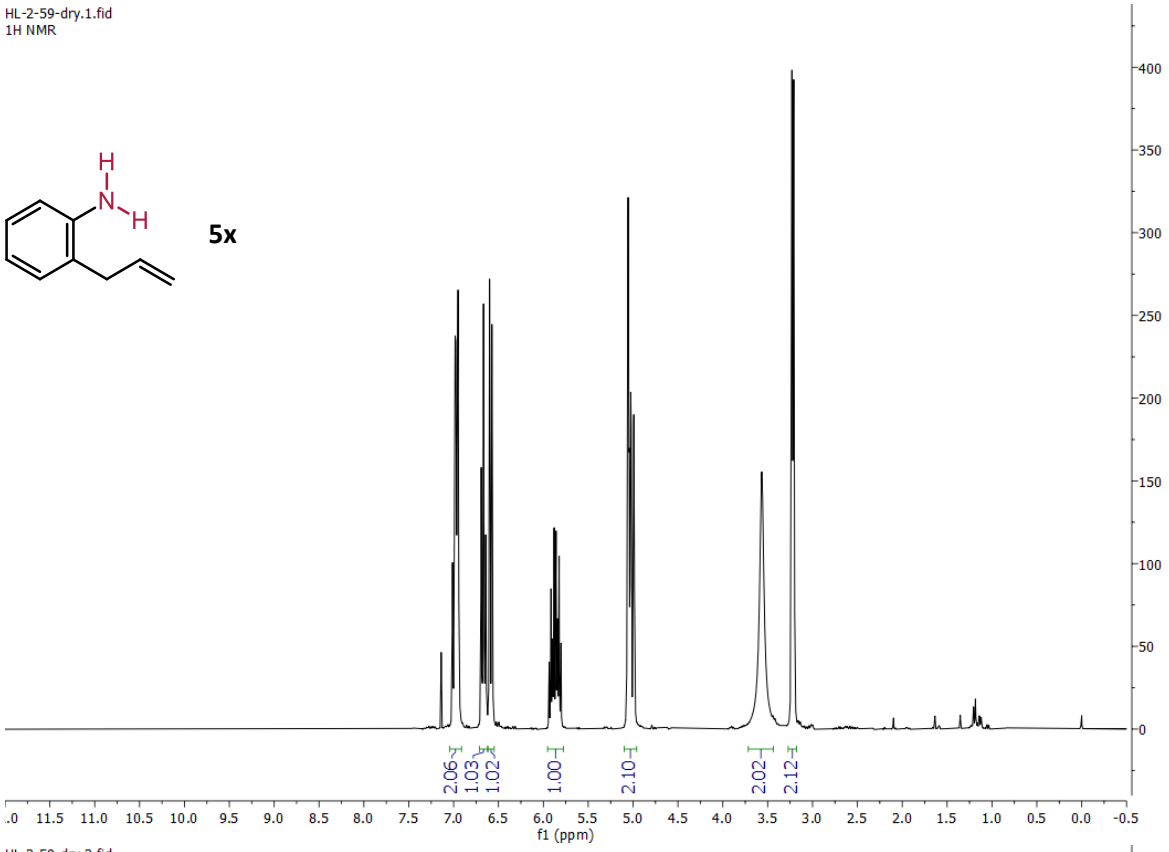

HL-1-123-MV.2.fid
13C
138.24
114.87
64.57
50.15
49.24
31.44
30.60
29.02
f1 (ppm)

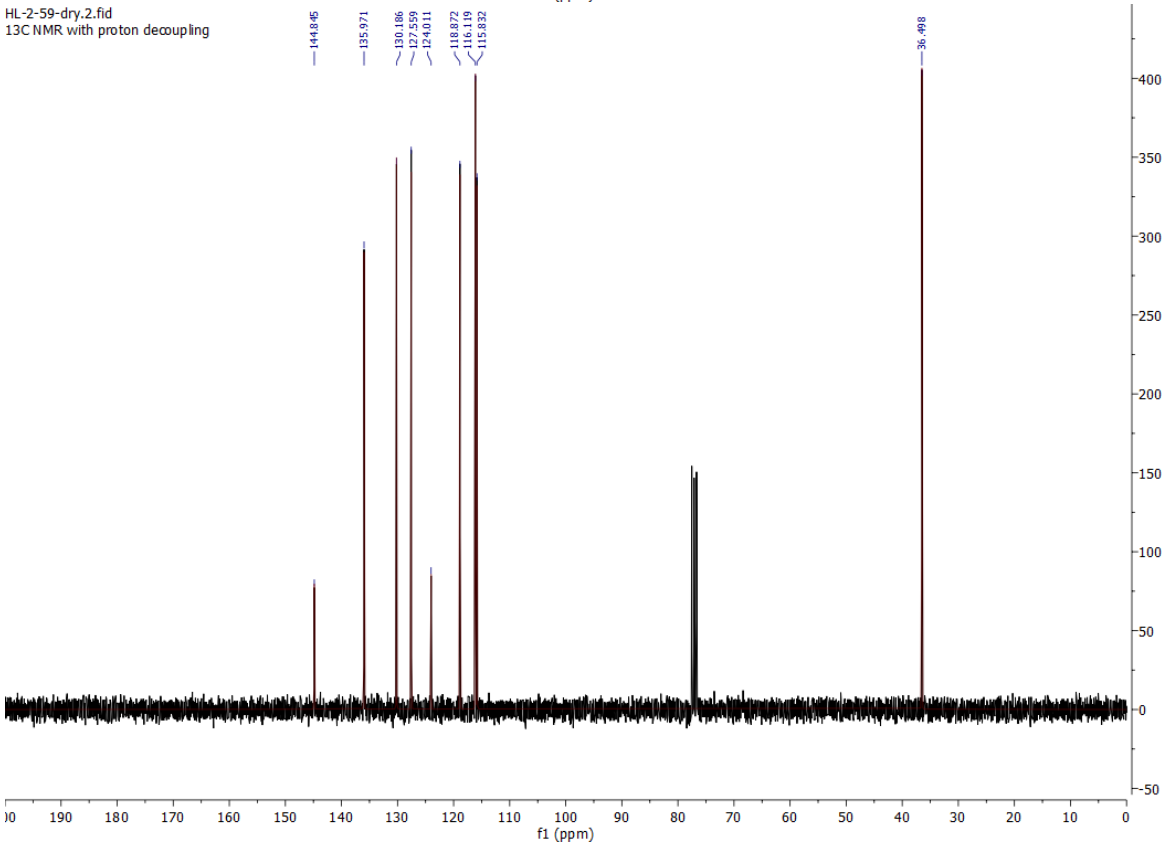

MAA GO-3-89p.1.fid
1H
H
N
HO
5v
2.27
3.13
0.99
1.05
1.00
1.04
1.05
1.03
1.07
1.08
2.80
2.10
f1 (ppm)

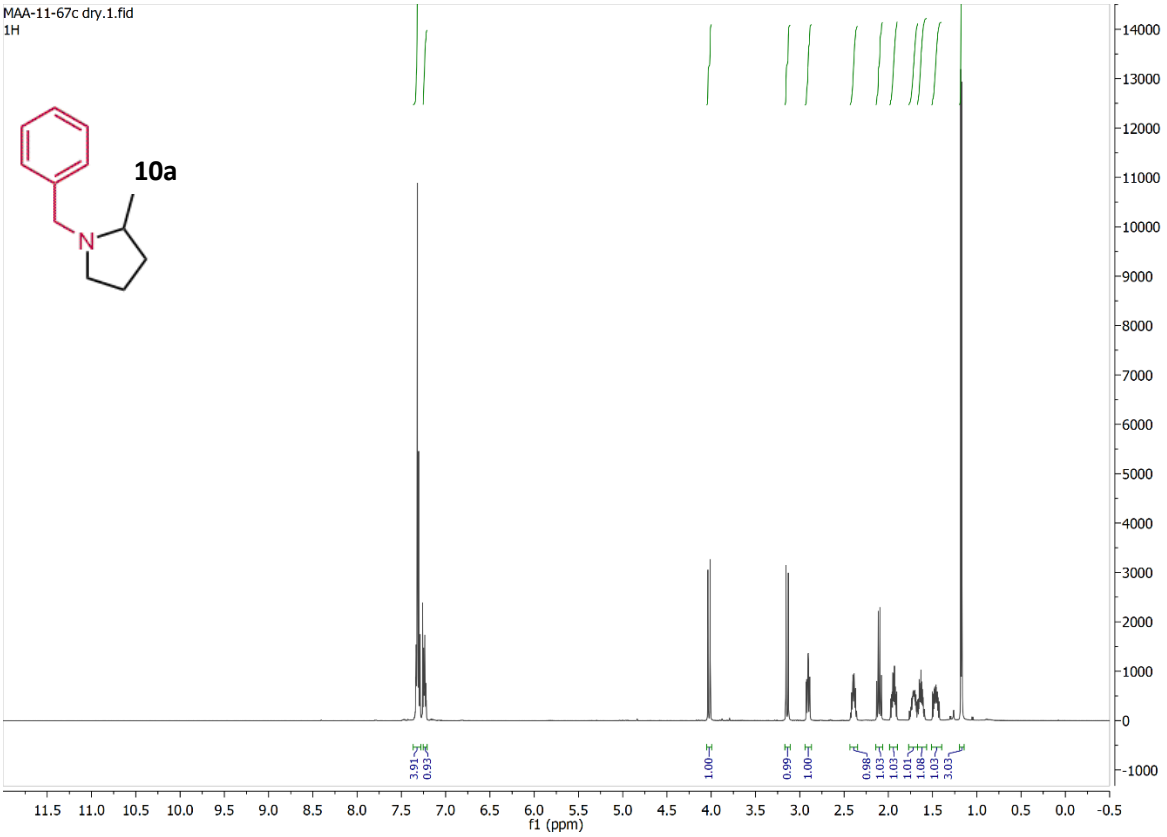

MAA GO-3-89p.2.fid
13C
140.85
138.36
128.60
127.55
127.05
114.68
66.53
64.49
46.77
31.43
29.43
f1 (ppm)

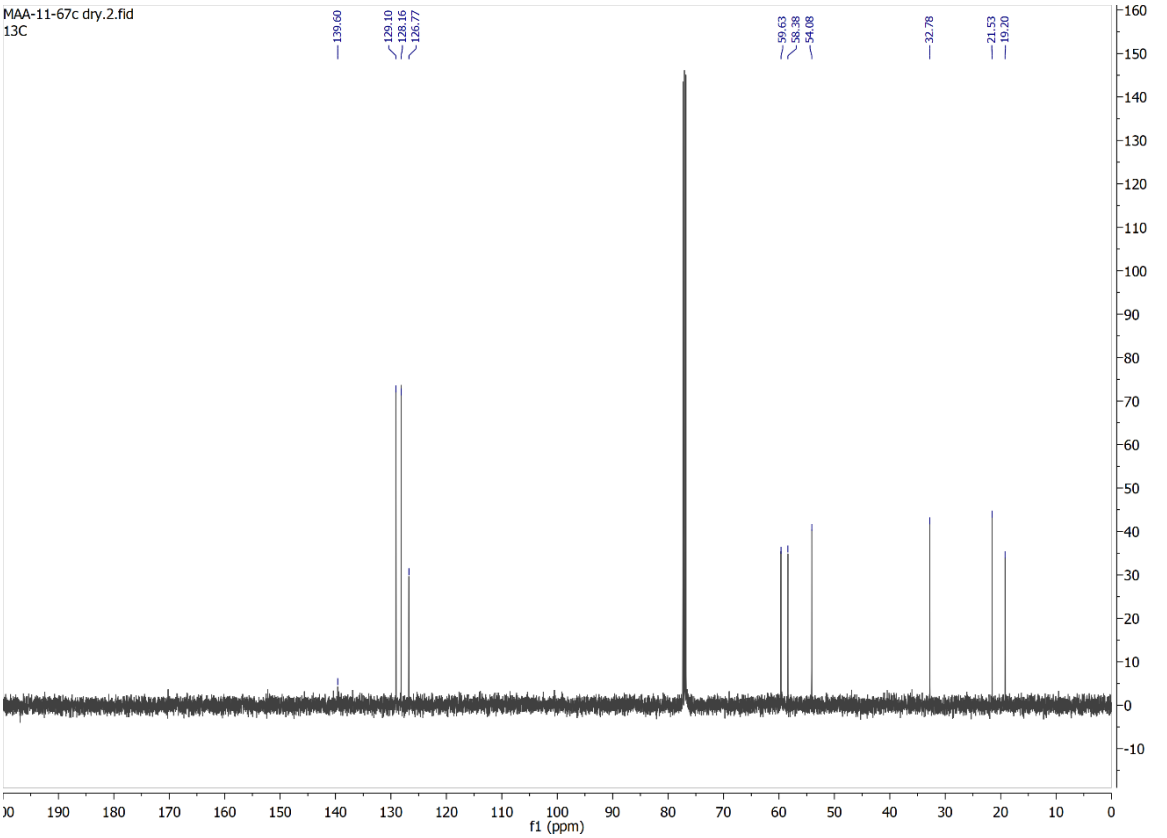

GO-3-140p charac.1.fid
1d_1H_16_scans CDCl3 D:\\ Beau 25
H
N
N
O
5w
0.99
1.04
0.97
4.04
1.88
1.96
2.09
3.84
1.93
2.49
f1 (ppm)

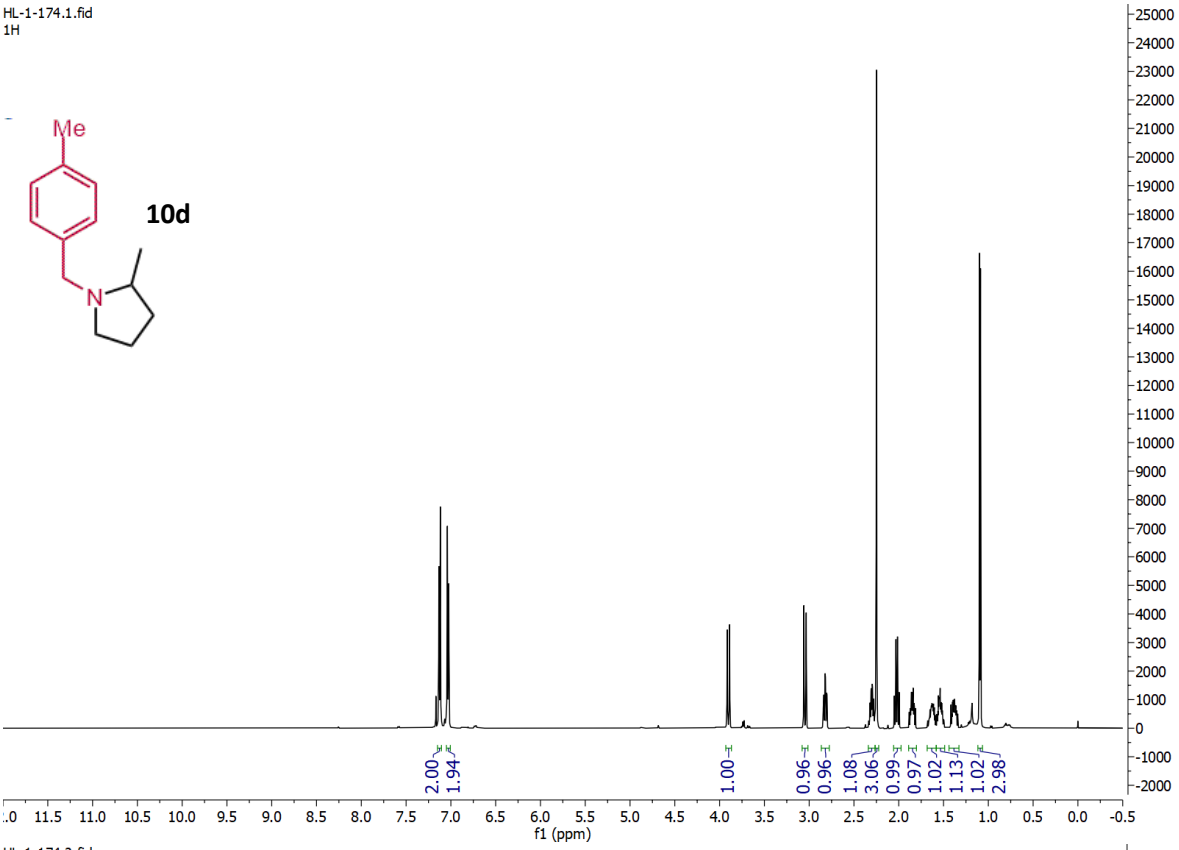

GO-03-140c dry charac.2.fid
1d_13C_20_minutes CDCl3 D:\\ Beau 23
138.39
114.65
67.01
58.25
53.72
49.45
46.05
31.51
29.09
f1 (ppm)

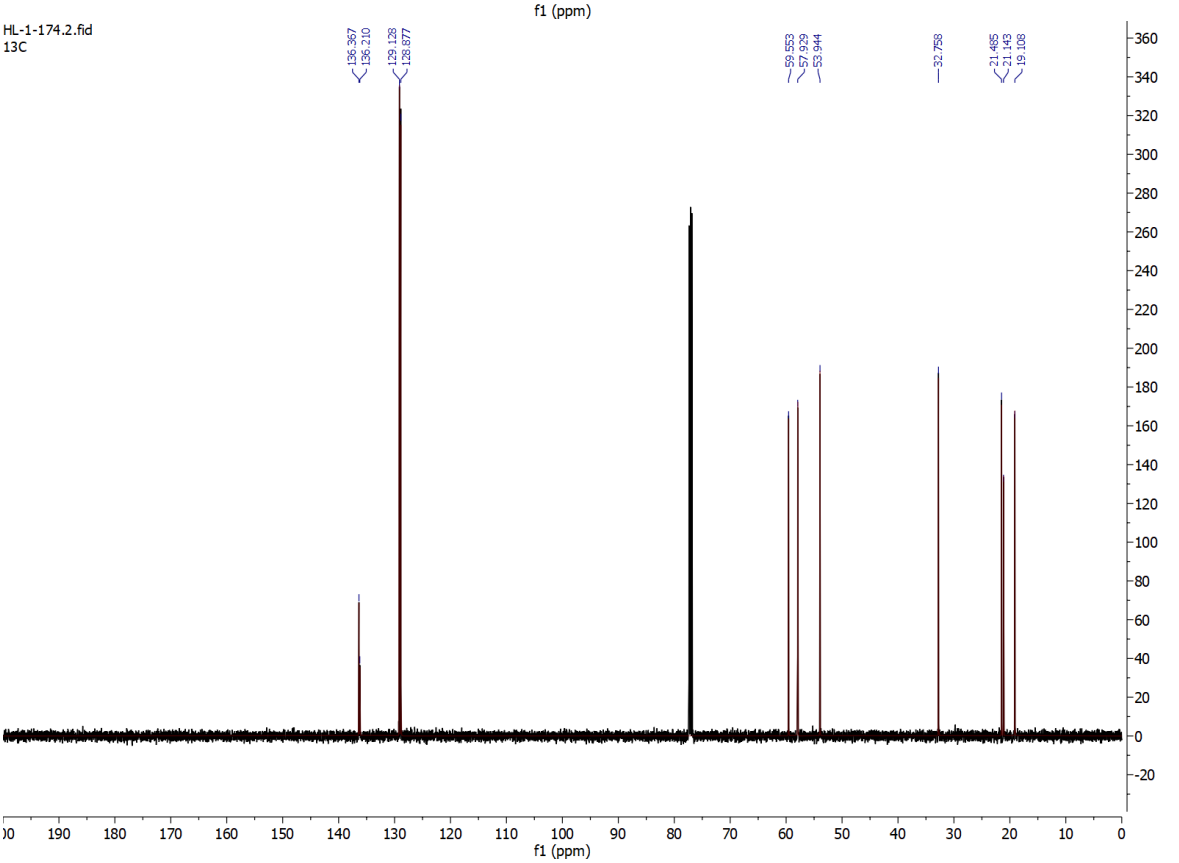

HL-2-59-dry.1.fid
1H NMR
5x
2.06
1.03
1.02
1.00
2.10
2.02
2.12
f1 (ppm)

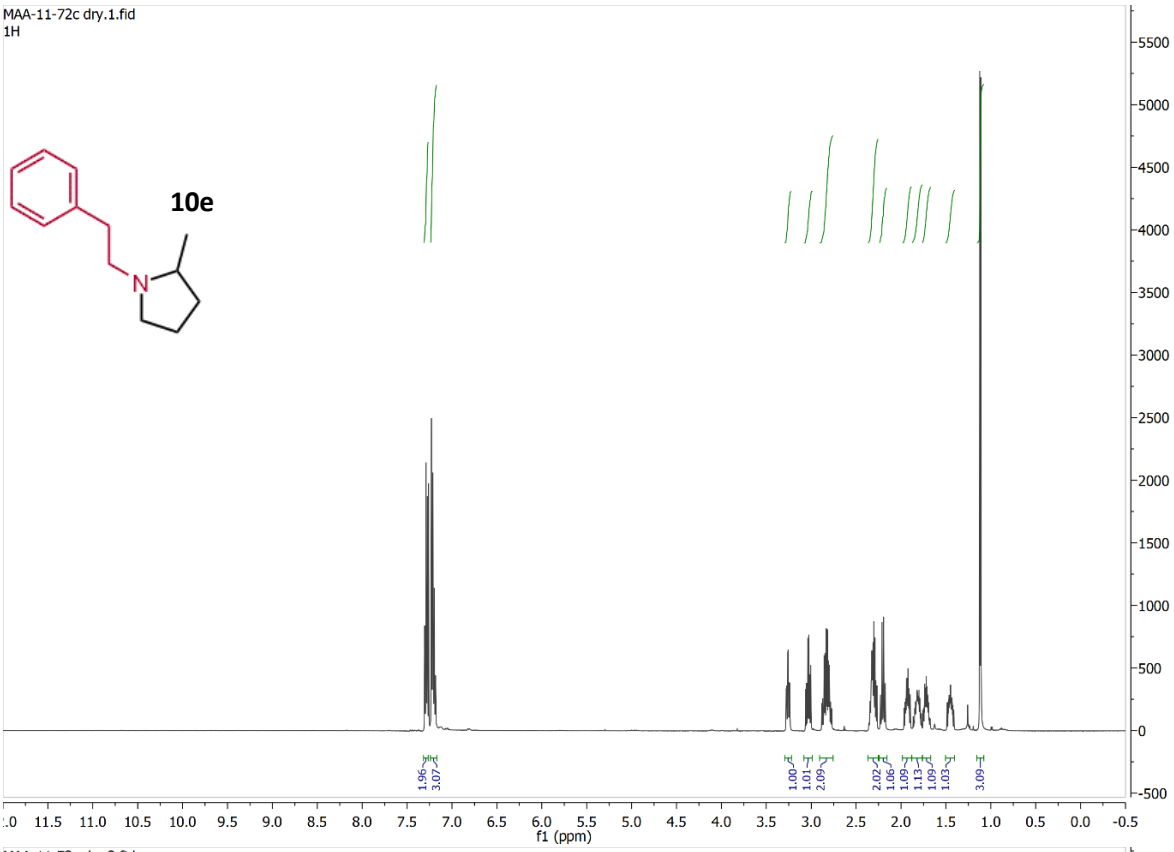

HL-2-59-dry.2.fid
13C NMR with proton decoupling
144.845
135.971
130.186
127.559
124.011
118.872
116.119
115.832
36.498
f1 (ppm)

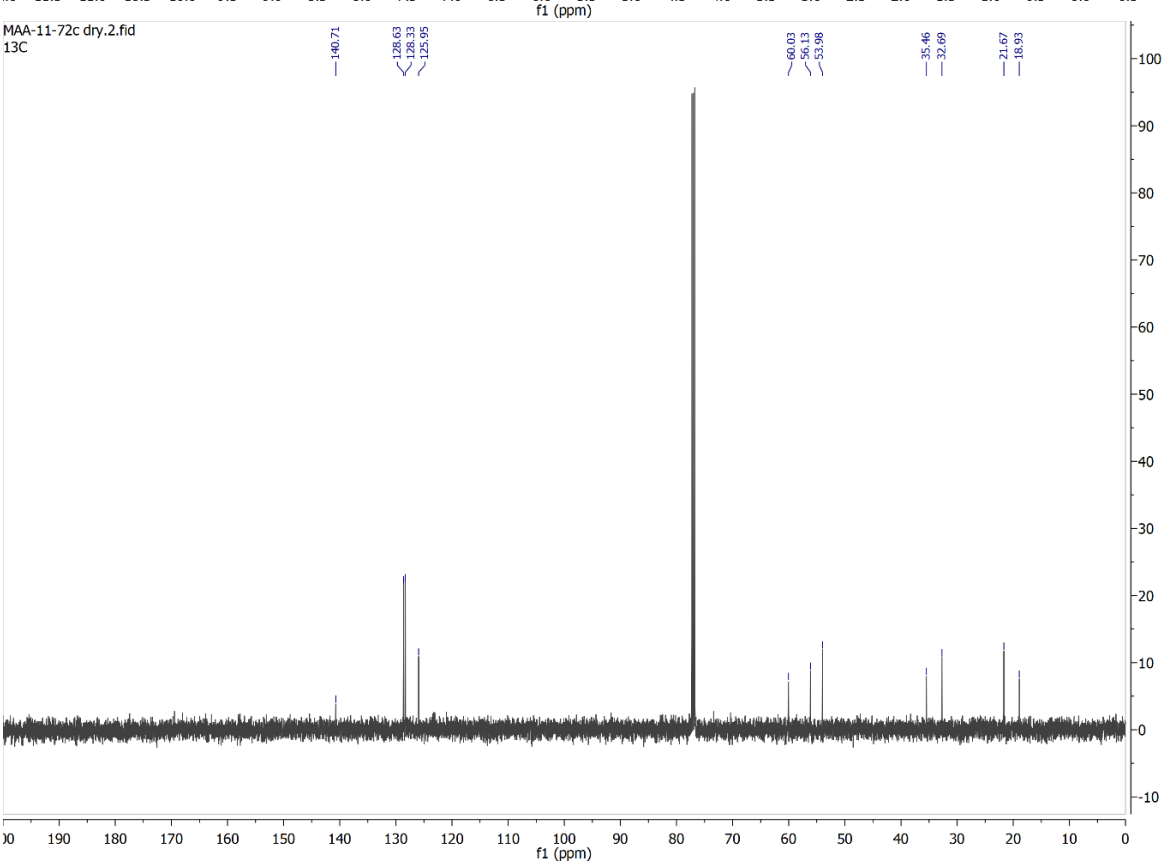

MAA-11-67c dry.1.fid
1H
10a
N
3.91
0.93
1.00
0.99
1.00
0.98
1.03
1.03
1.01
1.08
1.03
3.03
f1 (ppm)

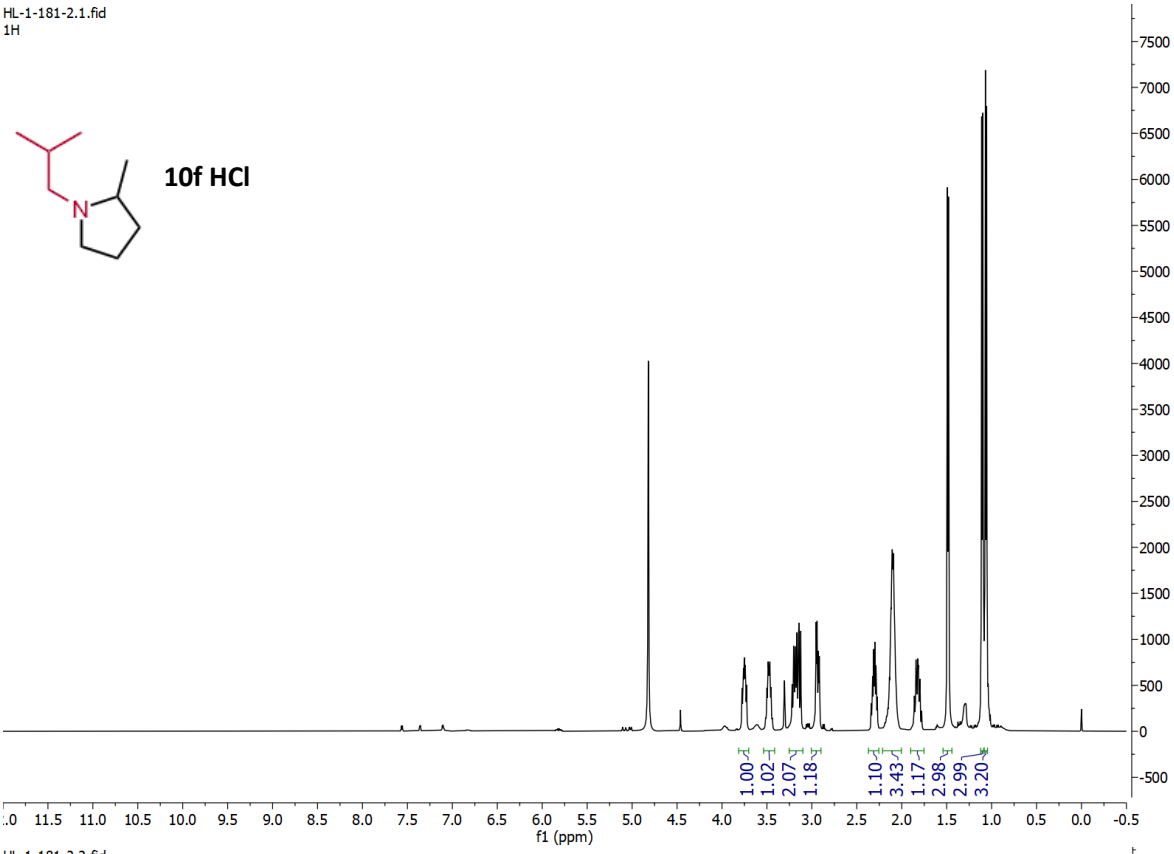

MAA-11-67c dry.2.fid
13C
139.60
129.10
128.16
126.77
59.63
58.38
54.08
32.78
21.53
19.20
f1 (ppm)

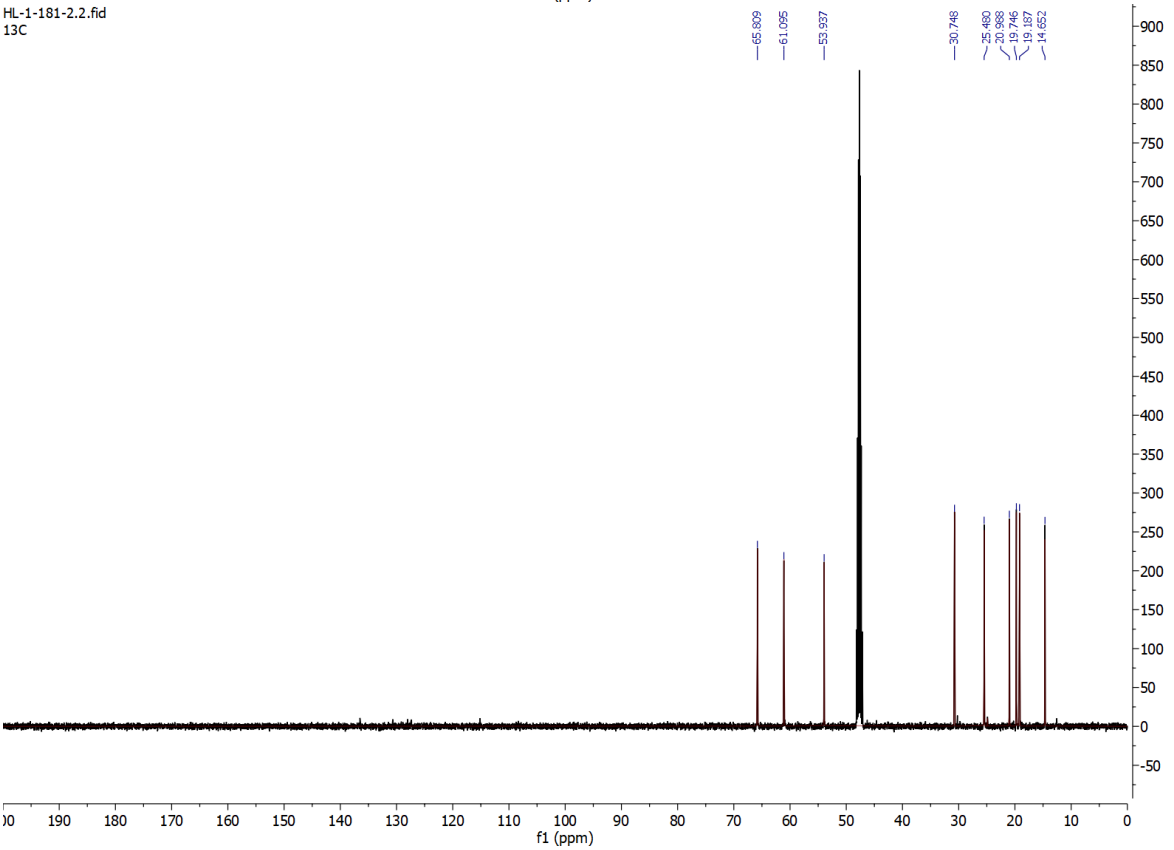

HL-1-174.1.fid
1H
Me
N
10d
2.00
1.94
1.00
0.96
0.96
1.08
3.06
0.99
0.97
1.02
1.13
1.02
2.98
f1 (ppm)

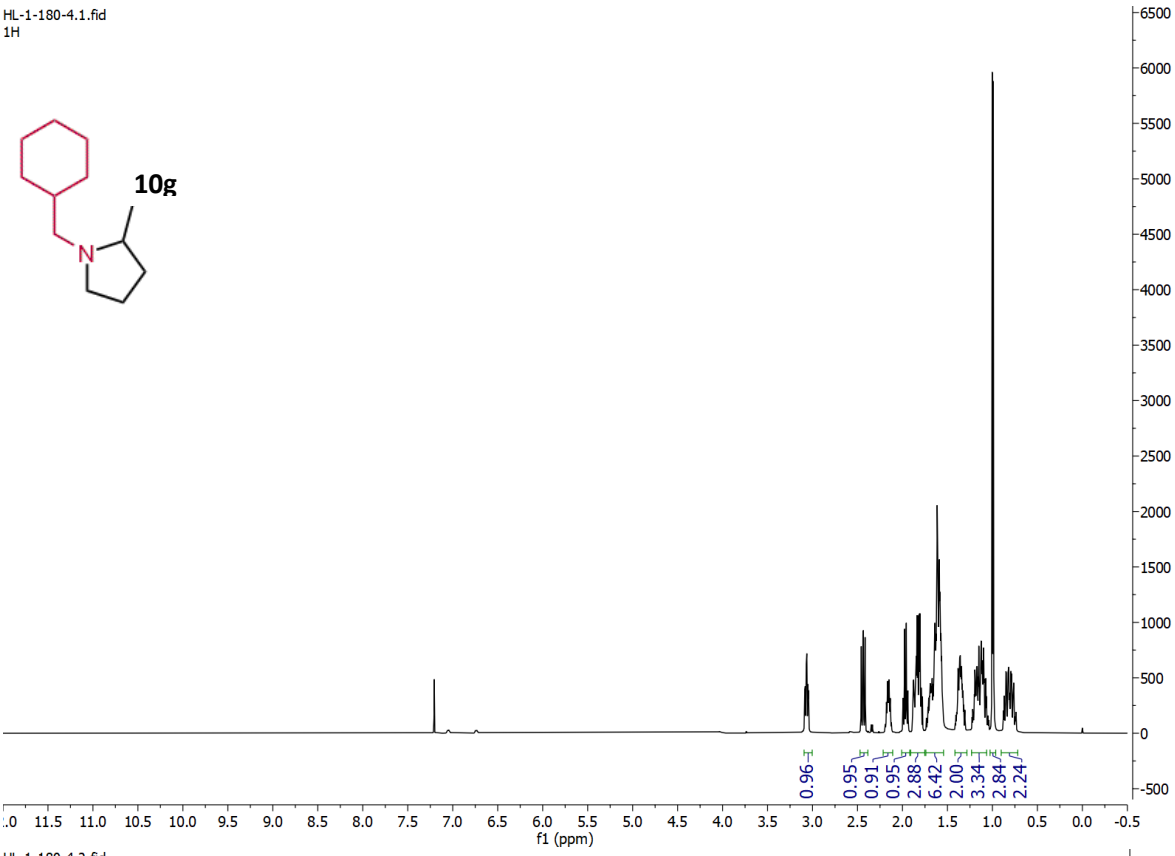

HL-1-174.2.fid
13C
136.367
136.210
129.128
128.877
59.553
57.929
53.944
32.758
21.485
21.143
19.108
f1 (ppm)

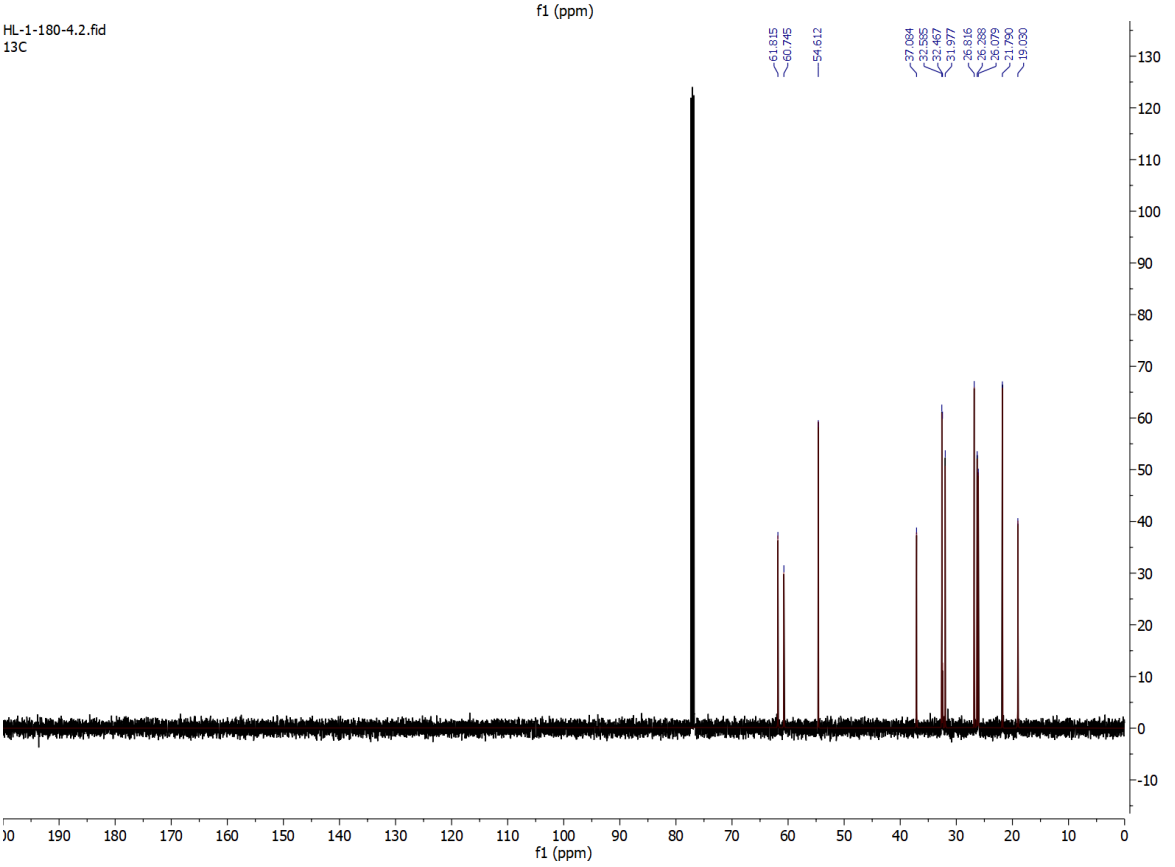

MAA-11-72c dry.1.fid
1H
10e
f1 (ppm)

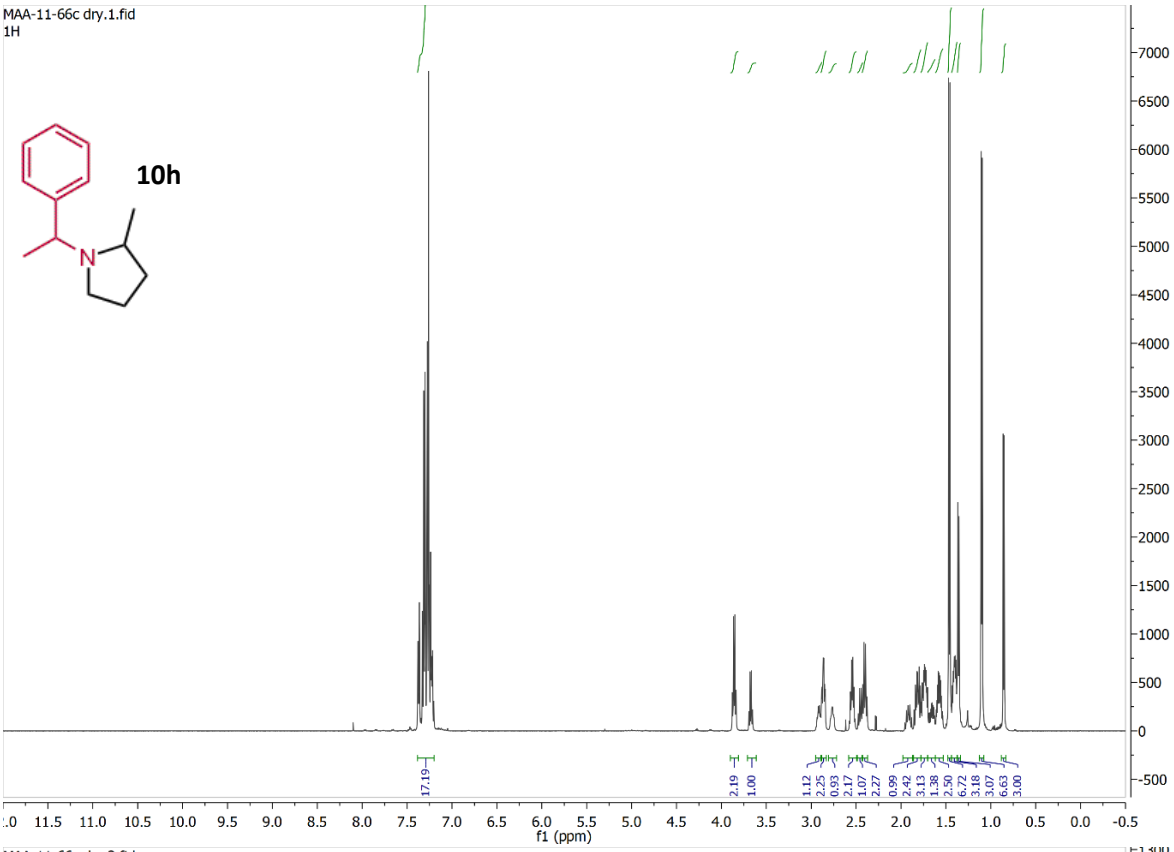

MAA-11-72c dry.2.fid
13C
140.71
128.63
128.33
125.95
60.03
56.13
53.98
35.46
32.69
21.67
18.93
f1 (ppm)

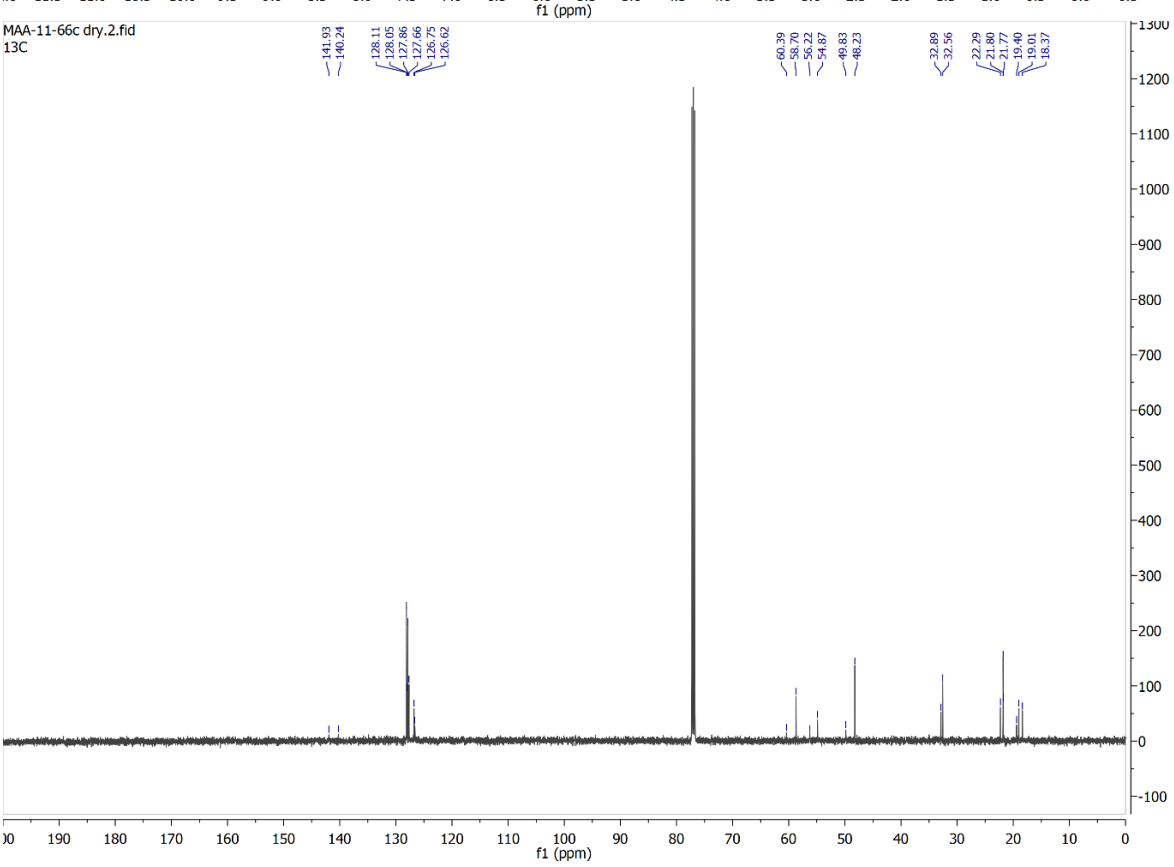

HL-1-181-2.1.fid
1H
10f HCl
1.00
1.02
2.07
1.18
1.10
3.43
1.17
2.98
2.99
3.20
f1 (ppm)

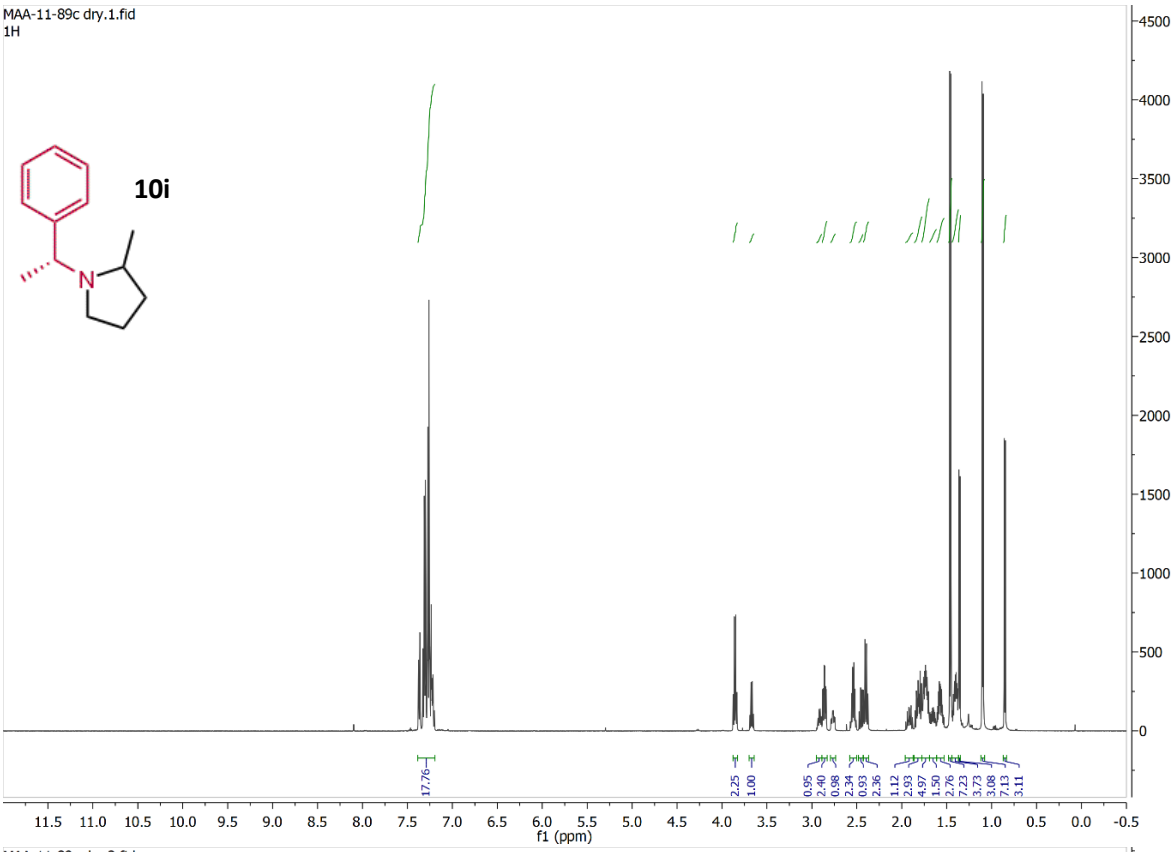

HL-1-181-2.2.fid
13C
65.809
61.095
53.937
30.748
25.480
20.988
19.746
19.187
14.652
f1 (ppm)

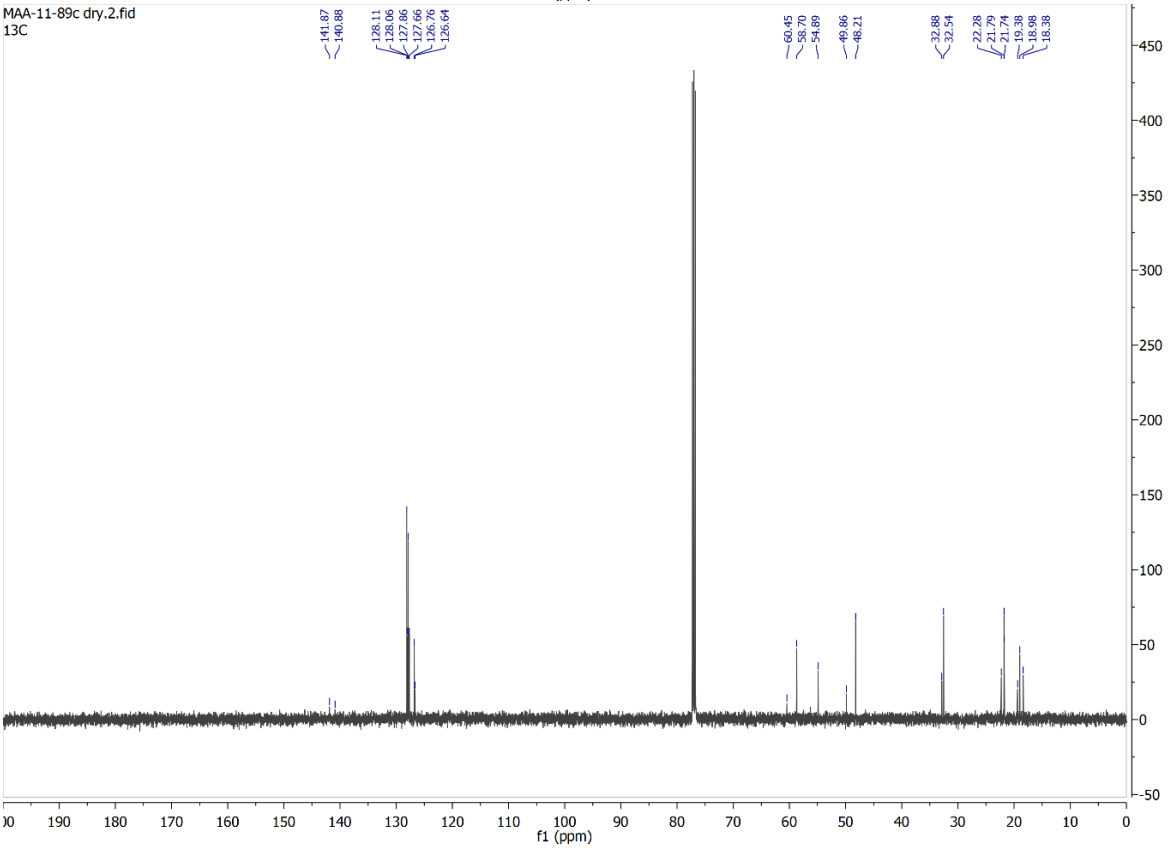

HL-1-180-4.1.fid
1H
10g
N
0.96
0.95
0.91
0.95
2.88
6.42
2.00
3.34
2.84
2.24
f1 (ppm)

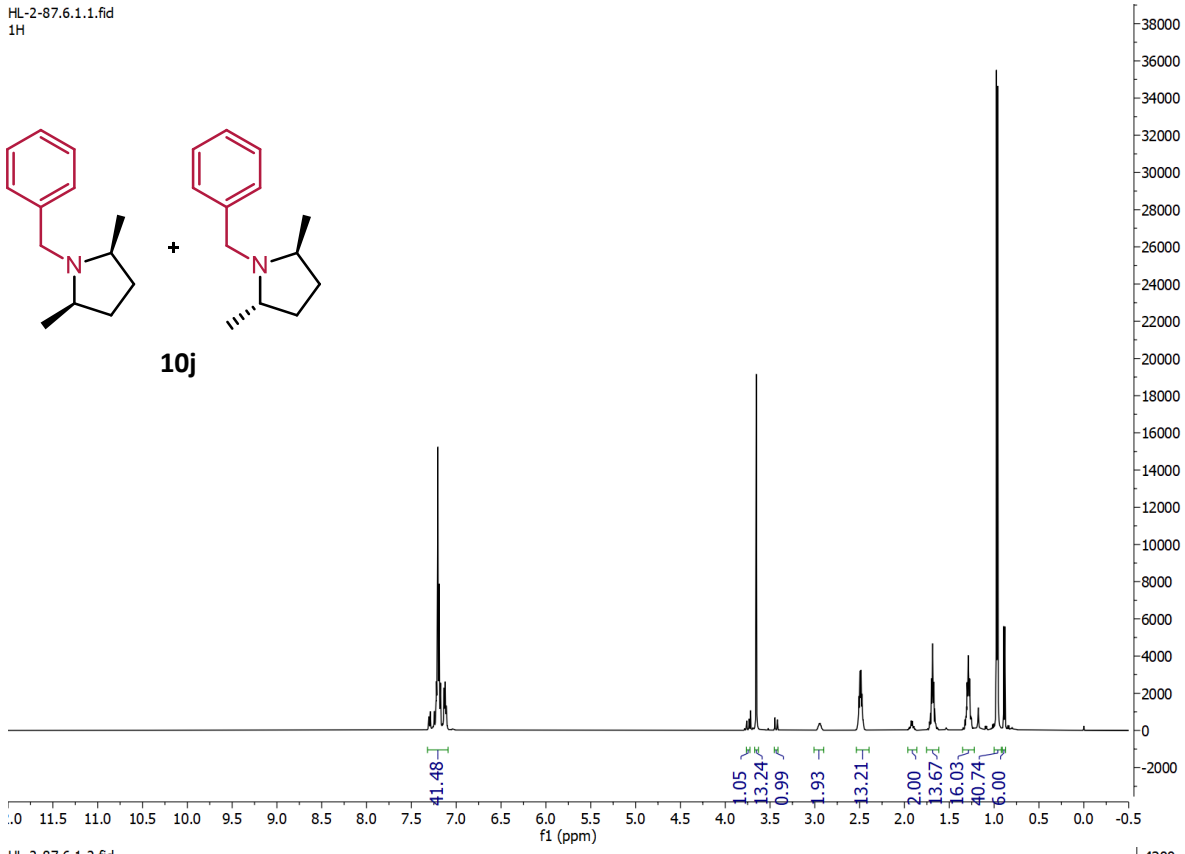

HL-1-180-4.2.fid
13C
61.815
60.745
54.612
37.084
32.585
32.467
31.977
26.816
26.288
26.079
21.790
19.030
f1 (ppm)


MAA-11-66c dry.1.fid
1H
10h
N
17.19
2.19
1.00
1.12
2.25
0.93
2.17
1.07
2.27
0.99
2.42
3.13
1.38
2.50
6.72
3.18
3.07
6.63
3.00
f1 (ppm)

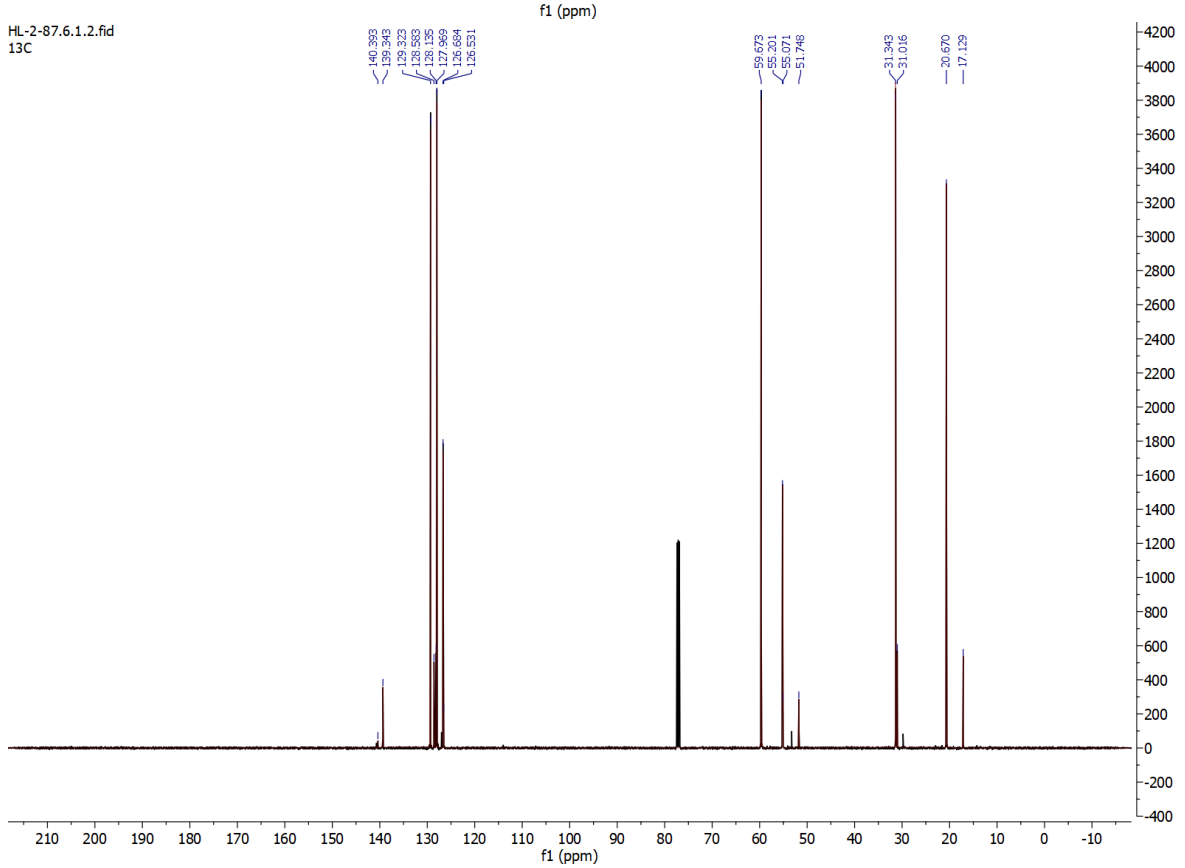

MAA-11-66c dry.2.fid
13C
141.93
140.24
128.11
128.05
127.86
127.66
126.75
126.62
60.39
58.70
56.22
54.87
49.83
48.23
32.89
32.56
22.29
21.80
21.77
19.40
19.01
18.37
f1 (ppm)


MAA-11-89c dry.1.fid
1H
10i
f1 (ppm)


MAA-11-89c dry.2.fid
13C
f1 (ppm)

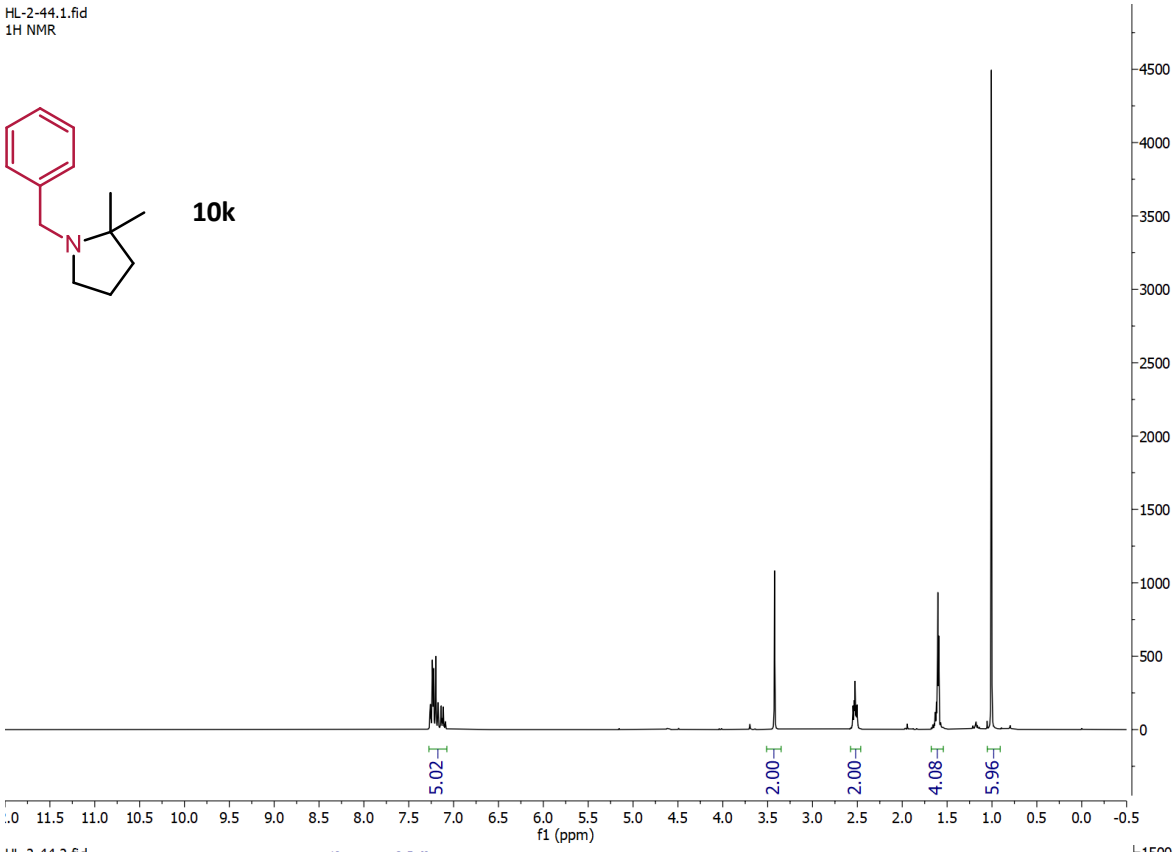

HL-2-87.6.1.1.fid
1H
41.48
1.05
13.24
0.99
1.93
13.21
2.00
13.67
16.03
40.74
6.00
f1 (ppm)

10j

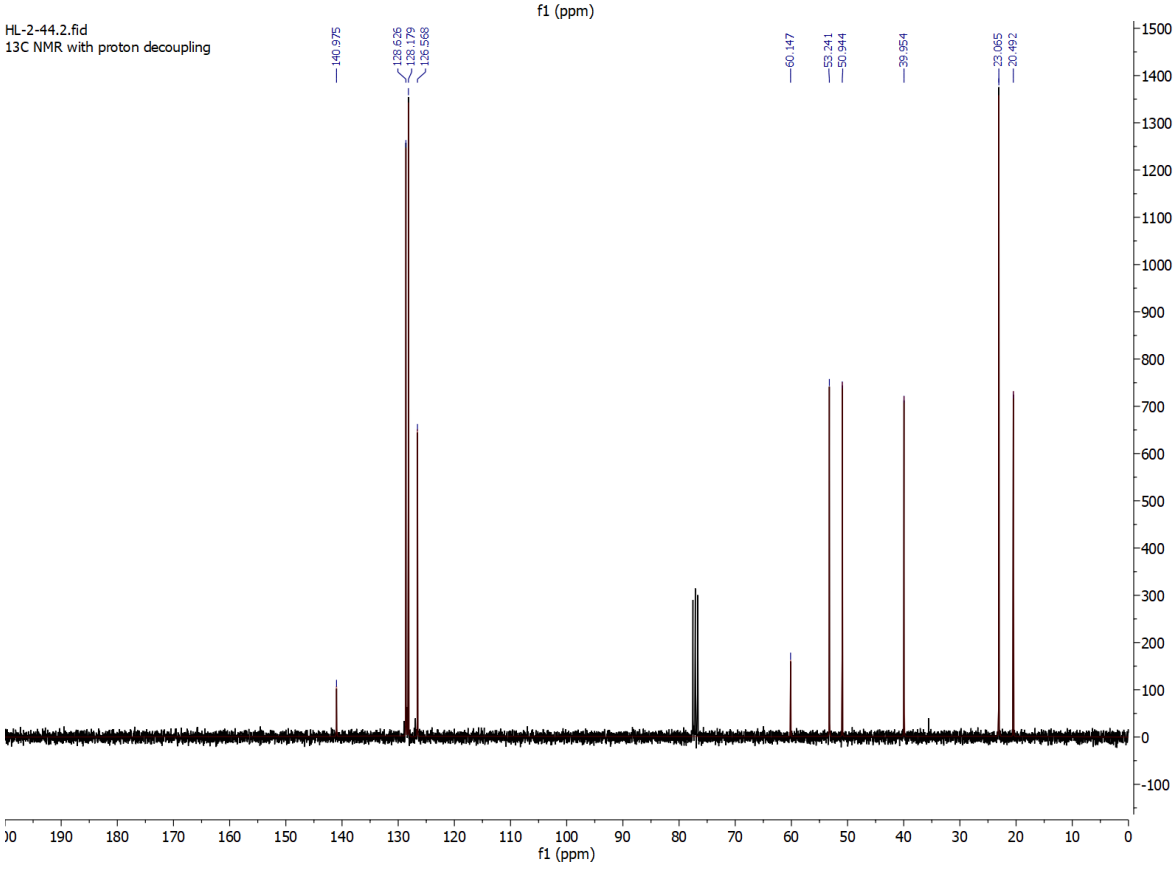

HL-2-87.6.1.2.fid
13C
140.393
139.343
129.323
128.583
128.135
127.969
126.684
126.531
59.673
55.201
55.071
51.748
31.343
31.016
20.670
17.129
f1 (ppm)

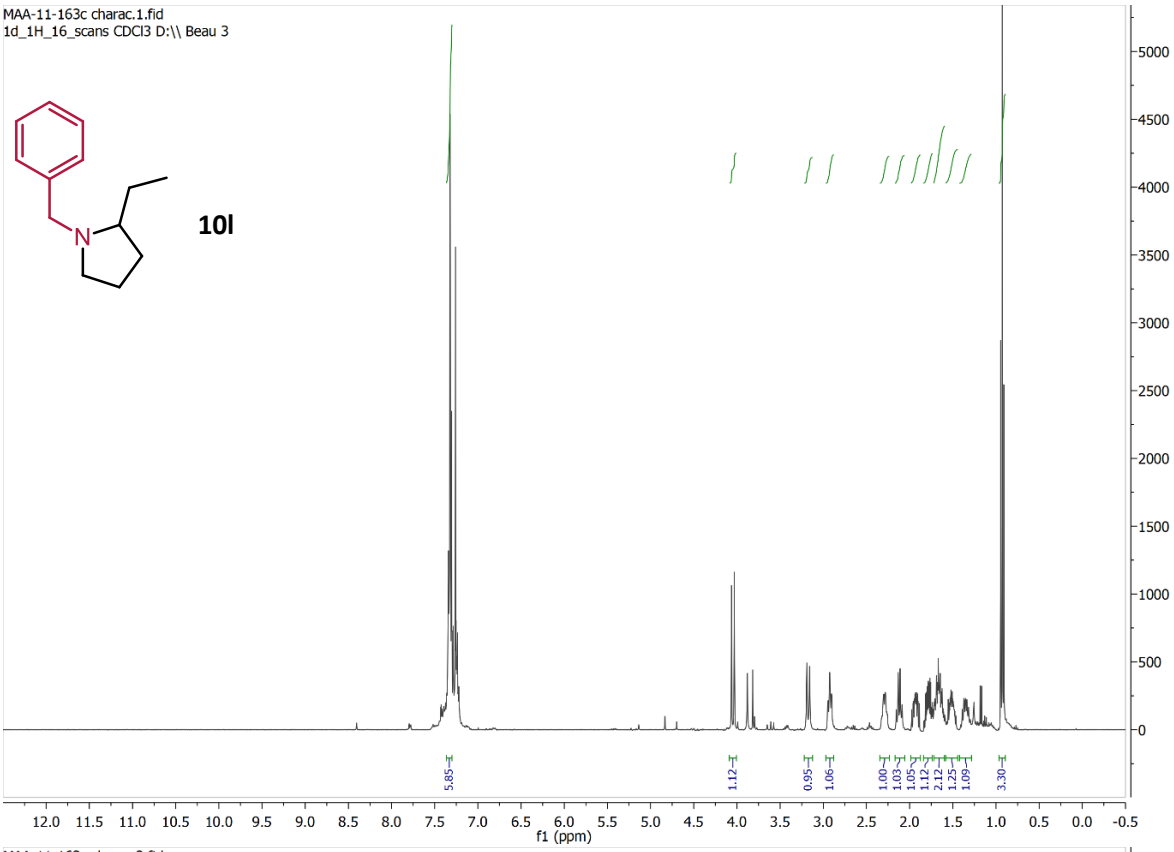
HL-2-44.1.fid
1H NMR

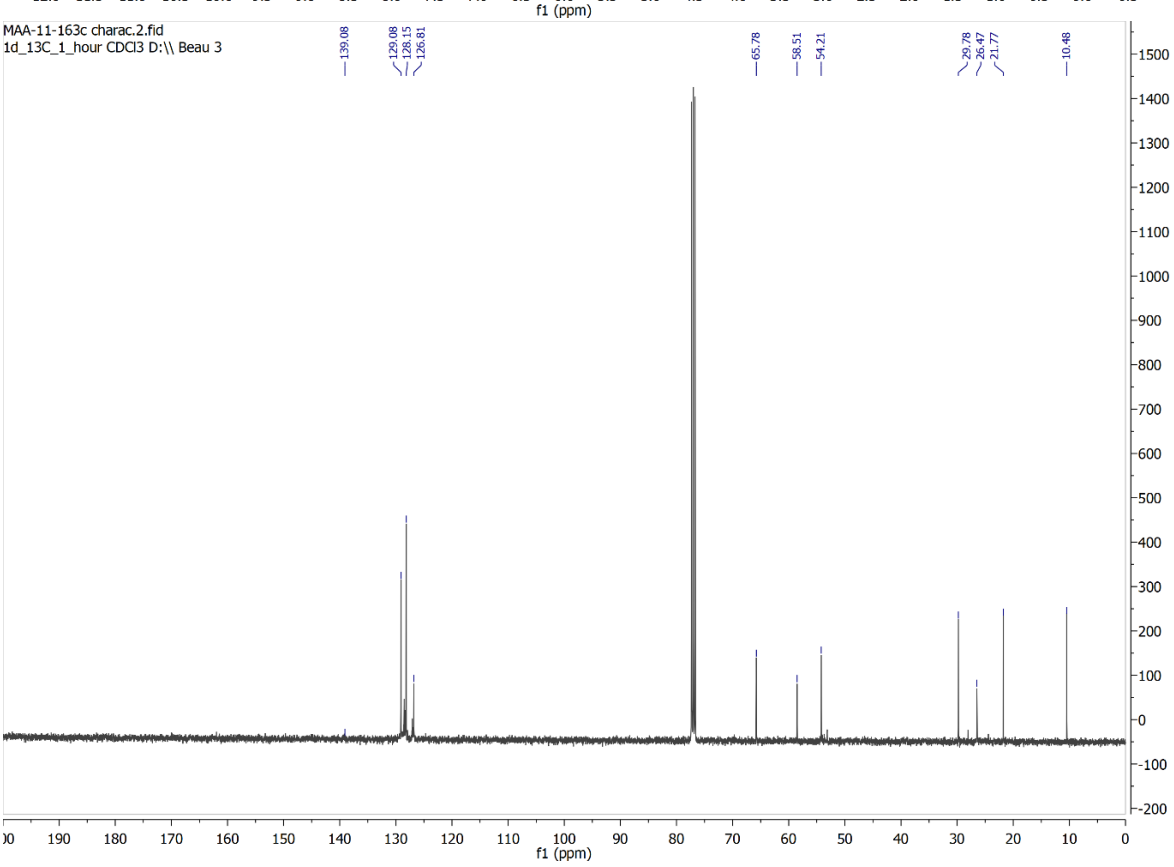
10k

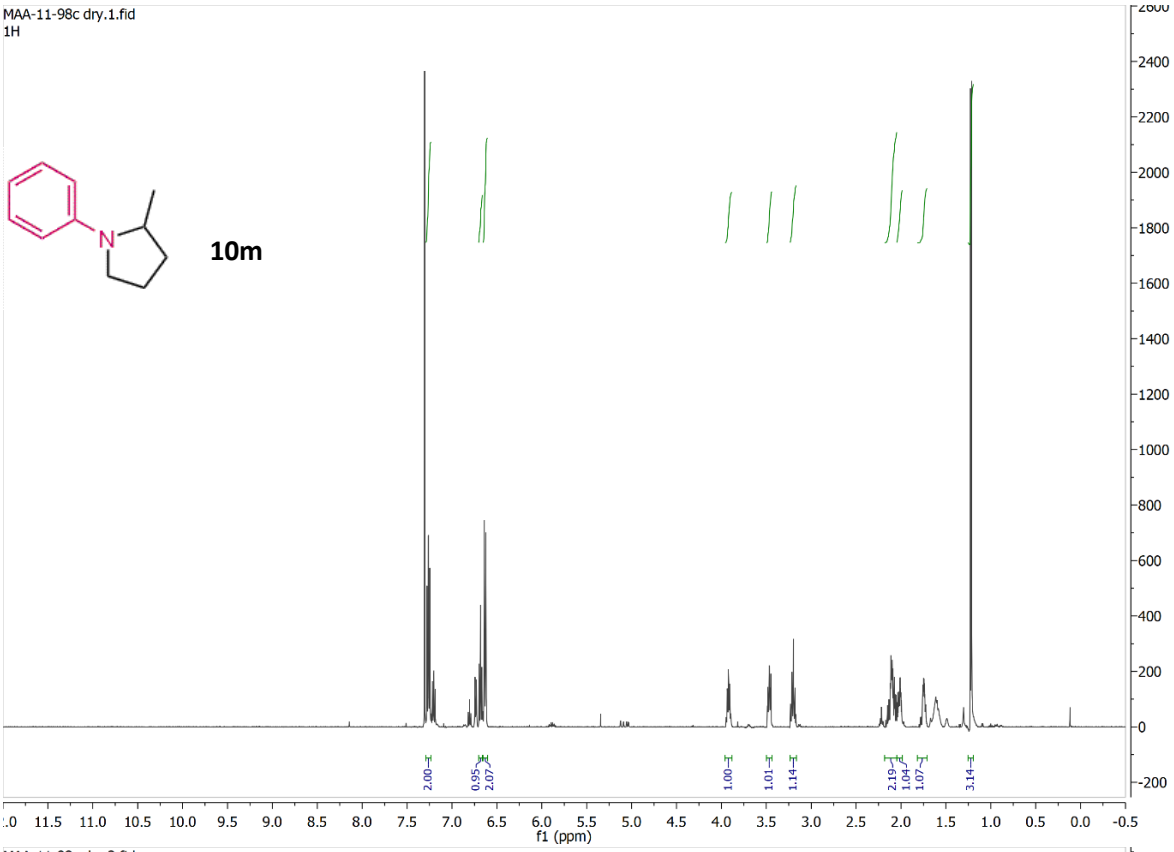


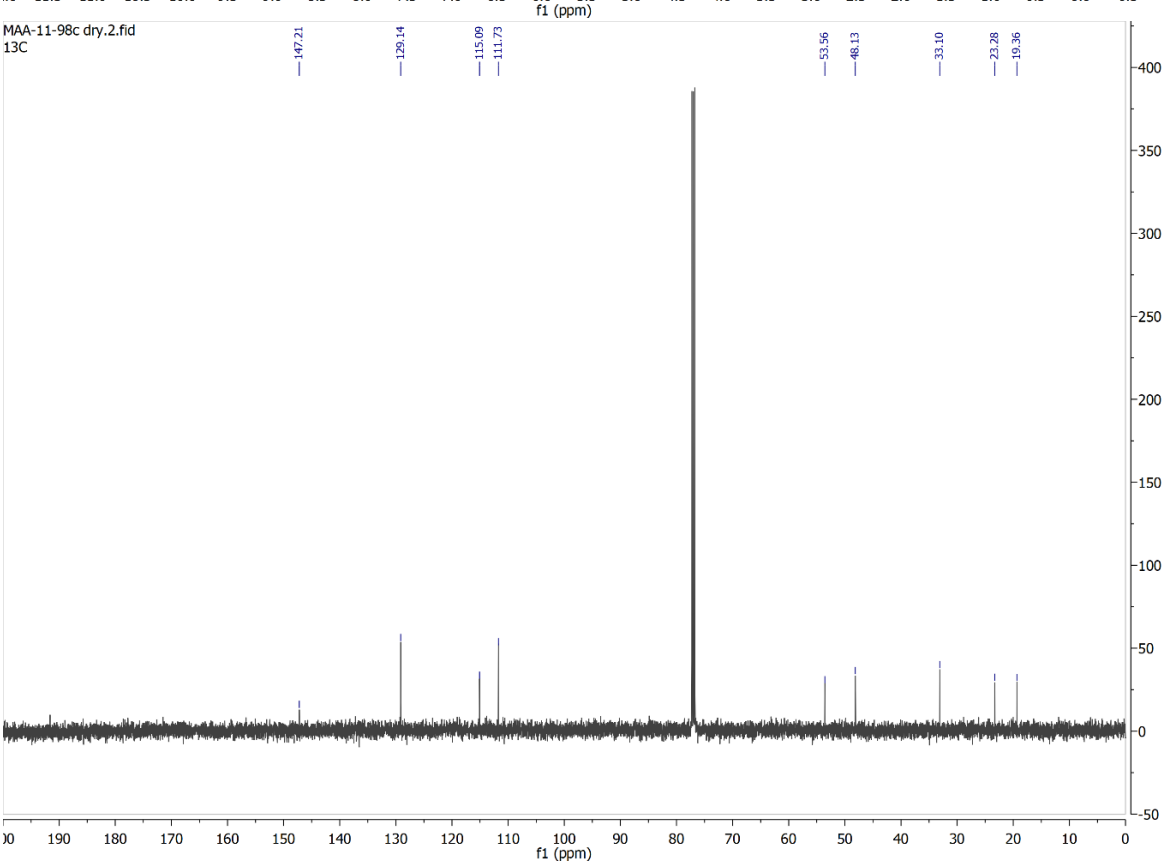
HL-2-44.2.fid
13C NMR with proton decoupling

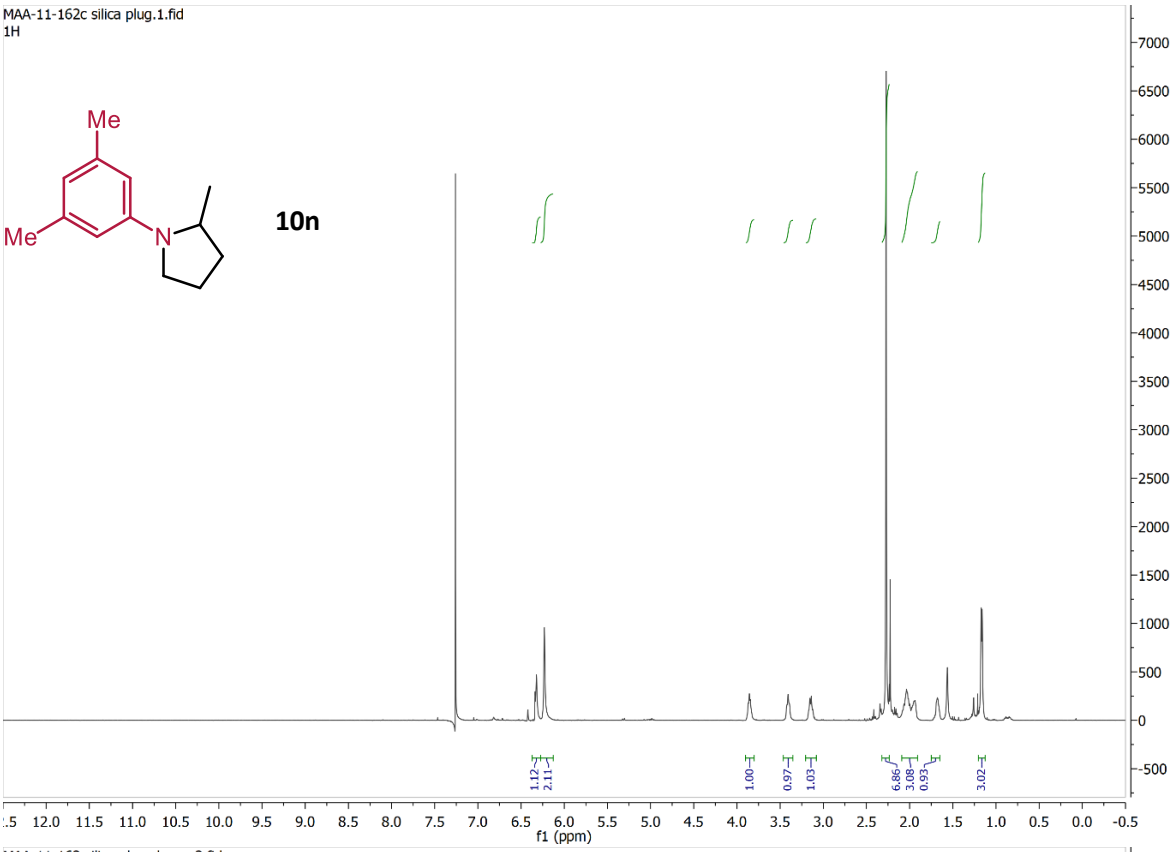


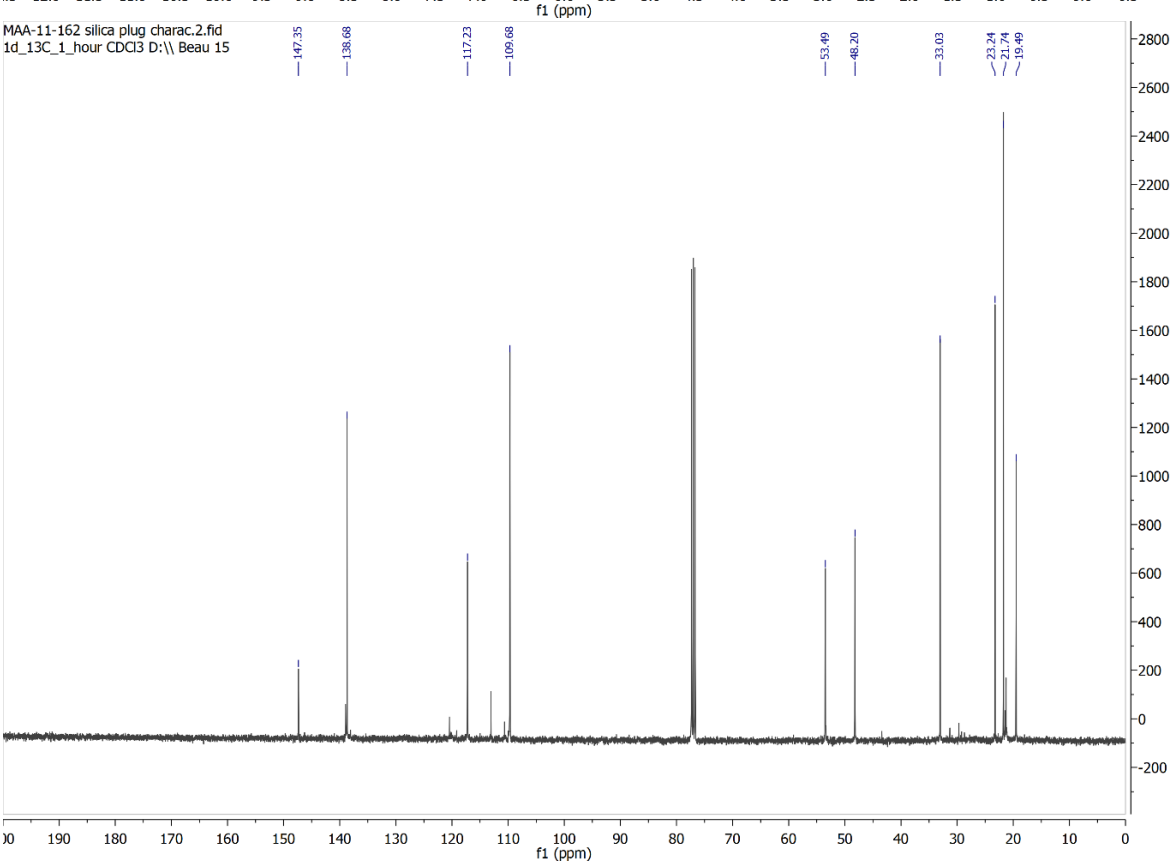

MAA-11-163c charac.1.fid
1d_1H_16_scans CDCl3 D:\\ Beau 3
10l
5.85
1.12
0.95
1.06
1.00
1.03
1.05
1.12
2.12
1.25
1.09
3.30
f1 (ppm)

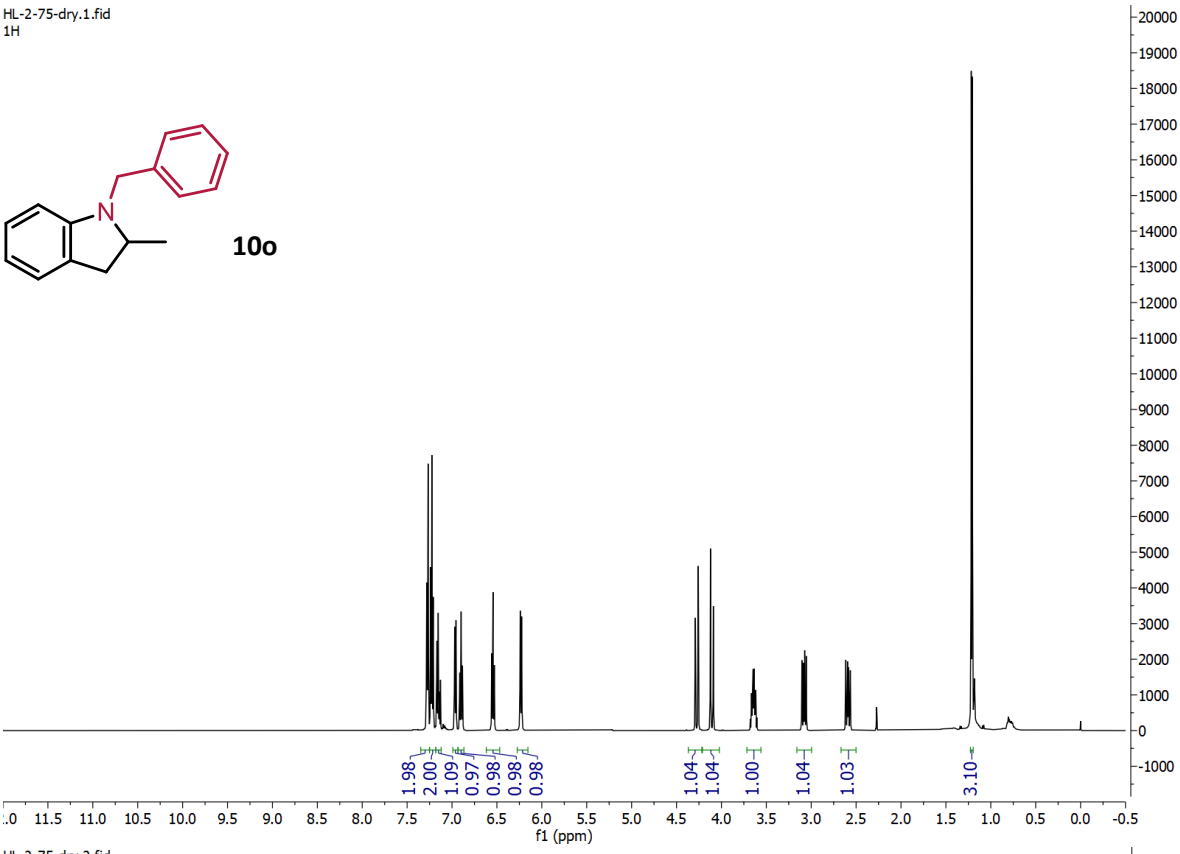

MAA-11-163c charac.2.fid
1d_13C_1_hour CDCl3 D:\\ Beau 3
139.08
129.08
128.15
126.81
65.78
58.51
54.21
29.78
26.47
21.77
10.48
f1 (ppm)

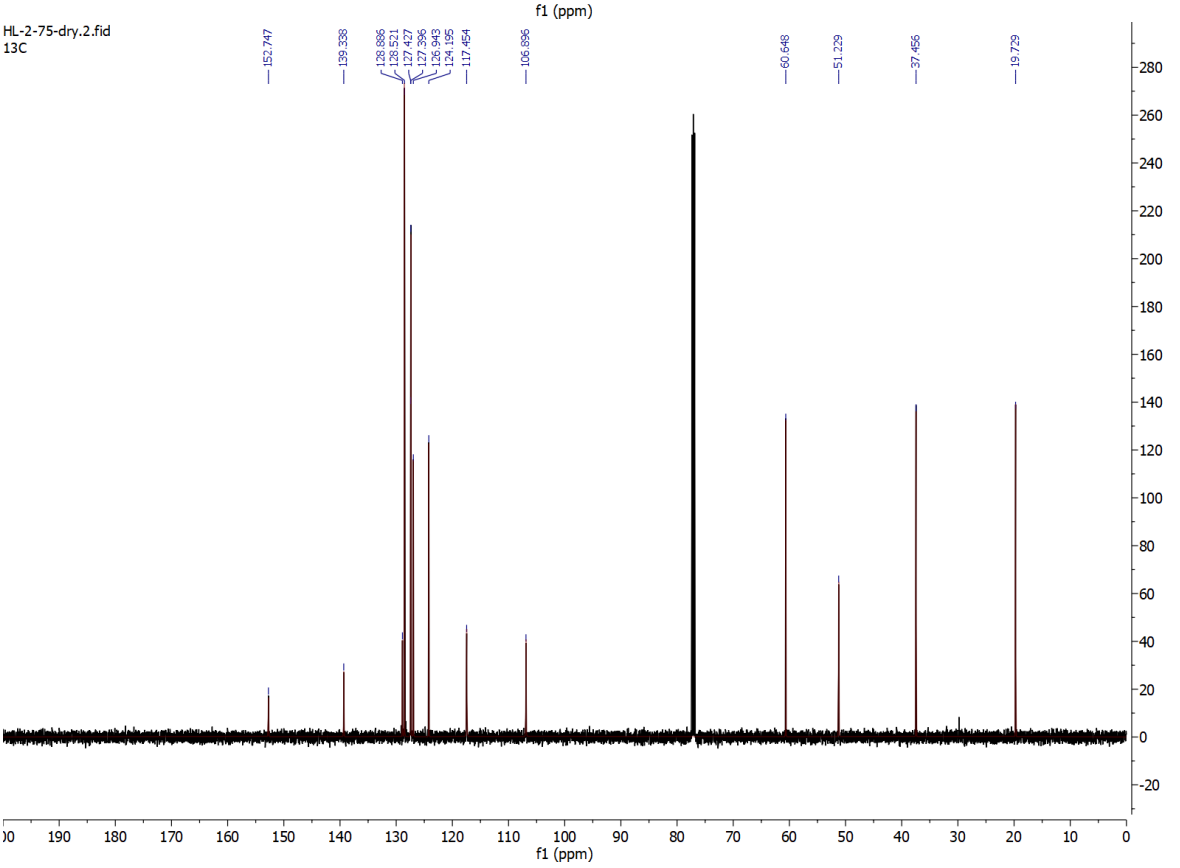

MAA-11-98c dry.1.fid
1H
10m
2.00
0.95
2.07
1.00
1.01
1.14
2.19
1.04
1.07
3.14
f1 (ppm)

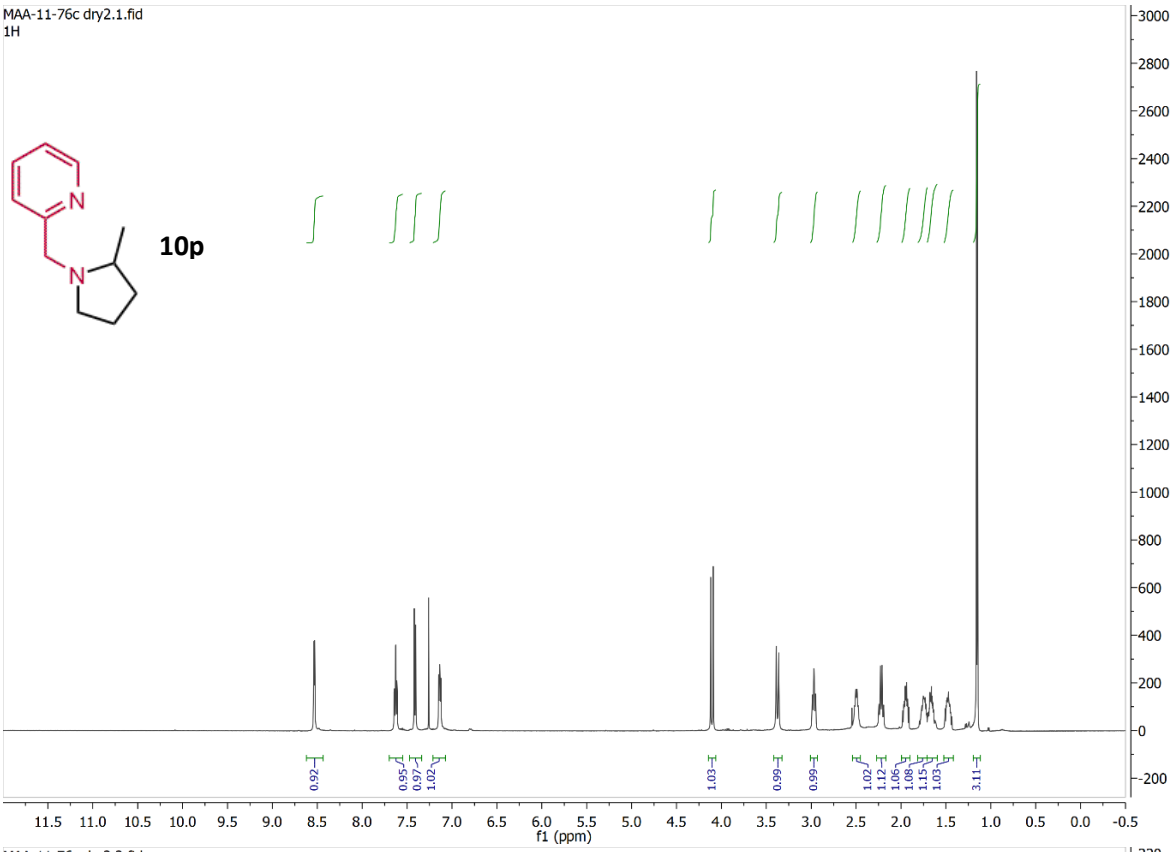

MAA-11-98c dry.2.fid
13C
147.21
129.14
115.09
111.73
53.56
48.13
33.10
23.28
19.36
f1 (ppm)

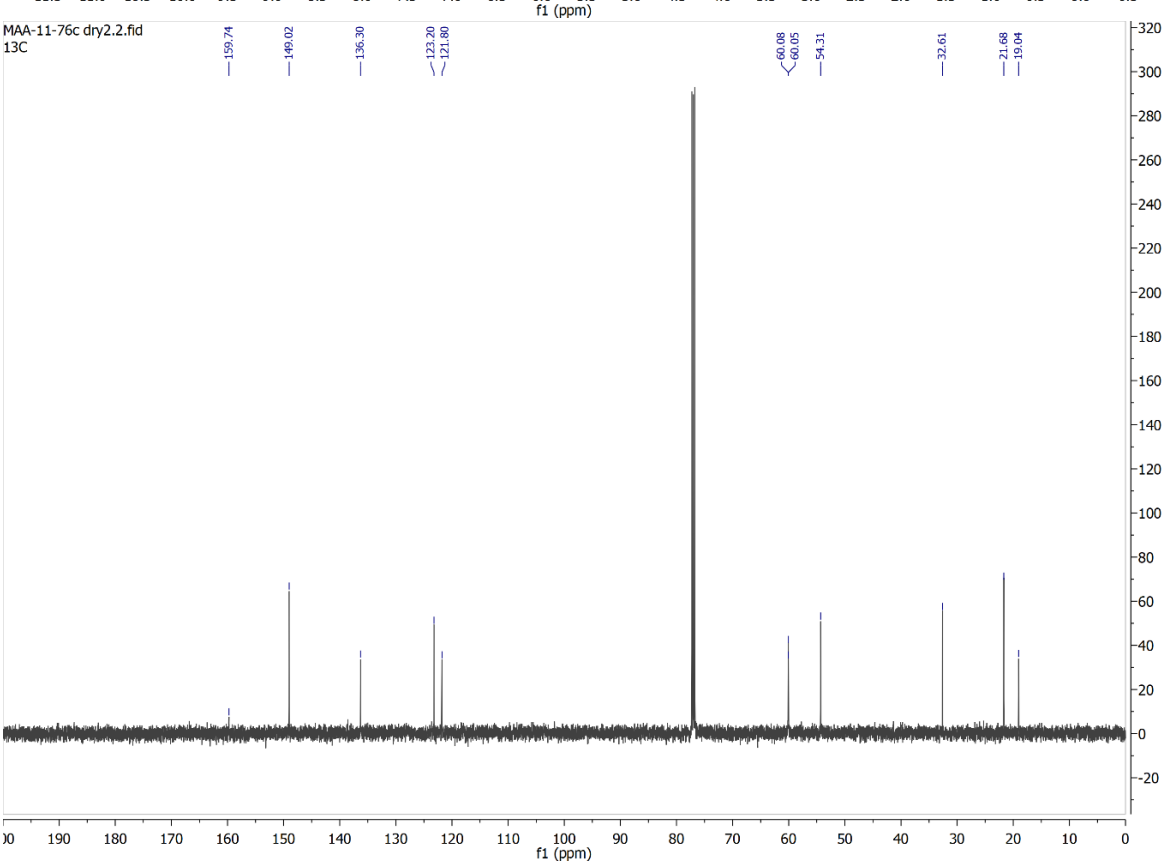

MAA-11-162c silica plug.1.fid
1H
Me
Me
N
10n
1.12
2.11
1.00
0.97
1.03
6.86
3.08
0.93
3.02
f1 (ppm)

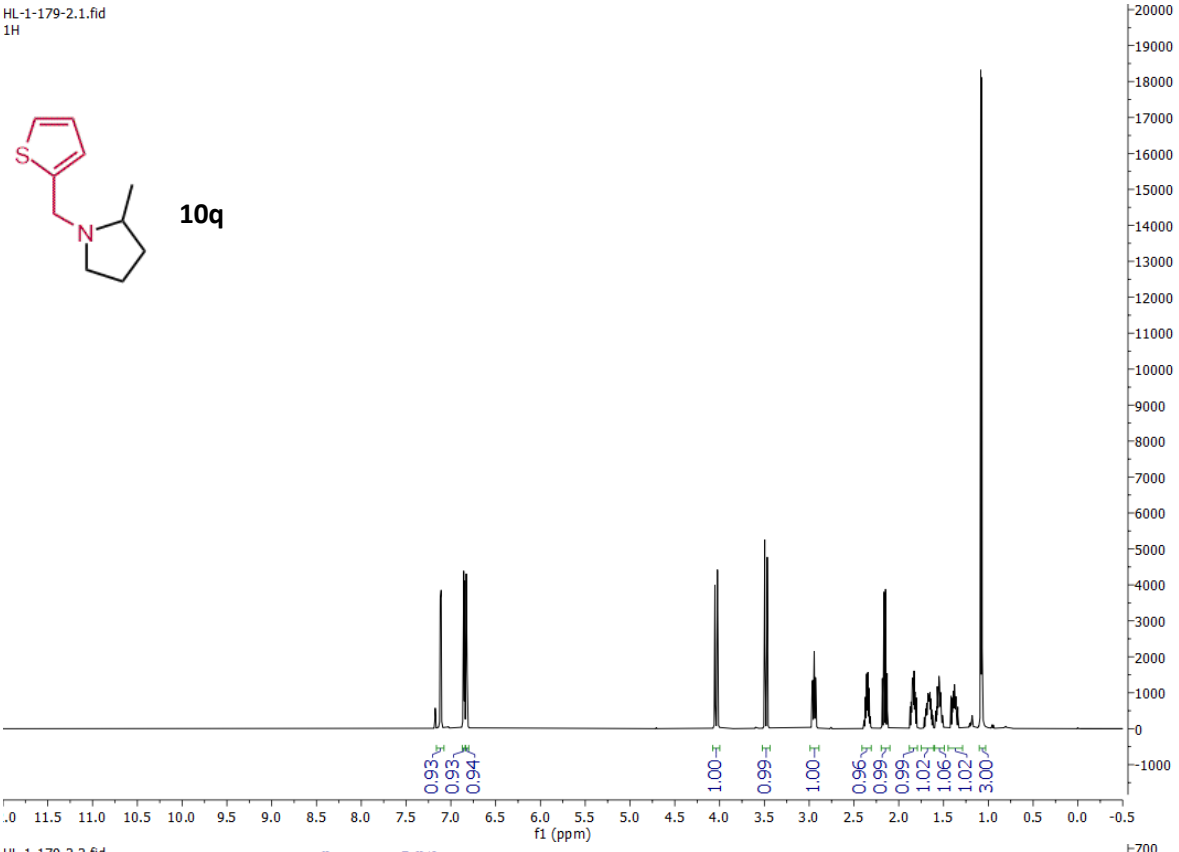

MAA-11-162 silica plug charac.2.fid
1d_13C_1_hour CDCl3 D:\\ Beau 15
147.35
138.68
117.23
109.68
53.49
48.20
33.03
23.24
21.74
19.49
f1 (ppm)

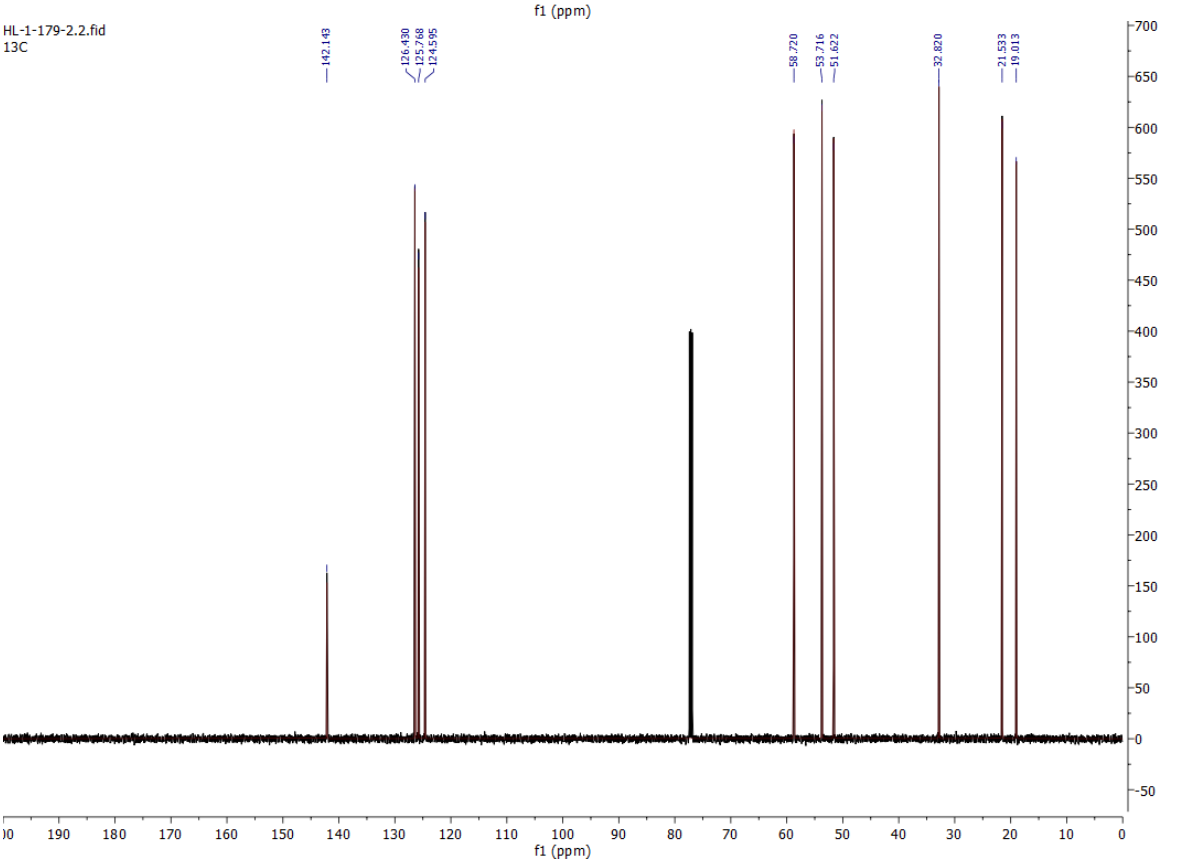

HL-2-75-dry.1.fid
1H
10o
1.98
2.00
1.09
0.97
0.98
0.98
0.98
1.04
1.04
1.00
1.04
1.03
3.10
f1 (ppm)

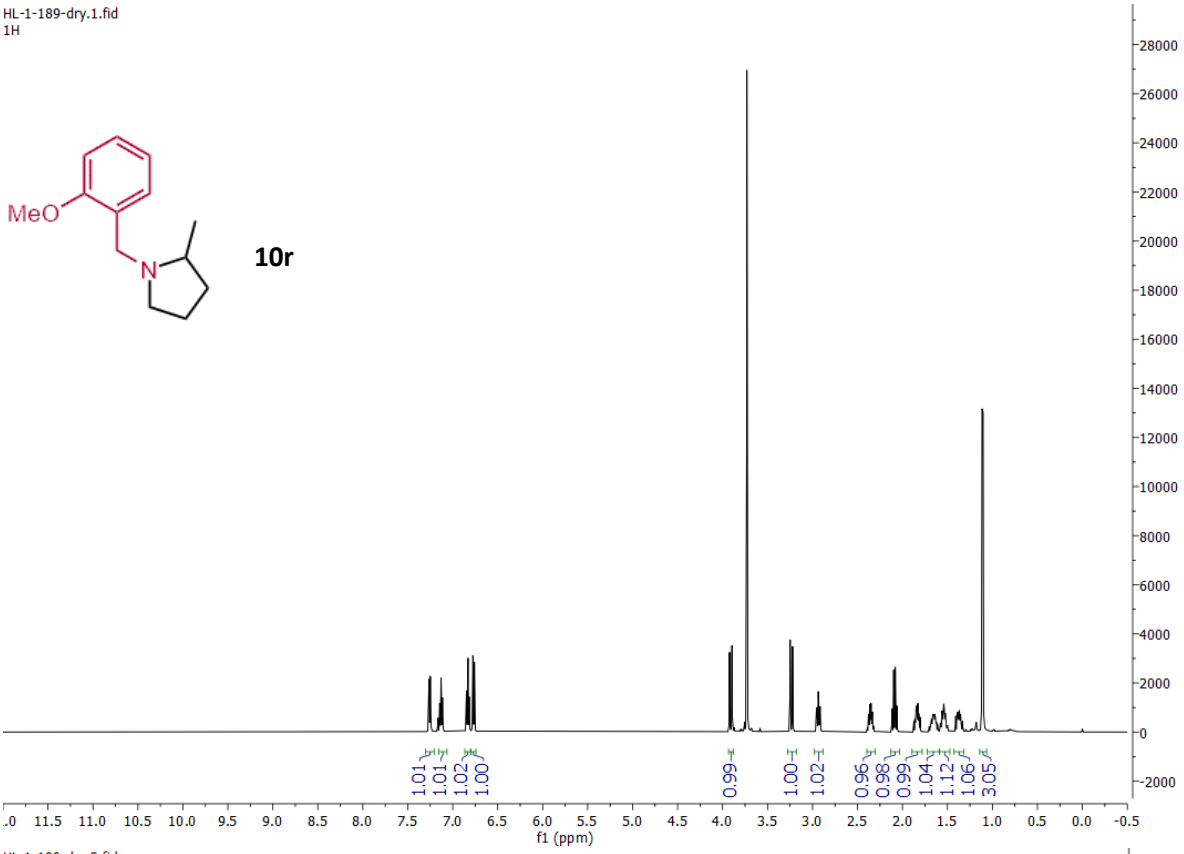

HL-2-75-dry.2.fid
13C
152.747
139.338
128.886
128.521
127.427
127.396
126.943
124.195
117.454
106.896
60.648
51.229
37.456
19.729
f1 (ppm)


MAA-11-76c dry2.1.fid
1H
10p
0.92
0.95
0.97
1.02
1.03
0.99
0.99
1.02
1.12
1.06
1.08
1.15
1.03
3.11
f1 (ppm)

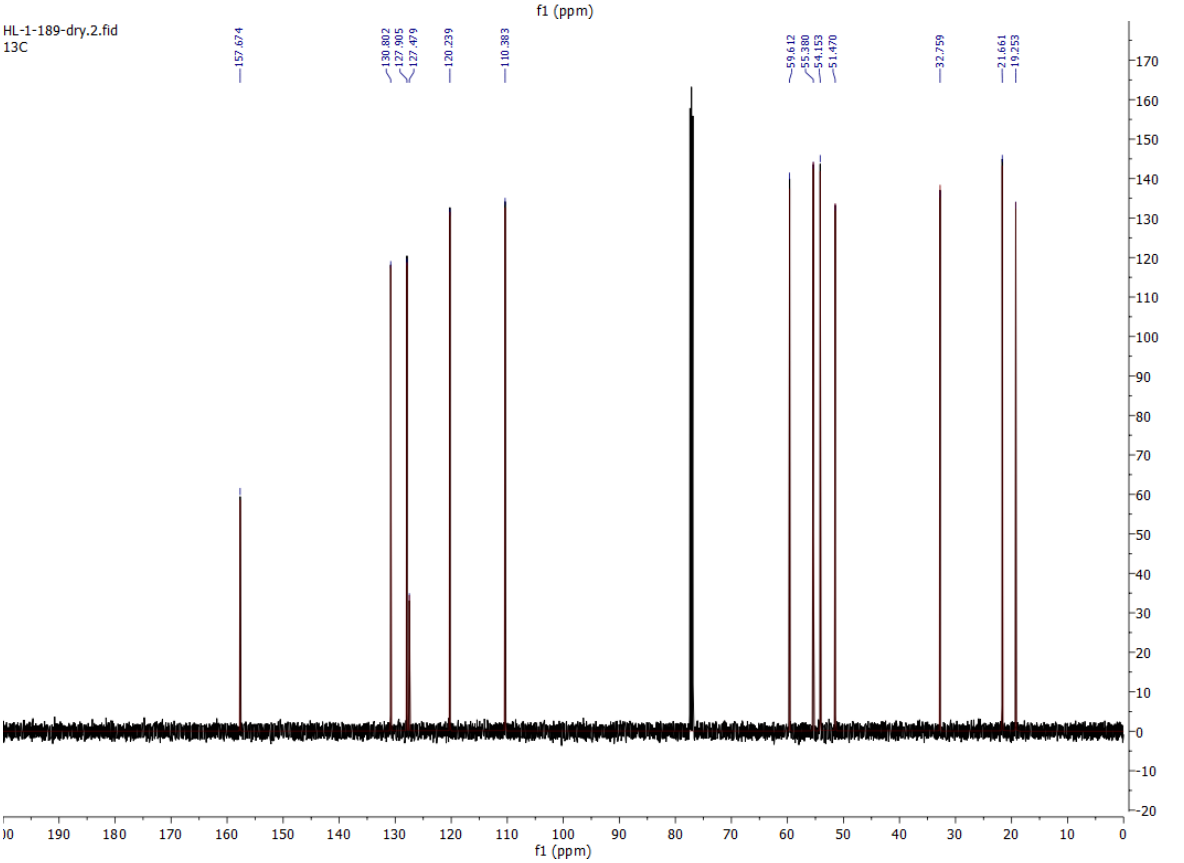

MAA-11-76c dry2.2.fid
13C
159.74
149.02
136.30
123.20
121.80
60.08
60.05
54.31
32.61
21.68
19.04
f1 (ppm)

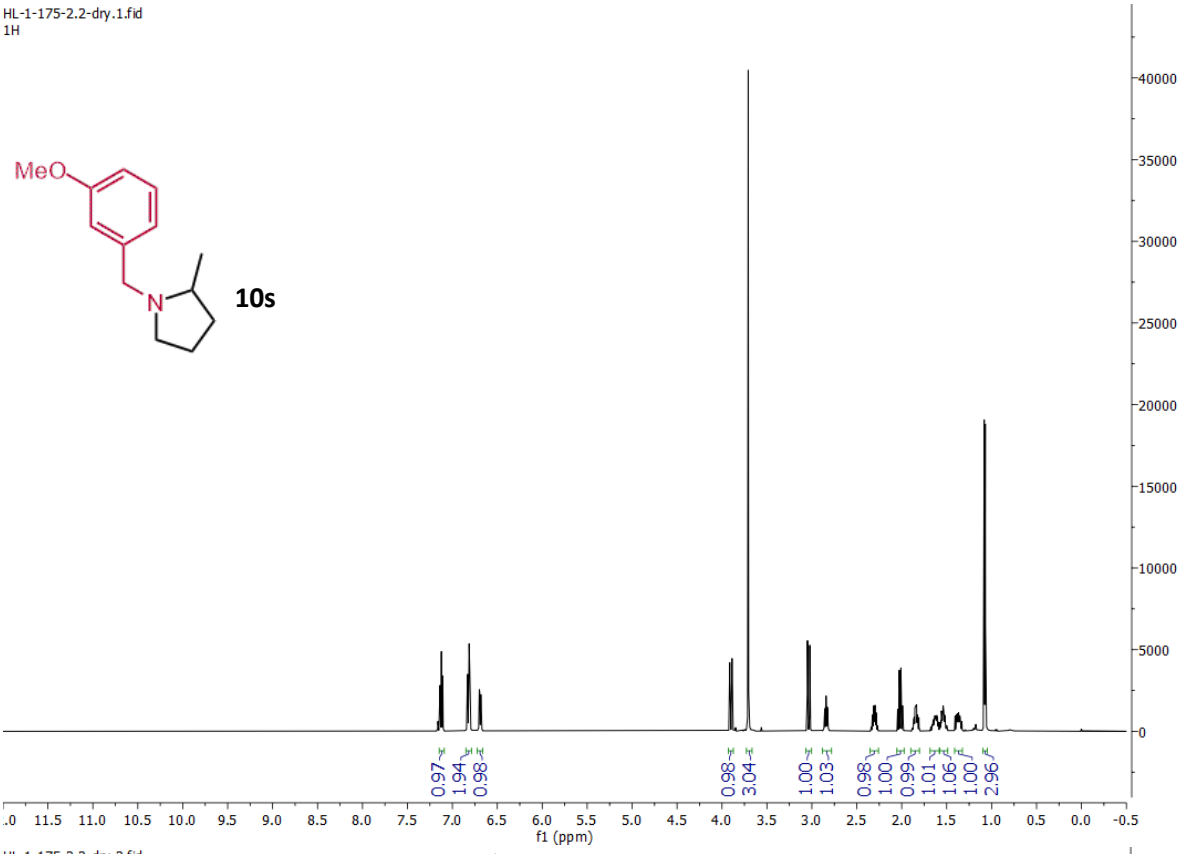

HL-1-179-2.1.fid
1H
10q
0.93
0.93
0.94
1.00
0.99
1.00
0.96
0.99
0.99
1.02
1.06
1.02
3.00
f1 (ppm)

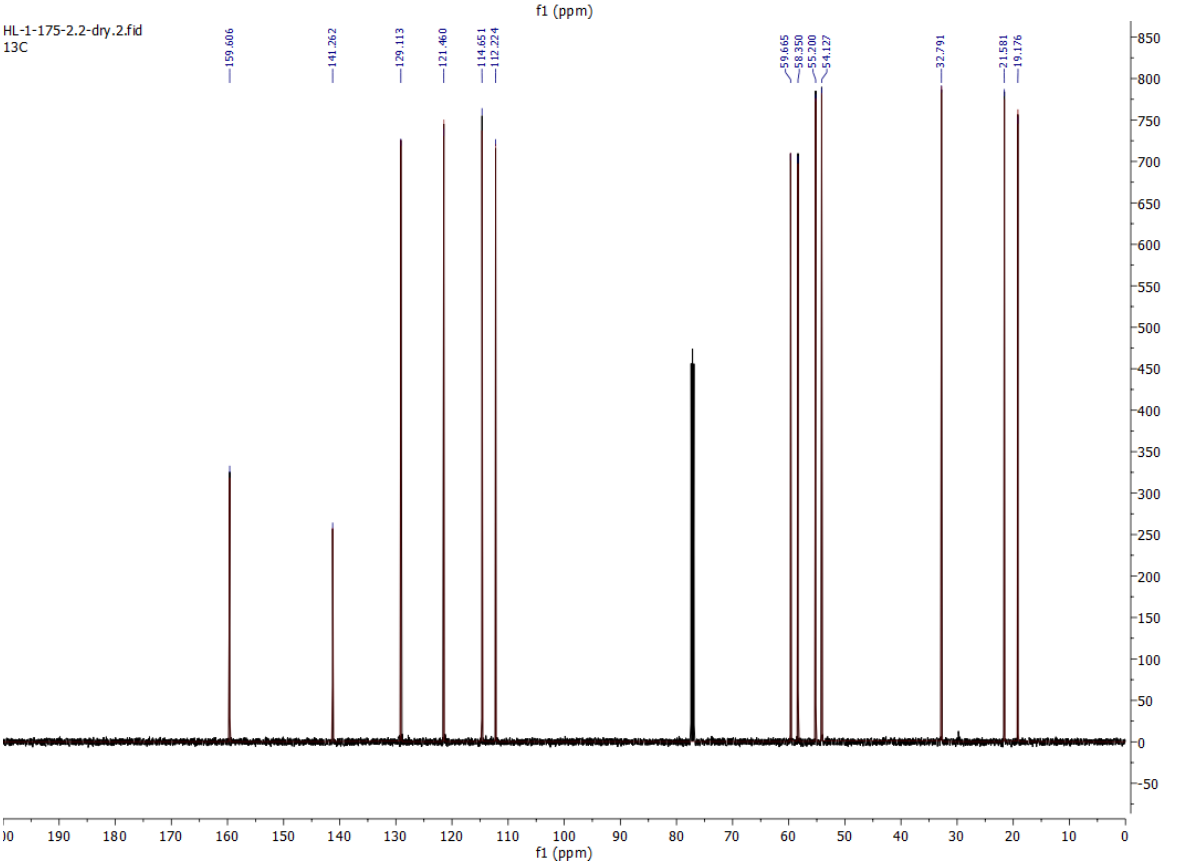

HL-1-179-2.2.fid
13C
142.143
126.430
125.768
124.595
58.720
53.716
51.622
32.820
21.533
19.013
f1 (ppm)

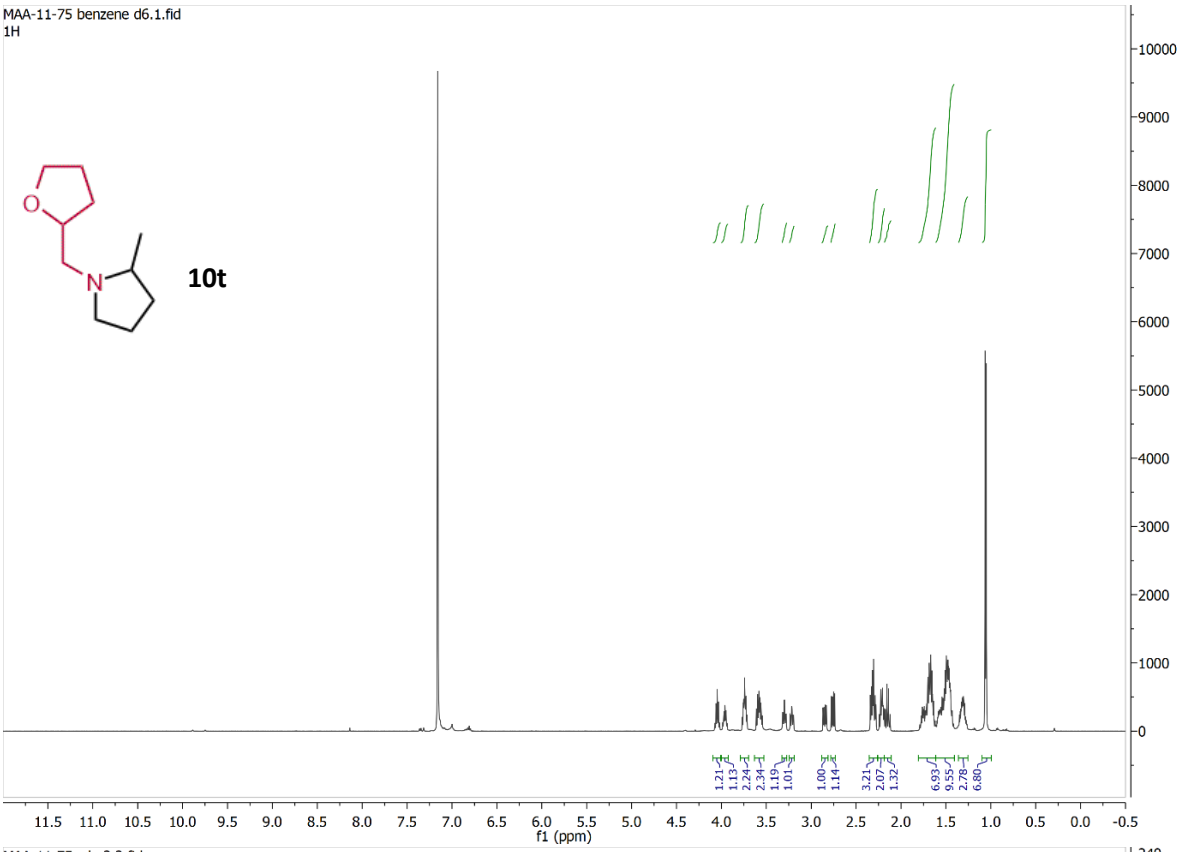

HL-1-189-dry.1.fid
1H
MeO
N
1.01
1.01
1.02
1.00
0.99
1.00
1.02
0.96
0.98
0.99
1.04
1.12
1.06
3.05
f1 (ppm)

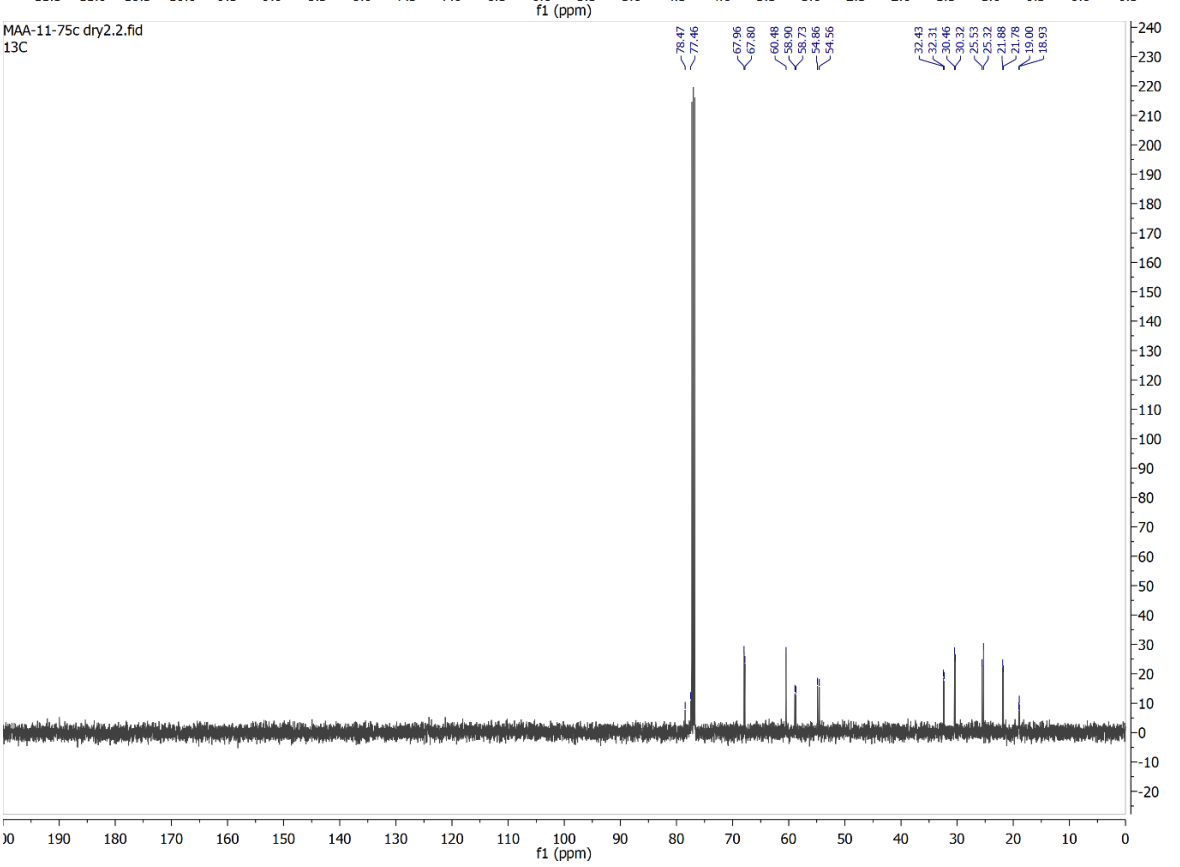
10r

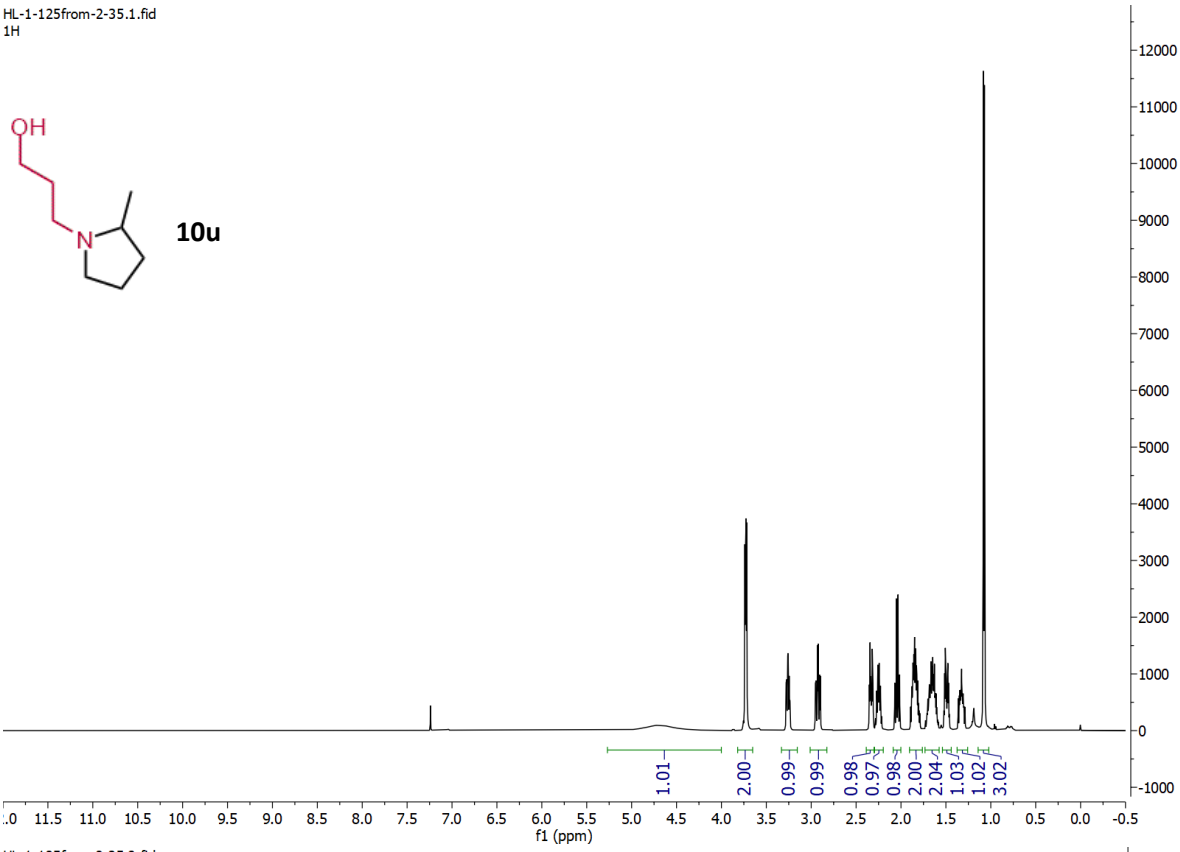

HL-1-189-dry.2.fid
13C
157.674
130.802
127.905
127.479
120.239
110.383
59.612
55.380
54.455
51.470
32.759
21.661
19.253
f1 (ppm)

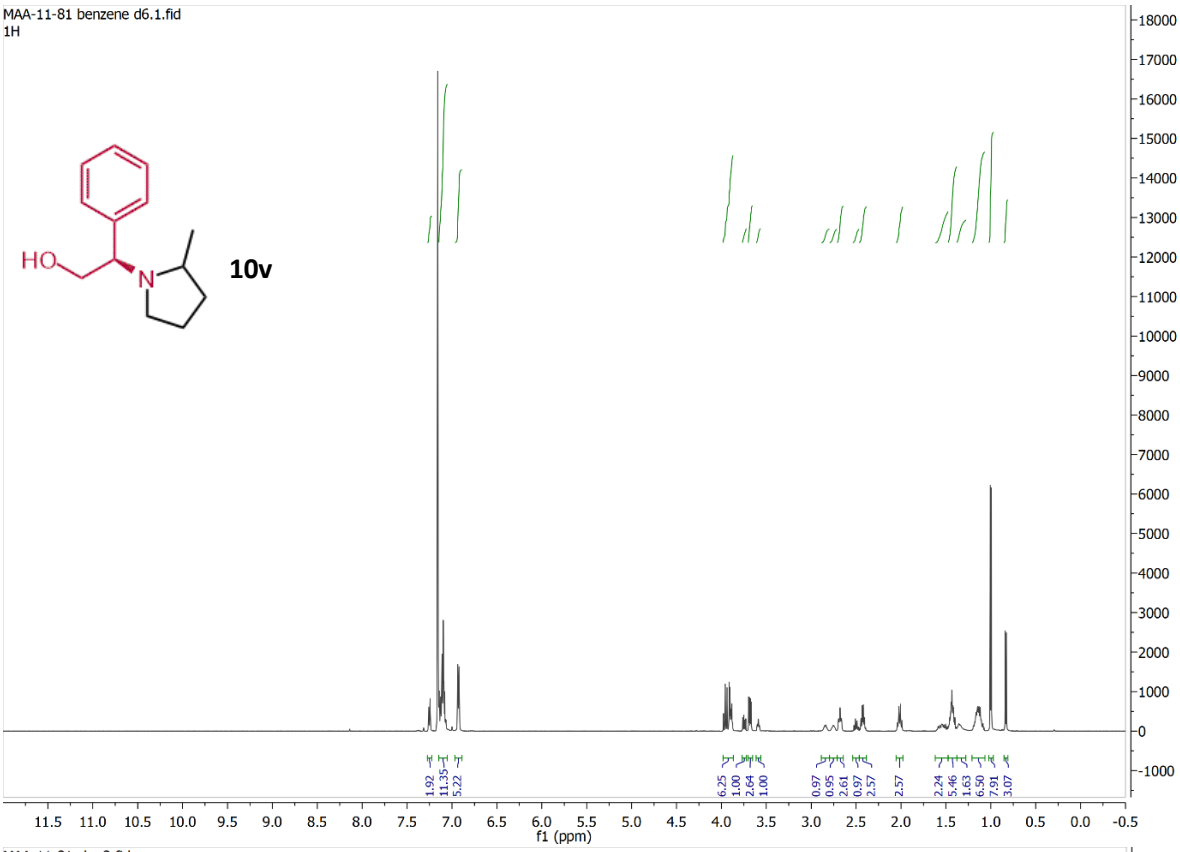

HL-1-175-2.2-dry.1.fid
1H
MeO
N
10s
0.97
1.94
0.98
0.98
3.04
1.00
1.03
0.98
1.00
0.99
1.01
1.06
1.00
2.96
f1 (ppm)

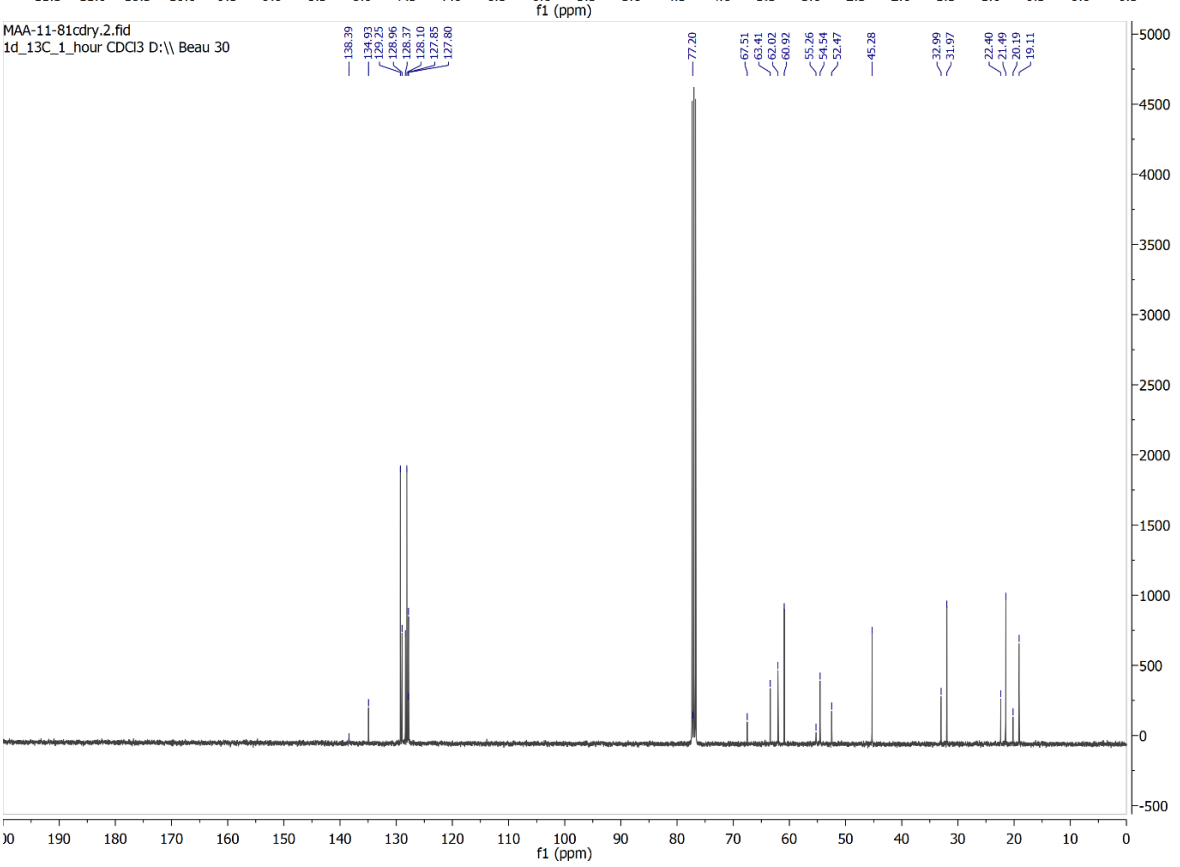

HL-1-175-2.2-dry.2.fid
13C
159.606
141.262
129.113
121.460
114.651
112.224
59.665
58.350
55.200
54.127
32.791
21.581
19.176
f1 (ppm)

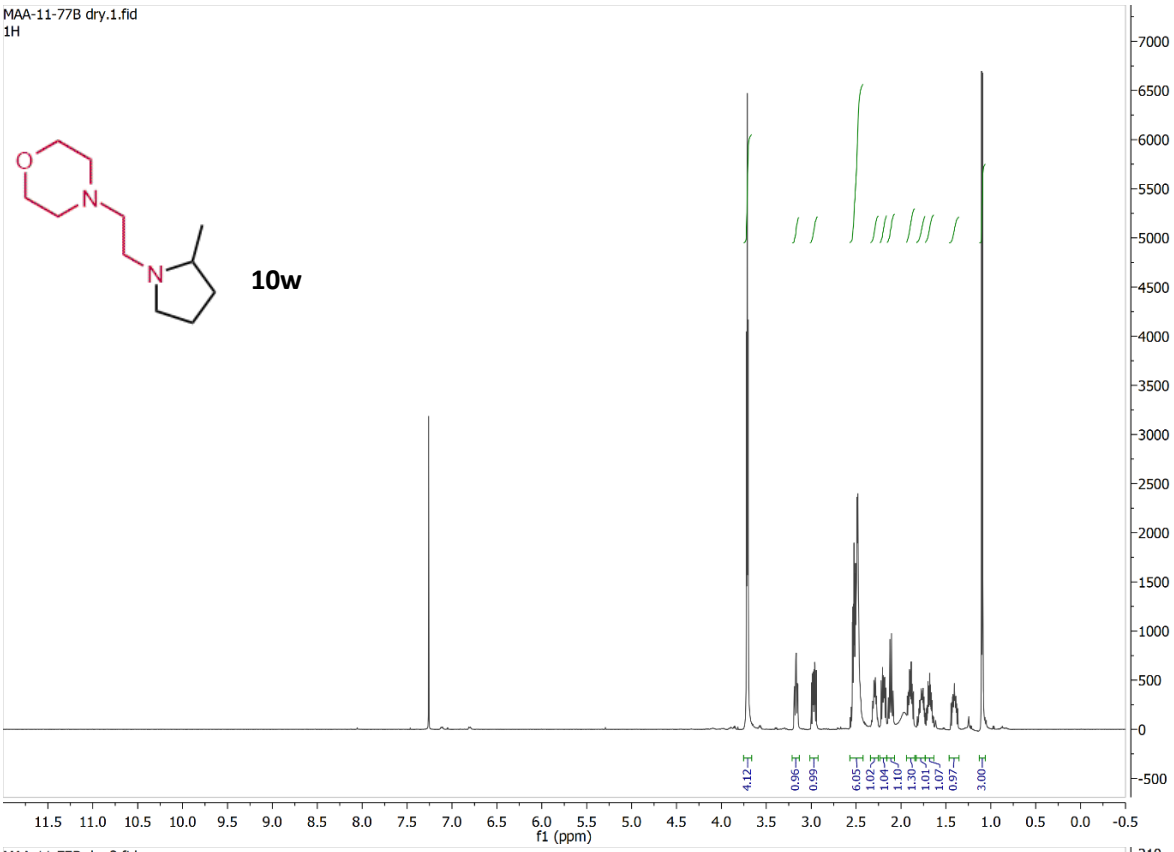

MAA-11-75 benzene d6.1.fid
1H
10t
f1 (ppm)

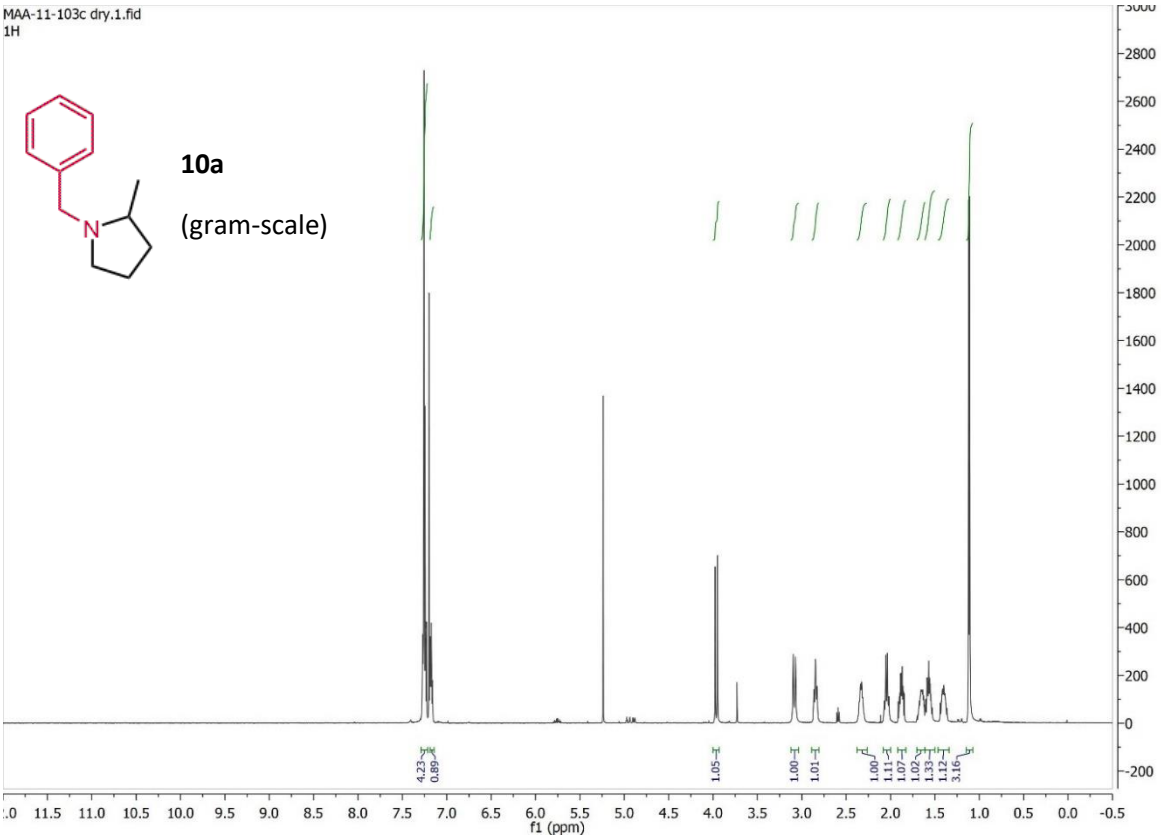

MAA-11-75c dry2.2.fid
13C
78.47
77.46
67.96
67.80
60.48
58.90
58.73
54.86
54.56
32.43
32.31
30.46
30.32
25.53
25.32
21.88
21.78
19.00
18.93
f1 (ppm)

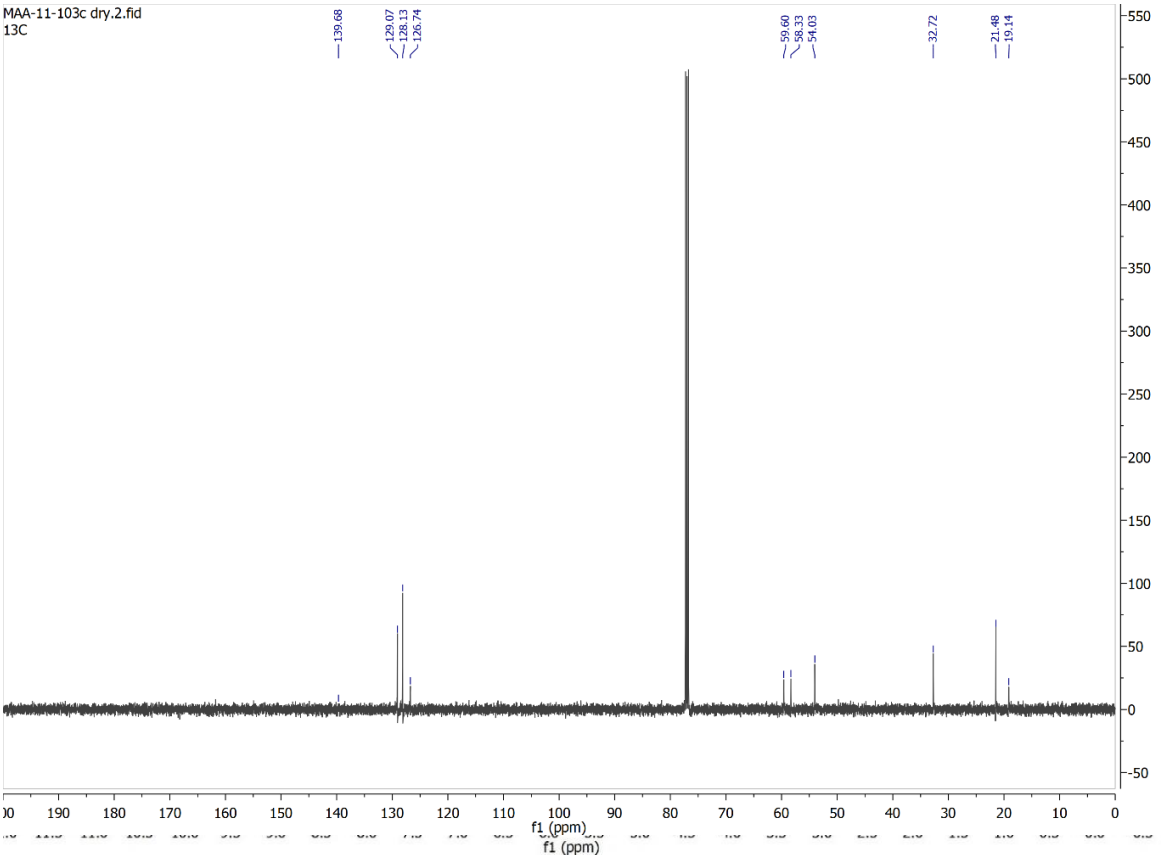

HL-1-125from-2-35.1.fid
1H
OH
N
10u
1.01
2.00
0.99
0.99
0.98
0.97
0.98
2.00
2.04
1.03
1.02
3.02
f1 (ppm)
HL-1-125from-2-35.2.fid
13C
77.358 CDCl3
77.103 CDCl3
76.849 CDCl3
64.637
60.365
54.231
53.993
32.639
29.108
21.639
18.956
f1 (ppm)

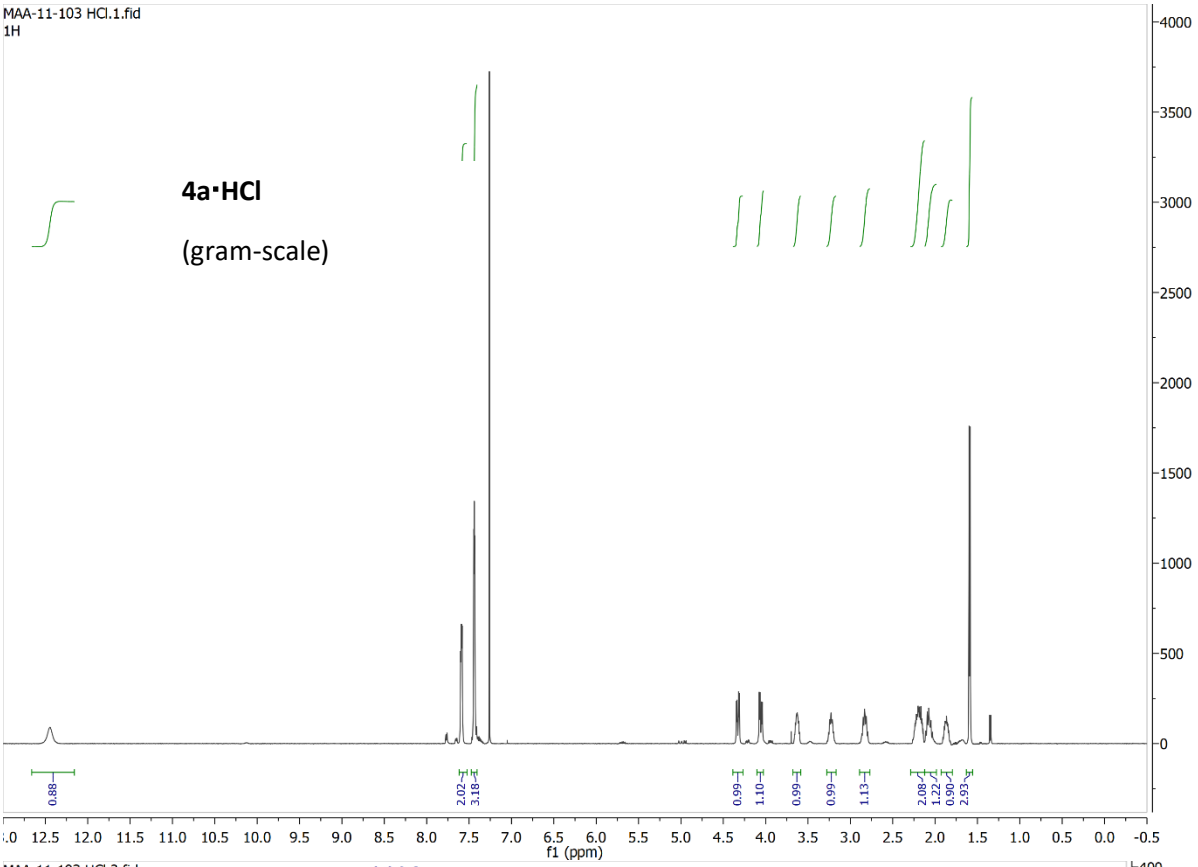

MAA-11-81 benzene d6.1.fid
1H
HO
N
10v
1.92
11.35
5.22
6.25
1.00
2.64
1.00
0.97
0.95
2.61
0.97
2.57
2.57
2.24
5.46
1.63
6.50
7.91
3.07
f1 (ppm)

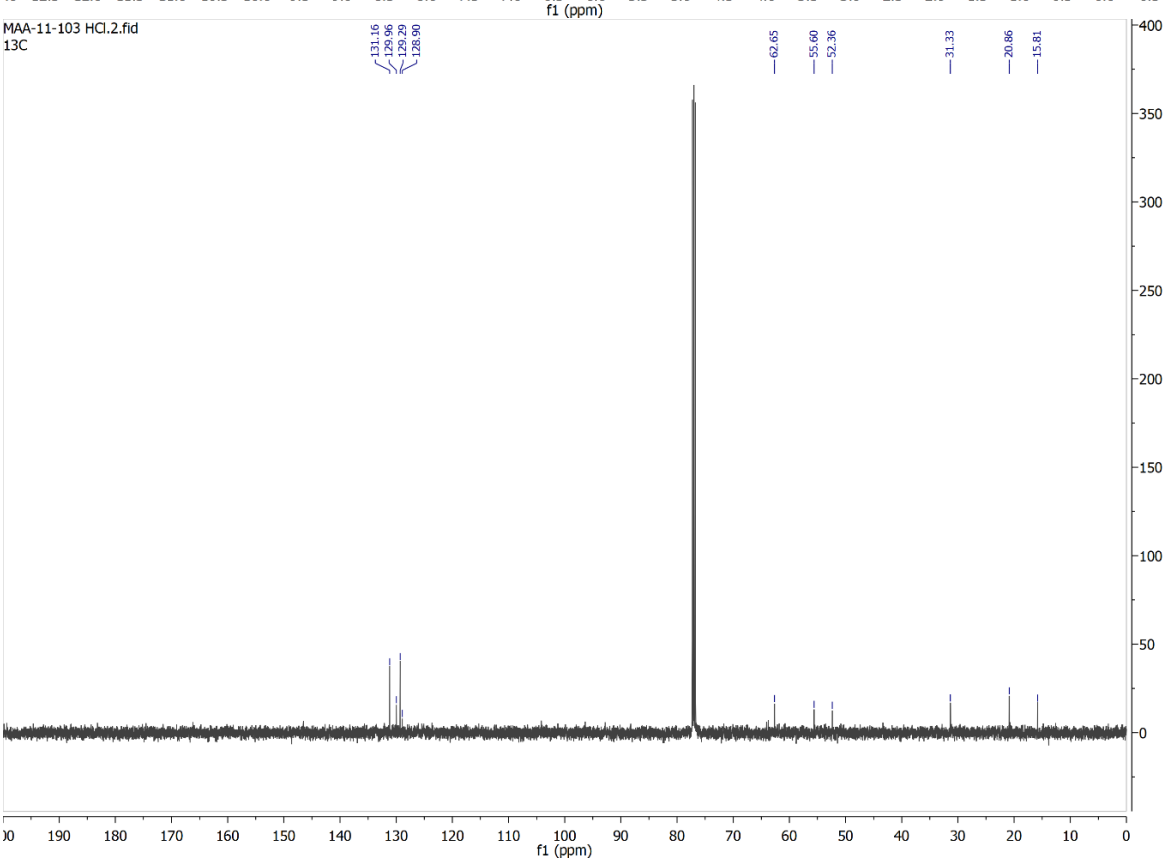

MAA-11-81cdry.2.fid
1d_13C_1_hour CDCl3 D:\\ Beau 30
138.39
134.93
129.25
128.96
128.37
128.10
127.85
127.80
77.20
67.51
63.41
62.02
60.92
55.26
54.54
52.47
45.28
32.99
31.97
22.40
21.49
20.19
19.11
f1 (ppm)


MAA-11-77B dry.1.fid
1H
10w
4.12
0.96
0.99
6.05
1.02
1.04
1.10
1.30
1.01
1.07
0.97
3.00
f1 (ppm)
MAA-11-77B dry.2.fid
13C
66.93
60.52
58.08
54.45
54.15
51.20
32.43
21.72
18.94
f1 (ppm)


MAA-11-103c dry.1.fid
1H
10a
(gram-scale)
f1 (ppm)


MAA-11-103c dry.2.fid
13C
139.68
129.07
128.13
126.74
59.60
58.33
54.03
32.72
21.48
19.14
f1 (ppm)

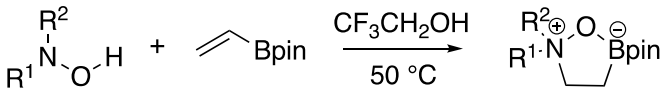

MAA-11-103 HCl.1.fid
1H
4a·HCl
(gram-scale)
f1 (ppm)


MAA-11-103 HCl.2.fid
13C
131.16
129.96
129.29
128.90
62.65
55.60
52.36
31.33
20.86
15.81
f1 (ppm)

6.4 Supporting Information for Chapter 4

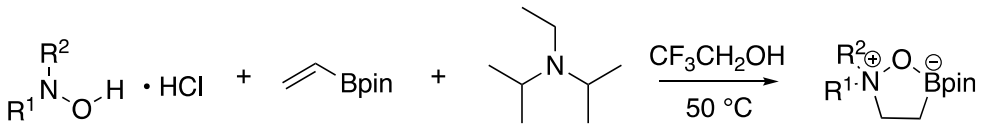
6.4.1 General Procedures

General procedure A: Cope-type hydroamination of pinacol vinylboronate



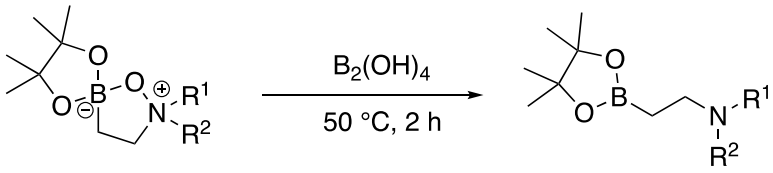
To a microwave vial charged with a stir bar was added vinylboronic acid pinacol ester (1.0 equiv) then CF_3CH_2OH (0.5 M), followed by the addition of hydroxylamine (1.5 equiv). The vial was sealed with a microwave cap and heated to 50 °C for 16 h. The reaction mixture was concentrated via rotary evaporation and the product was either purified by silica gel chromatography or recrystallization.

General procedure B: Cope-type hydroamination of pinacol vinylboronate using hydroxylamine HCl salts



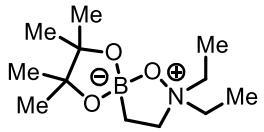
To a microwave vial charged with a stir bar was added vinylboronic acid pinacol ester (1.0 equiv) then CF_3CH_2OH (0.5 M), followed by the addition of hydroxylamine (1.5 equiv) and *N,N*-diisopropylethylamine (1.5 equiv). The vial was sealed with a microwave cap and heated to 50 °C for 16 h. The reaction mixture was concentrated via rotary evaporation and the product was purified by recrystallization.

General procedure C: Reduction of oxazaborolidines to aminoboronic esters



To a solution of crude oxazaborolidine (1.0 equiv) in CF_3CH_2OH (0.5 M) in a microwave vial was added $B_2(OH)_4$ (2.0 equiv). The vial was sealed with a microwave cap and heated to 50 °C for 2 h. The reaction mixture was concentrated via rotary evaporation and the product was used without any further purification.

6.4.2 Characterization



2,2-Diethyl-7,7,8,8-tetramethyl-1,6,9-trioxa-2-aza-5-boraspiro[4.4]nonan-2-ium-5-uide (4a)

The title compound was synthesized according to general procedure **A** using *N*,*N*-diethylhydroxylamine (0.077 mL, 0.75 mmol) and vinylboronic acid pinacol ester (0.077 g, 0.50 mmol) in CF_3CH_2OH (1.0 mL, 0.50 M). The crude product was isolated using flash chromatography (15% MeOH/EtOAc to 20% MeOH/EtOAc) to yield the title compound as a yellow oil (0.094 g, 77%).

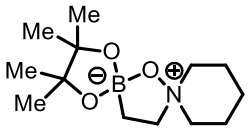
TLC R_f: 0.41 in 20% MeOH/EtOAc.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.50–3.39 (m, 4H), 3.22 (dq, *J* = 13.1, 7.2 Hz, 2H), 1.29 (t, *J* = 7.2 Hz, 6H), 1.11 (s, 12H), 0.89 (t, *J* = 8.2 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 78.3 (C), 66.4 (CH_2), 57.2 (CH_2), 24.9 (CH_2), 24.8 (CH_3), 24.6 (CH_3).

^{11}B NMR (95 MHz, $CDCl_3$): δ 12.1.

HRMS (ESI): Exact mass calcd for $C_{12}H_{27}BNO_3^+$ $[M+H]^+$: 265.1940. Found: 265.1970.



2,2,3,3-Tetramethyl-1,4,6-trioxa-7-aza-5-boradispiro[4.1.57.25]tetradecan-7-ium-5-uide (4e)

The title compound was synthesized according to general procedure **B** using *N*-hydroxypiperidine hydrochloride (0.054 g, 0.400 mmol), vinylboronic acid pinacol ester (0.041 g, 0.260 mmol) and *N,N*-diisopropylethylamine (0.056 mL, 0.40 mmol) in CF_3CH_2OH (0.52 mL, 0.50 M). The crude product was isolated using flash column chromatography to yield the title compound as a white solid (0.048 g, 73%).

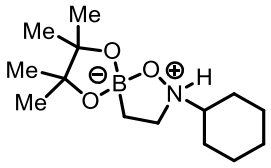
TLC R_f: 0.40 in 15% MeOH/EtOAc.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.58 (dt, *J* = 12.3, 4.0 Hz, 2H), 3.47–3.40 (m, 2H), 2.98 (td, *J* = 11.8, 3.3 Hz, 2H), 2.24 (dtt, *J* = 15.4, 11.7, 3.9 Hz, 2H), 1.78 (dq, *J* = 13.0, 4.3 Hz, 1H), 1.69 (dt, *J* = 14.6, 3.9 Hz, 2H), 1.41 (dtt, *J* = 13.3, 11.7, 3.9 Hz, 1H), 1.14 (s, 12H), 0.94 (t, *J* = 8.2 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 78.2 (C), 69.8 (CH_2), 63.1 (CH_2), 50.0 (CH_2), 24.9 (CH_2), 21.7 (CH_2), 21.1 (CH_3).

^{11}B NMR (160 MHz, $CDCl_3$): δ 12.3.

HRMS (ESI): Exact mass calcd for $C_{13}H_{26}BNNaO_3^+$ $[M+Na]^+$: 277.1940. Found: 277.1915.



2-Cyclohexyl-7,7,8,8-tetramethyl-1,6,9-trioxa-2-aza-5-boraspiro[4.4]nonan-2-ium-5-uide (4h)

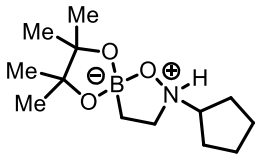
The title compound was synthesized according to a general procedure **A** using *N*-cyclohexylhydroxylamine (0.086 g, 0.75 mmol) and vinylboronic acid pinacol ester (0.077 g, 0.50 mmol) in CF_3CH_2OH (1.0 mL, 0.50 M). The crude product was isolated via recrystallization (EtOAc/acetone) to yield the title compound as a white solid (0.076 g, 56%).

^{1}H NMR (400 MHz, DMSO-*d_6*): δ 10.7 (br, s, 1H), 3.29–3.18 (m, 1H), 2.94– 2.82 (m, 2H), 2.13 (d, *J* = 10.9 Hz, 1H), 1.91–1.88 (m, 1H), 1.72–1.68 (m, 2H), 1.54 (d, *J* = 12.6 Hz, 1H), 1.37–1.09 (m, 4H), 1.07-0.99 (m, 1H), 0.94 (s, 3H), 0.92 (s, 3H), 0.89 (s, 3H), 0.88 (s, 3H), 0.41-0.37 (m, 2H).

^{13}C NMR (100 MHz, DMSO-*d_6*): δ 77.0 (C), 65.2 (CH), 54.4 (CH_2), 27.3 (CH_2), 26.6 (CH_2), 25.32 (CH_3), 25.0 (CH_3), 24.0 (CH_2), 23.8 (CH_2). *Two separate CH_3 signals for the pinacol.

^{11}B NMR (95 MHz, DMSO-*d_6*): δ 11.8.

HRMS (ESI): Exact mass calcd for $C_{14}H_{29}BNO_3^+$ $[M+H]^+$: 291.2096. Found: 291.2070.



2-Cyclohexyl-7,7,8,8-tetramethyl-1,6,9-trioxa-2-aza-5-boraspiro[4.4]nonan-2-ium-5-uide (4m)

The title compound was synthesized using according to general procedure **A** using *N*-cyclohexylhydroxylamine (0.034 g, 0.30 mmol) and vinylboronic acid pinacol ester (0.031 g, 0.20 mmol) in

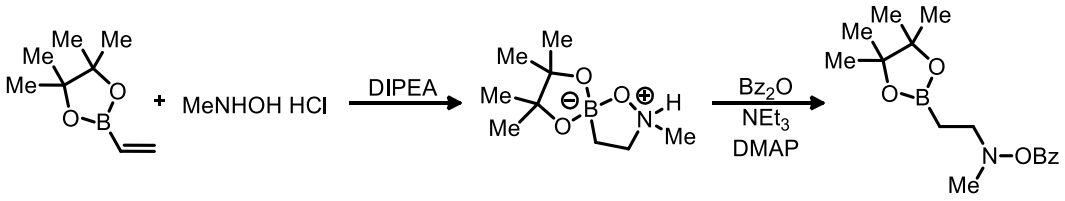
CF_3CH_2OH (0.4 mL, 0.5 M). The reaction mixture was concentrated under reduced pressure and recrystallized (Et_2O/DCM) to yield the title compound as white crystals (0.030 g, 56%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 11.60 (br s, 1H), 3.58–3.41 (m, 2H), 3.07 (q, *J* = 9.8 Hz, 1H), 2.16 (dq, *J* = 14.4, 7.6 Hz, 1H), 2.00–1.83 (m, 3H), 1.83–1.70 (m, 2H), 1.62–1.46 (m, 2H), 1.08 (s, 12H), 0.89 (dt, *J* = 12.4, 9.7 Hz, 1H), 0.71 (ddd, *J* = 13.0, 8.4, 4.2 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 83.2 (C), 67.1 (CH), 56.4 (CH), 28.9 (CH_2), 26.4 (CH_2), 25.2 (CH_3), 25.0 (CH_2), 24.7 (CH_3). *Two separate CH_3 signals for the pinacol.

^{11}B NMR (160 MHz, $CDCl_3$): δ 12.5.

HRMS (ESI): Exact mass calcd for $C_{13}H_{27}BNO_3^+$ $[M+H]^+$: 277.1940. Found: 277.1922.



***O*-Benzoyl-*N*-methyl-*N*-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)hydroxylamine (13i)**

The oxazaborolidine was synthesized according to general procedure **B** using *N*-methylhydroxylamine hydrochloride (0.084 g, 1.0 mmol), vinylboronic acid pinacol ester (0.231 g, 1.50 mmol) and *N,N*-diisopropylethylamine (0.18 mL, 1.0 mmol) in CF_3CH_2OH (2 mL, 0.5 M). Upon completion, the crude reaction mixture was concentrated via rotary evaporation, and was used in the following step without further purification

The crude oxazaborolidine (2,7,7,8,8-pentamethyl-1,6,9-trioxa-2-aza-5-boraspiro[4.4]nonan-2-ium-5-uide) was dissolved in DCM (3.3 mL, 0.30 M). To this solution Et_3N (0.42 mL, 3.0 mmol) and a catalytic amount of DMAP (0.012 g, 0.10 mmol) were added. It was followed immediately by the slow addition of benzoic anhydride (0.679 g, 3.00 mmol). Upon completion (17 h), the crude reaction mixture was concentrated via rotary evaporation, then diluted with DCM. The crude reaction was washed with saturated bicarbonate solution (x1). The aqueous phase was collected and extracted with DCM (x1). The combined organic phases were washed with brine (x1), then dried with Na_2SO_4 and filtered. The filtrate was concentrated via rotary evaporation and the crude product was isolated using flash column

chromatography (20% EtOAc/DCM to 50% EtOAc/DCM) to yield the title compound as an off-white solid (0.128 g, 42% over 2 steps).

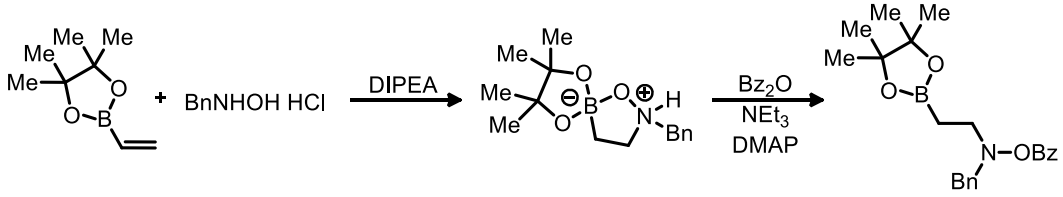
TLC R_f: 0.23 in 10% EtOAc/DCM

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.03–7.97 (m, 2H), 7.57–7.51 (m, 1H), 7.46–7.38 (m, 2H), 3.14–3.07 (m, 2H), 2.87 (s, 3H), 1.23 (s, 12H), 1.17 (dd, *J* = 9.6, 7.3 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 165.2 (C), 136.6 (C), 132.9 (CH), 129.4 (CH), 128.3 (CH), 83.3 (C), 56.6 (CH_2), 46.2 (CH_3), 24.7 (CH_3), 24.6 (CH_2).

^{11}B NMR (160 MHz, $CDCl_3$): δ 34.0.

HRMS (ESI): Exact mass calcd for $C_{16}H_{25}BNO_4^+$ $[M+H]^+$: 305.1732. Found: 327.1737.



***O*-Benzoyl-*N*-methyl-*N*-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)hydroxylamine (13j)**

The oxazaborolidine was synthesized according to general procedure **B** using *N*-benzylhydroxylamine hydrochloride (0.239 g, 1.50 mmol), vinylboronic acid pinacol ester (0.154 g, 1.00 mmol) and *N,N*-diisopropylethylamine (0.26 mL, 1.5 mmol) in CF_3CH_2OH (2 mL, 0.5 M). Upon completion, the crude reaction mixture was concentrated via rotary evaporation, and was used in the following step without further purification

The crude oxazaborolidine (2-benzyl-7,7,8,8-tetramethyl-1,6,9-trioxa-2-aza-5-boraspiro[4.4]nonan-2-ium-5-uide) was dissolved in DCM (3.3 mL, 0.3 M). To this solution, Et_3N (0.42 mL, 3.0 mmol) and a catalytic amount of DMAP (0.012 g, 0.10 mmol) were added. It was followed immediately by the slow addition of benzoic anhydride (0.679 g, 3.00 mmol). Upon completion (19 h), the crude reaction mixture was concentrated via rotary evaporation, then diluted with DCM. The crude reaction was washed with saturated bicarbonate solution (x1). The aqueous phase was collected and extracted with DCM (x1). The combined organic phases were washed with brine (x1), then dried with Na_2SO_4 and filtered. The filtrate was concentrated via rotary evaporation and the crude product was isolated using flash column

chromatography (10% EtOAc/DCM to 5% MeOH/DCM) to yield the title compound as an off-white solid (0.194 g, 51% over 2 steps).

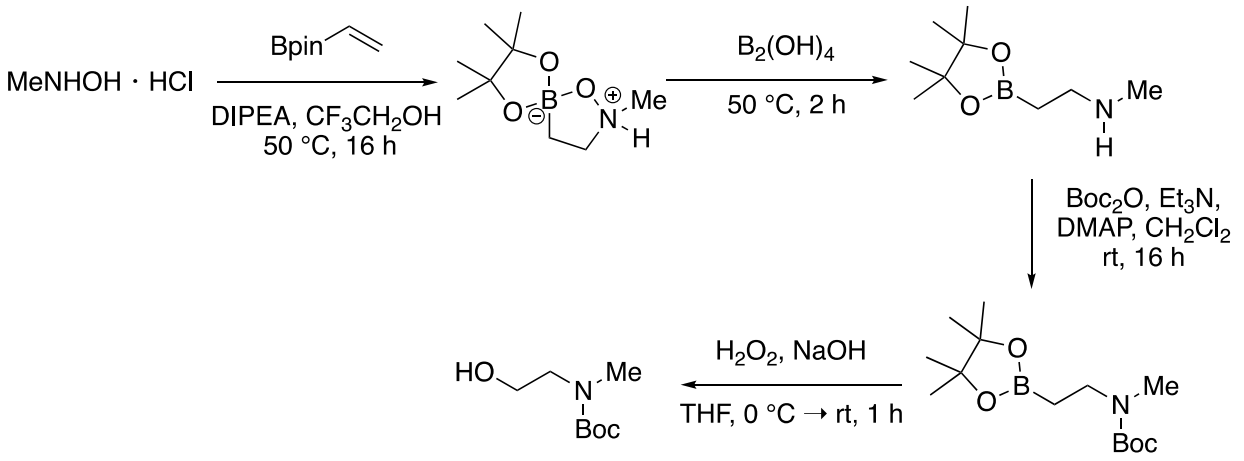
TLC R_f: 0.65 in 15% EtOAc/DCM

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91-7.88 (m, 2H), 7.56-7.49 (m, 1H), 7.45-7.40 (m, 2H), 7.40–7.35 (m, 2H), 7.30-7.26 (m, 2H), 7.24-7.19 (m, 1H), 4.16 (s, 2H), 3.23–3.15 (m, 2H), 1.22 (s, 12H), 1.21–1.16 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 165.2 (C), 136.0 (C), 132.7 (CH), 129.5 (CH), 129.4 (CH), 129.4 (C), 128.2 (CH), 128.2 (CH), 127.5 (CH), 83.2 (C), 62.8 (CH_2), 54.2 (CH_2), 24.8 (CH_3), 23.3 (CH_2).

^{11}B NMR (160 MHz, $CDCl_3$): δ 33.6.

HRMS (ESI): Exact mass calcd for $C_{22}H_{28}BNO_4^+$ $[M+H]^+$: 403.2045. Found: 403.2043.



***tert*-Butyl (2-hydroxyethyl)(methyl)carbamate (14i)**

The oxazaborolidine was synthesized according to general procedure **B** using *N*-methylhydroxylamine hydrochloride (0.063 g, 0.75 mmol), vinylboronic acid pinacol ester (0.077 g, 0.50 mmol) and *N,N*-diisopropylethylamine (0.13 mL, 0.75 mmol) in CF_3CH_2OH (1 mL, 0.5 M). The reaction mixture was used in the following step without further purification or concentration.

With the crude solution of 2,7,7,8,8-pentamethyl-1,6,9-trioxa-2-aza-5-boraspiro[4.4]nonan-2-ium-5-uide, general procedure **C** was conducted using $B_2(OH)_4$ (0.090 g, 1.0 mmol). The reaction mixture was allowed

to warm to room temperature after 2 h. The reaction mixture was concentrated via rotary evaporation and the crude amine was used in next step without purification.

The crude *N*-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethan-1-amine was dissolved in DCM (0.33 mL, 1.5 M). To this solution, Et_3N (0.11 mL, 0.75 mmol) and a catalytic amount of DMAP (0.006 g, 0.05 mmol) was added. It was followed immediately by dropwise addition of di-*t*-butyl dicarbonate (0.17 mL, 0.75 mmol). Upon completion (16 h at room temperature), the reaction mixture was concentrated via rotary evaporation, then diluted with DCM. The crude reaction mixture was washed with water (x3). The organic phase was collected and dried with Na_2SO_4 and filtered. The filtrate was concentrated via rotary evaporation and used without further purification.

To the crude *tert*-butyl methyl(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)carbamate was added THF (5 mL, 0.1 M). This mixture was then cooled to 0 °C. A solution of H_2O_2 (30% in H_2O, 1.25 mL) in aqueous NaOH (2.0 M, 2.5 mL) was added. The reaction mixture was stirred for 1 h at room temperature. Upon completion, the reaction mixture was evaporated and diluted further with water (5 mL). The aqueous phase was extracted with DCM (x3). The combined organic phases were collected and then dried with Na_2SO_4 and filtered. The filtrate was concentrated via rotary evaporation and the crude product was isolated using flash column chromatography (80% EtOAc/Hexanes) to yield the title compound as a colorless oil (0.037 g, 42% over 4 steps).

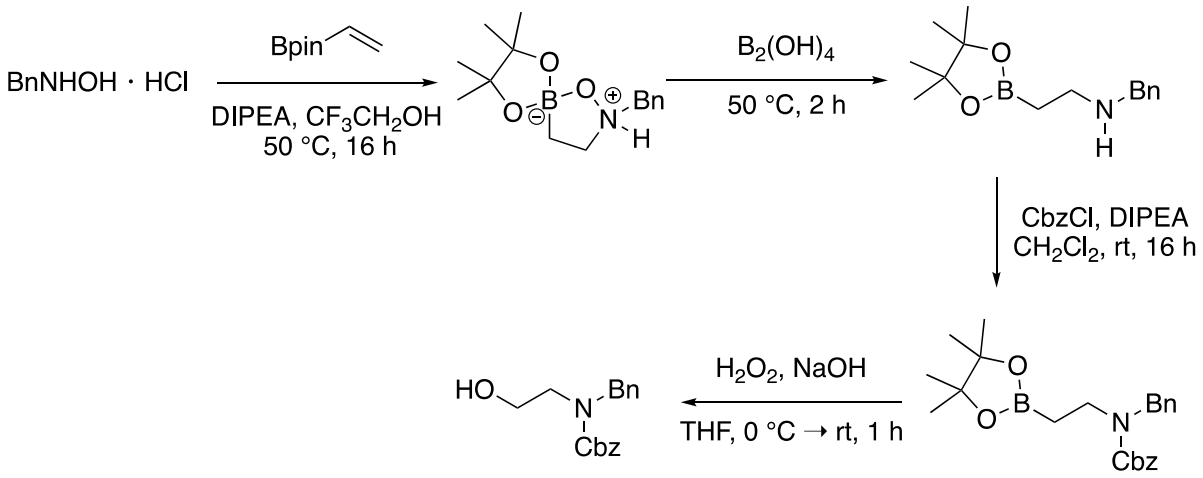
The characterization data below is in good agreement with previously reported data.[237]

TLC R_f: 0.20 in 80% EtOAc/Hexanes.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.75-3.71 (m, 2 H), 3.38 (t, *J* = 5.3 Hz, 2H), 2.91 (s, 3H), 1.45 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 157.6 (C), 80.0 (C), 61.8 (CH_2), 51.5 (CH_2), 35.6 (CH_3), 28.4 (CH_3).

[237] Söveges, B.; Imre, T.; Szenda, T.; Póti, Á. L.; Cserép, G. B.; Hegedüs, T.; Kele, P.; Németh, K. *Org. Biomol. Chem.* **2016**, *14*, 6071.



Benzyl benzyl(2-hydroxyethyl)carbamate (14j)

The oxazaborolidine was synthesized according to general procedure **B** using *N*-benzylhydroxylamine hydrochloride (0.063 g, 0.75 mmol), vinylboronic acid pinacol ester (0.077 g, 0.50 mmol) and *N,N*-diisopropylethylamine (0.013 mL, 0.75 mmol) in CF_3CH_2OH (1 mL, 0.5 M). The reaction mixture was used in the following step without further purification or concentration.

With the crude solution of 2-benzyl-7,7,8,8-tetramethyl-1,6,9-trioxa-2-aza-5-boraspiro[4.4]nonan-2-ium-5-uide, general procedure **C** was conducted using $B_2(OH)_4$ (0.090 g, 1.0 mmol). The reaction mixture was allowed to warm to room temperature after 2 h. The reaction mixture was concentrated via rotary evaporation and the crude amine was used in next step without purification.

The crude *N*-benzyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethan-1-amine was dissolved in DCM (0.33 mL, 1.5 M). To this solution DIPEA (0.013 mL, 0.75 mmol) was added, and followed immediately by dropwise addition of benzyl chloroformate (0.011 mL, 0.75 mmol). The reaction was stirred overnight. Upon completion, reaction was diluted with DCM. The crude reaction mixture was washed with a saturated sodium bicarbonate solution (x3). The organic phase was collected and dried with Na_2SO_4 and filtered. The filtrate was concentrated via rotary evaporation and used without further purification.

To the crude benzyl benzyl(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)carbamate was added THF (5 mL, 0.1 M). This mixture was then cooled to 0 °C. A solution of H_2O_2 (30% in H_2O, 1.25 mL) in aqueous NaOH (2.0 M, 2.5 mL) was added. The reaction mixture was stirred for 1 h at room temperature. Upon completion, the reaction mixture was evaporated and diluted further with water (5 mL). The organic phase was extracted with DCM (x3). The combined organic phases were collected and then dried with

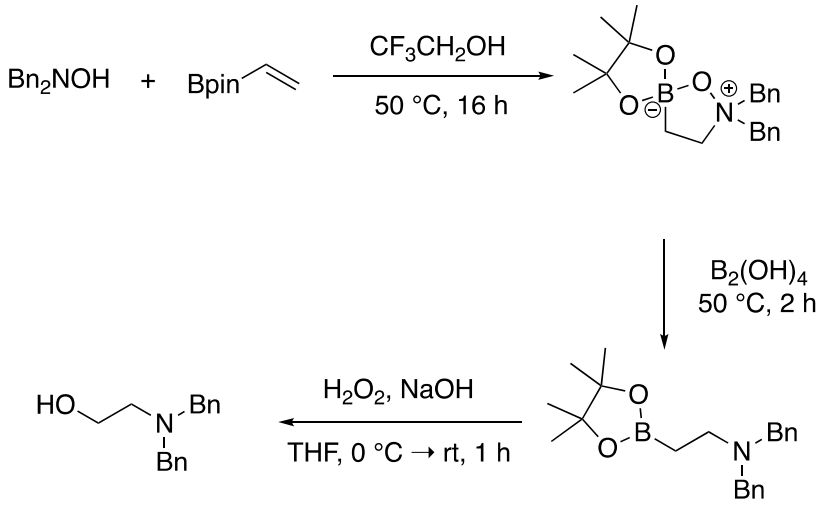
Na_2SO_4 and filtered. The filtrate was concentrated via rotary evaporation and the crude product was isolated using flash column chromatography (70% EtOAc/Hexanes) to yield the title compound as a colorless oil (0.050 g, 35% over 4 steps).

Characterization data is in good agreement with previously reported data.[238]

TLC R_f: 0.10 in 70% EtOAc/Hexanes.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37-7.18 (m, 10H), 5.20 (s, 2H), 4.60-4.57 (m, 2H), 3.73-3.67 (m, 2H), 3.46-3.40 (m, 2H), 2.89 (br s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 157.6 (C), 137.4 (C), 136.2 (C), 128.6 (CH), 128.4 (CH), 128.0 (CH), 127.9 (CH), 127.4 (CH), 127.2 (CH), 67.6 (CH_2), 61.5 (CH_2), 51.5 (CH_2), 50.0 (CH_2).



2-(Dibenzylamino)ethan-1-ol (15d)

The oxazaborolidine was synthesized according to general procedure **A** using *N,N*-dibenzylhydroxylamine (0.096 g, 0.45 mmol) and vinylboronic acid pinacol ester (0.046 g, 0.30 mmol) in CF_3CH_2OH (1.2 mL, 0.25 M). The reaction was heated to 50 °C for 48 h. The reaction mixture was used in the following step without further purification or concentration.

[238] Pal, R.; O'Brien, S. C.; Willis, M. C. *Chem. Eur. J.* **2020**, *26*, 11710.

With the crude solution of 2,2-dibenzyl-7,7,8,8-tetramethyl-1,6,9-trioxa-2-aza-5-boraspiro[4.4]nonan-2-ium-5-uide general procedure **C** was conducted using $B_2(OH)_4$ (0.054 g, 0.60 mmol). The reaction mixture was allowed to warm to room temperature after 2 h. The reaction mixture was concentrated via rotary evaporation and the crude amine was used in next step without purification.

To the crude *N,N*-dibenzyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethan-1-amine was added THF (0.3 mL, 0.1 M). This mixture was then cooled to 0 °C. A solution of H_2O_2 (30% in H_2O, 0.75 mL) in aqueous NaOH (2.0 M, 1.5 mL) was added. The reaction mixture was stirred for 1 h at room temperature. Upon completion, the reaction mixture was evaporated and diluted further with water (3 mL). The organic phase was extracted with DCM (x3). The organic phase was extracted with DCM (x3). The combined organic phases were collected and then dried with Na_2SO_4 and filtered. The filtrate was concentrated via rotary evaporation and the crude product was isolated using flash column chromatography (33% EtOAc/Hexanes) to yield the title compound as a white solid (0.027 g, 39% over 3 steps).

Characterization data is in good agreement with previously reported data.[239]

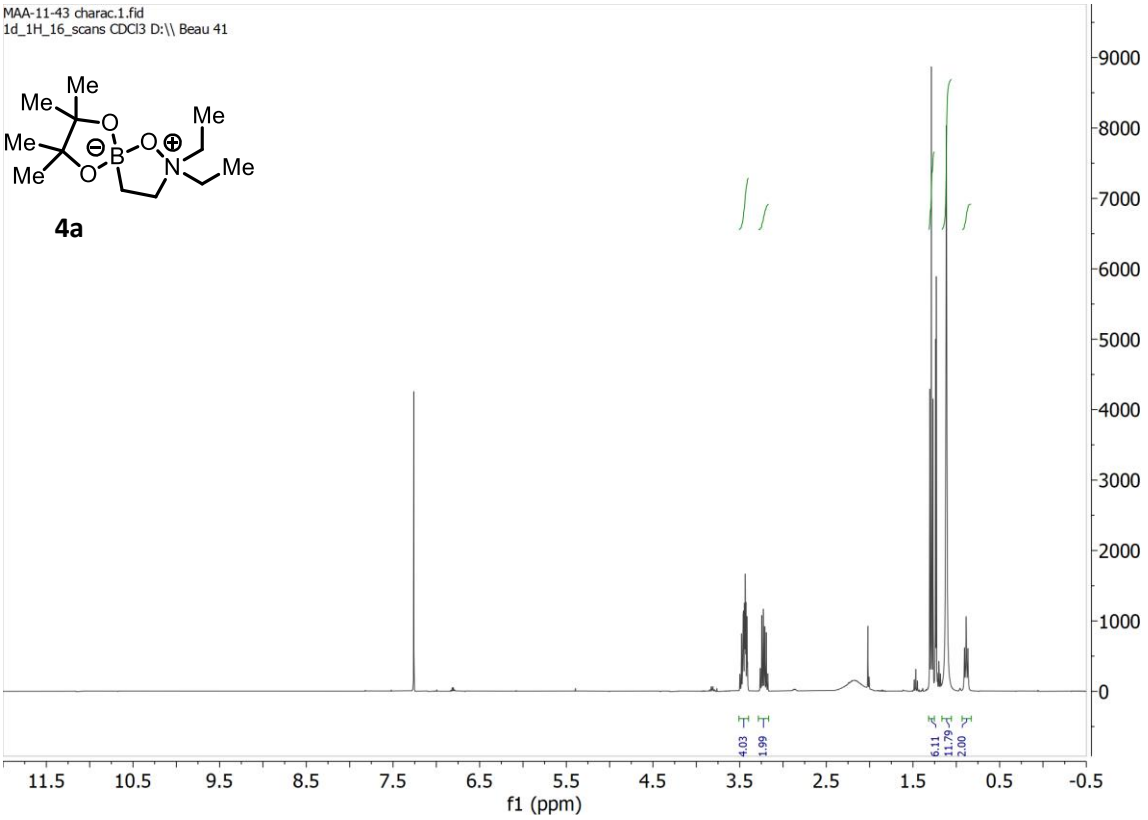
TLC R_f: 0.30 in 33% EtOAc/Hexanes.

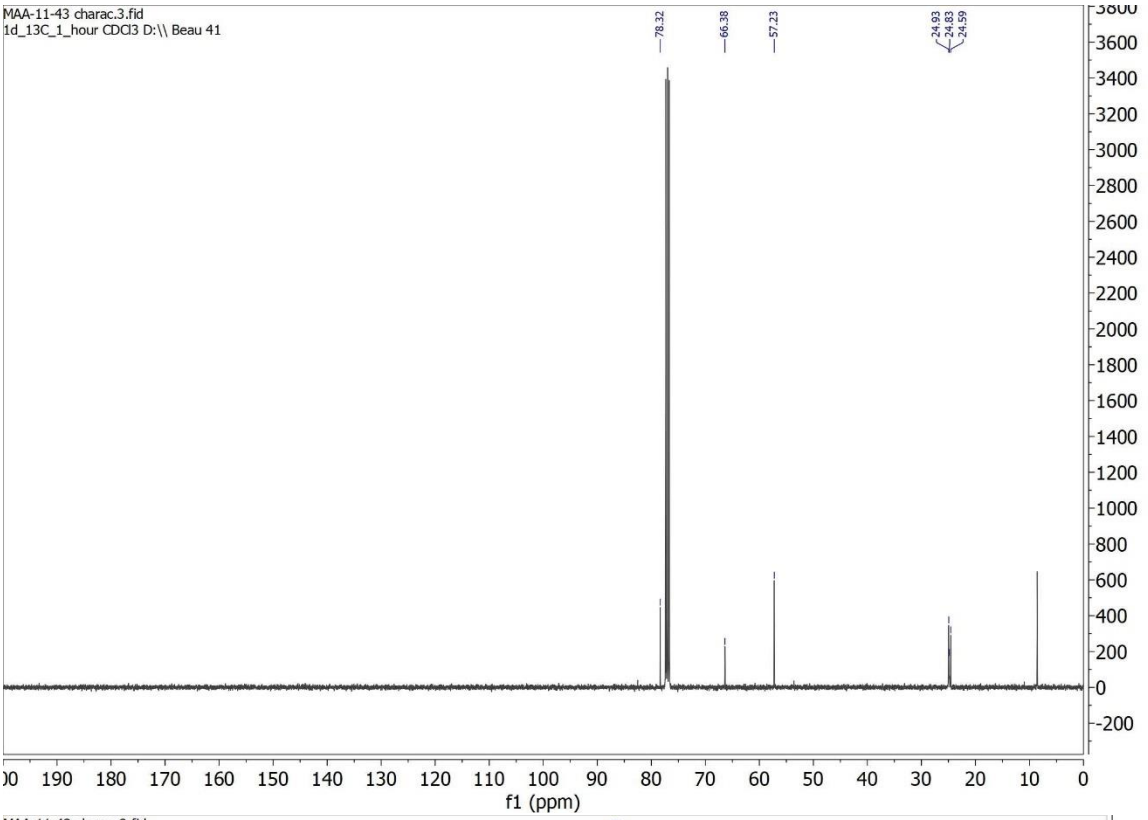
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36-7.29 (m, 8H), 7.28-7.25 (m, 2H), 3.63 (s, 4H), 3.59 (t, *J* = 5.3 Hz, 1H), 2.68 (t, *J* = 5.4 Hz, 1H), 2.55 (br s, 1H).

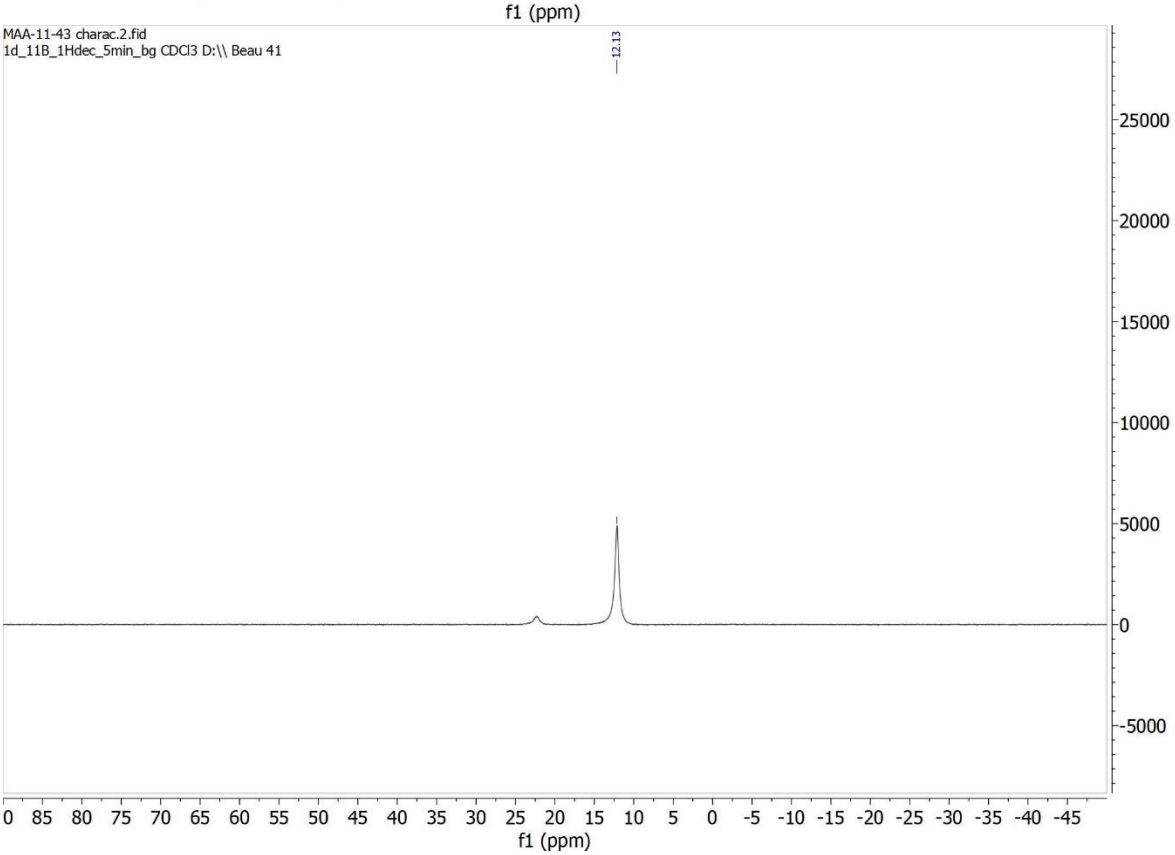
^{13}C NMR (125 MHz, $CDCl_3$): δ 138.7 (C), 129.0 (CH), 128.4 (CH), 127.2 (CH), 58.5 (CH), 58.2 (CH_2), 54.8 (CH_2).

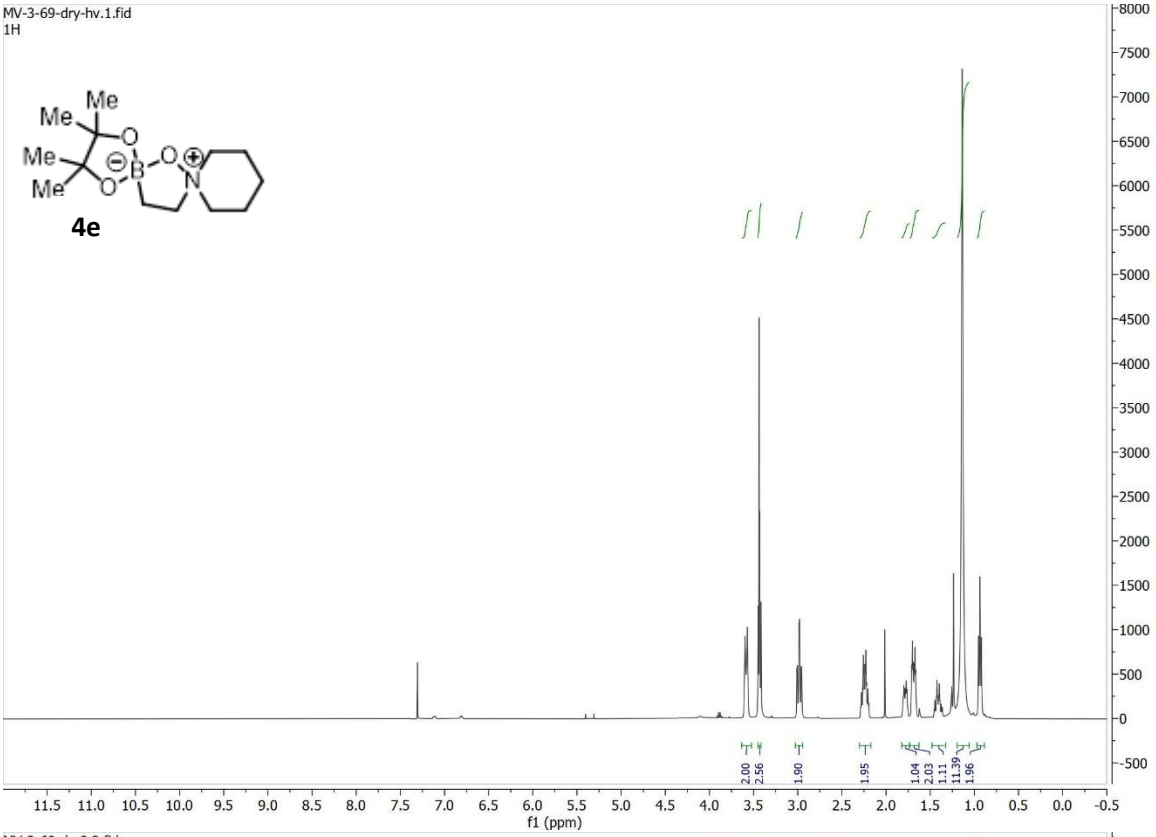
[239] Zimmermann, B. M.; Ngoc, T. T.; Tzaras, D.-I.; Kaicharla, T.; Teichert, J. F. *J. Am. Chem. Soc.* **2021**, *143*, 16865.

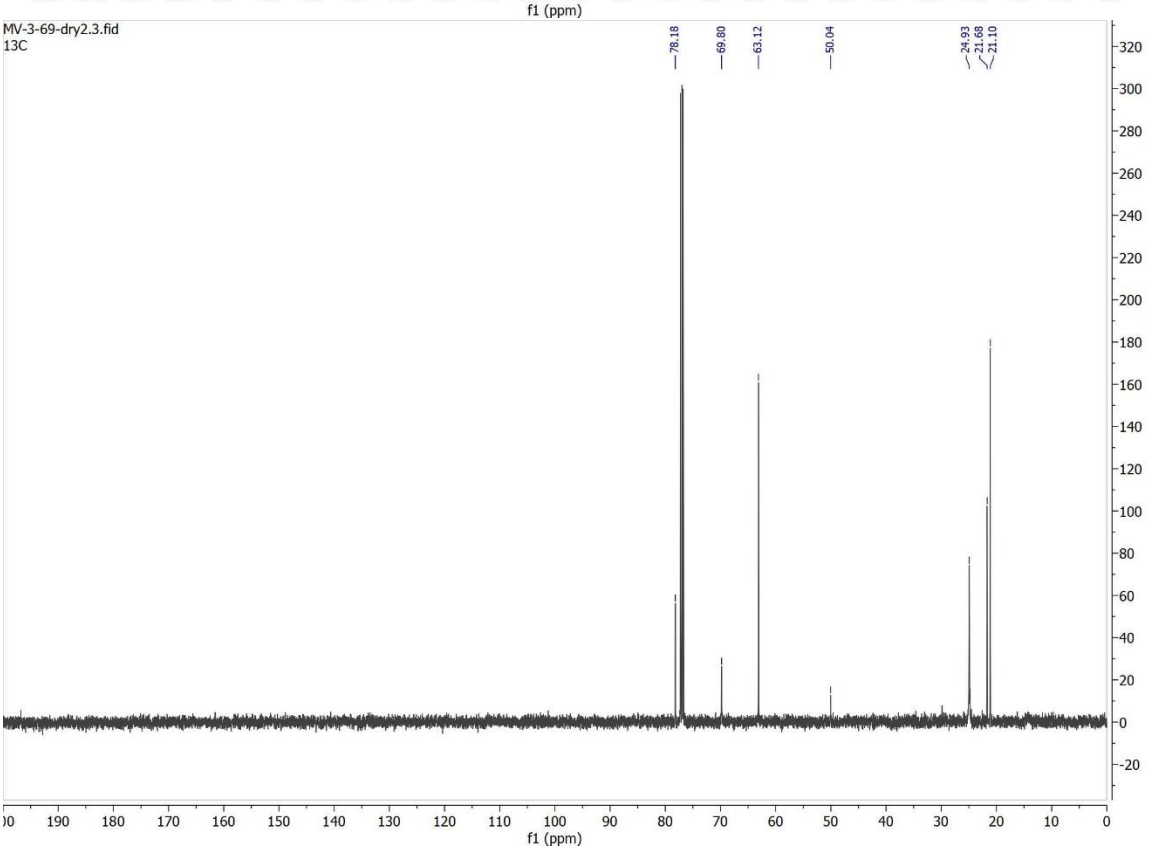
6.4.3 NMR spectra

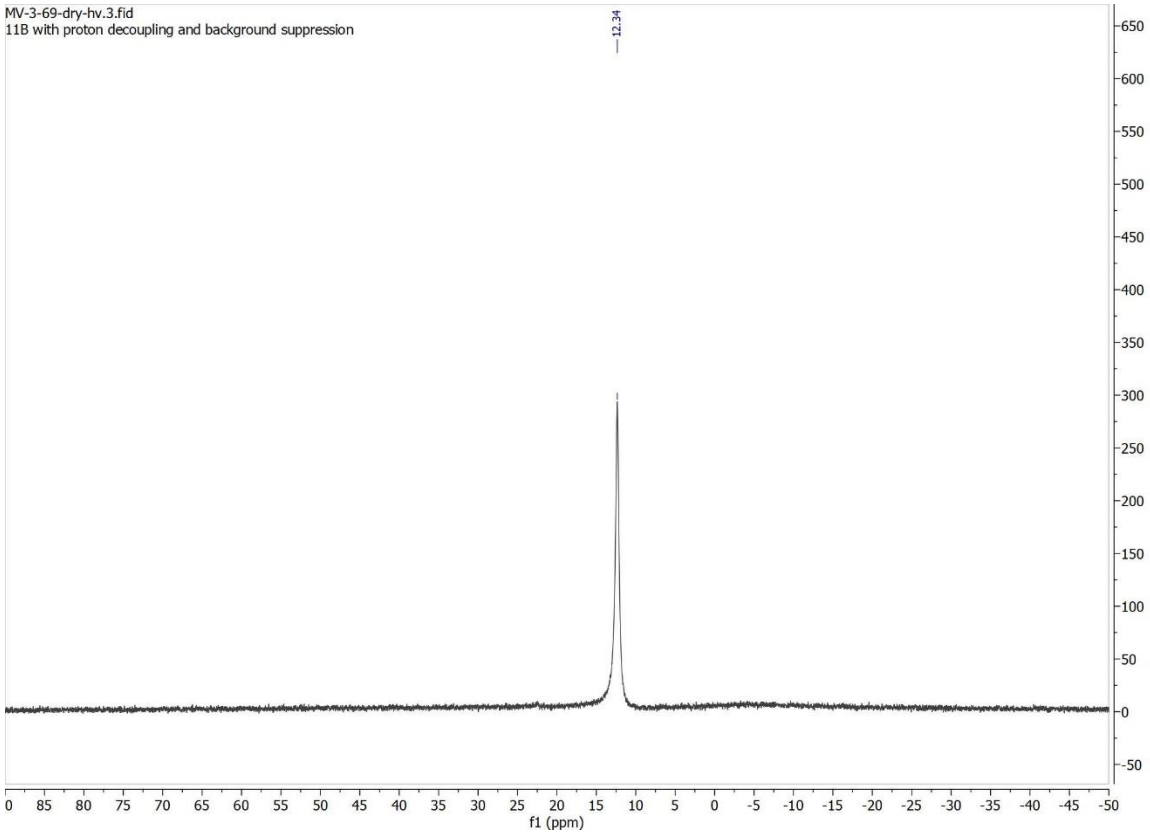


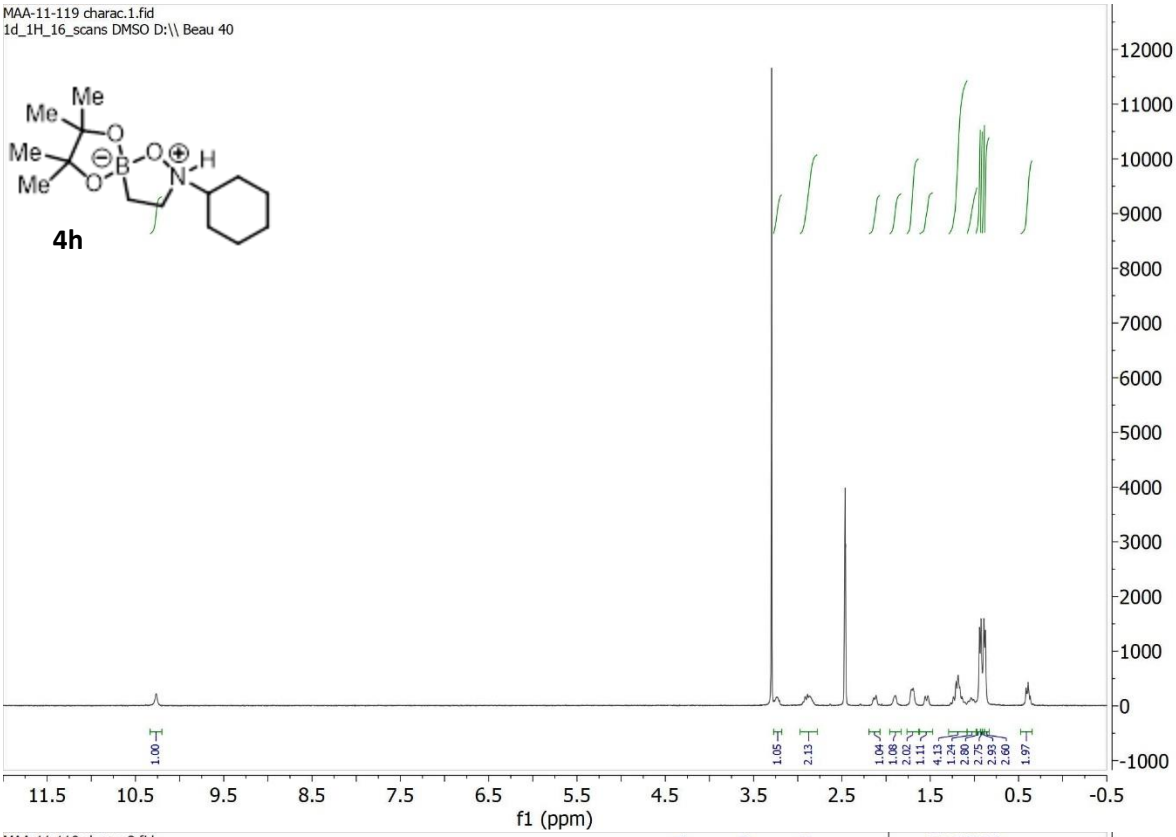

MAA-11-43 charac.3.fid
1d_13C_1_hour CDCl3 D:\\ Beau 41
78.32
66.38
57.23
24.93
24.83
24.59
f1 (ppm)

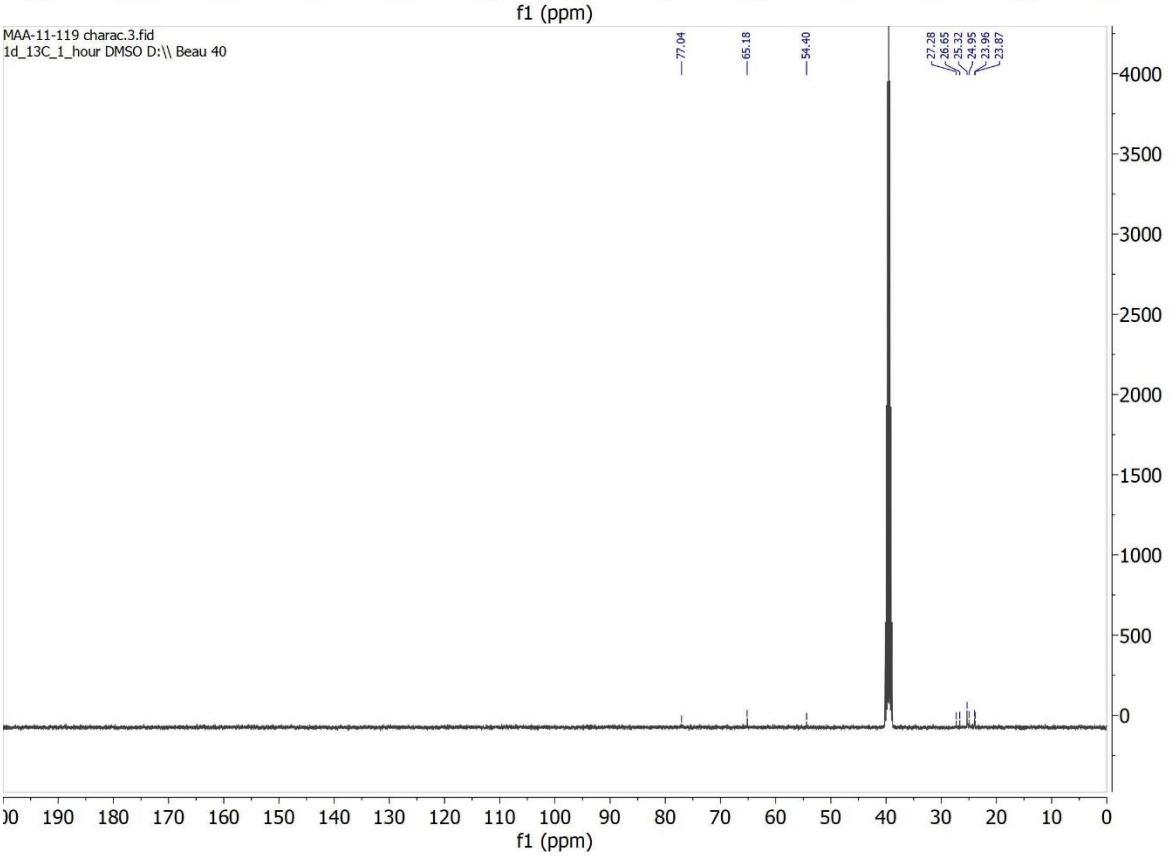

MAA-11-43 charac.2.fid
1d_11B_1Hdec_5min_bg CDCl3 D:\\ Beau 41
12.13
f1 (ppm)

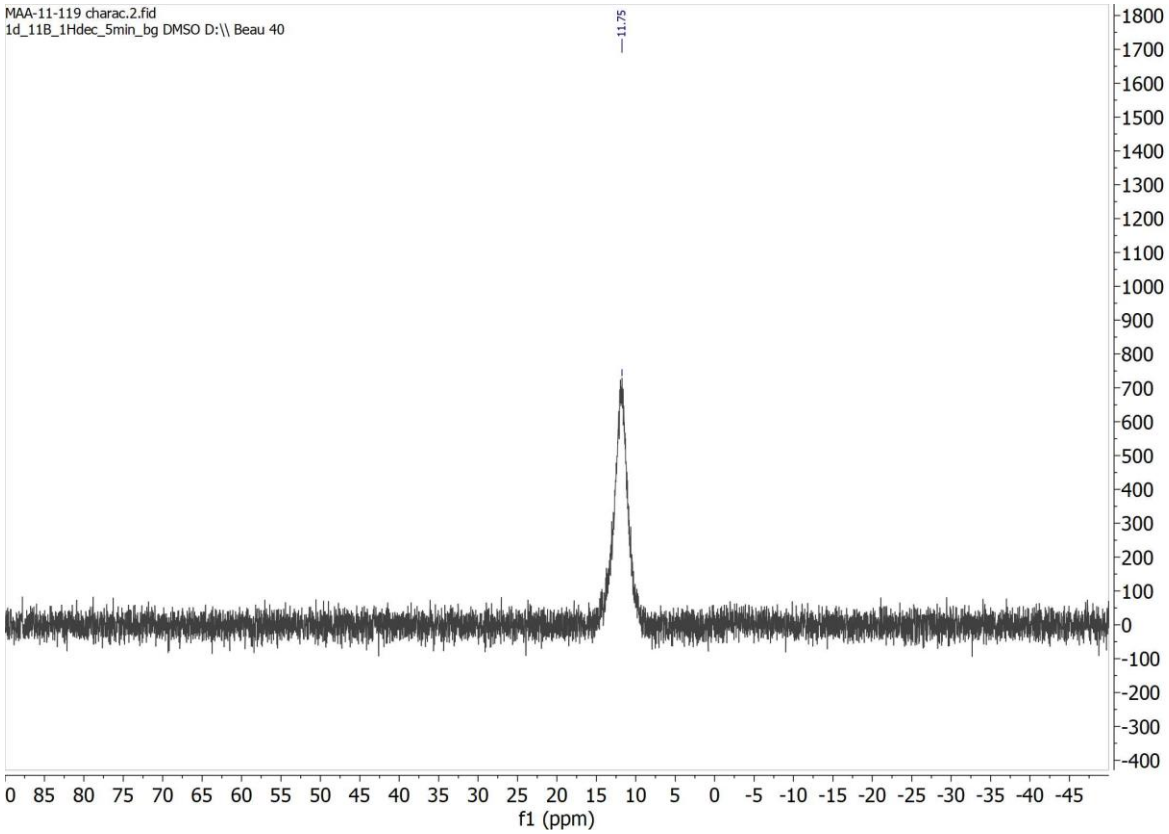

MV-3-69-dry-hv.1.fid
1H
Me
Me
Me
Me
O
O
B
O
N
4e
2.00
2.56
1.90
1.95
1.04
2.03
1.11
11.39
1.96
f1 (ppm)

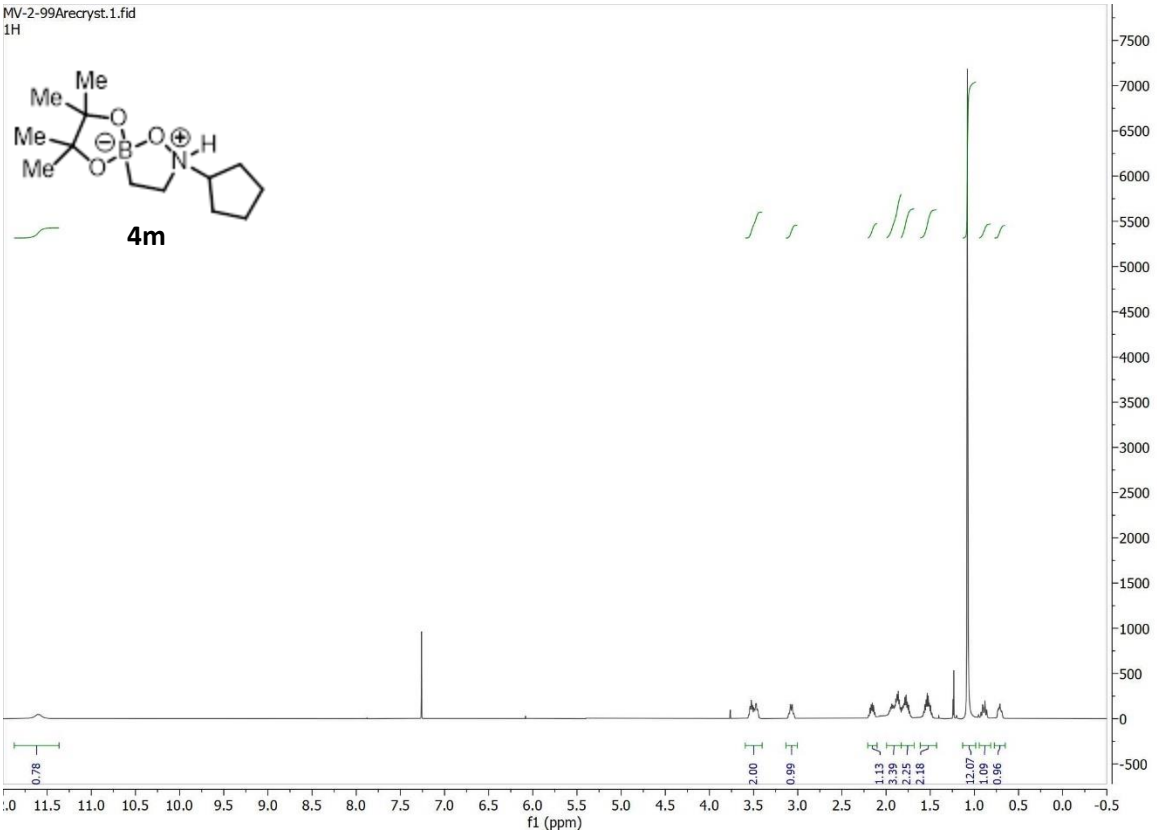

MV-3-69-dry2.3.fid
13C
78.18
69.80
63.12
50.04
24.93
21.68
21.10
f1 (ppm)

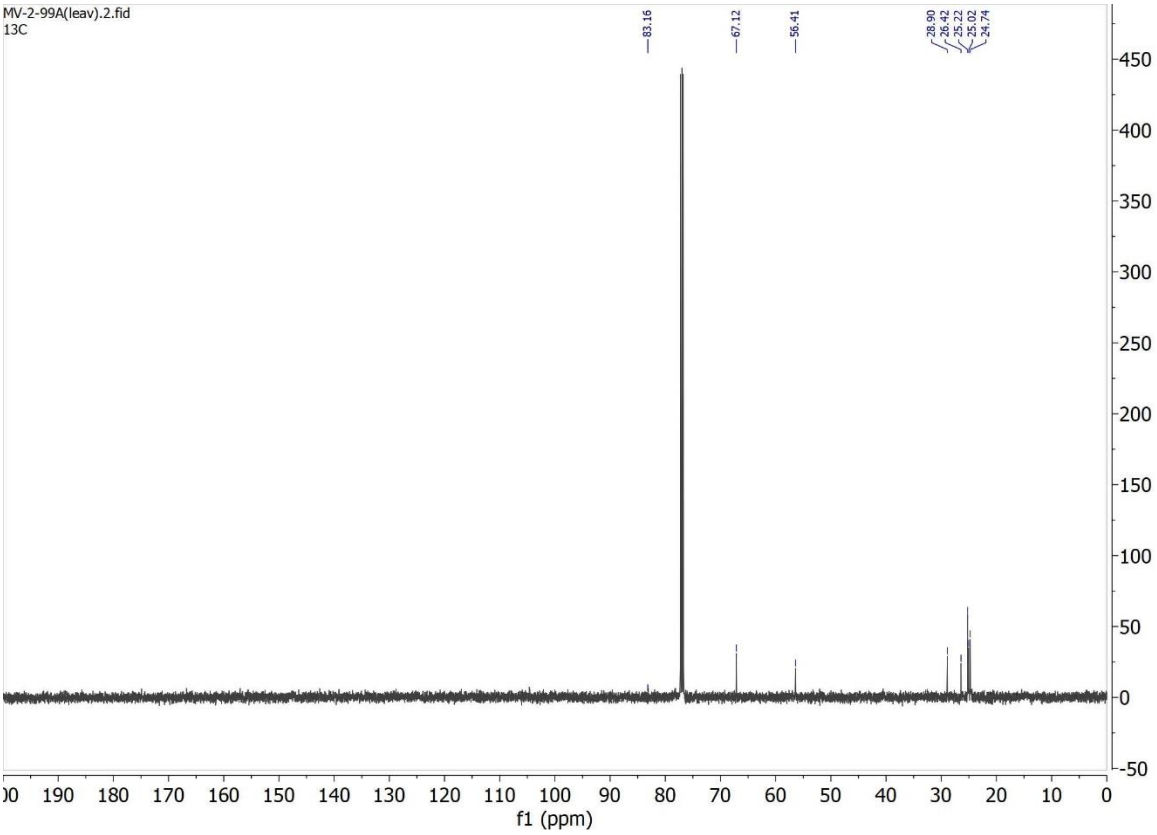

MV-3-69-dry-hv.3.fid
11B with proton decoupling and background suppression
12.34
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
0 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0 -5 -10 -15 -20 -25 -30 -35 -40 -45 -50
f1 (ppm)

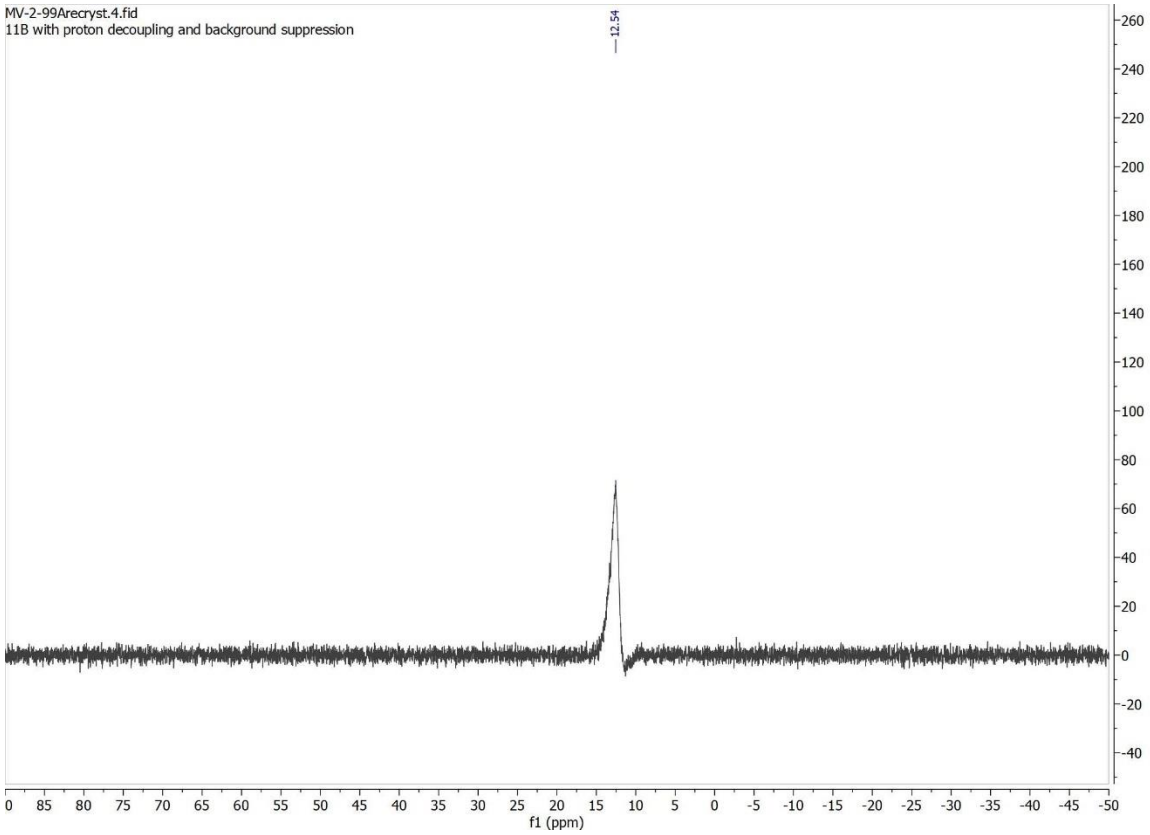

MAA-11-119 charac.1.fid
1d_1H_16_scans DMSO D:\\ Beau 40
Me
Me
Me
Me
O
O
B
O
H
N
4h
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
1.00
1.05
2.13
1.04
1.08
2.02
1.11
4.13
1.24
2.80
2.75
2.93
2.60
1.97
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f1 (ppm)

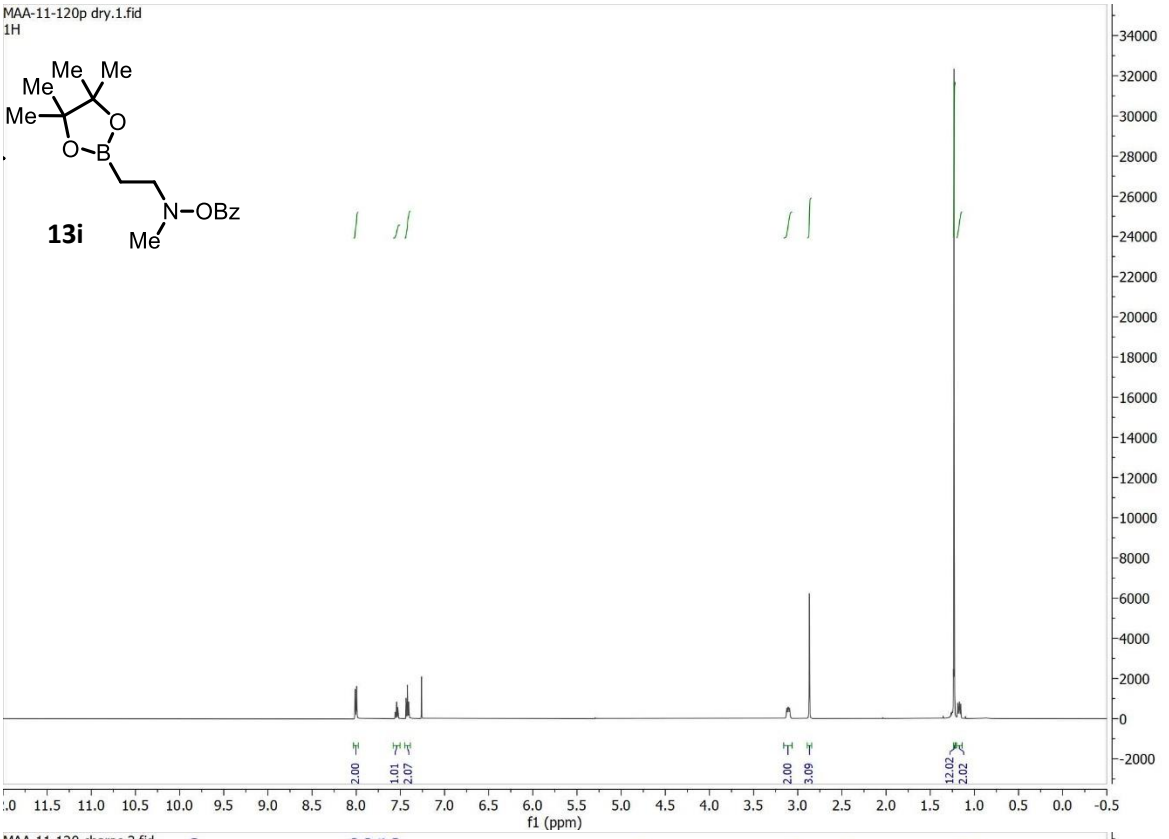

MAA-11-119 charac.3.fid
1d_13C_1_hour DMSO D:\\ Beau 40
77.04
65.18
54.40
27.28
26.65
26.32
24.95
23.96
23.87
4000
3500
3000
2500
2000
1500
1000
500
0
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

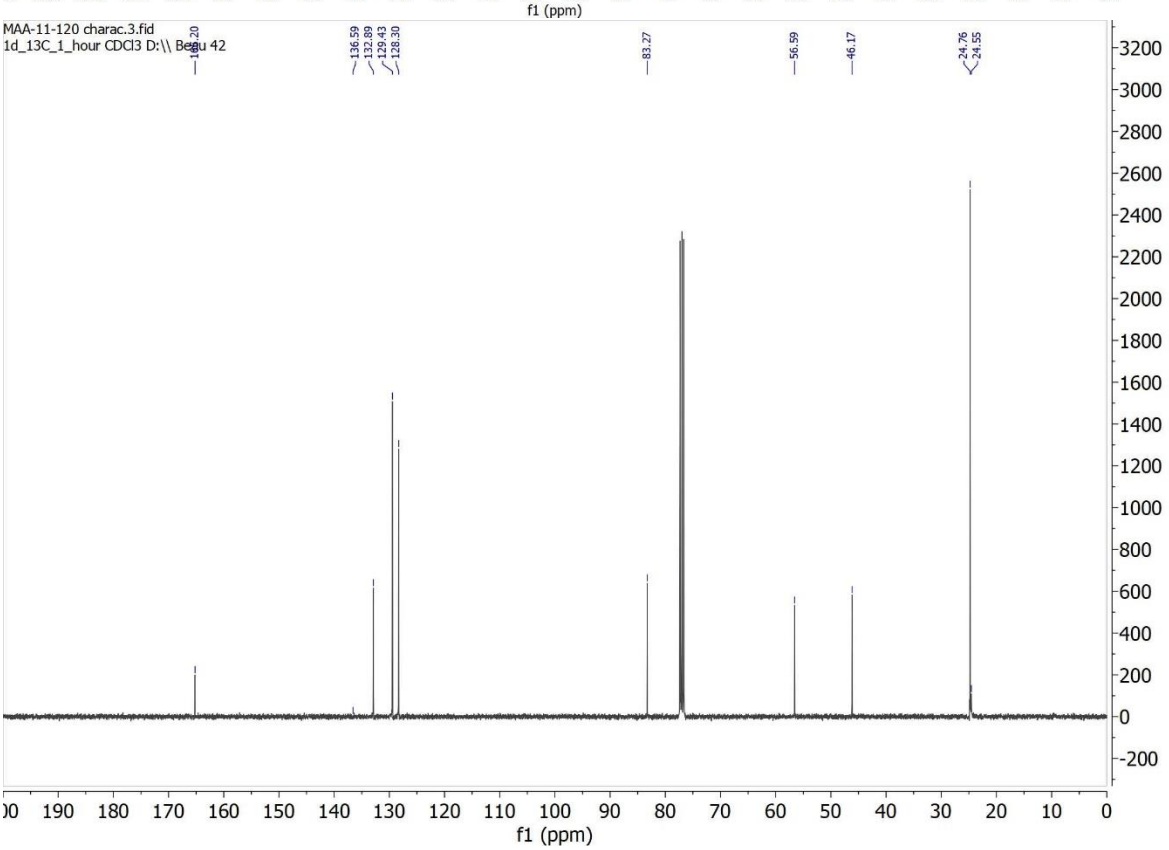

MAA-11-119 charac.2.fid
1d_11B_1Hdec_5min_bg DMSO D:\\ Beau 40
11.75
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
-200
-300
-400
0 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0 -5 -10 -15 -20 -25 -30 -35 -40 -45
f1 (ppm)

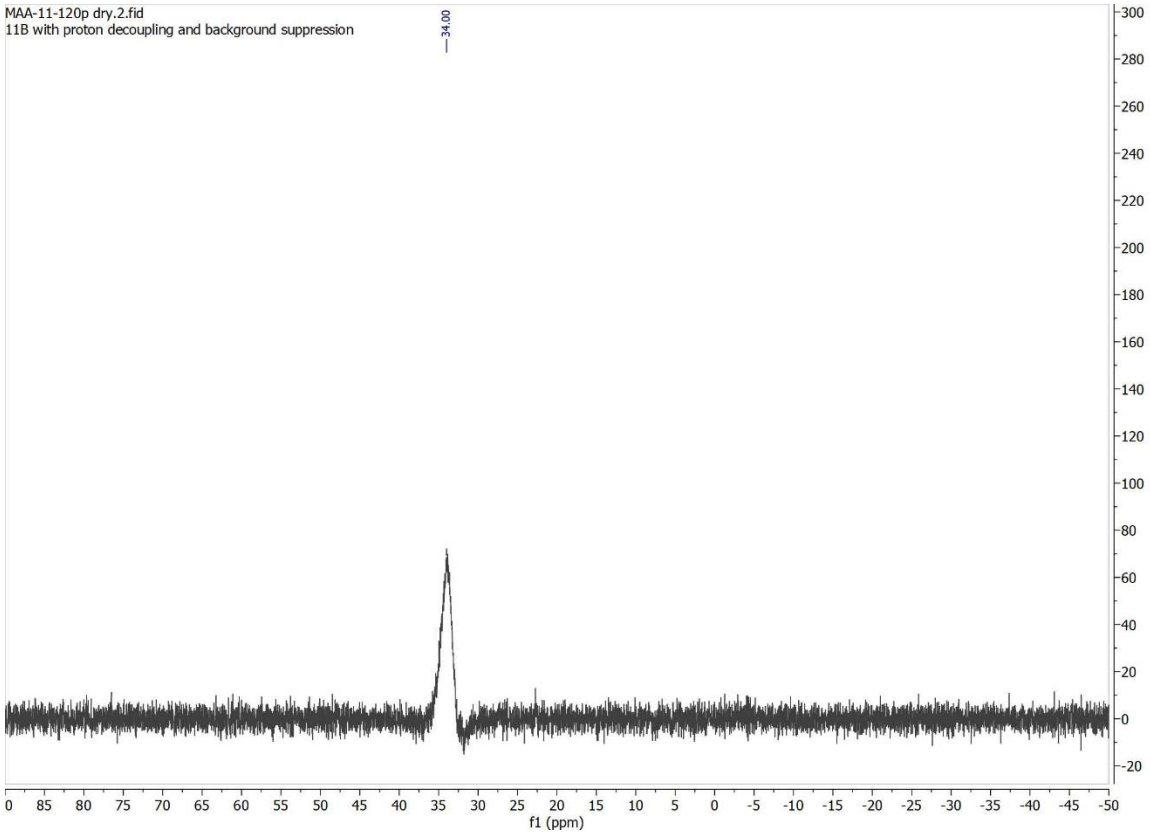

MV-2-99Arecryst.1.fid
1H
Me
Me
Me
Me
O
B
O
O
H
N
4m
0.78
2.00
0.99
1.13
3.39
2.25
2.18
12.07
1.09
0.96
f1 (ppm)

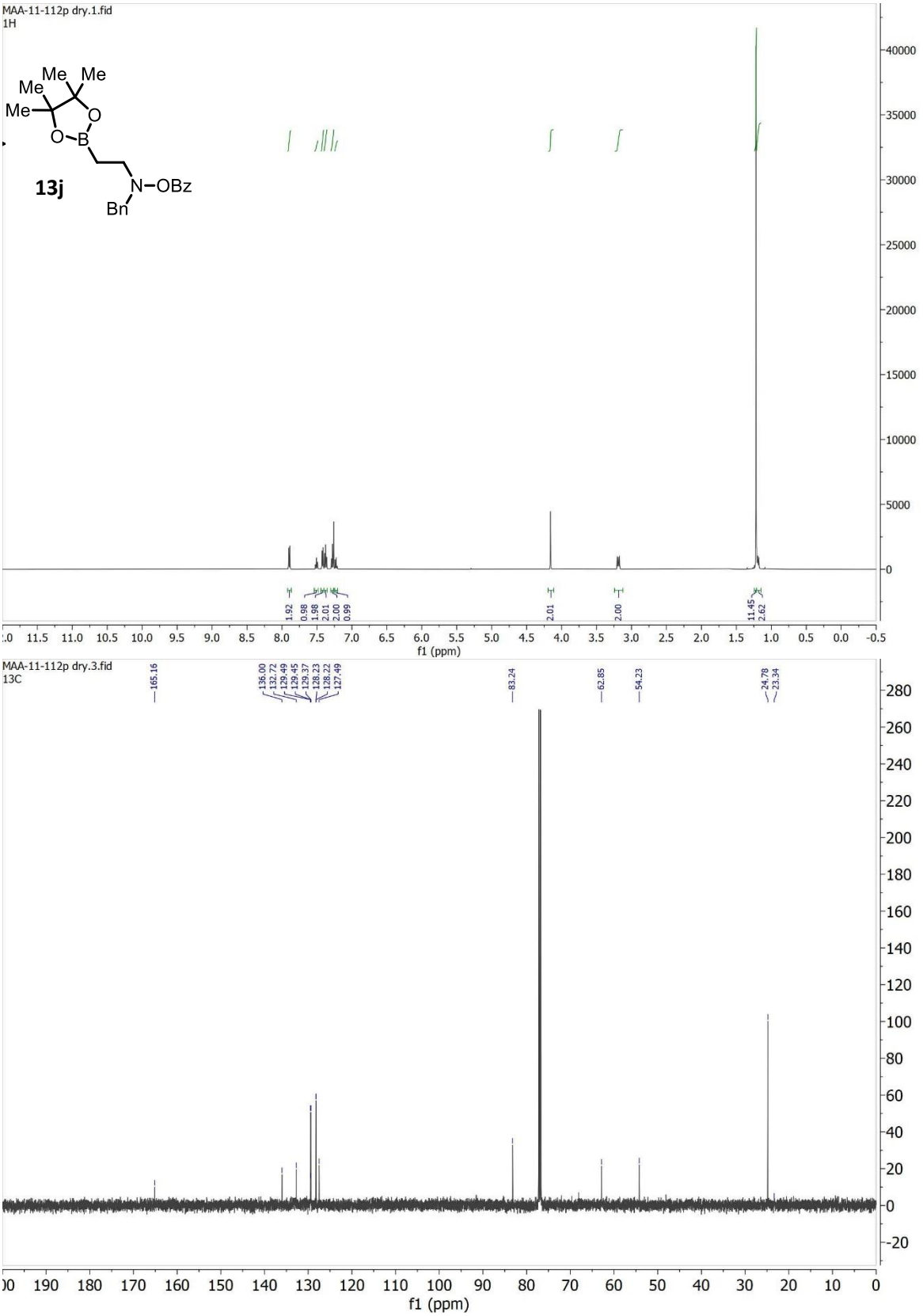

MV-2-99A(leav).2.fid
13C
83.16
67.12
56.41
28.90
26.42
25.22
25.02
24.74
f1 (ppm)

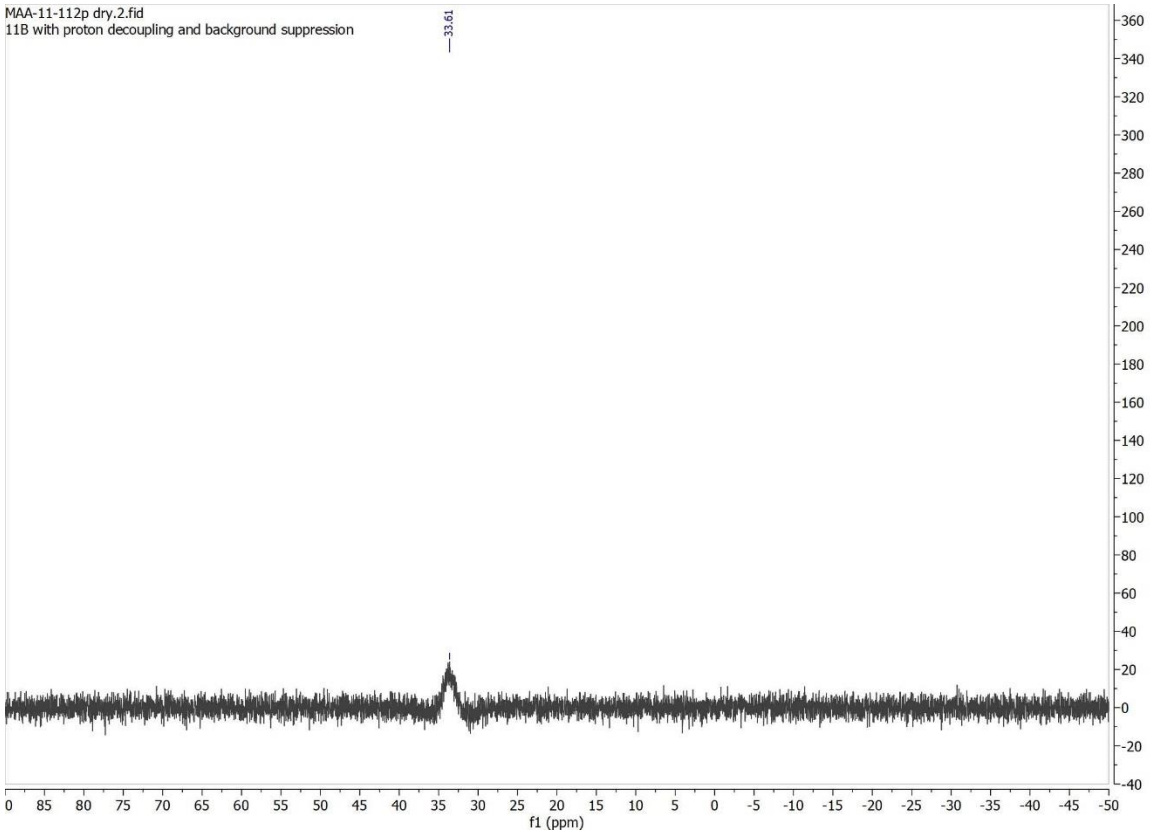

MV-2-99Arecryst.4.fid
11B with proton decoupling and background suppression
12.54
260
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
-40
0 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0 -5 -10 -15 -20 -25 -30 -35 -40 -45 -50
f1 (ppm)

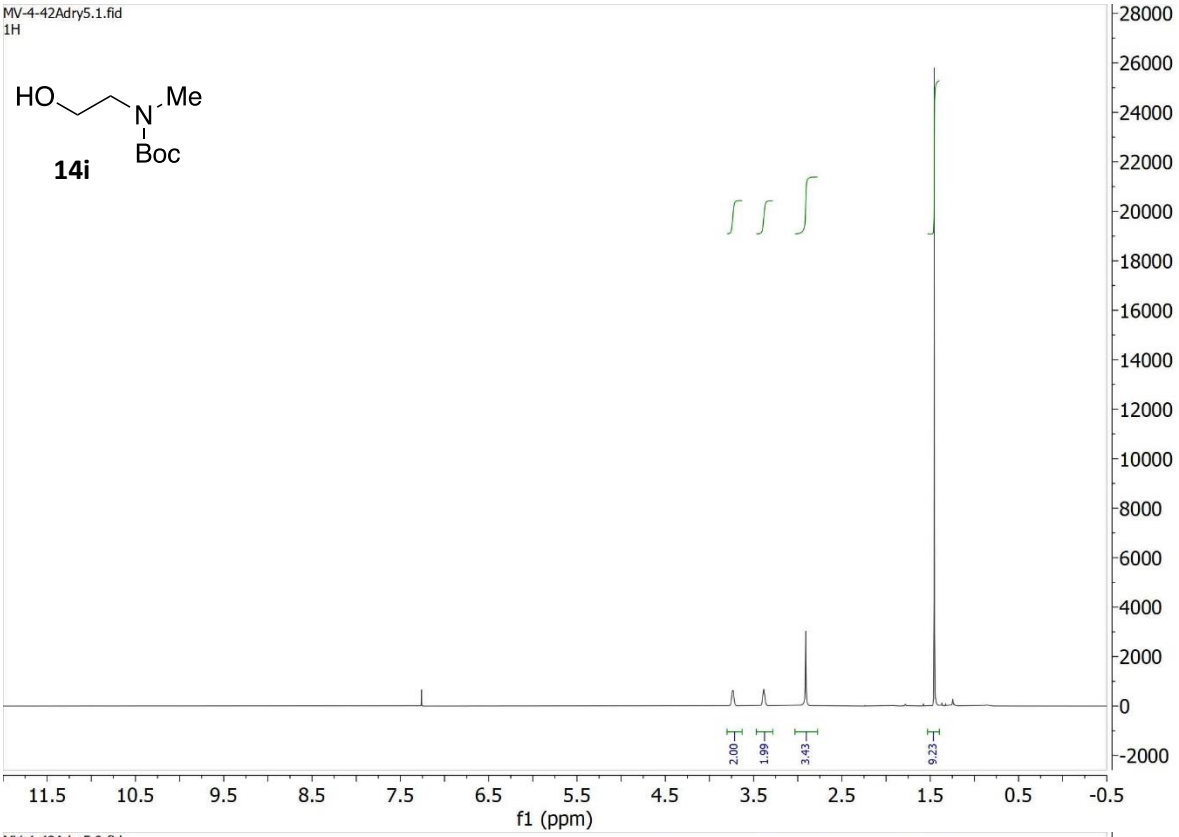

MAA-11-120p dry.1.fid
1H
Me
Me
Me
Me
O
O
B
N–OBz
Me
13i
2.00
1.01
2.07
2.00
3.09
12.02
2.02
f1 (ppm)

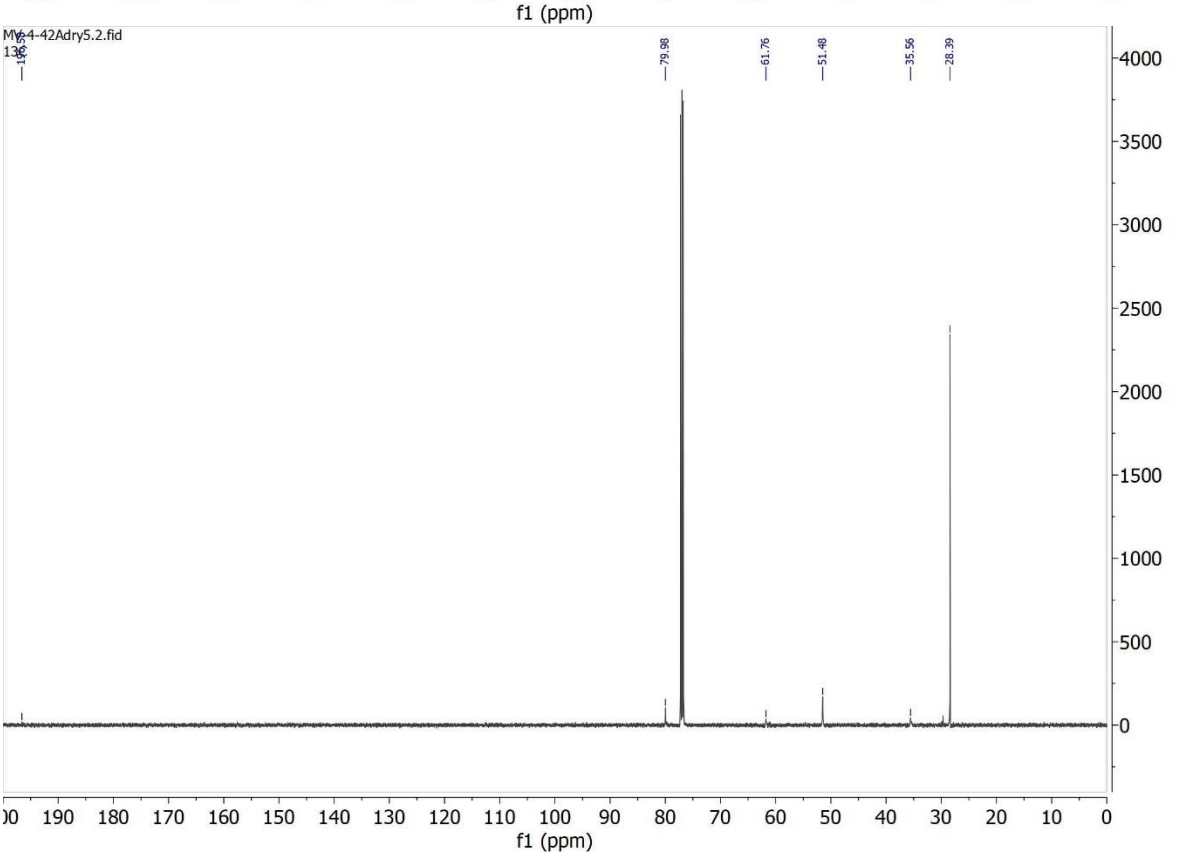

MAA-11-120 charac.3.fid
1d_13C_1_hour CDCl3 D:\\ Begu 42
168.20
136.59
132.89
129.43
128.30
83.27
56.59
46.17
24.76
24.55
f1 (ppm)

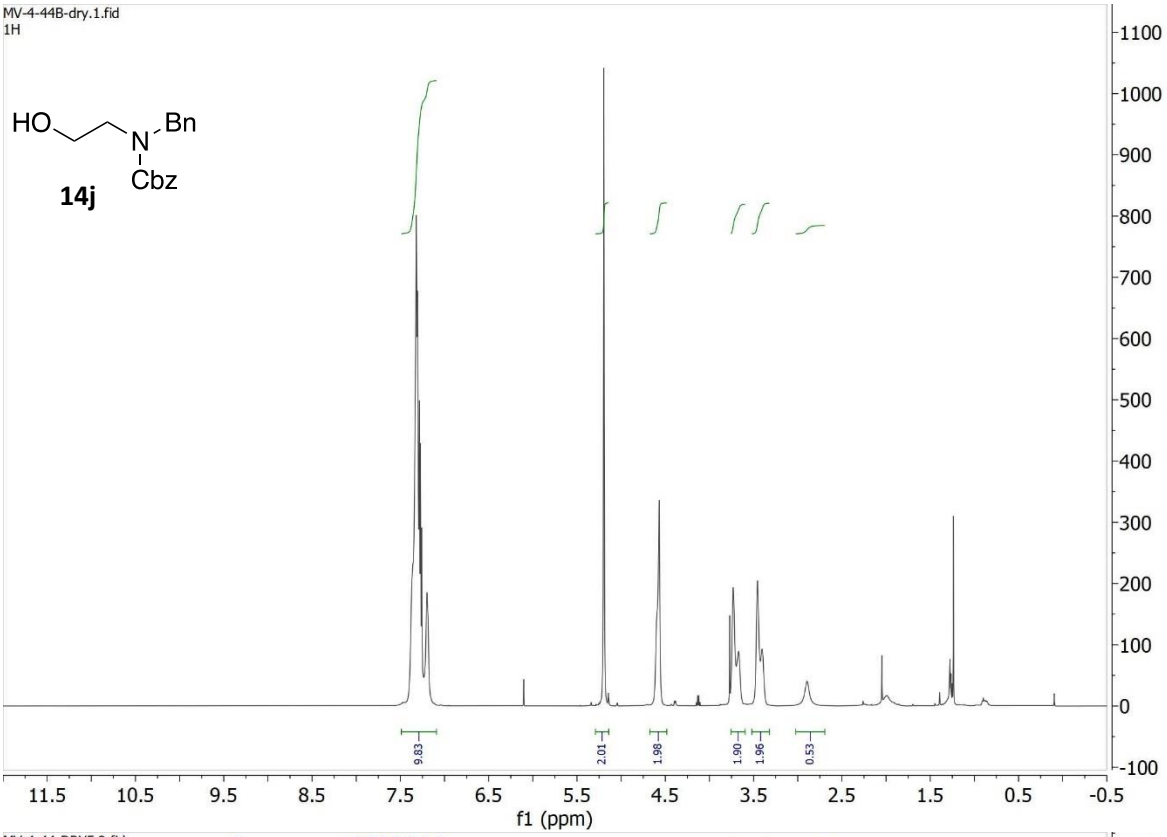

MAA-11-120p dry.2.fid
11B with proton decoupling and background suppression
34.00
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
0 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0 -5 -10 -15 -20 -25 -30 -35 -40 -45 -50
f1 (ppm)

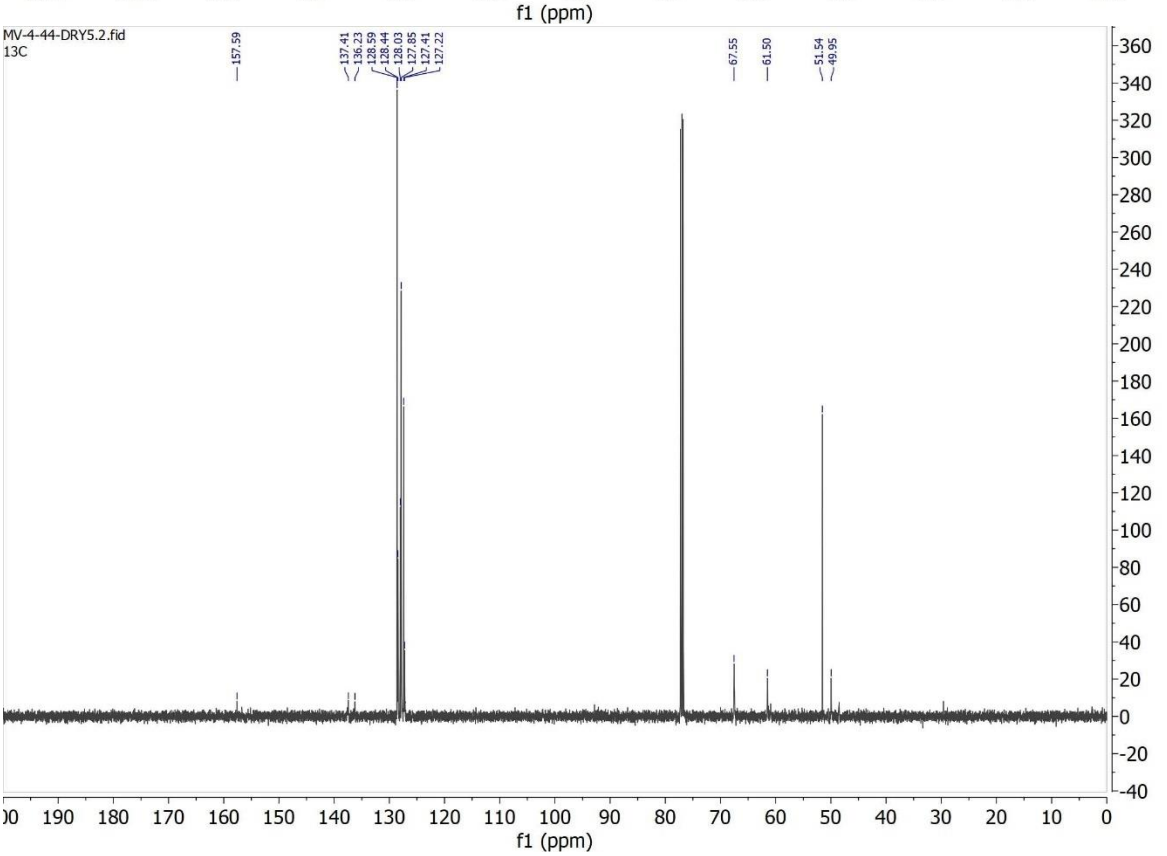

MAA-11-112p dry.1.fid
1H
Me
Me
Me
Me
O
O
B
N–OBz
Bn
13j
1.92
0.98
1.98
2.01
2.00
0.99
2.01
2.00
11.45
2.62
f1 (ppm)
MAA-11-112p dry.3.fid
13C
165.16
136.00
132.72
129.49
129.45
129.37
128.23
128.22
127.49
83.24
62.85
54.23
24.78
23.34
f1 (ppm)

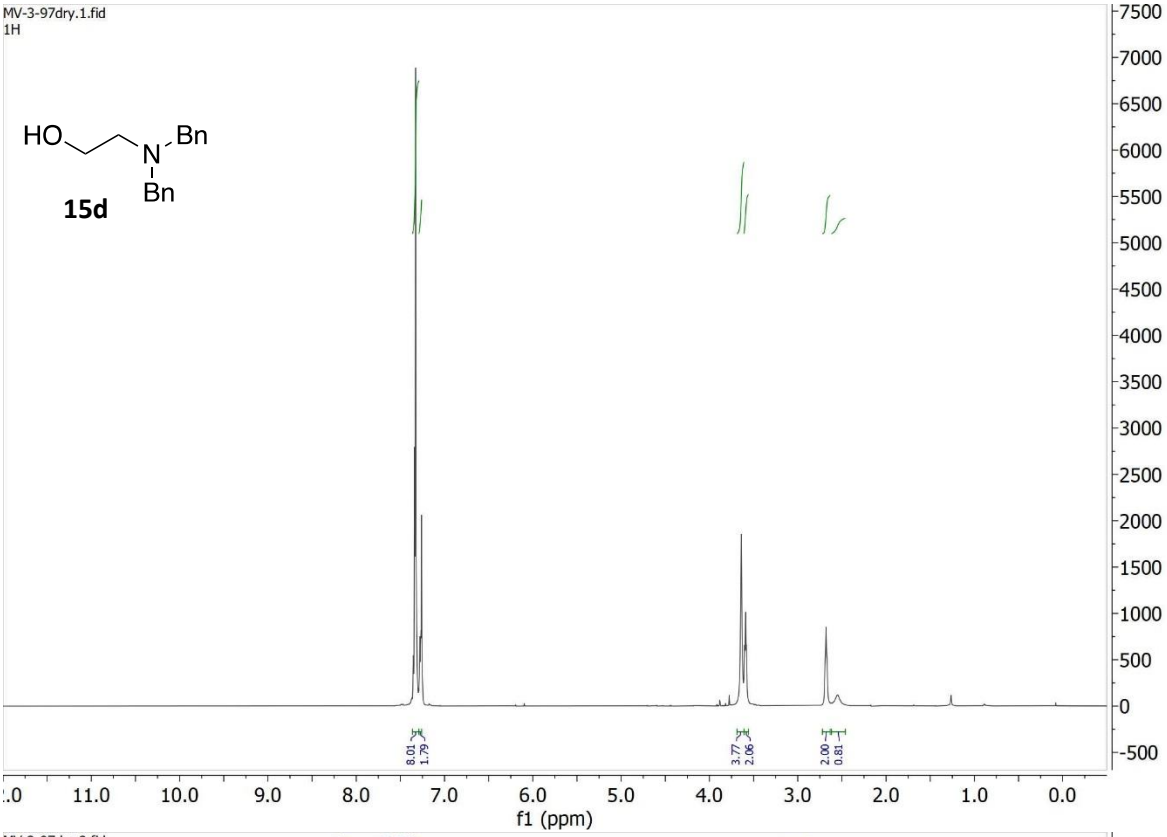

MAA-11-112p dry.2.fid
11B with proton decoupling and background suppression
33.61
360
340
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
-40
0 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0 -5 -10 -15 -20 -25 -30 -35 -40 -45 -50
f1 (ppm)

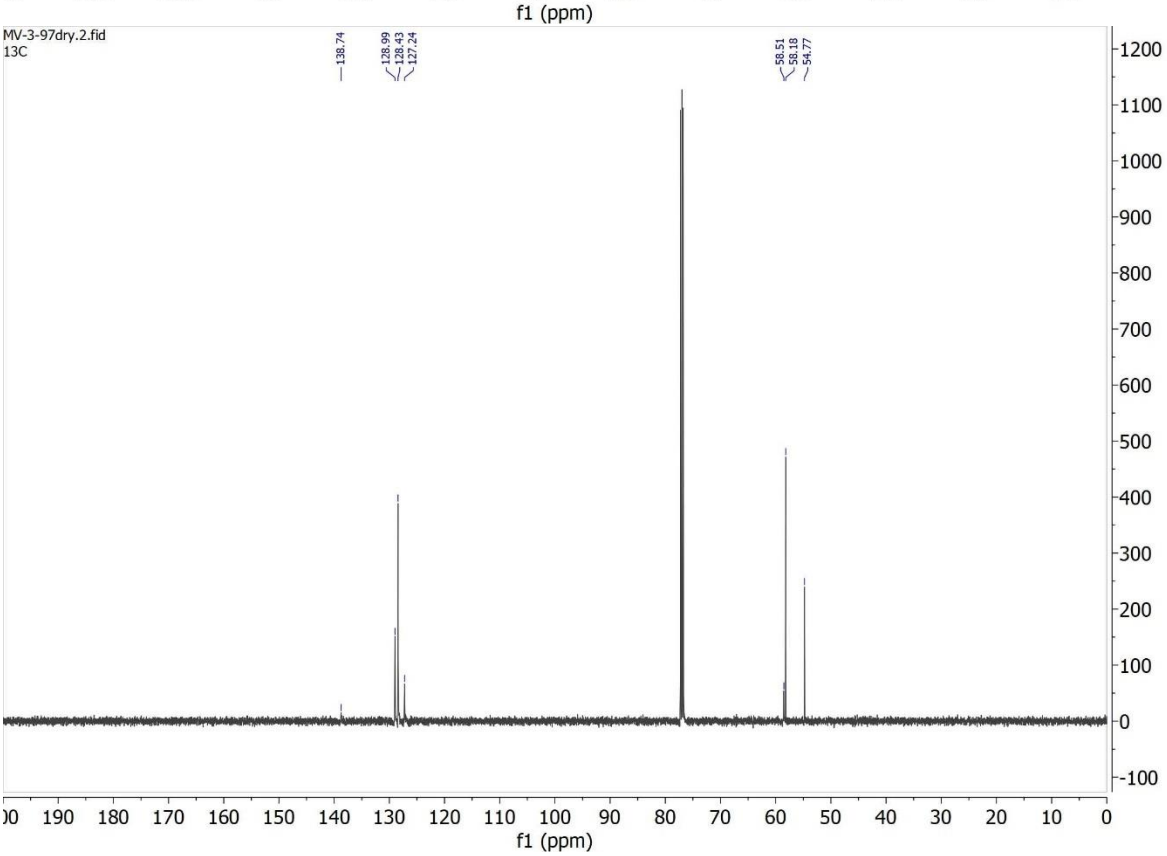

MV-4-42Adry5.1.fid
1H
HO
N
Me
Boc
14i
2.00
1.99
3.43
9.23
f1 (ppm)


MV-4-42Adry5.2.fid
79.98
61.76
51.48
35.56
28.39
f1 (ppm)

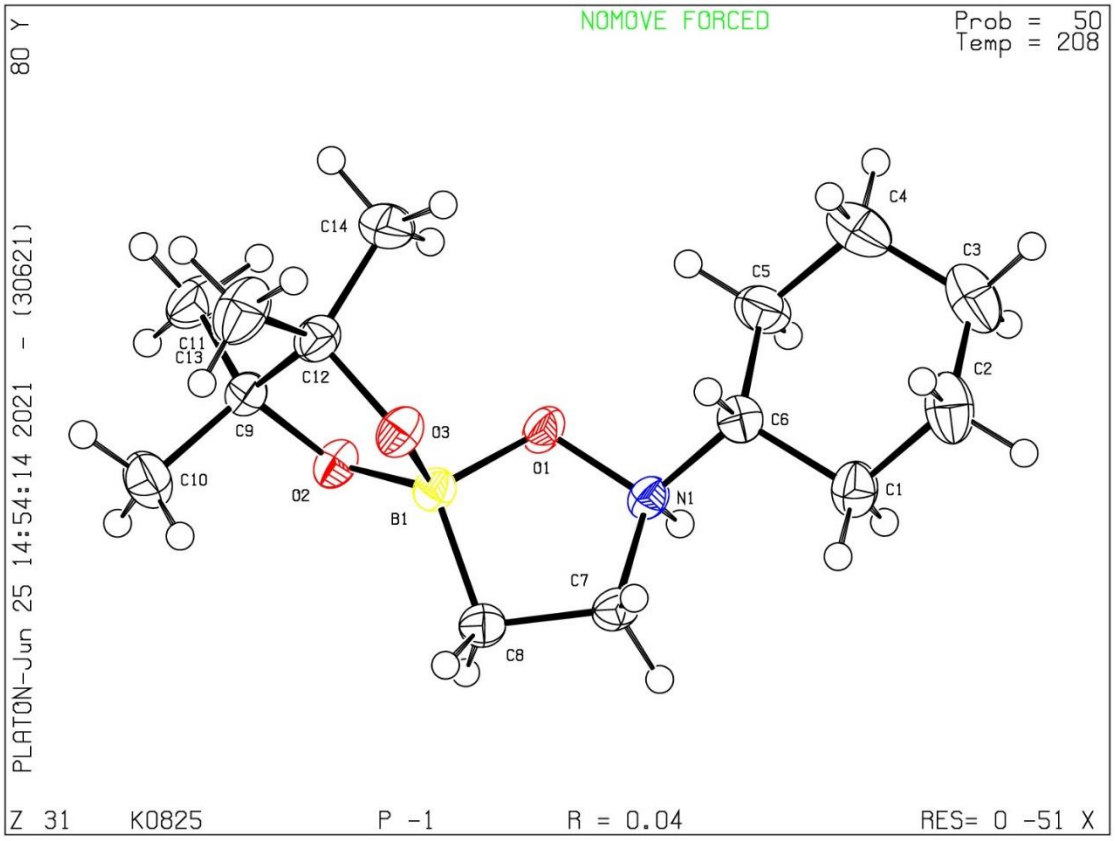

MV-4-44B-dry.1.fid
1H
HO
N
Bn
Cbz
14j
9.83
2.01
1.98
1.90
1.96
0.53
f1 (ppm)


MV-4-44-DRY5.2.fid
13C
157.59
137.41
136.23
128.59
128.44
128.03
127.85
127.41
127.22
67.55
61.50
51.54
49.95
f1 (ppm)


MV-3-97dry.1.fid
1H
HO
N
Bn
Bn
15d
8.01
1.79
3.77
2.06
2.00
0.81
f1 (ppm)


MV-3-97dry.2.fid
13C
138.74
128.99
128.43
127.24
58.51
58.18
54.77
f1 (ppm)

6.4.4 X-Ray Structures



Bond precision: C-C = 0.0016 A Wavelength=0.71073

Cell: a=8.5157(3) b=8.5439(3) c=11.1177(4)
alpha=105.979(2) beta=94.647(2) gamma=91.201(2)
Temperature: 208 K

	Calculated	Reported
Volume	774.29(5)	774.29(5)
Space group	P -1	P -1
Hall group	-P 1	-P 1
Moiety formula	C14 H28 B N O3	C14 H28 B N O3
Sum formula	C14 H28 B N O3	C14 H28 B N O3
Mr	269.18	269.18
Dx,g cm-3	1.155	1.155

Z	2	2
Mu (mm-1)	0.078	0.078
F000	296.0	296.0
F000’	296.13	
h,k,lmax	12,12,16	12,12,16
Nref	5525	5518
Tmin,Tmax	0.975,0.991	0.720,0.746
Tmin’	0.958	

Correction method= # Reported T Limits: Tmin=0.720 Tmax=0.746

AbsCorr = MULTI-SCAN

Data completeness= 0.999 Theta(max)= 32.335

R(reflections)= 0.0441(4139) wR2(reflections)= 0.1280(5518)

S = 1.020 Npar= 176