Intermolecular Cope-type hydroamination with boron-containing species

By

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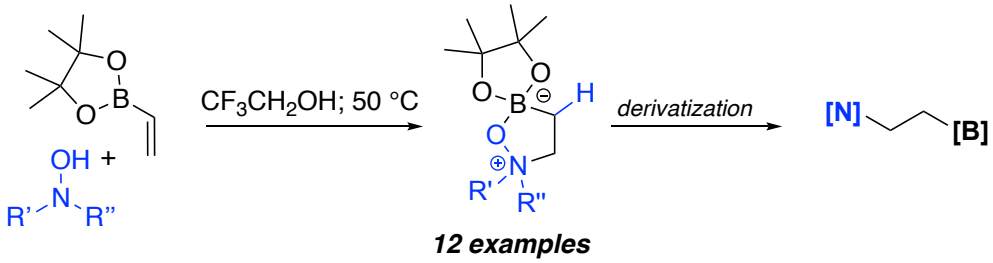
ABSTRACT

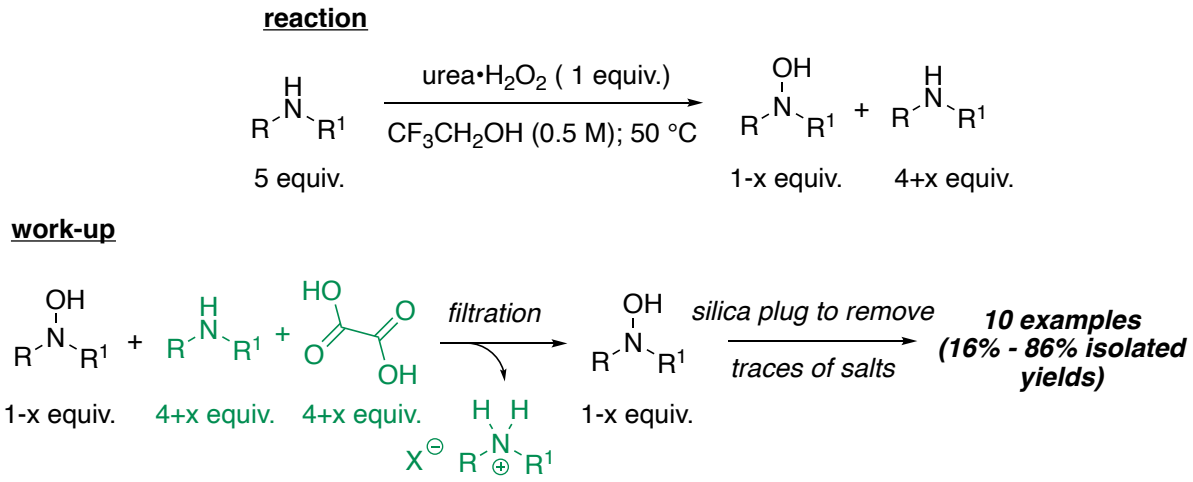
Advances in synthesis of boron-containing molecules significantly enlarged the usage of boron-containing subunits in medicinal chemistry. Interestingly, few recently approved drugs are boron analogues of natural amino acid derivatives. They contain an aminoboronic subunit. This subunit is also known to serve as a useful synthetic intermediate. However, despite its unique properties, limited examples of its synthesis are reported.

In this work, a new method of obtaining aminoboronic acids derivatives is discussed. In Chapter 2 conditions towards obtaining β-aminoboronic acid derivatives via anti-Markovnikov Cope-type hydroamination are presented. Cope-type hydroamination with boron containing species have shown to proceed at lower temperatures compared to unsubstituted alkene derivatives. The products of Cope-type hydroamination reaction are new: to our knowledge similar oxazaborolidine heterocycles have not been reported. Despite reduced stability of the synthesised products and their proneness to conduct bora-Cope type elimination reaction, it was possible to demonstrate oxazaborolidine synthetic utility by various derivatization reactions. A scope with primary and secondary hydroxylamines is presented for a vinylboronate substrate.



This work required access to a range of hydroxylamines. Recently our group discovered simple conditions to oxidize amines to hydroxylamines. In Chapter 3 an investigation of isolation conditions for a variant of this newly developed hydroxylamine synthesis is presented. While the oxidation is generally efficient in the presence of excess amine, the main challenge proved to be

the propensity of the unreacted amine and hydroxylamine product to interact together. The efficiency and main limitations of different isolation strategies are presented. In general, the best results of removal of the excess amine via filtration were obtained using oxalic acid to form the corresponding amine salt. This filtration was followed by a short silica plug to further remove the amine salt causing contamination.



ACKNOWLEDGEMENTS

My first interview with Dr. André Beauchemin was definitely one of my top three most significant life-changing events. At the very start of our online meeting, I quickly felt that this opportunity and the environment was precisely where I wanted to grow. I initially started working in André's group as a Mitacs student for my summer internship. Thereafter, I had the great pleasure to come back and work on my Master's degree here in his group. As a supervisor, André has always motivated me to push myself and to keep a solid attitude towards work even when things did not work out. André was really patient and always made me look at things optimistically.

Furthermore, it would be tough to imagine my graduate school experience without Meredith Allen. It was my great pleasure to learn from her. Meredith was very generous with her testing ideas and was always there to provide an answer when I had questions. Moreover, I felt that she pushed me to a better and more thorough chemist. For me, Meredith will always be a symbol of hard work, strong work ethics and efficiency.

Amongst my other lab-family members, I want to issue a big thank you to Julia and Bhavana, they showed me what girl power truly is! To Sherif, it was always fun to compare our life values. To Huy, my number one Vietnamese friend forever, even though he was the only close Vietnamese friend I had at the time. To Fred, who was always around to fix the high vacuum, which we surprisingly broke every second week. To William and Alshimaa, even though we did not overlap that much, it was always lovely to talk with you. And lastly, to Daniel, it was fun to work on the same project, I am thankful that you heroically kept working on it on your own.

I also must express my gratitude to the University of Ottawa and the Yu Scholarship that allowed me to cover my tuition fees. I really enjoyed studying here! I am convinced now that North America is a great place to pursue your degree.

I would also like to extend the warmest thank you to my parents and my brother Serhii. You are my biggest support through all this time, and I do everything to make you proud. Thanks to Alex, even though you are new in my life, you make me feel so confident and calm when we are together. Thanks to all my closest friends for staying strong and for fighting. I cannot wait for the day when I will get to hug you all in our amazing free Ukraine.

STATEMENT OF CONTRIBUTIONS

The work presented in this thesis was conducted in collaboration with PhD candidate Meredith Allen and Honours student Daniel Barriault, and I did my best to credit my colleagues during the thesis.

In Chapter 2, I quickly joined Meredith Allen project. After she discovered Cope-type hydroamination reactivity with vinylboronate, we worked together on the substrate scope. I was able to confirm with absolute certainty the structure of the product by X-ray crystallography. Meredith and myself worked together on derivatization of obtained products.

In Chapter 3, I was working on the isolation problem for the reaction conditions found and optimized by Meredith Allen. After a few months, Daniel Barriault joined the lab, and I helped mentor him. Daniel optimized the isolation process for hydroxylamines.

Dr. André Beauchemin was consulted at least biweekly throughout the project, discussing obtained results and new ideas to test.

Some spectra included in the thesis to allow comparison have been reproduced with the express permission of the publishers.

TABLE OF CONTENTS

LIST OF SCHEMES

LIST OF FIGURES

LIST OF TABLES

ABBREVIATIONS

°C – degrees Celsius
^{1}H – proton
^{11}B – boron-11
^{13}C – carbon-13
^{19}F – fluorine-19
Å – angstrom
Ac – acetyl
Anti – apart, opposite side
Ar – generic aryl
aq. – aqueous
Bn – benzyl
Boc – *tert*-butyloxycarbonyl
Bu – butyl
Bz – benzoyl
C – carbon
calcd - calculated
cat – catalyst
Cbz – benzyloxycarbonyl
Cy – cyclohexyl
DCM – dicloromethane
DMAP – 4-dimethylaminopyridine
DMSO – dimethyl sulfoxide
dr – diastereomeric ratio
E – *Ger.*, entgegen
ee – enantiomeric excess
equiv – stoichiometric equivalent
eq. – equation
er – enantimeric ratio
ESI – electrospray ionization
Et – ethyl
g – gram
h – hour
HA – hydroamination
HRMS – high-resolution mass spectroscopy
Hz – Hertz
i – i
J – coupling constant
L – liter, levorotatory
M – molar
Me – methyl
MeCN – acetonitrile
mL – milliliter
mmol – millimole
mol – mole

NMR – nuclear magnetic resonance
n-Pr – *n*-propyl
Ns – 2-nitrobenzenesulphonyl
PG – protecting group
Ph – phenyl
ppm – parts per million
pyr – pyridine
R – generic group
R – Latin, *rectus*
R_f – retention factor
rt – room temperature
S – Latin, sinister
syn – together, same side
t-Bu – *tert*-butyl
t-BuOH – *tert*-butanol
TFA – trifluoroacetic acid
TFE – 2,2,2-trifluoroetanol
THF – tetrahydrofuran
TLC – thin-layer chromatography
Ts – *para*-toluenesulfonyl
TS – transition state
UHP – urea - hydrogen peroxide
UV – ultraviolet
vac – vacuum
δ – chemical shift in parts per million
μm – micrometer

CHAPTER 1: INTRODUCTION

In this chapter, natural amino acids, and their structural analogues are briefly presented. After, the attention focuses on chemical and physical properties of aminoboronic acids. Their application, with an emphasis in drug development is discussed. Finally, known synthetic methods and a short review on Cope-type hydroamination, as one of potential synthetic methods towards obtaining aminoboronic derivatives, are presented.

1.1 ON THE IMPORTANCE OF AMINOBORONIC ACIDS

1.1.1 Natural amino acids and their structural analogues

Proteins are large biomolecules that play a crucial role in living organisms.[1] In most cases, they are composed of 20 standard amino acids. Even though this number seems relatively small, many possible combination sequences of amino acids exist. For a reference, the largest known protein – titin – consists of ~27 000 to ~35 000 amino acids (differentiate from splice isoform) in a unique order.[2]

Therefore, such large diversity of combinations allows proteins to accomplish various functions in the living cells. Among them are enzyme catalysis, DNA replication, transportation and more.[1]

Although natural amino acids have such prominent roles, their functions are limited to standard 20 species. Incorporating artificially made amino acids and their structural analogs can improve such protein drawbacks as:[3]

[1] Whitford, D. *Proteins: Structure and Function*, John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex, England, **2005**, 1–544.
[2] Sela, B.-A. *Harefuah*, **2002**, *141*, 631.
[3] Lenci, E.; Trabocchi, A. *Chem. Soc. Rev.* **2020**, *49*, 3262.

- lack of stability towards proteolysis;
- poor absorption and transportation due to high molecular masses result in excretion;
- poor selectivity, interaction with unwanted targets due to N-C_α and C_α-CO rotational bonds flexibility.

Due to reasons mentioned prior, unnatural amino acids, and other peptide- or protein-mimetic compounds (with other heteroatoms) have been largely explored for the last decades. Peptide- or protein-mimetic is a broadly used term that represents the compound that mimics the peptide/protein structure and can interact with different targets with the same biological effect.[3]

Here, we will briefly show some prominent examples of proteinomimetic species and how their structural difference results in different functions (*Figure 1.1*). While this is a broad area of the literature, this chapter aims to focus mostly on one subunit: β-aminoboronic acids.

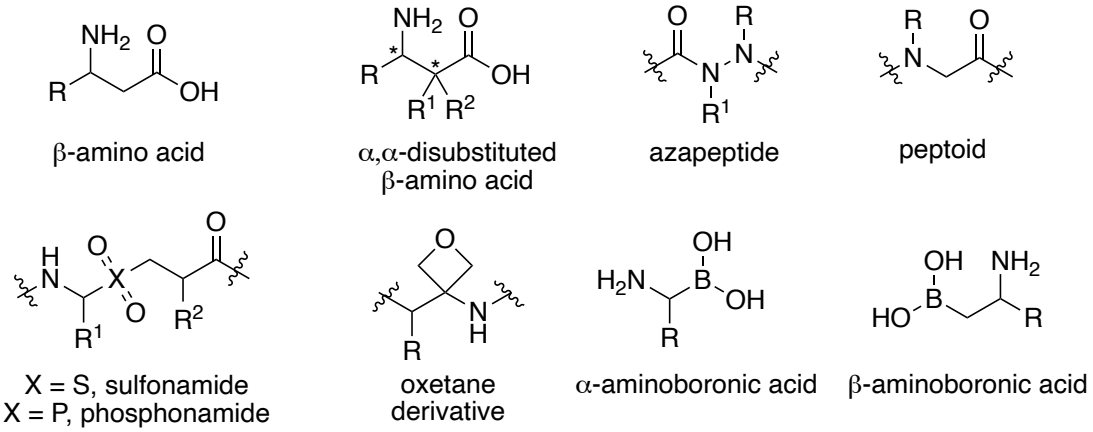


Figure 1.1: Examples of peptidomimetic species

β-Amino acids, similarly, to α-amino acids, contain amino and carboxyl terminus groups.[4] Although, β-amino acids are shown to be resistant to proteolysis compared to their α-analogs. For

[4] Steer, D. L.; Lew, R. A.; Perlmutter, P.; Smith, A. I.; Aguilar, M.-I. *Curr. Med. Chem.* **2002**, *9*, 811.

example, *Figure 1.2* shows how the addition of the carbon atom prevents displacing of the scissile bond from the active Zn-bound water molecule, and no further breakdown of protein occurs.

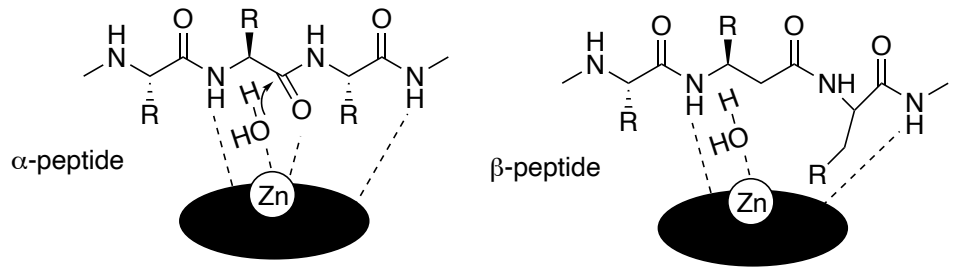


Figure 1.2: Schematic binding of peptides to the active site of species

In contrast to α-amino acids, the main terminus groups are separated by 2 carbon groups, resulting in the possibility of forming 4 diastereomers. Two stereogenic centers in β-amino acid significantly expand the diversity of β-amino acids, leading to enormous scope for molecular design which is not possible with natural amino acids. Further, they found their usage as receptor agonists and antagonists, protease inhibitors, DNA binding peptides, and more.[4]

Another example of a peptidomimetic compound is azapeptide. Replacing the α-carbon center with a nitrogen atom results in conformational restrictions.[5] This leads to different favoured geometry and facilitates the interactions with selected targets.

Another strategy is the conversion of peptides to peptoids (also known as *N*-substituted glycines) is discussed.[6] These changes result in compound with equivalent antimicrobial activity to the peptide species, although peptoids show improved proteolytic stability with increased half-life. Similarly to azapeptides, this structural modification removes stereochemical information, and can therefore facilitate the synthesis.

[5] Proulx, C.; Sabatino, D.; Hopewel, R.; Spiegel, J.; Ramos, Y. G.; Lubell, W. D. *Future Med. Chem.* **2011**, *2*, 1139.
[6] Green, R. M.; Bicker, K. L. *Int. J. Antimicrob. Agents*, **2020**, *56*, 106048.

Following same ideas of improving some protein features, α- and β-aminoboronic acids were closely studied. This introduction will first discuss their main physical and chemical properties.

1.1.2 Physical and chemical properties of organoboron compounds

The high interest towards aminoboronic derivatives can be explained by the unique nature of boron. The sp^2-hybridized boron atom has a vacant *p*-orbital and acts as a Lewis acid. Boronic compounds can be easily converted to negatively charged four coordinated borates and obtain tetrahedral geometry. The difference in electronegativity (B = 2.05, C = 2.55) makes boron primarily an electrophilic atom. At the same time, the carbon-boron bond has nucleophilic properties and can participate in cross-coupling reactions with organic electrophiles (*Figure 1.3*).[7]

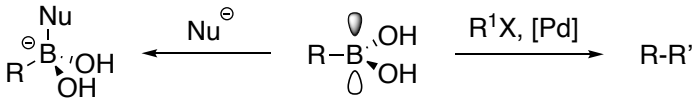


Figure 1.3: Boron reactivity with electrophiles and nucleophiles

When functionalized with an amino group at α- and β- positions, boronic acids can be characterized as a different class of compounds – aminoboronic acids, which act as amino acid bioisosteres (*Figure 1.4*).

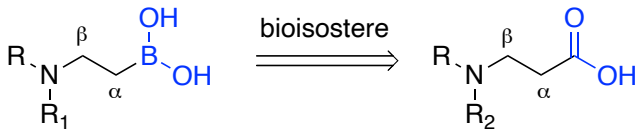


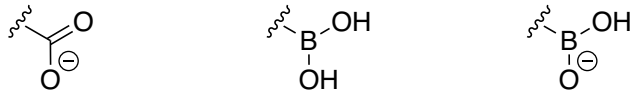
Figure 1.4: Amino acid and aminoboronic acids bioisosterism

[7] Hall, D. G. *Boronic Acids*, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, FRG, **2006**, 1–99.

In contrast to carboxylic acid, aminoboronic acids and their derivatives can adopt coordination modes. Primarily, tri-coordinated boron species can fulfil the octet rule and form anionic tetra-coordinated adducts upon interaction with basic molecules. This type of interaction is reversible.[8] This main feature significantly increased the interest to studying this class of compound as they may bind covalently to biological targets.

Boron-containing functional groups are commonly used in drug discovery. Some of its properties, which differentiate it from other class of compounds are:

a) boronic acids are neutral and uncharged at physiological pH (*Figure 1.5*). The higher p*Ka* of boronic acids compared to their bioisosteres make these compounds valuable in medicinal chemistry;[9]



pKa ~ 4-5 physiological *pH ~ 7.4* $pKa_1 \sim 9$

Figure 1.5: Comparison of pKa of different functional groups

b) boronic acids can mimic tetrahedral intermediates of the amide group in peptide substrate (*Figure 1.6a*).[10] At the same time, boronic acids can be a better reversible covalent group compared to aldehydes or nitriles. In contrast to nitriles, boronic acids are more electrophilic and can easily become tetra-coordinated (*Figure 1.6b-1.6d*).[11] Compared to aldehydes, boronic acids are considered safer to use in medicinal chemistry (aldehydes are highly reactive species and tend to form adducts with

[8] Diaz, D. B. and Yudin, A. K. *Nat. Chem.* **2017**, ***9***, 731.
[9] Westmark, P. R.; Gardiner, S. J.; Smith, B. D. *J. Am. Chem. Soc.* **1996**, *118*, 11093.
[10] Plescia, J.; Cesco, S. D.; Patrascu, M. B.; Kurian, J.; Trani, J. D.; Dufresne, C.; Wahba, A. S.; Janmamode, N.; Mittermaier, A. K.; Moitessier, N. *J. Med. Chem*. **2019**, *62*, 7874.
[11] Plescia, J. and Moitessier, N. *Eur. J. Med. Chem.* **2020**, *195*, 112270.

macromolecules, which can lead to mutations, cause cancer and other disorders.[12] Aldehydes can also generate free radicals and cause oxidative stress);

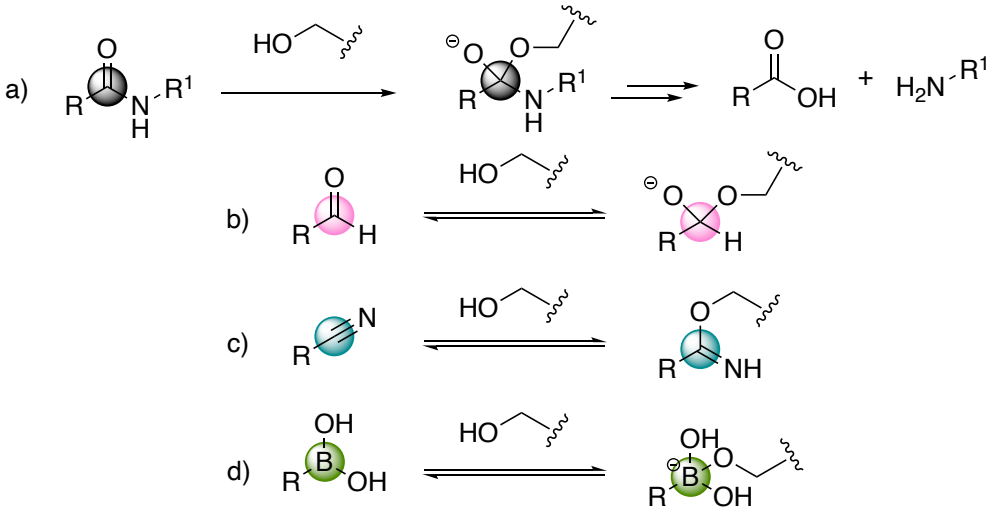
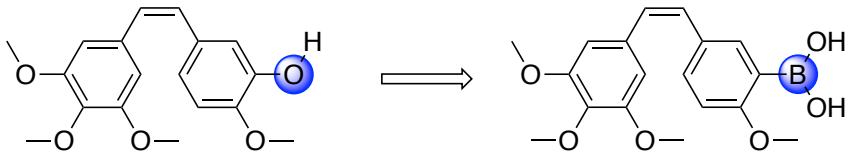


Figure 1.6: Covalent inhibition with different functional groups

c) replacement of different functional groups with a boron analogue impacts the octanol-water partition coefficient (logP) and the distribution coefficient (logD). For example, switching phenol to a boron moiety results in almost two times better solubility and at the same time requires smaller amount for inhibition (*Figure 1.7*).[11]



Combretastatin A-4
Tubulin IC_{50} = 2.0 ± 0.1 μM
solubility @ pH 2: 18.9 μg/mL

Boro-combretastatin A-4
Tubulin IC_{50} = 1.5 ± 0.2 μM
solubility @ pH 2: 33.8 μg/mL

Figure 1.7: Improved properties by switching alcohol to the boronic acid group

[12] Younus, H. and Laskar, A. A. *Drug Metabolism Rev.* **2019**, *51*, 42.

In addition, as it was mentioned before, organoboron compounds show low toxicity.[7] For example, the LD_{50} of boric acid, main metabolite, is 3,500-4,100 mg/kg (rat, oral) can be compared to the toxicity of table salt 3,000 mg/kg (rat, oral).

1.1.3 Applications of aminoboronic compounds

Currently, there are three drugs on the market that contain α-aminoboronic subunits (*Figure 1.8*). Despite the desirable properties, the use of aminoboronic acids remain somewhat underdeveloped in drug discovery, notably because of synthetic challenges.

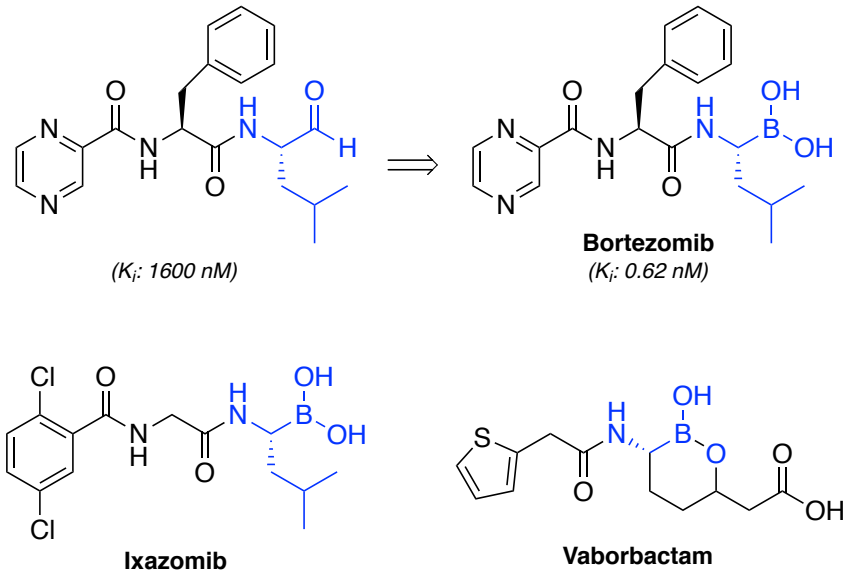


Figure 1.8: Approved aminoboron containing drugs

Bortezomib (commercial name Velcade®) was approved by Health Canada in 2008. This medication is used for previously untreated multiple myeloma (cancer of plasma cells).[13] The lead structure for Bortezomib was firstly discovered in the form of peptidic aldehyde (*Figure 1.8*), which had low selectivity for the 20S proteasome. It was proposed that switching an aldehyde to

[13] Arkwright, R.; Pham, T. M.; Zonder, J. A.; Dou, Q. P. *Expert Opin. Drug Discov.* **2017**, *12*, 225.

a boronic acid moiety can facilitate the binding of the hydroxyl group of threonine at the active site of the proteasome. Aminoboronic derivative showed to be more selective (K_i 0.6 nM) for inhibition the enzyme and by knowing this it was selected for intensive studies.[14]

To improve the pharmacokinetic properties of this medication, a large screening of boron-containing proteasome inhibitors was conducted. Based on the results, it was found that Ixazomib has higher efficacy and fewer side effects compared to Bortezomib, although both compounds act through a similar mechanism.[15] Ixazomib showed superior pharmacokinetic properties compared to it is previous generation: the maximal plasma concentration (C_{max}) of ixazomib was 17 000 ng/mL, while for bortezomib it was 321 ng/mL. Moreover, it had around 16 times greater plasma exposure and five times higher drug distribution from blood into tissues. Health Canada approved the second generation of medication in 2016 and it is now sold under the commercial name Ninlaro®.

The last approved drug containing aminoboronic moiety is Vabomere™. It is a combination drug, which contains Vaborbactam (*Figure 1.8)* and used to treat bacterial infections.[16] It was designed by modifying previously known active analogues. Vaborbactam contains a boronic group, which acts as a reversible covalent inhibitor. Furthermore, the cyclic boronic acid of Vaborbactam allows selectivity between mammalian and native serine proteases because it is large enough that it does not fit in the active site of native serine proteases.

Apart from the above listed drugs, various α- and β-aminoboronic species are in clinical trials. Aminoboronic acid shows activity against *Mycobacterium tuberculosis* and was discovered through the screening of α,β-disubstituted β-aminoboronic esters and acids, which, in general,

[14] Adams J. *Cancer Cell*, **2004**, *5*, 417.
[15] Muz, B.; Ghazarian, R. N.; Ou, M.; Luderer, M. J.; Kusdono, H. D.; Azab, A. K. *Drug Des. Dev. Ther*. **2016**, *10*, 217.
[16] Lee, Y.; Kim, J.; Trinh, S. *P T.*, **2019**, *44*, 110.

show higher activity than α-monosubstituted species.[17] Other studies conducted by Yudin's group with aminoboronic derivative shows complete inhibition of α/β-hydrolase domain 3 (ABHD3) in human cells, with no reactivity against other serine hydrolases.[18] Similar mechanism of enzyme inactivation for different α-aminoboronic species led to a broad range of biologically active compounds and some others biological active compounds are shown in *Figure 1.9*.[19]

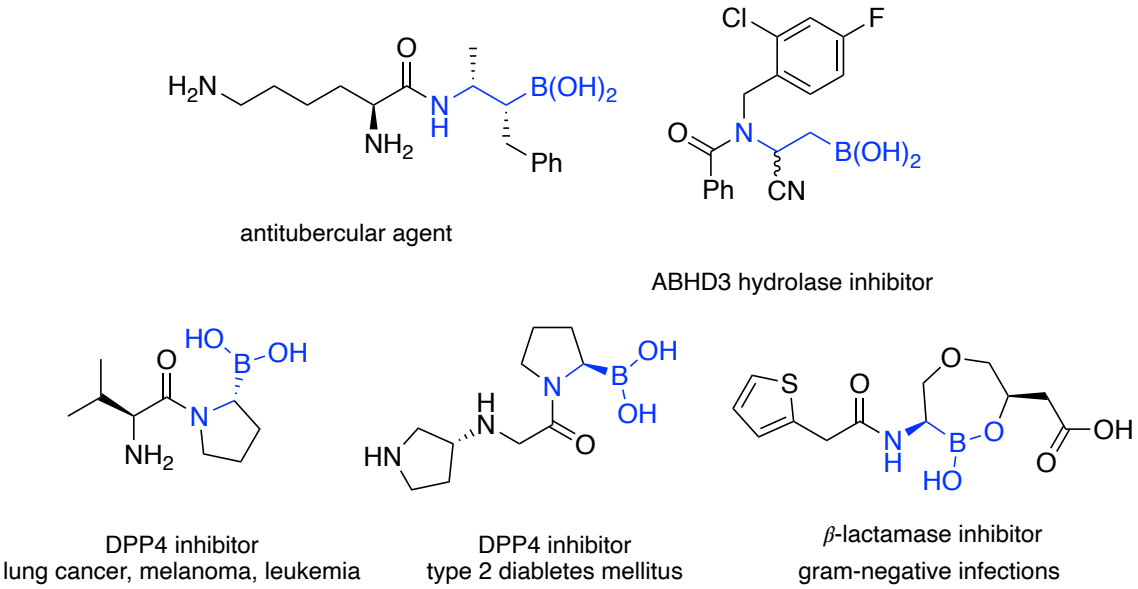
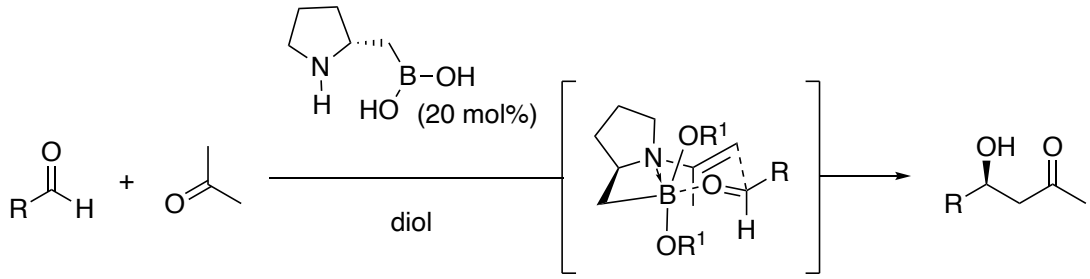


Figure 1.9: Aminoboronic derivatives that show biological activity

Reversible covalent interaction with boron allows aminoboronic species also find an application as bifunctional catalysts in catalysis. These species can direct amide formation, facilitate the hydrolysis of chlorohydrin, or function as aldol catalysts.[20] Some of known catalysts are chiral and able to control enantioselectivity. For example, forming of high enantioselective

[17] Gorovoy, A. S.; Gozhina, O.; Svendsen, J.-S.; Tetz, G. V.; Domorad. A.; Tetz. V.V.; Lejon, T. *J. Pept. Sci.* **2013**, *19*, 613.
[18] 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.
[19] (a) Andrés, P.; Ballano, G.; Calaza, M. I.; Cativiela C. *Chem. Soc. Rev*. **2016**, *45*, 2291; (b) Das, B. C.; Thapa, P.; Karki, R.; Schinke, C.; Das, S.; Kambhampati, S.; Banerjee, S. K.; Veldhuizen, P. V.; Verma, A.; Weiss, L. M.; Evans, T. *Future Med. Chem.* **2013**, *5*, 653.
[20] Georgiou, I.; Ilyashenko, G.; Whiting A. *Acc. Chem. Res*. **2009**, *42*, 756.

aldol adduct is catalysed by chiral β-aminoboronic species and is shown in *Scheme 1.1*. To compare, its shorter α-aminoboronic homologue boroproline does not provide any asymmetric induction. The transition state suggests that aldehyde activation occurs by the boronic acid functional group. Changing the substitution on boron to different diols (OR^1) and increasing it is Lewis's acidity, tightens the transition state and resulting in higher enantioselection for the formation of the aldol product the product to being more enantioenriched.

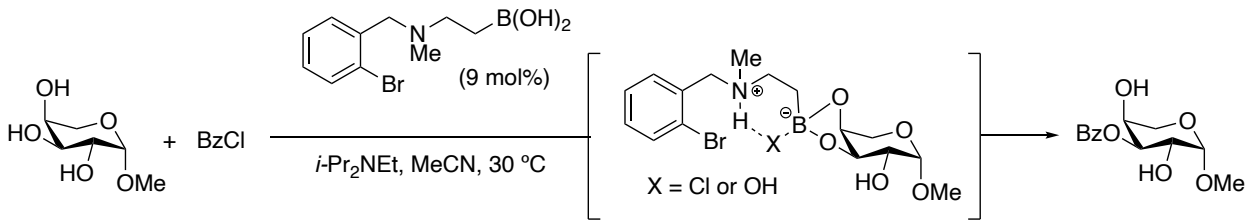


Scheme 1.1: Proposed transition state involving bifunctional catalyst

Another remarkably important diol-binding property of β-aminoboronic acids were shown by Yudin and Taylor groups on sugar derivatives.[21] Relatively high p*K*a values of boronic acids (usually 7-10 p*K*a) cause lower affinity of β-aminoboronic acids to diols by making them prospective carbohydrate receptors (*Scheme 1.2*). An association constant to different sugars of substituted β-aminoboronic species was studied using fluorescence. These resulted prompted a study on interactions with diols on cell-surface glycans. What is more, these studies had some other outcomes. Carbohydrate-binding ability facilitate the reaction regioselectivity and functionalization of the equatorial oxygen in the sugar (*Scheme 1.2*). Switching catalyst to unfunctionalized boronic acid led to lower reactivity of a substrate. This suggests that the amino

[21] Garrett, G. E.; Diaz, D. B.; Yudin, A. K.; Taylor, M. S. *Chem. Commun*. **2017**, *53*, 1809.

group is involved in this interaction. So, aminoboronic derivatives can be more active than other boron species in terms of carbohydrate-binding activity.



Scheme 1.2: Proposed mechanism of selective monobenzoylation

Aminoboronic derivatives are also used as useful synthetic building blocks. Even though boron is commonly found in nature, all aminoboronic acids are artificially made. Carbon-boron and carbon-nitrogen bonds can easily be derivatized and transformed into other groups.

In some schemes below, the symbol [B], which represents different substituted boron group (pinacol, MIDA, catechol, etc.), is used during this chapter. It was chosen here for simplicity, as there are general methods to interconvert boron derivatives.[22]

Typical reactions with boron functional groups include Suzuki-Miyaura cross-coupling reactions, oxidation, amination, halogenation and others (*Figure 1.10*).[23] Similarly to boron species, aminoboronic transformations from optically pure boronates allows controlled formation of stereocenters in new compounds, so these compounds can then be used in asymmetric synthesis.

[22] Churches, Q. I.; Hopper, J. F.; Hutton, C. A. *J. Org. Chem*. **2015**, *80*, 5428.
[23] (a) Fawcett, A.; Murtaza, A.; Gregson, C. H. U.; Aggarwal, V. K. *J. Am. Chem. Soc*. **2019**, *141*, 4573; (b) Yang, C.-H.; Han, M.; Li, W.; Zhu, N.; Sun, Zh.; Wang, J.; Yang, Zh.; Li, Y.-M. *Org. Lett.* **2020**, *22*, 5090; (c) Xie, Q.; Dong, G. *J. Am. Chem. Soc*. **2021**, *143*, 14422.

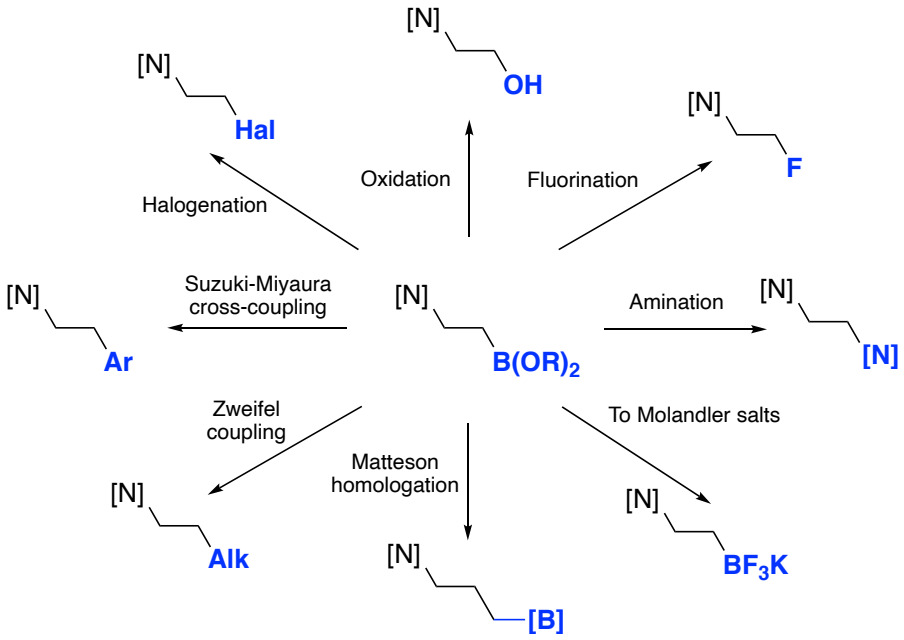


Figure 1.10: Possible synthetic transformations of the boronic ester group

The amino group in aminoboronic derivatives is nucleophilic. It participates in alkylation and acylation reaction. Protection with Cbz-, Ts-, Boc-, and Fmoc- of primary amino groups are mostly described in the literature (*Figure 1.11*).[23] The reverse reaction - deprotection - often proceeds under mild conditions.

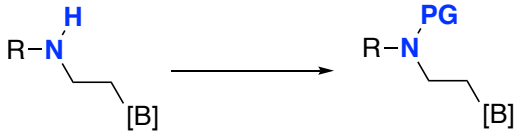


Figure 1.11: Protection of an amino group

In most cases aminoboronic derivatives are directly transformed to other motifs using reactions mentioned above, as there are some challenges associating with a direct isolation of these species. The most common approaches are converting aminoboronic acids to aminoalcohols or to Molandler's trifluoroborate salts.

1.2. DIFFERENT STRATEGIES TO OBTAIN β-AMINOBORONIC ACID DERIVATIVES

The lack of β-aminoboronic acids and their derivatives on the market can be explained by the fact reactions for their synthesis remains underdeveloped. Moreover, known methods forming β-aminoboronic acids have a narrow scope, require substrate pre-functionalization or precious metals for catalytic transformations.

In general, approaches to obtaining β-aminoboronic acids rely on hydro- or aminoboration. Fewer amination-based methods have been reported.

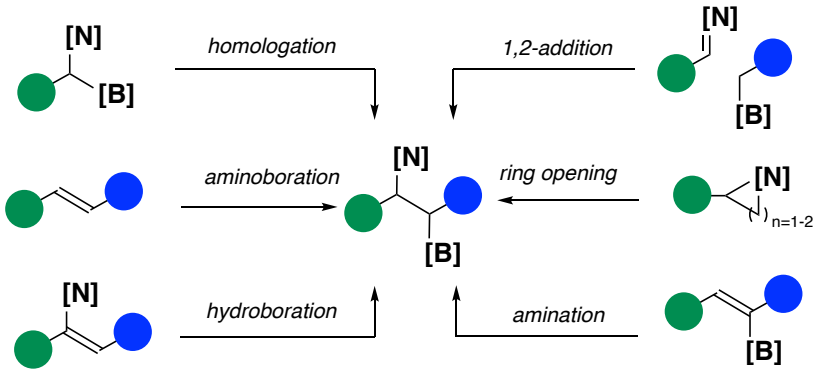


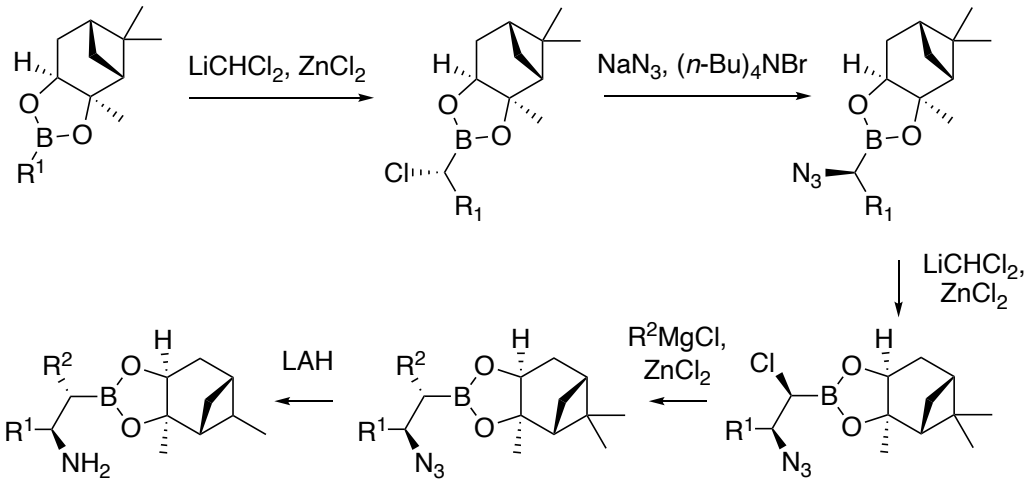
Figure 1.12: Methods to synthesize aminoboronic derivatives

1.2.1 Homologation

The first synthesis of a β-aminoboronic ester was reported by the Matteson group in 1986 (*Scheme 1.3*).[24] However, this early work was related mostly to the study of boronic ester homologation and new ways to introduce chiral centers to compounds. The authors did not show any direct interest to synthesize of β-aminoboronic ester. Among some other diols and insect pheromones, only one β-aminoboronic derivative was discussed in current paper. β-Aminoboronic

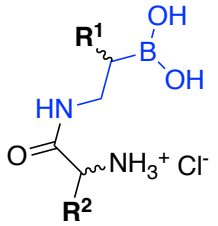
[24] Matteson, D. S.; Sadhu K. M.; Peterson, M. L. *J. Am. Chem. Soc.* **1986**, *108*, 810.

derivative is synthesized from optically pure pinanediol. The described reaction occurs in *syn* fashion with 99:1 dr in the formation of the product. Nowadays, this reaction is known as a "Matteson homologation", and it involves formal carbenoid insertion to carbon-boron bonds.



Scheme 1.3: Synthesis of aminoalkylboronate via Matteson homologation

The scope of the Matteson homologation reaction was slightly expanded by Lejon group in 2013.[25] It was shown that starting from pinanediol, some other β-aminoboronic acids (*Figure 1.13*) are possible to obtain. The main motivation this time was to obtain a range of β-aminoboronic specious for further testing for the activity against *Mycobacterium tuberculosis*.



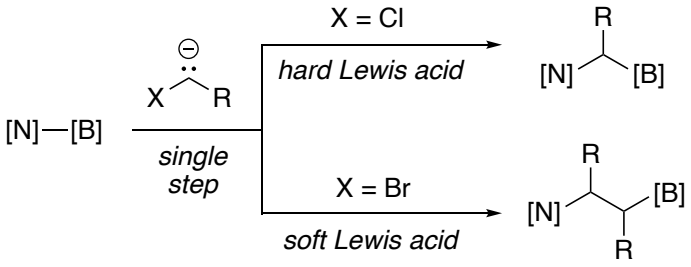
*where **R¹** = H, methyl, phenethyl, benzyl, 4-(F)-benzyl, 4-(CF_3O)-benzyl, 2-naphtylmethyl, phenyl*

***R²** = remaining portion of (L)- or (D)-Lys, (L)-Phe, (L)-Ala, (L)-Arg*

Figure 1.13: General scaffold for the library of aminoboronic species

[25] Gorovoy, A. S.; Gozhina, O.; Svendsen, J.-S.; Tetz, G. V.; Domorad. A.; Tetz. V.V.; Lejon, T. *Chem. Biol. Drug Des.* **2013**, *81,* 408.

In 2021, Dong published an aza-Matteson variant of this reaction.[23c] The reaction proceeds via controlled mono- and double- insertion of methylene into a nitrogen-boron instead of regular carbon-boron insertion. In contrast to traditional Matteson homologation, mono- or double-methylene insertion is controlled by the choice of Lewis acid activators and the leaving group (*Scheme 1.4*). In the proposed explanation, authors suggest that the repulsion between the lone pair on nitrogen and the vicinal formal negative charge on boron destabilize an intermediate. When carbenoid has a good leaving group (Br^-) a spontaneous *N*-1,2-migration occurs. It is promoted by low-lying C-Br σ* orbital. Excess of carbenoid leads to double insertion. However, mono insertion is preferred when the nitrogen atom used in the system is electron deficient. This method has a diverse functional group tolerance and could be used for late-stage diversification of amines. When the leaving group is Cl^-, the intermediate is more stable due to higher C-Cl σ* orbital. *N*-1,2 migration occurs at low temperature and prevents double insertion.

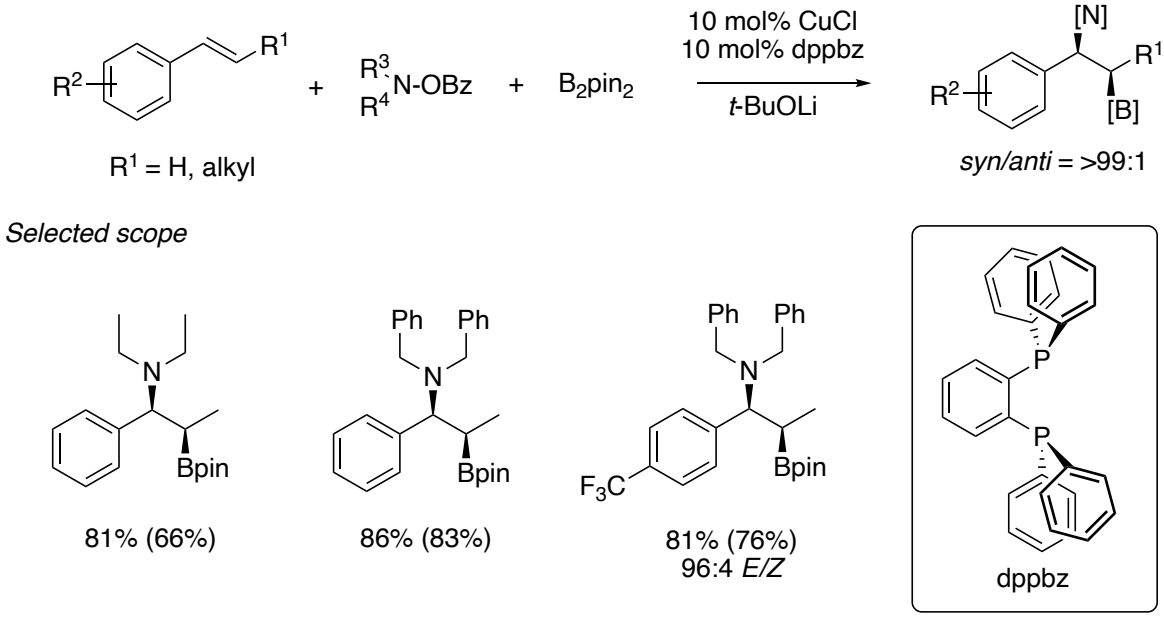


Scheme 1.4: Mono- and double-methylene insertion into the nitrogen-boron bond

1.2.2 Aminoboration (inter- and intramolecular reactions)

Currently, β-aminoboronic synthesis mostly rely on aminoboration method, as it is widely studied mostly by Hirano and Miura. The first Cu-catalyzed aminoboration reaction was reported

by Hirano and Miura in 2013 on substituted styrenes.[26] The amino group here is incorporated through an umpolung electrophilic strategy with *O*-benzoyl-*N,N*-dialkylhydroxylamines. Regardless of the size and electronic properties of the alkyl groups on the hydroxylamine, aminoboration of *(E)*-styrenes proceeds in *syn* fashion with an excellent diastereo- (*syn:anti* > 99:1) and regioselectivity (*Scheme 1.5*). The amine group is installed at the benzylic position; the boron group at the homobenzylic position. For *(Z)*-substrates the diastereoselectivity is opposite (*syn:anti* < 1:99). The scope of this early work from 2013 was limited to alkyl- or H-substituted styrene derivatives.

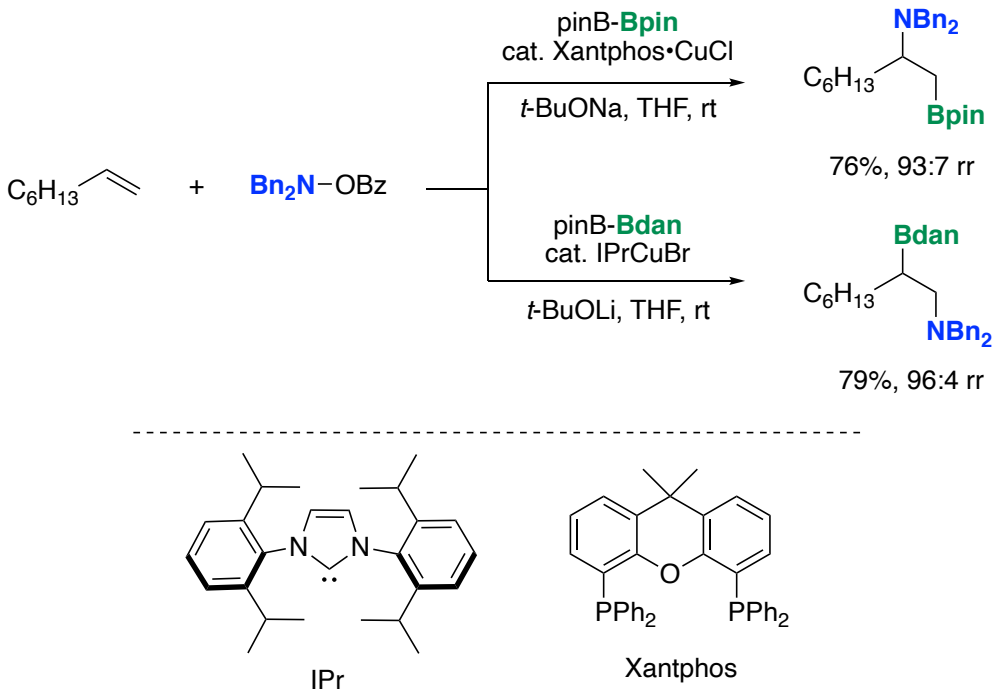


Scheme 1.5: Metal-catalyzed aminoboration of styrenes

After further studying of this reaction with other alkene species, it was noticed that during unsymmetrical difunctionalization for some compounds only one regioisomer is obtained successfully. Previously it was not possible to obtain selectively another regioisomer, at best a mixture of regioisomers was formed. In 2015 Hirano and Miura reported a ligand-controlled,

[26] Matsuda, N.; Hirano, K.; Satoh, T.; Miura M. *J. Am. Chem. Soc.,* **2013**, *135*, 4934.

regiodivergent aminoboration reaction (*Scheme 1.6*).[27] By choosing different ligands both regioisomers could be obtained from same terminal alkene with high regioselectivity. Such regioselectivity was explained by the electronic and steric factors of catalysts during the insertion step.

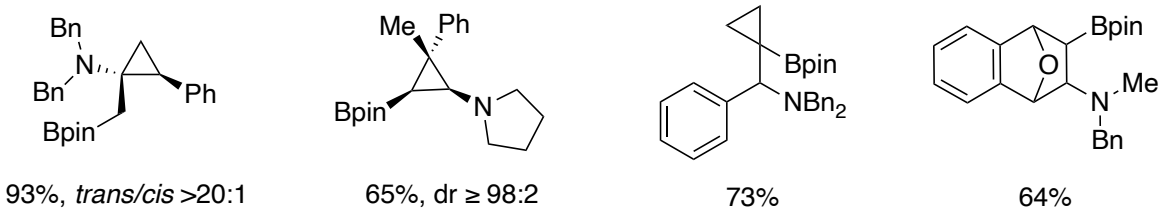


Scheme 1.6: Ligand-controlled regiodivergent aminoboration

This aminoboration Cu-catalyzed method was applied later to other alkene derivatives (*Figure 1.14*), mostly to obtain cyclopropane derivatives, as cyclopropane ring is common in pharmaceutical studies.[28] The Hirano and Miura group showed reactivity with methylenecyclopropane with yields up to 93% and >20:1 trans/cis product ratio.[29] Then, the Tortosa group show reactivity with cyclopropenes (er up to 98:2, dr up to ≥ 98:2),[30] and the Shi

[27] Sakae, R.; Hirano, K.; Miura M. *J. Am. Chem. Soc.,* **2015**, *137*, 6460.
[28] Talele, T. T. *J. Med. Chem*. **2016**, *59*, 8712.
[29] Sakae, R.; Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2014**, *16*, 1228.
[30] Parra, A.; Amenós, L.; Guisán-Ceinos, M.; López, A.; Ruana, J. L. G.; Tortosa M. *J. Am. Chem. Soc.* **2014**, *136*, 15833.

group with benzylidenecyclopropane (47-88% yields, 44-94% ee).[31] Bicyclic alkenes were also studied (up to 99% yield, up to 96:4 er).[32]

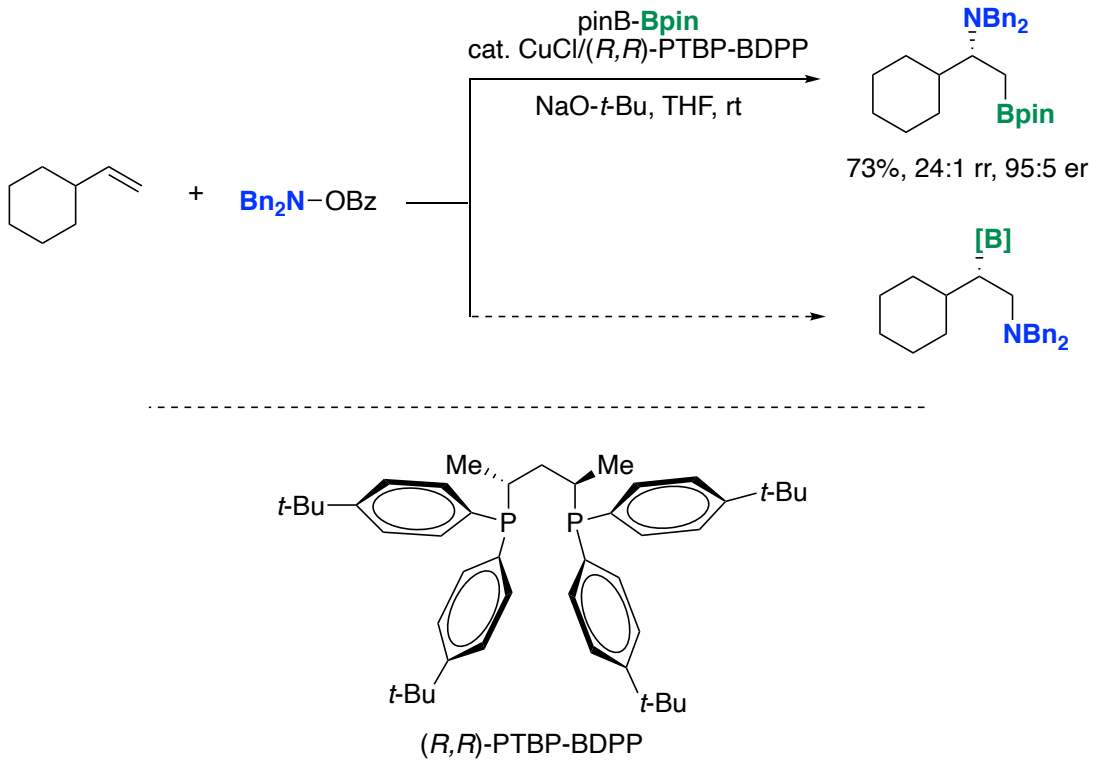


93%, *trans/cis* >20:1 | 65%, dr ≥ 98:2 | 73% | 64%

Figure 1.14: Representative examples of aminoboration of strained alkenes

Among the limitations of the copper-catalyzed 1,2-aminoboration reaction described above is that it occurs only with *O*-acylated hydroxylamine, and features only copper catalysts. Studying this reaction with other transition metals could expand the scope and allow to overcome the unsolved problem of enantioselective aminoboration leading to internally borylated products (*Scheme* 1.*7*).[33]

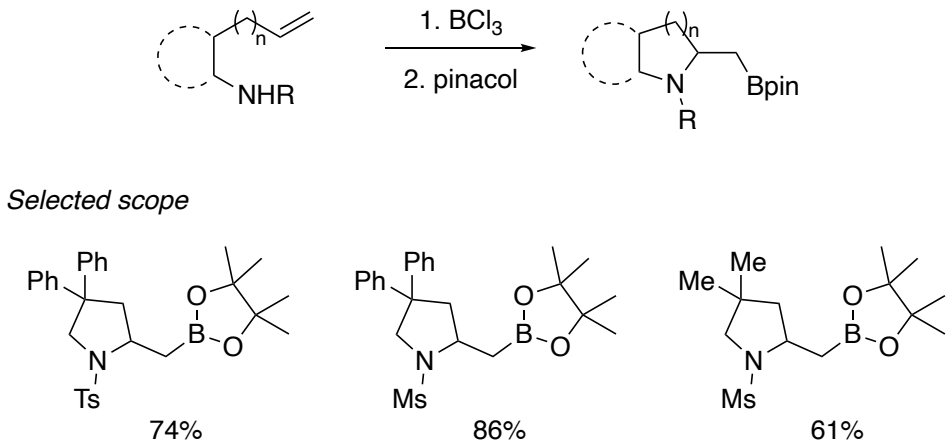
[31] Jiang, H.-Ch.; Tang, X.-Y.; Shi, M. *Chem. Commun.* **2016**, *52*, 5273.
[32] Sakae, R.; Hirano, K.; Satoh, T.; Miura M. *Angew. Chem., Int. Ed.* **2015**, *54*, 613.
[33] Hirano, K.; Miura M. *J. Am. Chem. Soc.* **2022**, *144*, 648.



Scheme 1.7: Regio- and enantioselective aminoboration

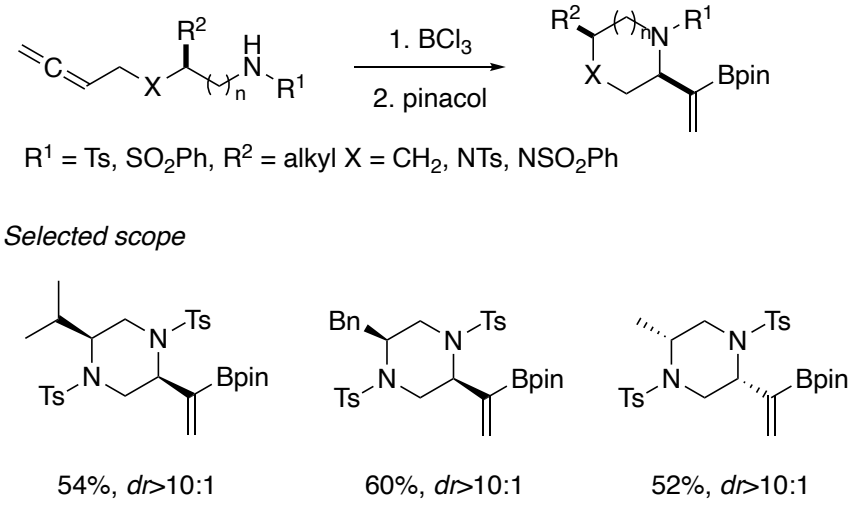
In contrast to this reaction, the Li group worked on conditions for the intramolecular aminoboration of unfunctionalized alkenes (*Scheme 1.8*).[34] The intramolecular reaction requires milder condition (room temperature with no catalyst) and proceeds with 1 equivalent of boron trichloride. Based on NMR studies, it was concluded that the reaction proceeds upon interaction of boron with nitrogen, where the Lewis pair N-BCl_2 is formed. The next step of the mechanism is intermolecular aminoboration which occurs in similar fashion to a hydroboration reaction. Basicity and nucleophilicity of the nitrogen atom are crucial for this reaction. The scope is limited to the sulfonamide derivatives (tosyl, mesyl or another group on nitrogen).

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



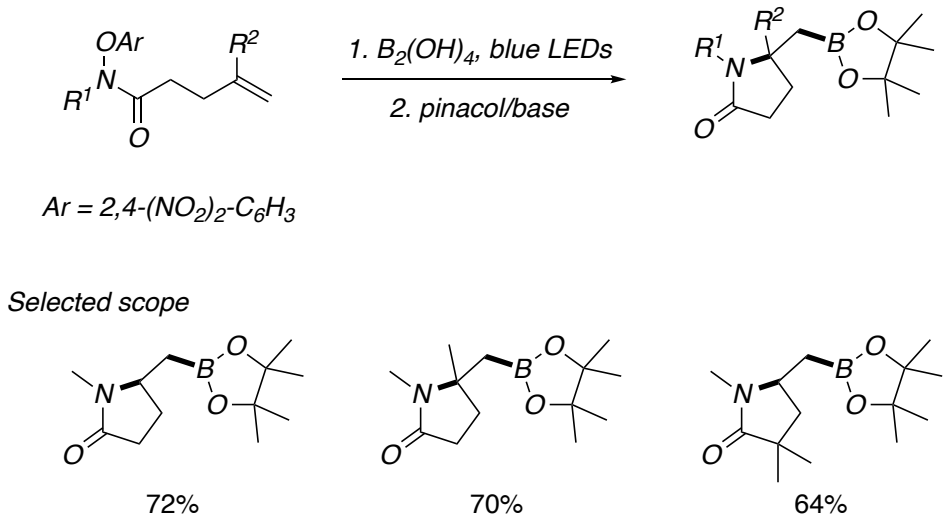
Scheme 1.8: Direct intramolecular amination

Five years later, the same group expanded the substrate scope of this intramolecular aminoboration to allenylsulfonamides (*Scheme 1.9*). The conditions of this reaction were slightly modified (small excess 0.2 eq of BCl_3 showed better yields compared to previous 1:1 ratio). The aminoboronic species were obtained in yields from 51% to 80% with high diastereoselectivity (dr > 10:1).[23b] This strategy can be also applied to obtain indoles via the aminoboration of allenes



Scheme 1.9: Intramolecular aminoboration of allenes

However, this is not the only possible conditions for intramolecular metal-free aminoboration of unactivated alkenes. Another approach was published in 2021 by Studer.[35] It is the first reported aminoboration reaction that proceeds via a radical mechanism. Aryloxyamide *N*-radical precursor enables the chain reaction, while $B_2(OH)_4$ traps the cyclized radical (*Scheme 1.10*). Current results provide a broad scope of cyclic 1,2-aminoboronic esters.



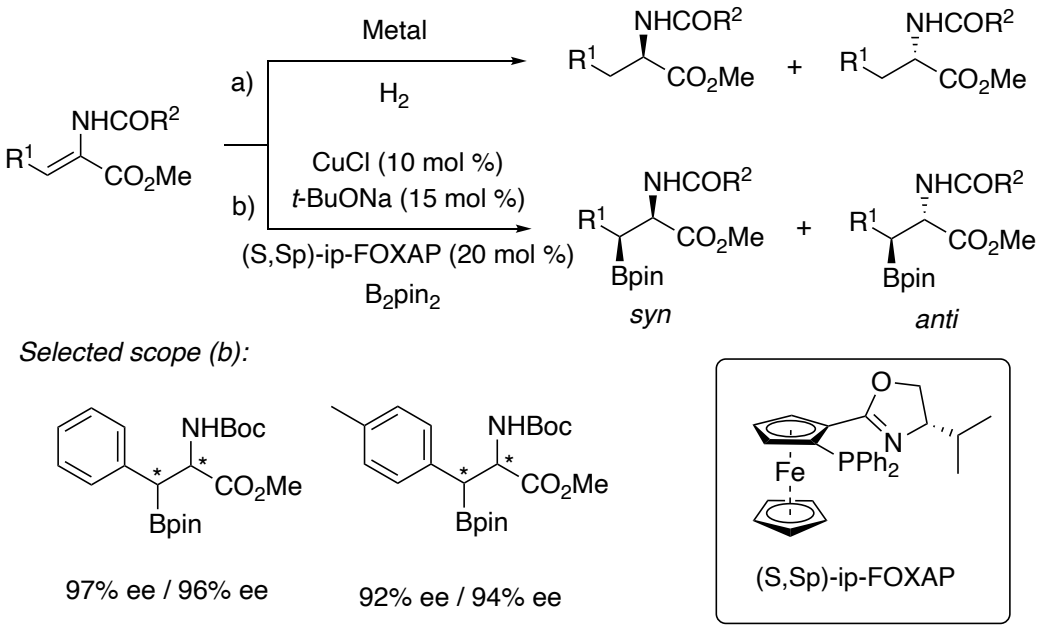
Scheme 1.10: Radical aminoboration of unactivated alkenes

1.2.3 Borylation or hydroboration

Cu-catalysts are also used for synthesizing of β-aminoboronic derivatives *via* hydroboration method. This reaction is commonly recognized as a practical method to obtain chiral compounds. Similar to metal-catalyzed hydrogenation reaction of α-dehydroamino acids to obtain chiral aminoacids (*Scheme 1.11a*), β-aminoboronic chiral acids can be formed. Hydrogen gas was replaced by boron species, while metal catalysts such as Rh, Ru or Ir were replaced by Cu. The hydroboration reaction of β-substituted-α-dehydroamino derivative (*Scheme 1.11b*) was

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

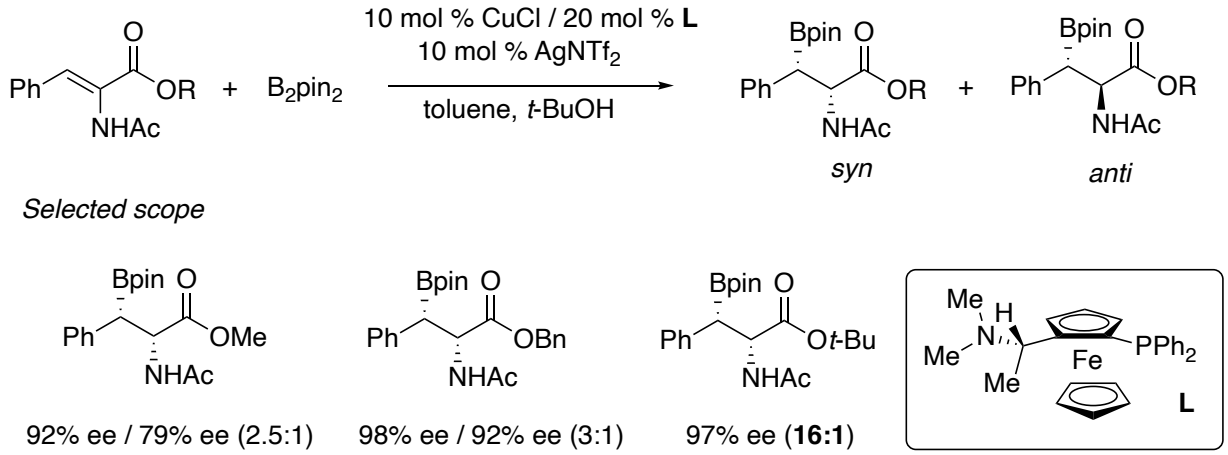
established by Lin and Tian in 2014.[36] This rection shows high combined yields (83-99%); high enantioselectivity (92-98% ee) with *syn*- and *anti*- β-aminoboronic products with around 1:1 dr (*Scheme 1.11b*).



Scheme 1.11: Hydrogenation (a) and hydroboration (a) of in the presence of metal catalysts

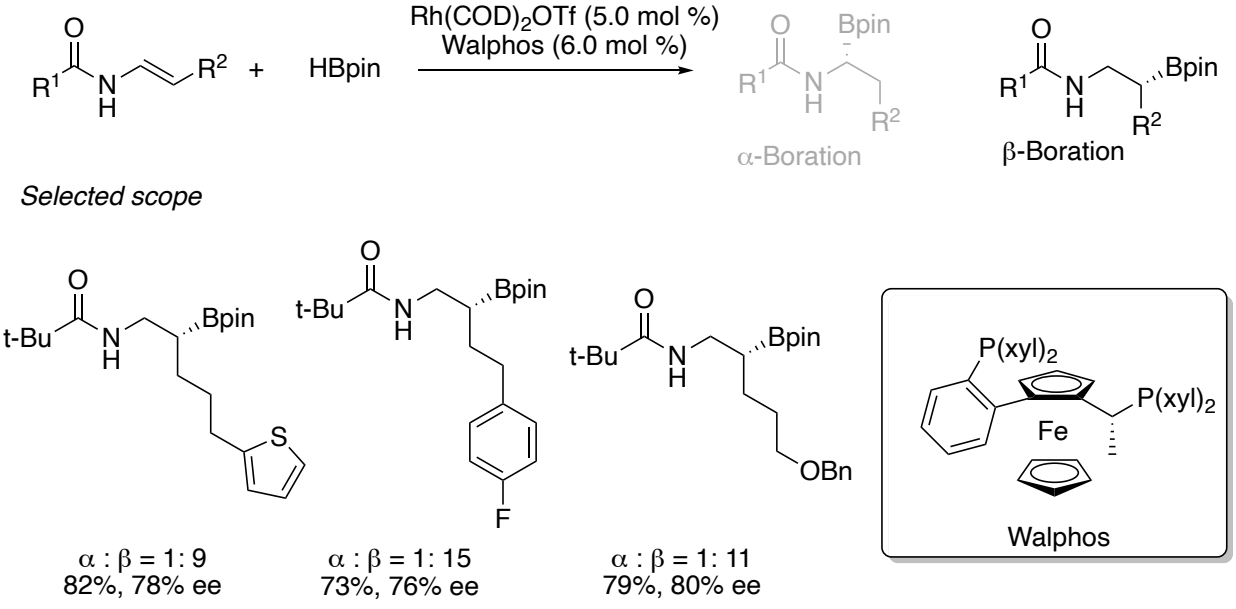
The diastereoselectivity of this reaction was improved 2 years later by Li group.[37] A weaker base, increased steric bulk and pK_a of used alcohol allowed to achieve 16:1 *syn:anti* diastereoselectivity for hydroboration reaction. Although, these conditions were described for only one substrate (*Scheme 1.12*).

[36] He, Z.-T.; Zhao, Y.-S.; Tian, P.; Wang, C.-C.; Dong, H.-Q.; Lin, G.-Q. *Org. Lett.* **2014**, *16*, 1426.
[37] Xie, J.-B.; Lin, S.; Qiao, S.; Li, G. *Org. Lett*. **2016**, *18*, 3926.



Scheme 1.12: Improves diastereoselectivity for hydroboration reaction

In 2019, Li reported a rhodium-catalyzed asymmetric borylation reaction that allowed for high diastereo-, regio- and enantioselectivity (*Scheme 1.13*).[38]

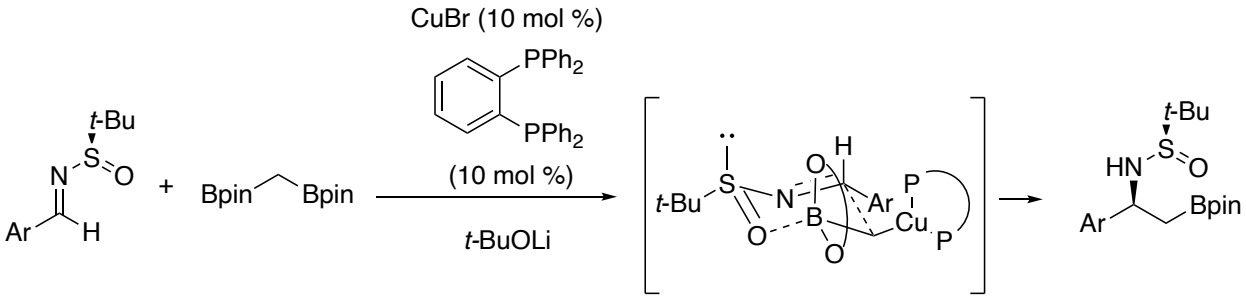


Scheme 1.13: Borylation in the presence of rhodium catalyst

[38] Bai, X.-Y.; Zhao, W.; Sun, X.; Li, B.-J. *J. Am. Chem. Soc*. **2019**, *141*, 19870.

1.2.4 Addition

In 2016, Cho presented a different approach towards chiral β-aminoboronic derivatives (*Scheme 1.14*).[39] Chemo- and diastereoselective alkylation of *N*-*tert*-butanesulfinyl aldimines by 1,1-diborylmethane can be conducted with good yields (57-96% of isolated corresponding amine). The high diastereoselectivity of this reaction is achieved in the presence of copper catalyst and bidentate phospine ligand. Running this reaction under metal-free conditions lead to very poor diastereoselectivity. Authors suggest that the reaction proceeds *via* a 6-membered chair-like transition state. The primary limitation of this reaction is that the aldimine substrate must be aromatic.



Scheme 1.14: Copper-catalyzed diastereoselective addition of diborylmethane to aldimines

Another downside to this reaction is the necessity of using *N*-sulfonyl imines. One year later, they were switched to more accessible *N*-protected imines (*Figure 1.15*).[40] A stoichiometric amount of chiral auxiliary was replaced by CuBr/chiral phosphoramidite catalyst. The reactions proceed with an excellent diastereo- (up to >20:1) and enantioselectivity (up to 99% *ee*).

[39] Park, J.; Lee, Y.; Kim, J.; Cho, S. W. *Org. Lett.,* **2016**, *18*, 1210.
[40] Kim, J.; Ko, K.; Cho, S. W. *Angew. Chem. Int. Ed*., **2017**, *56*, 11584.

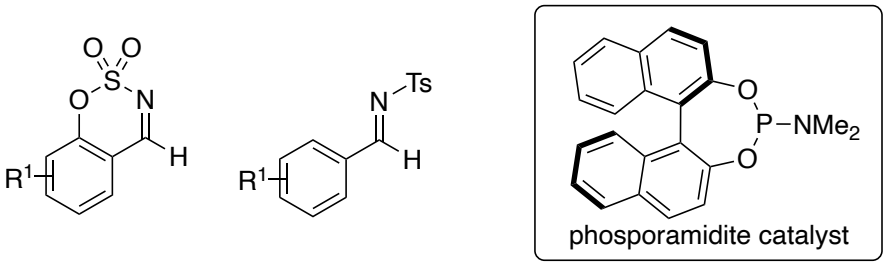
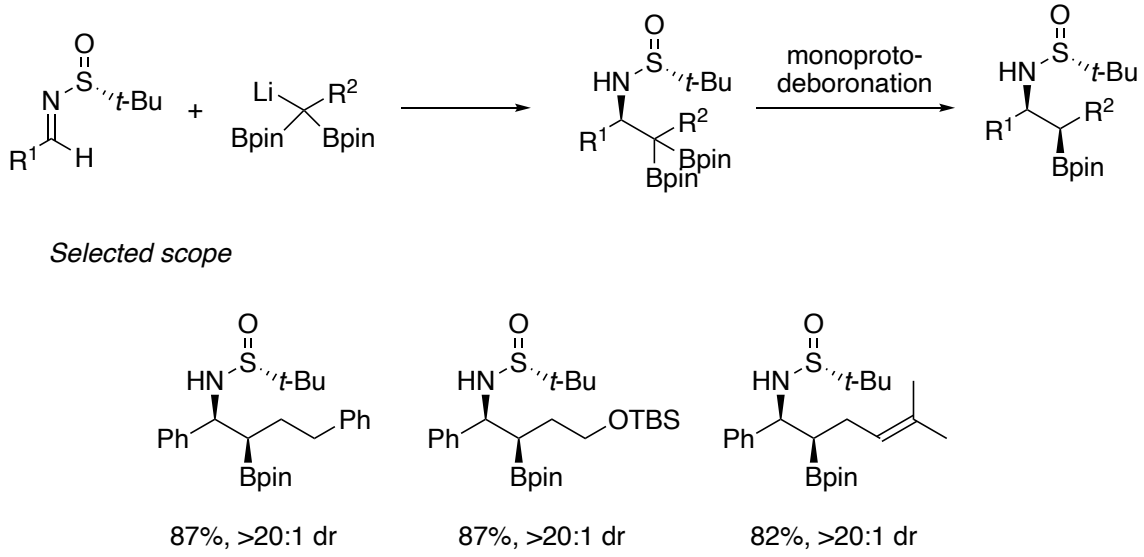


Figure 1.15: Examples of N-protected amines and new catalyst

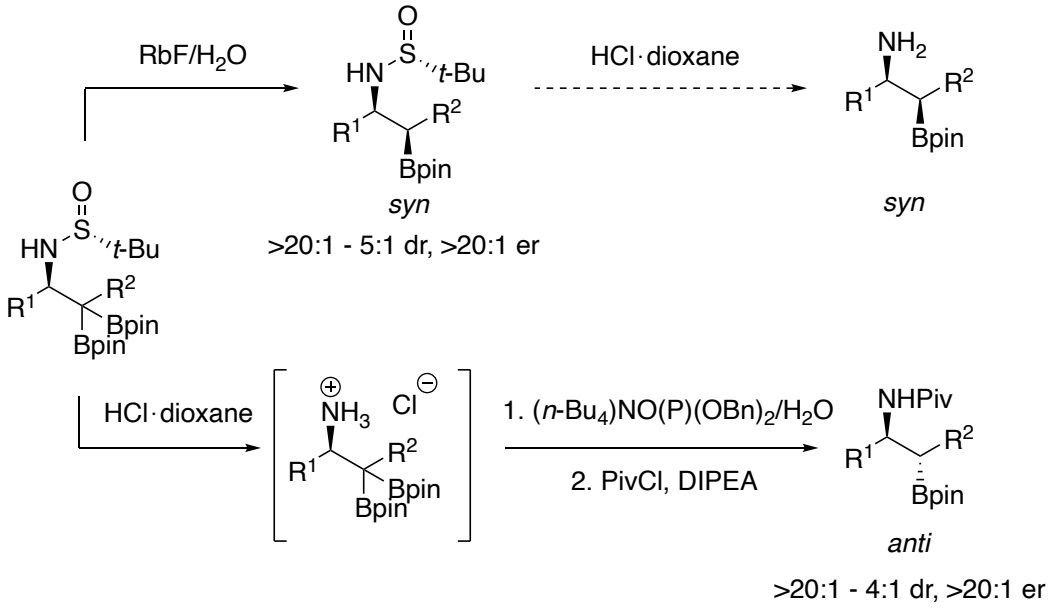
One year later, Li and Hall published a paper starting from the same *N-tert*-butanesulfinyl aldimine substrate using a significantly different approach.[41] 1,2-Addition proceeds with 1,1-diborylalkane lithiated species (*Scheme 1.15*). This multi-step reaction requires a diastereoselective protodeboronation step. Rubidium fluoride and water were found as optimal conditions. It was also noticed that compared to other fluorides, RbF reduces the amount of elimination product. The yield of obtained β-aminoalkylboronates varies from 39 to 99% and diastereoselectivity ranges from >20:1 to 4:1 dr.



Scheme 1.15: 1,2-addition of lithiated 1,1-diborylalkane to aldimine

[41] Li, X.; Hall, D. G. *Angew. Chem. Int. Ed*. **2018**, *57*, 10304.

In another work Li and Hall expanded the possibilities of this reaction and designed a route towards *anti*-diastereomers.[42] The conditions were developed by changing the sequence of desulfinylation and protodeboronation step (*Scheme 1.16*). It was possible to obtain up to >20:1 dr.

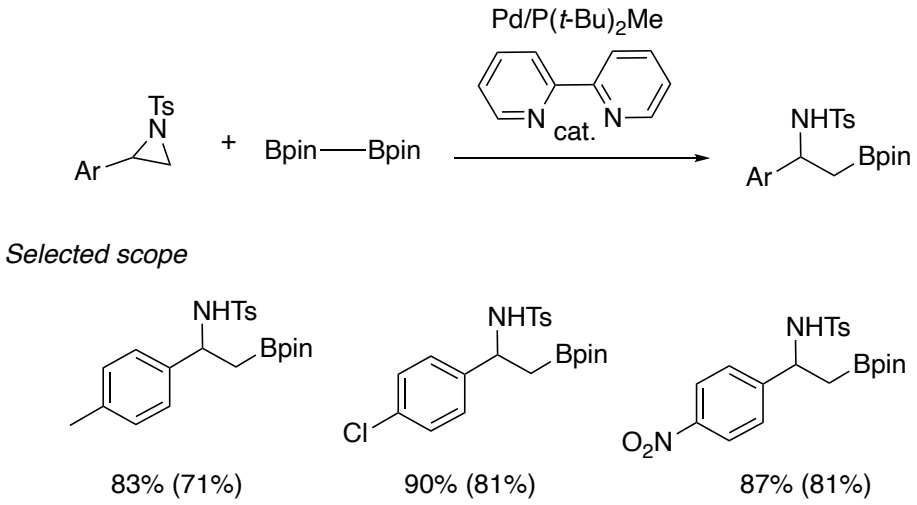


Scheme 1.16: Desulfinylation and protodeboronation step sequence leading to syn/anti product

1.2.5 Ring opening

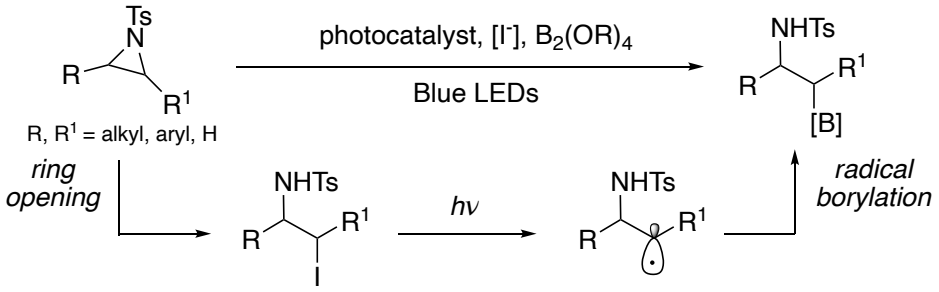
Another method to obtain β-aminoboronic derivatives is *via* the ring opening reaction of 2-arylaziridines.[43] This reaction shows catalyst-dictated regioselectivity. Ring opening (oxidative addition) of aziridines proceeds in an S_N2 fashion and no epimerization is observed (*Scheme 1.17*). Starting from various racemic substrates, a 58-81% yield can be achieved.

[42] Li, X.; Hall, D. G. *J. Am. Chem. Soc.* **2020**, *142*, 9063.
[43] Takeda, Y.; Kuroda, A.; Sameera, W. M. C.; Morokuma, K.; Minakata, S. *Chem. Sci.* **2016**, *7*, 6141.



Scheme 1.17: Metal-catalyzed ring opening of aziridines

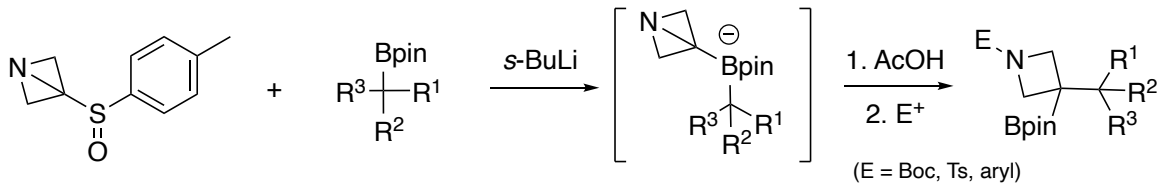
A variety of other aziridines found their application in another reaction which was described in 2022 by Lee.[44] The synthetic method relies on a cascade reaction (*Scheme 1.18*): firstly ring-opening by nucleophilic attack of iodide occurs followed by visible-light mediated radical borylation. It was shown that the boron source is crucial for the borylation step and only particular diboron (B_2cat_2) reagents lead to good yields (range from 21 to 77%).



Scheme 1.18: Nucleophilic ring opening and further radical borylation of aziridines

[44] Park, S.; Koo, J.; Kim, W.; Lee, H. G. *Chem. Commun*. **2022**, *58*, 3767.

A ring-opening strategy was also applied to 4-membered rings (*Scheme 1.19*).[23a] The driving force of this reaction is decreasing the strain present in the ring system. After lithiation, the formed intermediate can undergo 1,2-metallate rearrangement. Primary, secondary, tertiary, aryl and alkenyl boronic esters are applicable to these conditions.

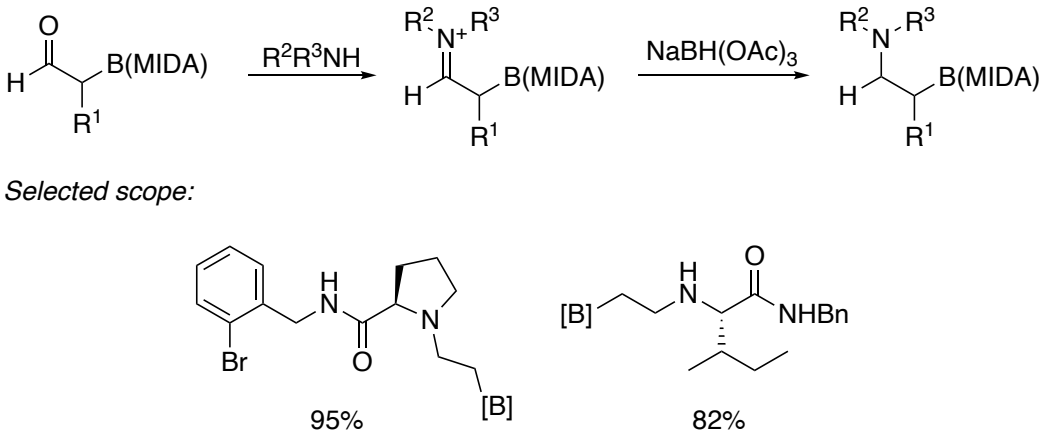


Scheme 1.19: Lithiation of azabicyclo[1.1.0]cyclobutane

1.2.6 Amination

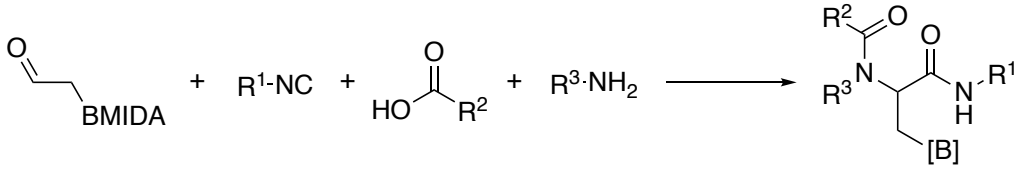
There have been relatively few studies related to amination methods to obtain β-aminoboronic derivatives. All of them have been reported by the Yudin group. The first paper with new method was published in 2016.[45] The reaction focuses closely on reactivity of MIDA-protected α-boryl aldehydes. Adding an amine to the system leads to the iminium ion, which could be further reduced to β-aminoboronic species (*Scheme 1.20*).

[45] Diaz, D. B.; Scully, C. C. G.; Liew, S. K.; Adachi, S.; Trinchera, P.; Denis, J. D. St.; Yudin, A. K. *Angew. Chem. Int. Ed*. **2016**, *55*, 12659.



Scheme 1.20: Transformation of MIDA protected aldehyde to aminoboronate species

One year later Yudin also described the synthesis of β-aminoboronates via an Ugi 4-component reaction starting from α-borylaldehydes (*Scheme 1.21*).[46] To stabilize and to avoid premature protodeboronation, the boron species was protected by *N*-methyliminodiacetic (MIDA) group.



Scheme 1.21: Obtaining aminoboronates trough a four-component Ugi reaction

1.3 BACKGROUND ON COPE-TYPE HYDROAMINATION

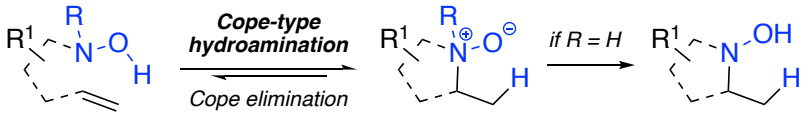
Another potential hydroamination method to obtain β-aminoboronic derivatives is Cope-type hydroamination. Our group conducted significant research efforts to develop this reaction.

[46] Kaldas, Sh. J.; Rogova, T.; Nenajdenko, V. G.; Yudin, A. K. *J. Org. Chem.* **2018**, *83*, 7296.

There are very detailed reviews of this reaction by Knight[47] and Beauchemin[48] in 2004 and 2013, respectively. Since that time, only minor improvements of Cope-type hydroamination have been reported.[49]

1.3.1 Mechanism of Cope-type hydroamination and reaction limitations

The Cope-type hydroamination is a concerted, direct amination of C-C π bonds using hydroxylamine derivatives (*Scheme 1.22*). It proceeds via a five-membered transition state, and it is the microscopic reverse of the Cope elimination.

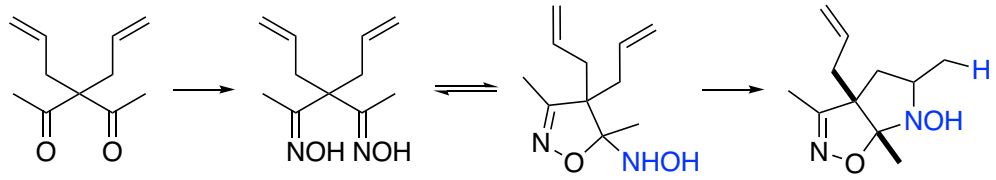


Scheme 1.22: The Cope-type hydroamination

The early studies of this reaction were conducted by Cope, Laughlin, Ciganek, House and Oppolzer, among others, during the second part of the 20th century.[50]

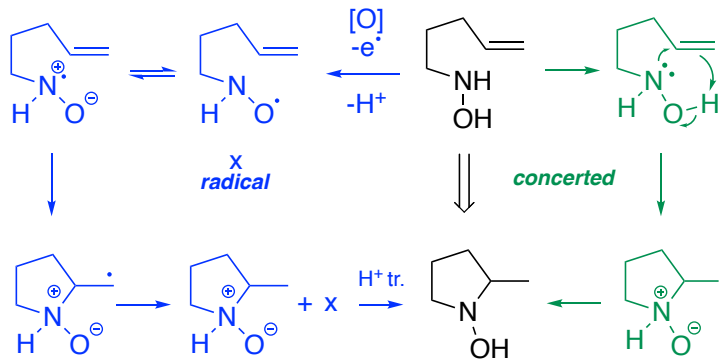
The first isolation of a Cope-type hydroamination product was conducted by House in 1976.[50C] Attempts to synthesize dioxime using standard conditions (reflux in dioxane) leaded to an unexpected cyclic product (*Scheme 1.23*). In further studies, House studied the reactivity of this reaction using simpler hydroxylamines.[51]

[47] Cooper, N. J.; Knight, D. W. *Tetrahedron*, **2004**, *60*, 243.
[48] Beauchemin, A. M. *Org. Biomol. Chem*. **2013**, *11*, 7039.
[49] Kang, D.; Cheug, Sh. T.; Kim, J. *Angew. Chem. Int. Ed*. **2021**, *60*, 16947.
[50] (a) Cope, A. C.; LeBel N. A. *J. Am. Chem. Soc.* **1960**, *82*, 4656; (b) Laughlin, R. G. *J. Am. Chem. Soc.* **1973**, *95*, 3295; (c) House, H.O.; Manning, D. T.; Melillo, D. G.; Lee, L. F.; Haynes, O. R.; Wilkes, B. E. *J. Org. Chem.* **1976**, *41*, 855; (d) Oppolzer, W.; Spivey, A. C.; Bochet, C. G. *J. Am. Chem. Soc.* **1994**, *116*, 3139.
[51] House, H.O.; Lee, L. F. *J. Org. Chem.* **1976**, *41*, 863.



Scheme 1.23: First reported Cope-type hydroamination reaction

Several likely mechanisms of this reaction were proposed[52] Some electrochemical measurements and impact of traces of oxidizing agents allowed to speculate that the reaction proceeds by radical-based mechanism. However, this hypothesis was not consistent with observations. For example, adding radical inhibitors did not impact the reaction rate.[53] Additionally, no product was formed from theoretically more stable radical intermediates. In contrast, a concerted mechanism was reported by Ciganek in 1990 and three years later by Oppolzer's group (*Scheme 1.24*).[50d,52]



Scheme 1.24: Proposed radical and concerted mechanism of the reaction

Ciganek reported a formation of single diastereomer as a Cope-type hydroamination product, where methyl group and the oxygen were in *cis* form (*Figure 1.16a*). Later, Oppolzer's group claimed that different diastereomers can be formed from corresponding starting *E/Z* alkenes

[52] (a) Ciganek, E. *J. Org. Chem.* **1990**, *55*, 3007; (b) Oppolzer, W. *Gazz. Chim. Ital.* **1995**, *125*, 207.
[53] Black, D. St. C.; Doyle, J. E. *Aust. J. Chem.* **1978**, *31*, 2317.

(*Figure 1.16b*). These supported a planar 5-membered transition state. The reaction yield also showed solvent dependency. This will be discussed in further details in section 1.3.3.

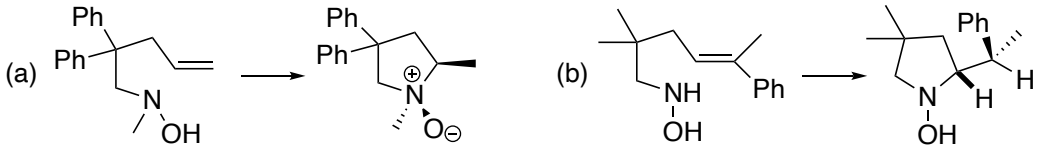


Figure 1.16: Reported Cope-type hydroamination products which supported concerted mechanism

Further studies of intramolecular reactivity with a range of substituted hydroxylamines allowed for several general conclusions:

a. *N*-methyl substituted hydroxylamines react faster than primary analogues;
b. distal substituents slow Cope-type hydroamination (methyl group seems to have little impact);[53]
c. an impact of Thorpe-Ingold effect (geminal di-substitution generally leads to more facile cyclization);
d. ring size: 5-membered ring cyclization are generally accessible, while 6-membered are difficult to form.

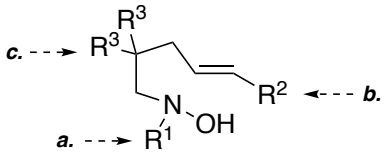


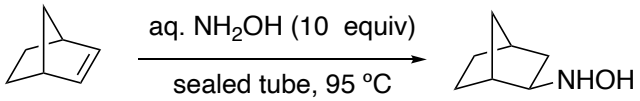
Figure 1.17: Intramolecular reactivity trends of Cope-type hydroamination

1.3.2 Our group's work on Cope-type hydroamination

A significant improvement of Cope-type hydroamination reactivity was achieved through optimization work by the Beauchemin group.

Initially reported in 2008,[54] it was shown that solvent effects are particularly important for intermolecular reactions. The conditions were initially reported for addition on alkynes did not show good reactivity with alkenes. Indeed, an intermolecular reaction was performed on norbornene and it was expected that partial strain release would provide a more energetically favourable profile. Through a solvent scan it was noticed that the reaction yield is highly dependent on a solvent (*Table 1.1*).

Table 1.1: Solvent effect in the hydroamination of norbornene



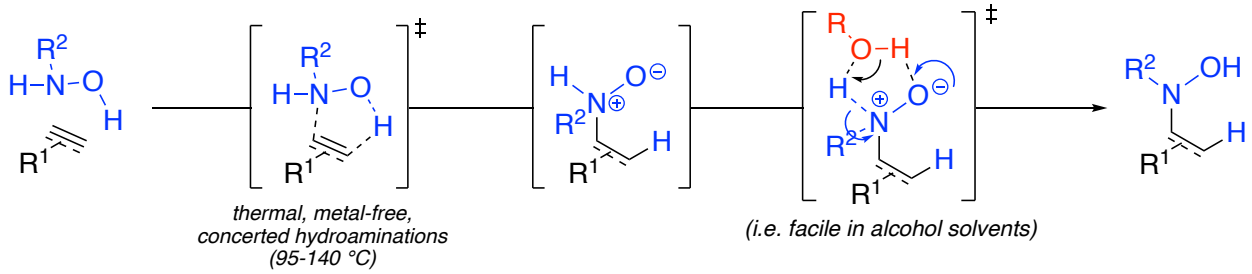
Solvent	Conversion [%]*
C_6D_6	0
Dioxane	3
$CDCl_3$	5
MeOH	26
EtOH	14
***i*-PrOH**	**48**
DMSO-d_6	22
No solvent	0

[*] NMR yield determined using styrene as an internal standard

It was proposed that such reactivity could be explained by hydrogen bonding. Indeed, the *N*-Oxide intermediate can be stabilized in presence of alcoholic solvents and the formation of a more stable intermediate helps to minimize the reverse reaction (Cope elimination). Moreover, alcoholic

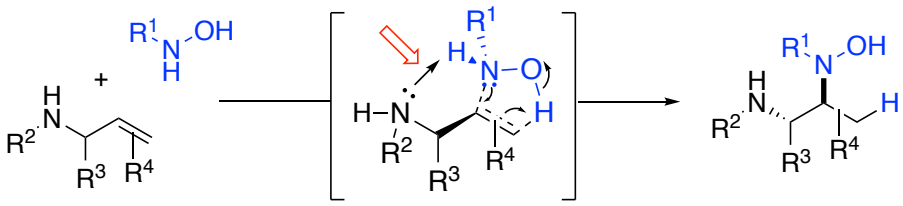
[54] Beauchemin, A. M.; Moran, J.; Lebrun, M.-E.; Séguin, C.; Dimitrijevic, E.; Zhang, L.; Gorelsky, S. I. *Angew. Chem. Int. Ed.* **2008**, *47*, 1410.

solvents could facilitate the proton transfer step. A detailed mechanism in such solvents was proposed (*Scheme 1.25*).



Scheme 1.25: Mechanism of Cope-type hydroamination in alcohol solvents

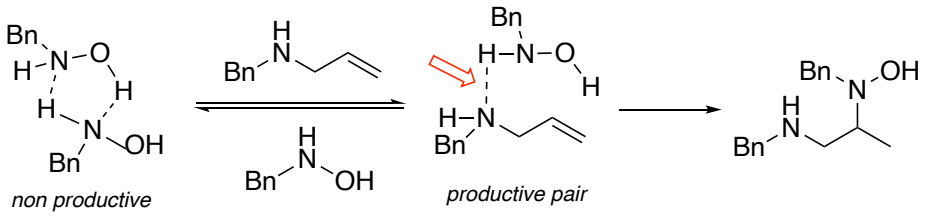
These results inspired further investigation of Cope-type hydroamination reactions. Keeping in mind that hydrogen bonding facilitates this reaction, this finding was exploited in follow up studies. The reaction rate can be accelerated by changing the nature of substrates or by adding catalyst. This way, transition states can be stabilized through a directed reaction,[55] and the reaction will require milder conditions. In 2012, a study on allylic amines was conducted (*Scheme 1.26*). It was possible to get 20 examples with yields up to 97%.



Scheme 1.26: Cope-type hydroamination with allylic amines

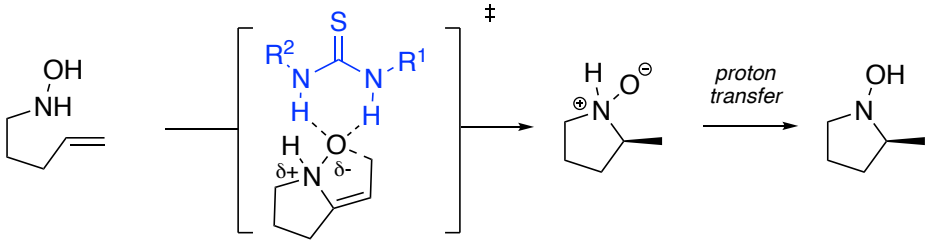
During the optimization it was noted that the better reaction outcome occurs if allylic amine is in excess. Excess amine helps to overcome the formation of unreactive hydroxylamine dimers and allows to obtain a desired product.[56]

[55] Hoveyeda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, 93, 1307.
[56] Zhao, Sh.-B.; Bilodeau, E.; Lemieux, V.; Beauchemin, A. M. *Org. Lett.* **2012**, *14*, 5082.



Scheme 1.27: Reaction equilibrium with hydroxylamine

In line with studies of our group, a hydrogen bonding stabilization of dipolar intermediate was shown with a chiral thiourea catalyst by Jacobsen in 2013.[57]



Scheme 1.28: Cope-type hydroamination using thiourea catalyst

Hydrazine derivatives are useful reagents in organic synthesis. Further development showed that hydrazines can engage in concerted hydroamination reactions.[58] Given the contents of this thesis focusing on hydroxylamines, the development with hydrazines will not be discussed in detail.

A reaction scope of intermolecular reaction of alkenes with hydroxylamines for some time was limited to strained alkenes, allylic amines and styrene species. To perform less favourable intermolecular Cope-type hydroamination reaction with other alkene species, temporary

[57] Brown, A. R.; Uyeda, C.; Brotherton, C. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2013**, *135,* 6747.
[58] (a) Cebrowski, P. H.; Roveda, J.-G.; Moran, J.; Gorelsky, S. I.; Beauchemin, A. M. *Chem. Commun.* **2008**, *492.* (b) Roveda, J.-G.; Clavette, Ch.; Hunt, A. D.; Gorelsky, S. I.; Whipp, Ch. J.; Beauchemin, A. M. *J. Am. Chem. Soc*. **2009**, *131*, 8740. (c) Loiseau, F.; Clavette, C.; Raymond, M.; Roveda, J.-G.; Burell, A.; Beauchemin, A. M. *Chem.Commun.* **2011**, *562.*

intramolecularity was exploited.[59] The goal was to use a catalyst forming a temporarily tether as shown on *Figure 1.18,* hoping to accelerate the rate of the reaction by 10^4-10^8 for 1 M reactants, which is predicted for temporary intramolecularity.[60] As it is illustrated, this catalytic approach does not require additional step for installing and removing tether, as is typically the case when temporary tethers are used.

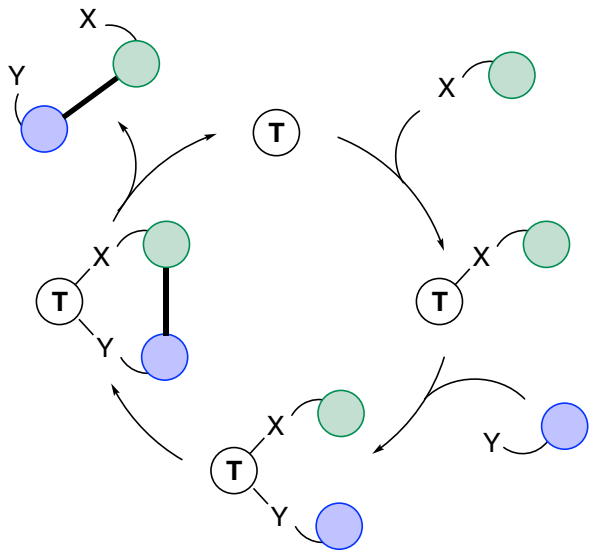
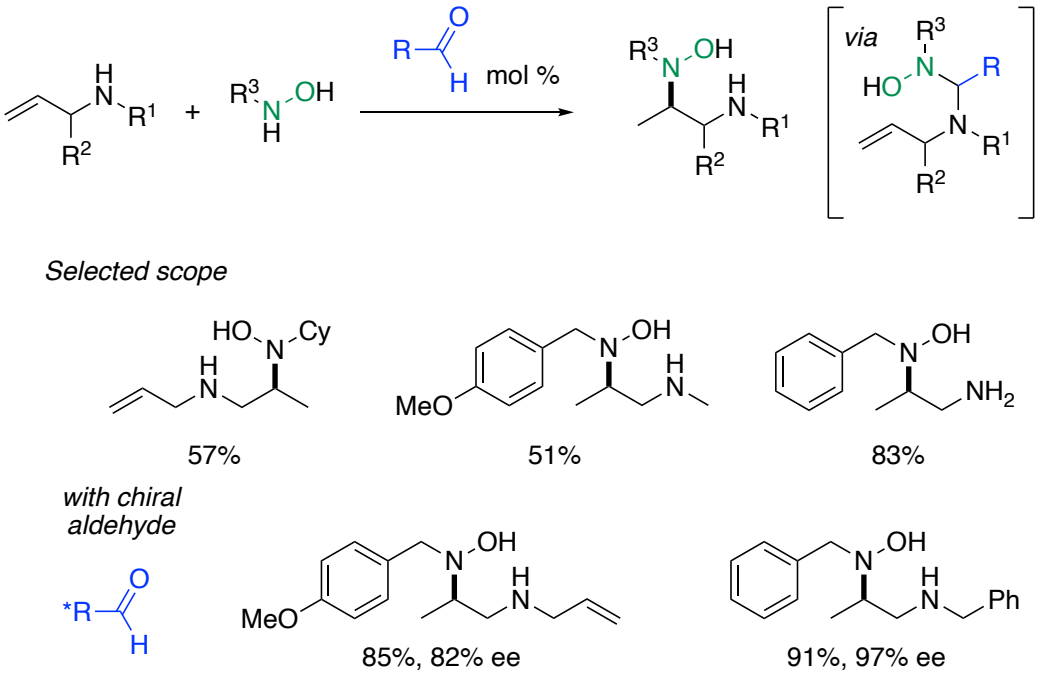


Figure 1.18: Catalytic cycle via temporary intramolecularity

In our approach as a tethering catalyst an aldehyde was used. This catalytic approach allowed for mild, metal-free conditions. Moreover, 1,2-diamine motifs can be obtained with high diastereoselectivity (starting from chiral hydroxylamine or chiral allylic amide) (*Scheme 1.29*).

[59] (a) MacDonald, M. J.; Schipper, D. J.; Ng, P. J.; Moran, J.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2011**, *20100.* (b) Hesp, C. R.; MacDonald, M.; Zahedi, M.; Bilodeau, D.A.; Zhao, S.-B.; Pesant, M.; Beauchemin, A. M. *Org. Lett.* **2015**, *17*, 5136.
[60] Jencks, W. P. *Adv. Enzymol. Relat. Areas Mol. Biol.* **1975**, *43*, 219.

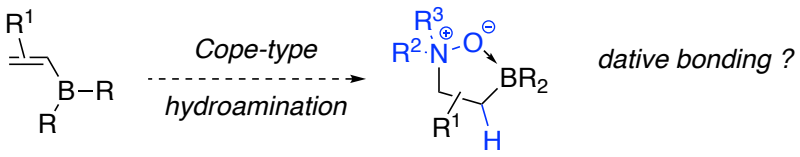


Scheme 1.29: Aldehyde-catalyzed Cope-type hydroamination

1.4 RESEARCH GOALS

As stated before, despite some interesting biological and synthetical values of β-aminoboronic acids, the broad usage of these compounds is limited due to the lack of their general synthetic methods. Therefore, in this thesis, an investigation towards a new possible way of synthesis of β-aminoboronic acids is conducted.

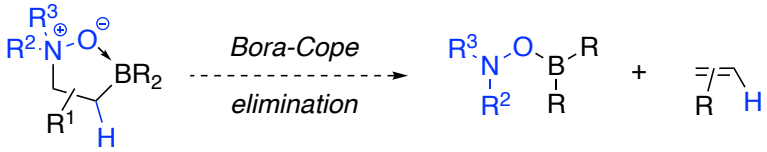
With experience in Cope-type hydroamination reaction, our group questioned the possibility of previously unexplored reactivity of hydroxylamines with vinylboronate species (*Scheme 1.30*). The presence of boron would impact the hydroamination conditions, while forming a dative bond may facilitate the reaction outcome.



Scheme 1.30: Cope-type hydroamination with boron species

Developing suitable conditions for further derivatization of obtained species would also enlarge the scope of β-aminoboronic acid derivatives.

At the same time, we were intrigued regarding the product stability and the possibility of a further almost unexplored Bora-Cope elimination reaction. Low stability of formed products would allow to obtain precursors for aminoboration reaction or give way towards forming product of elimination with stereocontrol (*Scheme 1.31*).



Scheme 1.31: Bora-Cope elimination

The poor commercial availability and high price of hydroxylamines, which are used as starting materials for scope investigation, inspired to develop improved oxidation conditions for amines. These results are presented in Chapter 3.

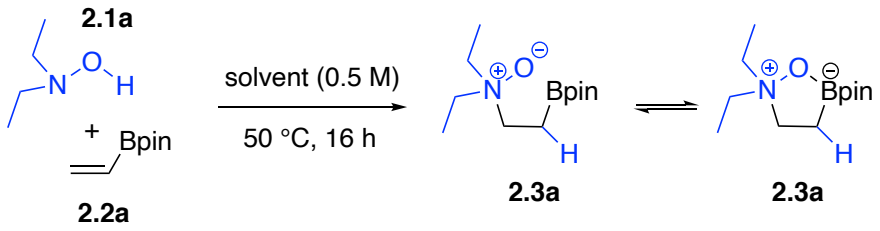
CHAPTER 2: COPE-TYPE HYDROAMINATION

In Chapter 2 the first examples of metal-free, anti-Markovnikov hydroamination of vinylboronates with hydroxylamines are presented. Newly formed oxazaborolidine ylide heterocycles have not been reported in the literature. The scope, reaction limitations and further derivatization to different substrates, including β-aminoboronic esters, are shown.

2.1 INTERMOLECULAR COPE-TYPE HYDROAMINATION OF VINYLBORONATES

As it was proposed before, dative bonding can have an impact on Cope-type hydroamination reactivity. Herein, investigations were initiated towards intermolecular reactions with boron-containing species. With prior experience in our group[48] in studying of Cope-type hydroamination, it was expected that reaction should be solvent dependent and sensitive to stoichiometry. Using *N,N*-diethylhydroxylamine **2.1a** as a commercially available secondary hydroxylamine and pinacol vinylboronate **2.2a** as the simplest boron-containing alkene the optimal reaction conditions were investigated (*Table 2.1*).

Table 2.1: Optimization of hydroamination reaction with vinylboronate[a]



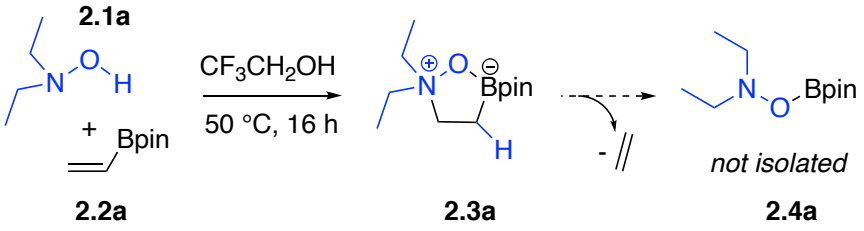
entry	equiv **2.1a**	equiv **2.2a**	solvent	yield (%)[b]
1	1.0	1.5	CF_3CH_2OH	88
2	**1.5**	**1.0**	**CF_3CH_2OH**	**93**
3[c]	1.5	1.0	CF_3CH_2OH	74
4[d]	1.5	1.0	CF_3CH_2OH	79
5	5.0	1.0	CF_3CH_2OH	86
6[e]	1.5	1.0	CF_3CH_2OH	92
7	1.5	1.0	$(CF_3)_2CHOH$	91
8	1.5	1.0	CH_3OH	82
9	1.5	1.0	*i*-PrOH	59
10	1.5	1.0	THF	0
11	1.5	1.0	toluene	0

(a) Conditions: boronate **2.1a** in solvent (0.5 M), Et_2NOH added, 50 °C, sealed tube, 16 h; (b) ^1H NMR yields using 1,3,5-trimetoxybenzene as internal standard; (c) rt instead of 50 °C; (d) 80 °C instead of 50 °C; (e) microwave heating 50 °C for 2 h.

Firstly, an optimal reaction solvent was identified. The results obtained were consistent with previous trends reported for Cope-type hydroamination,[54] and less polar solvents show no product formation (*Table 2.1, entries 10-11*). Fluorinated alcoholic solvents 2,2,2-trifluoroetanol (TFE)

and hexafluoroisopropanol (HFIP) were scanned and, surprisingly, their use led to a better outcome compared to MeOH and *i*-PrOH (*Table 2.1, entries 1-8*). Further investigations in conditions for vinylboronates, indicate that small excess of hydroxylamine is required, although the use of a larger amount is not beneficial (*Table 2.1, entries 1-2, 5*). Performing a reaction at room temperature or 80 °C led to longer reaction time or lower yield (*Table 2.1, entry 4*). It is worth highlighting that Cope-type hydroamination for unfunctionalized alkenes occurs above 100 °C and compounds which contain boron substituent allow milder conditions. Microwave irradiation provided nearly the same outcome of reaction in shorter time (*Table 2.1, entry 6*).

During an investigation of optimal conditions, it was noticed that holding a compound on high vacuum for a long time led to a bora-Cope elimination. Appearance of a small ethylene peak in ^{1}H NMR spectrum suggested that *O*-borylhydroxylamine **2.4a** was formed (*Scheme 2.1*). Obviously, ethylene is a gas, and it is difficult to quantify and thus observe its conversion rate by ^{1}H NMR. We were particularly interested in obtaining **2.4a** as it could be a potential reagent for a one-step alkene aminoboration under mild conditions. Although numerous attempts to isolate *O*-borylhydroxylamine **2.4a** was not successful. Holding this compound for a long time on a high vacuum under room temperature or at 50 °C led to decomposition of the product.

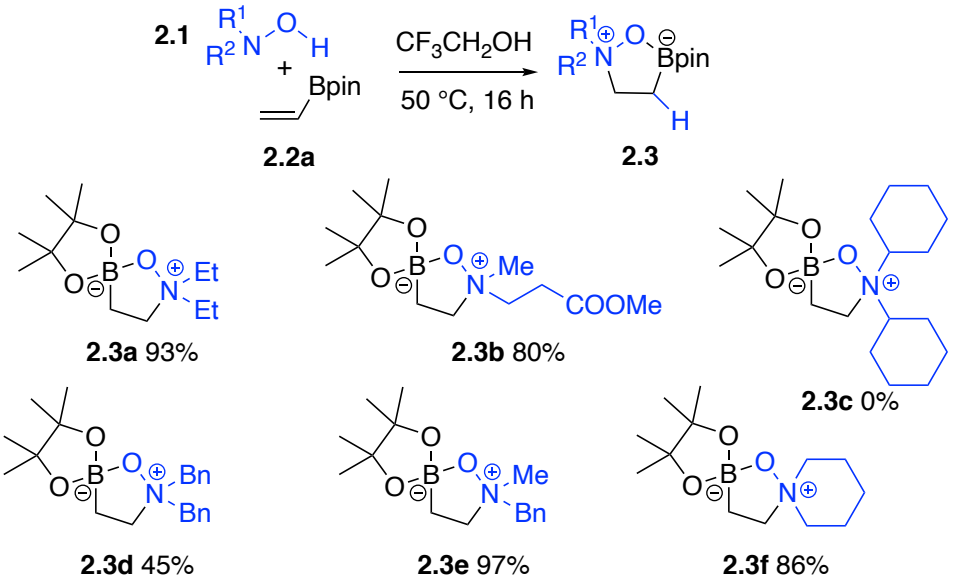


Scheme 2.1: Possible elimination reaction for Cope-type hydroamination with vinylboronate

Investigation of the reaction scope under optimized conditions revealed that a variety of *N, N*-disubstituted hydroxylamines afford Cope-type hydroamination with vinylboronates in yields

from 45% to 97% (*Table 2.2*). Significantly lower yield 45% of **2.3d** could be explained due to steric reasons, also no product was noticed for bulky **2.3c**.

Table 2.2: Reaction scope of Cope-type hydroamination with secondary hydroxylamines[ab]



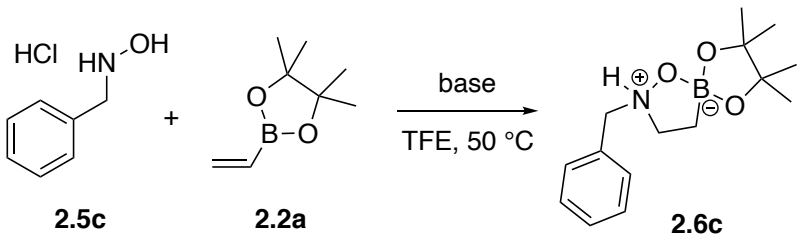
(a) Conditions: 1 equiv. boronate **2.2a** in CF_3CH_2OH (0.5 M), 1.5 equiv. R_2NOH added, 50 °C, sealed tube, 16 h; (b) ^1H NMR yields using 1,3,5-trimetoxybenzene as internal standard;

While secondary hydroxylamines for synthesizing **2.3a**, **2.3d** are commercially available, hydroxylamine for **2.3b** was obtained by addition of unsaturated ester to primary hydroxylamine salt,[61] hydroxylamine for **2.3f** was synthesized via aza-Michael addition of secondary amines to acrylonitrile followed by *N*-oxide formation and Cope elimination,[62] hydroxylamines for **2.3c**, **2.3e** were obtained through a new method developed by PhD student in our group and further optimized by collaboration with honours student Daniel Barriault. A detailed discussion of this oxidation method is presented in Chapter 3.

[61] Baldwin, J. E.; Harwood, L. M.; Lombard, M. J. *Tetrahedron Lett*. **1984,** 4363.
[62] O'Neil, I. A.; Cleator, E.; Tapolczay, D. *Tetrahedron Lett*. **2001**, *42*, 8247.

We were also interested in exploring the use of *N*-alkylhydroxylamines. Some *N*-monosubstituted hydroxylamines come as commercially available compounds in form of salts, so additional optimizations of reaction conditions were investigated (*Table 2.3*). As a model substrate salt **2.5c** was chosen.

Table 2.3: Optimization of Copy-type hydroamination with primary hydroxylamine[a]



2.5c **2.2a** **2.6c**

entry	base	yield (%)[b]
1	K_2CO_3	64
2	$KHCO_3$	60
3	**DIPEA**	**87**
4	DBU	80

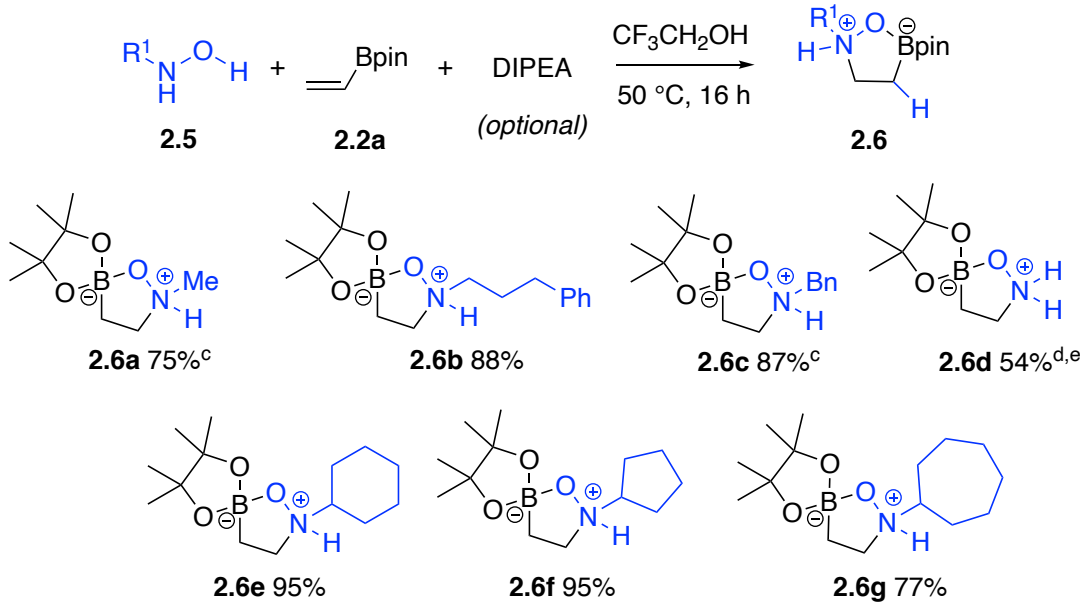
(a) Conditions: 1 equiv. boronate **2.2a** in CF_3CH_2OH (0.5 M), 1.5 equiv. amine salt **2.5c**, 1.5 equiv. base, 50 °C, sealed tube, 16 h; (b) ^1H NMR yields using 1,3,5-trimetoxybenzene as internal standard.

Better yields were observed with organic bases (*Table 2.3, entries 3-4*), while with inorganic bases the yields were fair and hit 60% and 64% (*Table 2.3, entries 1-2*). Weaker organic base DIPEA (pK_{aH}(water) = 12[63]) shows to be more effective compared to stronger base DBU

[63] Perrin, D. D. *Dissociation constants of organic acids and bases*; Butterworths: London, **1965**.

(pK_{aH}(water) = 10.75[64]). No further base screening was conducted as at this stage observed ^{1}H NMR yield was satisfied to proceed further. DIPEA was used in further reactions (*Table 2.3*).

Table 2.4:Reaction scope of Cope-type hydroamination with primary hydroxylamines[ab]



(a) Conditions: 1 equiv. boronate **2.2a** in CF_3CH_2OH (0.5 M), 1.5 equiv. RNHOH added, 50 °C, sealed tube, 16 h; (b) ^{1}H NMR yields using 1,3,5-trimetoxybenzene as internal standard; (c) 1.5 equiv. DIPEA added when hydroxylamine comes in form of hydrochloride salt; (d) hydroxylamine comes in aquas solution; (e) reaction time is 24 h instead of 16 h.

Good to excellent yields (54-95%) were obtained with primary hydroxylamines (*Table 2.4*). It was possible to increase the reaction yield of **2.6d** from 23% to 54% by using aqueous

[64] Granitza, D.; Beyermann, M.; Wenschuh. H.; Haber, H.; Carpino, L. A.; Truranb, G. A.; Bienerta, M. *J. Chem. Soc.* **1995**, *21*, 2223.

solution of NH_2OH instead of $NH_2OH{\cdot}HCl$. Longer reaction time for this reaction led to decomposition.

Due to the fact, that the products obtained have not been reported before in the literature, in addition to ^{1}H and ^{13}C NMR, and mass spectroscopy analysis, the structure of the oxazaborolidine was proved by an X-ray analysis for **2.6f** (*Figure 2.1*).

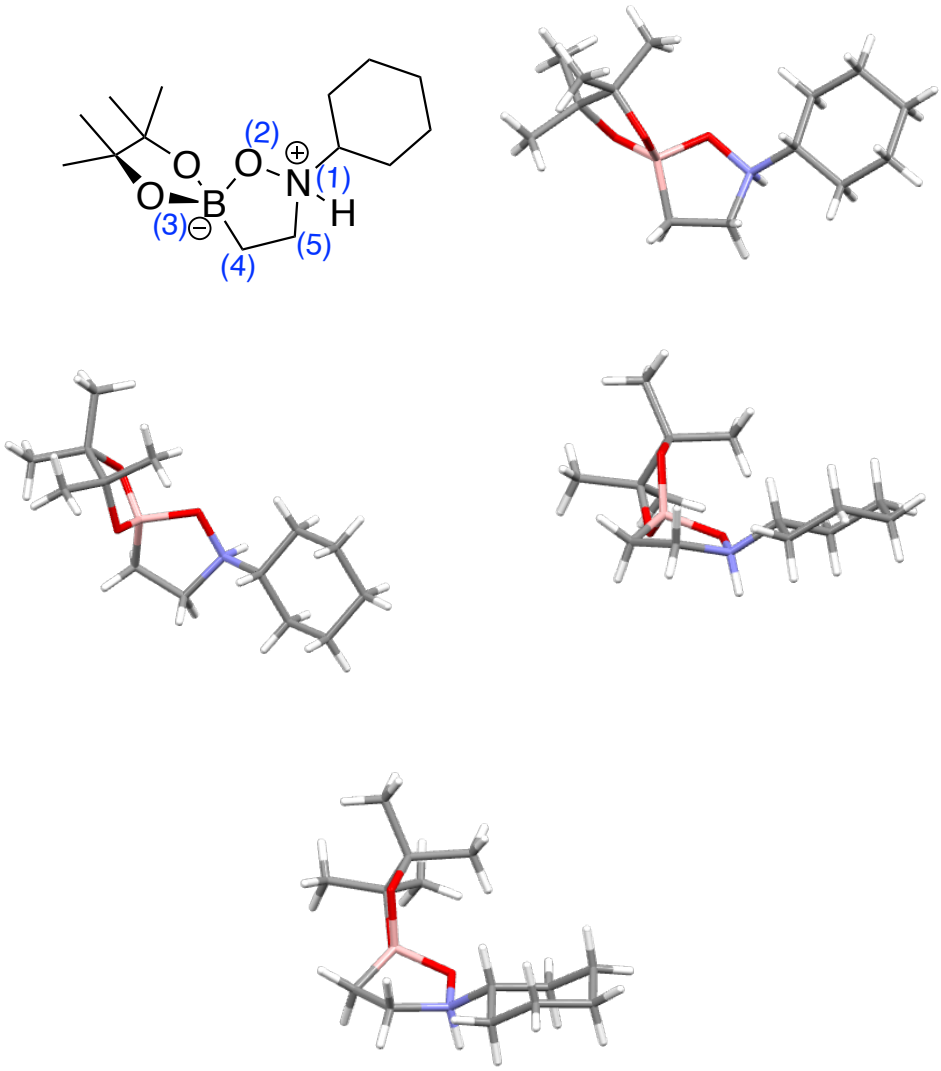


Figure 2.1: X-ray structure of oxazaborolidine from different angles

Selected structural information obtained from this X-ray crystal structure, bond lengths, are also presented in *Table 2.5* along with a comparison of normal bond lengths. The length of N(1)-O(2) bond is 1.41(2) Å and this length is slightly smaller than typical length for N-O bond (*Table 2.5*). In contrast, B(3)-O(2) bond is longer than it usually occurs (1.53(7) Å), typical number for trisubstituted B(3)-O(2) species ranges from 1.28 to 1.43 Å. This data suggests that obtained B(3)-O(2) bond should be more reactive. Interestingly, the difference is also noticed for C-Heteroatom bonds in cyclic formed compound. C(4)-B(3) bond is 1.61(5) Å, which is longer than typical length and also longer compared to C(5)-N(1) bond in other molecules. This feature would make this bond is also more reactive in comparison to C(5)-N(1). Measured C(5)-N(1)-O(2) angle is 100.7(2) deg, while C(4)-B(3)-O(2) angle less has less strain and reaches 108.9(2) deg.

Table 2.5: Comparison of bond lengths

Element 1- Element 2	Typical bond length, Å[65]	Bond length in **2.6f,** Å
N(1)-O(2)	1.46 (single bond)	1.41(2)[a]
B(3)-O(2)	1.28 – 1.43 (tricoordinate)[66]	1.53(7)
C(4)-B(3)	1.56	1.61(5)
C(5)-N(1)	1.48 (single bond)	1.51(9)

[a] bond lengths shown in brackets have been rounded to the nearest integer.

What is more, it is worth highlighting that although a molecule has a chiral center, the overall structure is centrosymmetric meaning the crystals are built from a 50:50 racemic mixture.

[65] Weast, R. C.; Astle, M. J. CRC handbook of chemistry and physics; Boca Raton, Fla.: The CRC Press, **1982**.
[66] Coulson, C. A.; Dingle, T.W. *Acta Cryst.* **1968**, *B24*, 153.

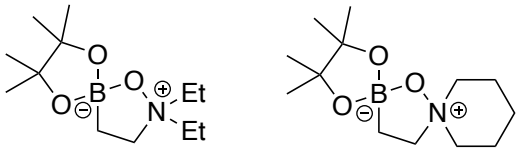
Same tendency is observed via ^{1}H NMR spectra, being especially easy to observe on oxazaborolidines which contain benzyl group.

2.2 EFFORTS TOWARDS ISOLATION AND FURTHER DERIVATIZATION OF OXAZABOROLIDINES

With a broad scope on hand, we were challenged to isolate synthesized compounds.

Firstly, it is worth to highlight that oxazaborolidines show moderate stability in air. After keeping compounds on a bench for a month no significant degradation was observed. Although due to their polarity these compounds proved to degrade on silica. Thus, it was difficult to isolate them in good yields using column chromatography. Also, due to their and unique structure they show degradation if placed under high vacuum.

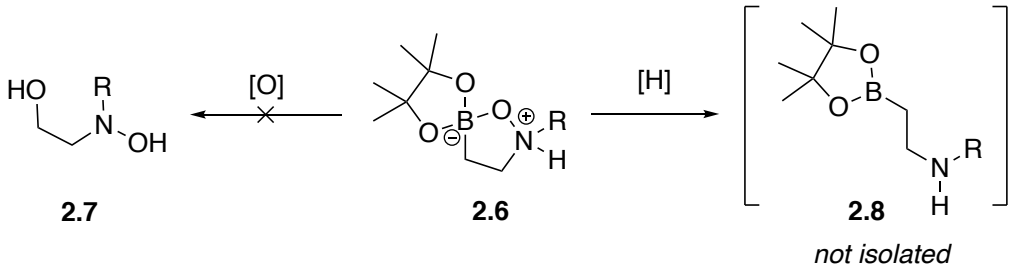
Preliminarily results of isolation via pipette column chromatography on small scale were encouraging, however showed to be difficult to scale-up to 0.3 mmol scale. A variety of solvent systems were tested for more efficient isolation. Unfortunately, only few substrates we were able to obtain good isolation yields (*Figure 2.2*). In most cases, the expected compound came with a hydroxylamine as a contaminant and significantly lower yield of product than what was expected after ^{1}H NMR analysis using an internal standard. Switching starting material ratio to excess of vinylboronate reagent led to significantly longer reaction time and poor yields. At this stage, we hypothesized that modifying silica with 1% Et_3N or 1% NH_4OH bases or 0.5% CH_3COOH acid could be helpful for isolation, however no difference was observed. Unfortunately, the same was true by switching silica to neutral aluminium oxide.



2.3a 93% (77%) **2.3f** 86% (73%)

Figure 2.2: Oxazaborolidines isolated via column chromatography: isolated yield is shown between parentheses

At this stage, the need for alternative purification method to support the yields determined by ^{1}H NMR analysis prompted the study of chemical properties of oxazaborolidines. Investigations were initiated towards oxidation and reduction reactions. Unfortunately, the appropriate conditions for an oxidation to β-alkoxyamine *N*-oxide **2.7** were not found. Gratifyingly, the reduction of this compound lead to β-aminoboronic ester **2.8** with almost up to 99% conversation (*Scheme2.2*).



Scheme 2.2: Oxidation and reduction of oxazaborolidine derivative

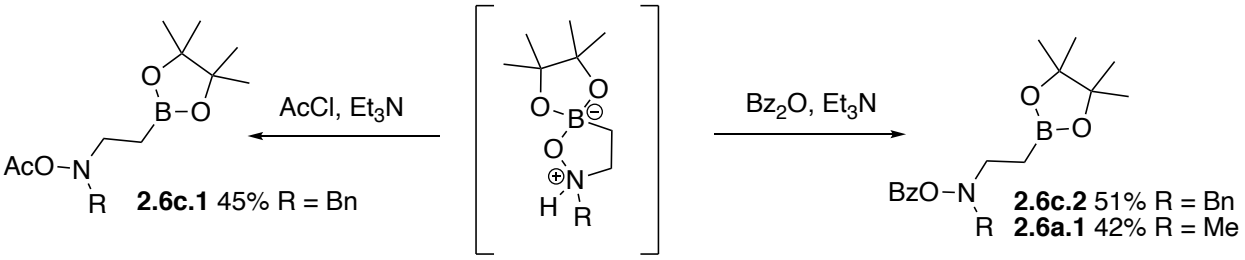
With this, efforts towards isolation using column chromatography were conducted on β-aminoboronic ester. Previous literature review stated that these compounds are also difficult to isolate via column chromatography.[67,23c] Nevertheless, we decided to conduct a few attempts. It was hypothesized that modification of silica with Et_3N could lead to either coordination of the nitrogen atom of Et_3N to the boron atom of pinacol, or simply to neutralization of traces of acid

[67] (a) Li, Q.; Liskey, C. W.; Hartwig, J. F. *J. Am. Chem. Soc*. **2014**, *136*, 8755; (b) Jones, M. R.; Fast, C. D.; Schley, N. D. *J. Am. Chem. Soc.* **2020**, *142*, 6488.

that could facilitate decomposition of the β-aminoboronate. However, no successful results were obtained.

Bearing this is mind, it was decided to investigate conditions for other derivatizations, where further isolation with acceptable mass recovery would be developed. Although, no general isolation method was found. Each compound required unique derivatization.

Several approaches were used for isolation of oxazaborolidines formed from primary hydroxylamines. By an acylation reaction, oxazaborolidines can form an amide bond, which has easier purification (*Scheme 2.2*). Although, acylation with acetyl chloride worked well,[68] the isolated yield for **2.6c.1** was 45% over 2 steps, with some traces of other compounds. This compares to a ^{1}H NMR yield for oxazaborolidine **2.6c** was 87%. However, in parallel the conditions with benzoic anhydride[69] show slightly better results. It was possible to obtain pure amphoteric *O*-acylhydroxylamine-substituted alkylboronic esters **2.6c.2** and **2.6a.1** with good yields (42% for **2.6a.1** and 51% for **2.6c.2**) over two steps.

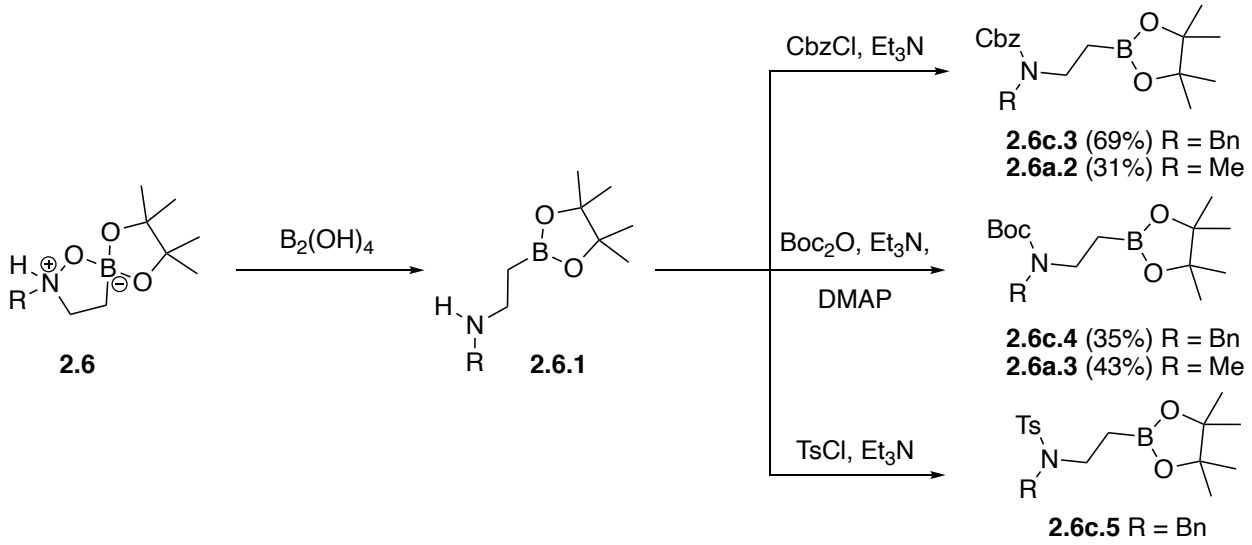


Scheme 2.3: Acylation reaction of oxazaborolidine

Another approach for further derivatization included a reduction reaction of species **2.6** to secondary β-aminoboronic ester **2.6.1** and their further *in-situ* protection with different protecting

[68] Heidlas, J. E.; Lees, W. J.; Pale, P.; Whitesides, G. M. *J. Org. Chem.* **1992**, *57*, 146.
[69] Osamu, I.; Masaaki, A.; Hidekatsu, Y.; Heitaro, O.; Hiroaki, O.; Hitoshi, K. *Chem. Lett.* **2000**, *29*, 304.

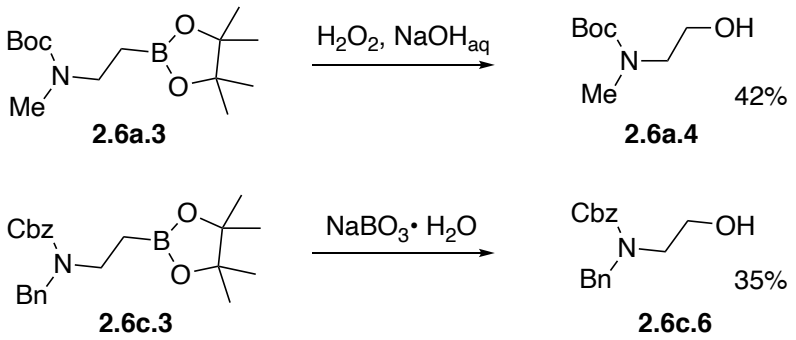
groups (*Scheme 2.4*).[70] Conducted reactions showed encouraging ^{1}H NMR yields over 3 steps, although, surprisingly, compounds **2.6a.2**-**2.6a.3** and **2.6c.3**-**2.6c.5** were difficult to purify. β-Aminoboronic esters **2.6a.2**-**2.6a.3**, **2.6c.3**-**2.6c.5** and *N*-protected amines (formed from excess of hydroxylamine; first step with vinylboronate) have similar polarity, and have too small R_f differences, despite attempts with many solvent systems attempted to achieve separation.



Scheme 2.4: Protection of β-aminoboronic esters

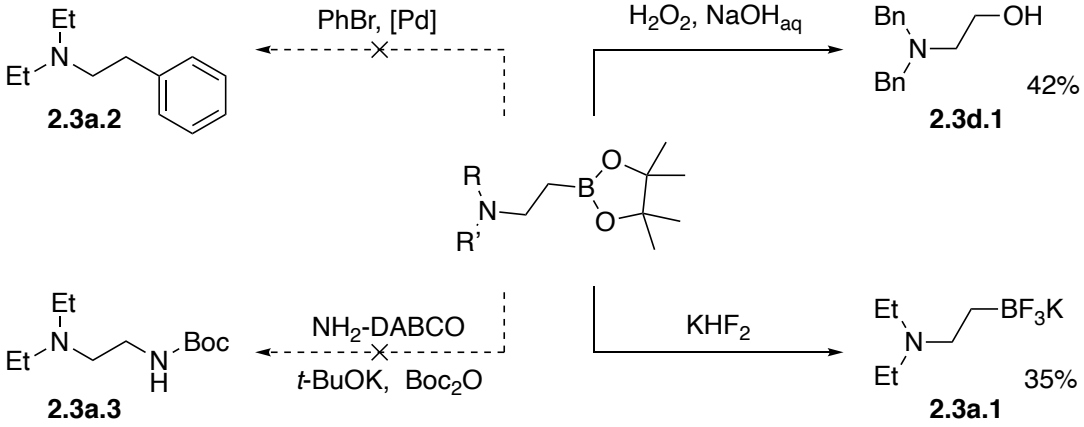
A fourth additional step was conducted. Switching β-aminoboronic ester to aminoalcohol significantly impacted on compound polarity. Two different oxidative conditions[23c,71] worked for substrates **2.6a.3** and **2.6c.3** (*Scheme 2.5*). Aminoalcohols **2.6a.4** and **2.6c.6** were isolated with yields 42% and 35%, respectively, over 4-step sequence, while ^{1}H NMR yield for the respective oxazaborolidines 75% and 87%.

[70] (a) Seashore-Ludlow, B.; Villo, P.; Häcker, C.; Somfai, P. *Org. Lett.* **2010**, *12*, 5274; (b) Choi G.; Hong, S. H. *Angew. Chem. Int. Ed.* **2018**, *57*, 6166. (c) Erb, W.; Wen, M.; Roisnel, T.; Mongin, F. *Synthesis* **2021**, *53*, 2612.
[71] Chandra, G.; Majik, M. S.; Lee, J. Y.; Jeong, L. S. *Org. Lett.* **2012**, *14*, 2134.



Scheme 2.5: β-Aminoboronic esters oxidation

Similarly, β-aminoboronic esters formed from secondary hydroxylamines were reduced. By further oxidation of boron group, it was possible to isolate **2.3d.1** with 42% yield over 3 steps (*Scheme 2.6*) while ^{1}H NMR yield for oxazaborolidine is 45%. With no further column synthetically attractive potassium trifluoroborate salt[67a] **2.3a.1** was obtained from diethylhydroxylsubstituted ester with 35% yield over 3 steps. It is worth to mention, that same derivatization conditions were tried with different β-aminoboronic esters, although no success was achieved. Products were obtained in low yields or isolation challenges did not allow the full purification of the substrates.



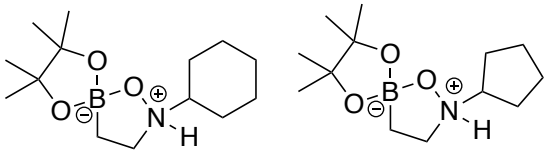
Scheme 2.6: Derivatization of β-aminoboronic esters

Other modifications were tried. Synthetically attractive Suzuki coupling was conducted with diethylsubstituted derivative to obtain amine **2.3a.2**. Unfortunately, tested conditions did not lead to the formation of the desired product. We believe that it can be explained due to reduced nucleophilicity of nitrogen. Accessing desired phenethylamines via Suzuki cross-coupling is limited to usage of *N*-aryl (*N*-phenyl,[23c] carbazole), amide and carbamate derivatives.[72] The latter species allow obtaining amines in free form after further appropriate deprotection of Boc and Cbz protecting groups.[72a] Synthesis of *N,N*-dialkyl phenethylamine derivatives from aminoboronic species via Suzuki coupling have not been reported previously and obtained result is consistent with known literature reports. Out of curiosity, an attempt to synthesize phenethylamine derivative from oxazaborolidine was accomplished. It was assumed that in the non-cyclic form an *N*-oxide could allow obtaining the desired product. A Suzuki cross-coupling was performed following Dong's protocol.[23c] No formation of desired product was observed. At this stage we decided to proceed with other derivatizations and no other screening of Suzuki conditions with oxazaborolidines were tested.

The right conditions for the amination of pinacol boronate compounds were not developed. After unsuccessful attempt of using as the amination reagent a freshy prepared free methoxylamine,[73] we switched to a less sensitive novel approach with aminoazanium of DABCO.[74] However, no expected product **2.3a.3** was registered in this case.

[72] (a) Molander, G. A.; Vargas, F. *Org. Lett.* **2007**, *9*. 203; (b) Katayyama, K.; Ishii, K.; Tsuda, E.; Yotsumoto, K.; Hiramoto, K.; Suzuki, M.; Yasumatsu, I.; Igarashi, W.; Torihata, M.; Ishiyama, T.; Katagiri, T. *Bioorg. Med. Chem. Lett.* **2020**, *30*, 127475; (c) Harris, M. R.; Li, Q.; Lian, Y.; Xiao, J.; Londregan, A. T. *Org. Lett.* **2017**, *19*, 2450; (d) Oeschger, R.; Su, B.; Yu, I.; Ehinger, C.; Romero, E.; He, S.; Hartwig, J. *Science*, **2020**, *368*, 736.
[73] Mlynarski, S. N.; Karns, A. S.; Morken, J. P. *J. Am. Chem. Soc.* **2012**, *134*, 16449.
[74] Liu, X.; Zhu, Q.; Chen, D.; Wang, L.; Jin, L.; Liu, C. *Angew. Chem. Int. Ed.* **2020**, *59*, 2745.

Gratifyingly, it was possible to obtain pure oxazaborolidines **2.6e** and **2.6f** by recrystallization with relatively good yields (*Figure 2.3*). Unfortunately, for other oxazaborolidines no other tested recrystallization conditions show any sign of forming crystals.

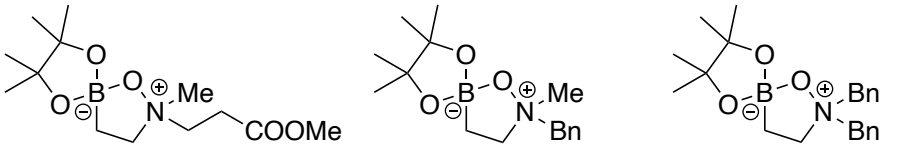


2.6e 95% (56%) **2.6f** 95% (34%)

Figure 2.3: Isolated oxazaborolidines yields via recrystallization

Also, appropriate purification conditions for oxazaborolidines **2.3b**, **2.3e**, and **2.3d** could not be identified (*Figure 2.4*). Although, their structures were proven by crude ^{1}H NMRs. Simple purification via column chromatography without derivatization leads to a mixture of the desired product, contaminated by some of the unreacted hydroxylamine starting material. It also seems that compounds **2.3b**, **2.3e**, and **2.3d** are prone to degrade on silica gel. The same is true for holding these compounds under high vacuum. For compound **2.3b** the isolated yield is 32% while the ^{1}H NMR yield is 80%. However, 32% is the isolated mass of hydroxylamine observed by NMR analysis, after holding this compound for 1 day on high vacuum. We believe that partial amount of hydroxylamine comes from degradation of oxazaborolidine **2.3b**, while other amount can be from respective hydroxylamine which was used as starting material. Unfortunately, changing the ratio of reagents, as it was mentioned previously, lead to significantly lower yields. For compound **2.3e** the isolated yield 27% with 23% of impurities of isolated mass from hydroxylamine. Compound **2.3d** was isolated in form of oxazaborolidine too. Although better result was obtained during its derivatization which was mentioned earlier. While not perfect from a preparative perspective, the samples obtained after purification do support the structure of the assigned

reaction product, and more broadly, both specific isolation procedures (**2.3b** and **2.3e**) or derivatization reactions support that the synthesis of the desired heterocycles was achieved.



2.3b 80% (32%) **2.3e** 97% (27%) **2.3d** 45% (11%)

Figure 2.4: Compounds partially purified via column chromatography

2.3 POSSIBILITY OF COPE-TYPE HYDROAMINATION WITH OTHER BORON SPECIES AND BORA-COPE ELIMINATION

Over the course of this research, we were intrigued to explore other reactivity pathways of these reagents. For example, the ethylene peak sometimes observed upon standing in ^{1}H NMR suggested that bora-Cope elimination can occur. Previous literature search showed that the most detailed and related studies were reported by three independent groups in 1963, 1989 and 1994. However, since that time no further investigation was conducted.

In 1963, Kuhn group reported obtaining BON (Boron Oxygen Nitrogen)-BON heterocycle from hydroxylamine solution and di-*n*-butylborinic acid.[75] A formed crystalline solid structure composition was confirmed by elemental analysis, while molecular weight determination indicated that it is dimer (*Figure 2.5*). Crystals show to be stable in air and easy to recrystalize from organic solvents.

[75] Inatome, M.; Kuhn, L.P. *J. Am. Chem. Soc*. **1963**, *85*, 1206.

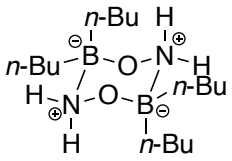
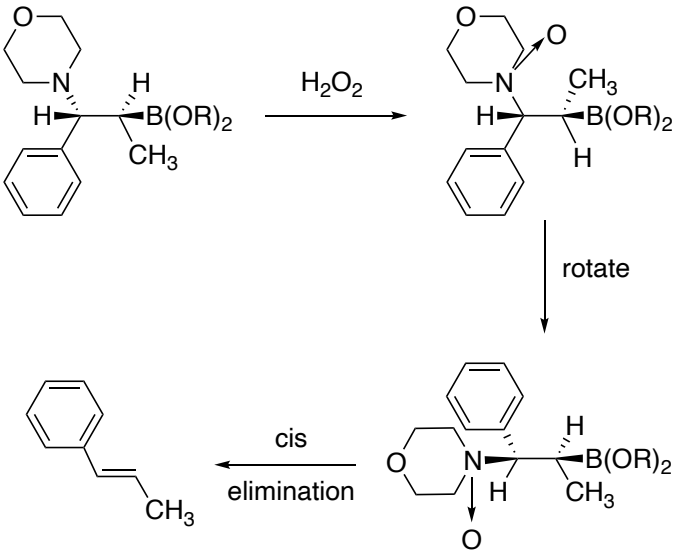


Figure 2.5: BON-BON dimer

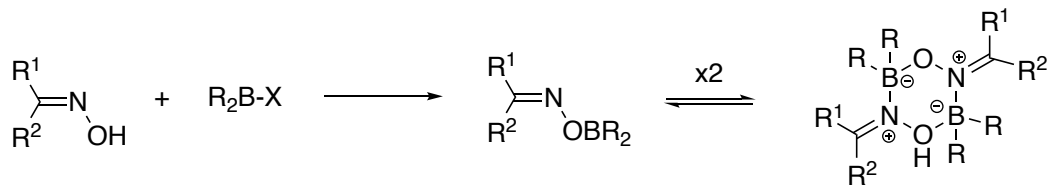
In 1989, Brown group conducted a hydroboration of enamines followed by methanolysis.[76] A product of stereospecific elimination was reported (*Scheme 2.7*). The proposed mechanism for this reaction included coordination of nitrogen atom with an oxygen although no other intermediate were proposed or isolated.



Scheme 2.7: Forming of trans-alkenes via elimination reaction

In 1994, a collaboration of the Kliegel and Rettig groups published more detailed studies on BON-BON structures.[77] A range of oxime diarylborinates were synthesized via reaction of diarylborinic acid or anhydride with an oxime (*Scheme 2.8*).

[76] Singaram, B.; Goralski, C. T.; Rangaishvenvi, M. V.; Brown, H. C. *J. Am. Chem. Soc*. **1989**, *111*, 384.
[77] Kliegel, W.; Nanninga, D.; Riebe, U.; Rettig, S. J.; Trotter, J. *Can. J. Chem.* **1994**, *72*, 1735.



Scheme 2.8: Formation of BON-BON dimer from oximes

Obtained structures of BON-BON heterocycles were confirmed by ^{11}B NMR, IR and X-ray analysis. The ^{11}B NMRs show signals between δ = 6.5 and 8.0 ppm, which is an indicator of tetra-coordinated boron in a solution (^{11}B NMR characteristically shifts briefly discussed further in this chapter). Weakened phenyl ring stretching in IR also suggested that tetra-coordinated phenylboron center is formed.

It was hypothesized that changing the Lewis acidity at boron would allow bora-Cope elimination to occur, and as a result *O*-borylhydroxylamine (NOB-compound) is produced, which can be used further for 1-step aminoboration reaction of alkene would be formed.

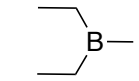
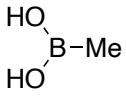
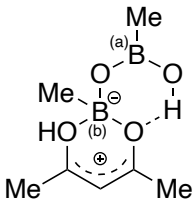
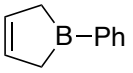
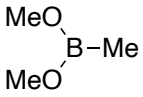
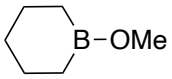
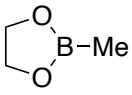
In this part of chapter, the investigation towards the incorporation of different boronates and attempts to generate and trap *O*-borylhydroxylamine are discussed.

It is worth mentioning that ^{11}B NMR spectra were taken to help analyze the reaction outcome. Indeed, the broad range (250 ppm) allows to observe shift differences even with minor electronic or structural changes.[78] ^{11}B NMR is also helpful to differentiate tri- and tetra-coordinated boron species. Replacing neighbor carbon atoms with 1 heteroatom (O or N) leads to significant decrease of shift by approximately 30 ppm, while with two oxygens the boron shift is ~30 ppm (*Table 2.6*).[79] For four coordinated compounds this number reaches ~10 ppm depending on

[78] Schmid, G. *Compr. Het. Chem.* **1996**, *3*, 739.
[79] Wrackmeyer, B. *Nuclear Magnetic Resonance Spectroscopy of Boron Compounds Containing Two-, Three- and Four-Coordinate Boron;* Annual reports on NMR spectroscopy, Academic Press, **1988**, 203.

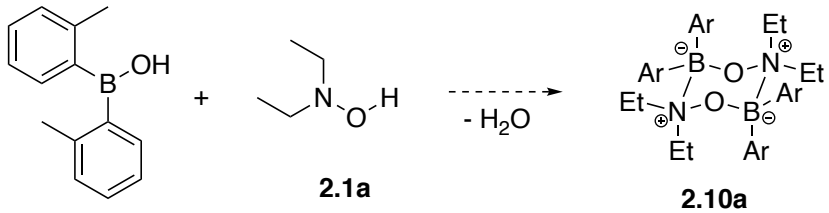
substitutes. For compounds **2.3a-2.3f** and **2.6a-2.6g** which were investigated during a scope at Chapter **2.1**, boron shift ~12 ppm is typical.

Table 2.6: Impact of substituents on ^{11}B NMR shift

	δ ^{11}B, ppm		δ ^{11}B, ppm		δ ^{11}B, ppm
	86.1		31.9		31.8 (a) 7.3 (b)
	86.2		29.5		
	52.2		34.2		

2.3.1 Attempts towards obtaining *O*-borylhydroxylamines and BONBON dimers

Inspired by publication of Kuhn[75] a reaction of borinic acid and hydroxylamine was conducted. Diarylborinic acid **2.9** was chosen as a reactive boron species due to its known air/moisture stability in comparison to alkyl boronic analogues (*Scheme 2.9*). Diarylborinic acids can be easily obtained from aryl magnesium halides with alkylboronate and further purified as crystalline solids after their treatment with 2-aminoethanol.[80] As a nitrogen source, a secondary *N,N*-diethylhydroxylamine **2.1a** was chosen due to its commercial availability.



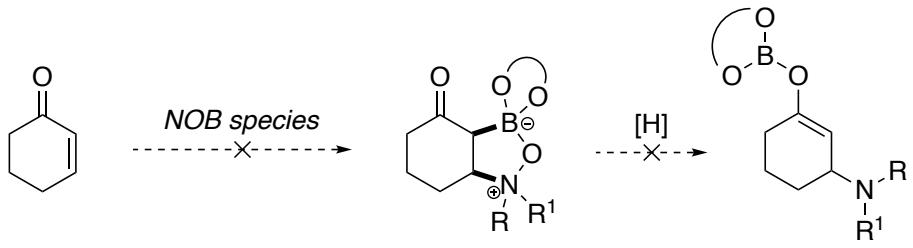
2.9 **2.1a** **2.10a**

Scheme 2.9: Possibility of forming NOB dimer

[80] Chen, X.; Ke, H.; Chen, Y.; Guan, C.; Zou, G. *J. Org. Chem.* **2012**, *77*, 7572.

^{11}B NMR shift 13.24 ppm suggested that tetra-coordinated boron species could be formed. Unfortunately, it was impossible to purify and to further confirm the structure of formed product after an overnight reaction at room temperature in MeOH. Adding molecular sieves to the flask to absorb water did not impact the reaction outcome and same results were obtained.

In further studies, addition of reactive alkynes and alkenes directly to the flask to trap formed products was implemented. Cyclohexenone and cyclopentenone were chosen as model substrates. While the β-position of unsaturated ketone can react with the nucleophilic site of nitrogen atom, boron can be stabilized via its coordination with oxygen and further reduction of compounds would lead to boron migration (*Scheme 2.10*). It was assumed that a large excess of unsaturated ketones would be beneficial for reaction occurrence. Unfortunately, heating at 50 °C overnight in CF_3CH_2OH led to degradation of hydroxylamine and arylborinic acid, although no ketone was consumed. The reaction with such alkynes as bulky 1-octyne and phenylacetylene did not show any sign of reactivity either.

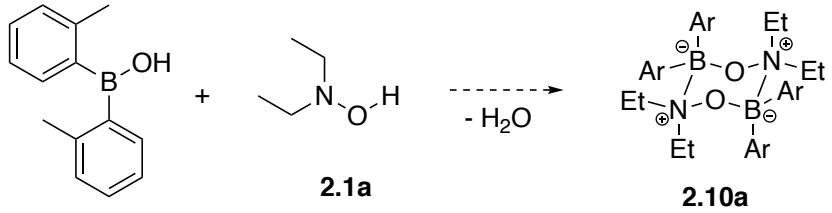


Scheme 2.10: Possibility of trapping NOB compound in presence of alkene

At this stage, it was decided to look for more favourable conditions to form *O*-borylhydroxylamine. A solvent scan was conducted (*Table 2.7*). This time, trimethyl orthoformate was used as a dehydrating agent. All experiments showed that after 6 hours of reaction no borinic acid **2.9** was left. Peaks ranging from 7 to 11 ppm suggested that tetra-coordinated boron species could be formed. However, diethyl peaks from hydroxylamine pointed that the starting material

did not react at all or it was fully converted to another species. Only one triplet and one quartet were observed on ^{1}H NMR in respective area. Also, we did not expect that signals can overlap due to their slightly different neighboring groups.

Table 2.7: Solvent scan of forming BONBON



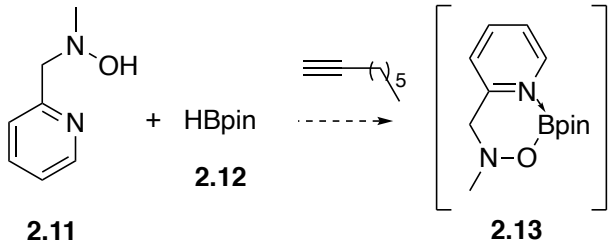
2.9 **2.1a** **2.10a**

Solvent	Boron chemical shift δ, ppm		
	6 hours	22 hours	48 hours
CF_3CH_2OH	**9.1**; 3.2	**8.7**; 3.1	3.5
MeOH	29.2; 43.0	28.7	27.9; 18.7
ACN	29.0; **11.0**; **7.4**; 4.8	30; **7.2**; 4.2	30; **8**; 2.1
Toluene	30.4; 45.0	30.5; 1.5	30.5; 1.4
DCM	30.0	30.3; 1.3	32.4; 20.7; 4.9

(a) Conditions: 1 equiv of boronic acid in solvent (0.5 M), 1 equiv of hydroxylamine, 1.5 equiv of trimethyl orthoformate, stir for 6 h at rt, 22 h (50 ºC) and 48 h (50 ºC)

At this stage, it was proposed that a promising peak from tetra-coordinated boron could be obtained from boron atom coordination with solvents. However, background experiments of mixing acid with respective solvents did not show same tendency. Peaks with δ = 40-45 ppm were observed.

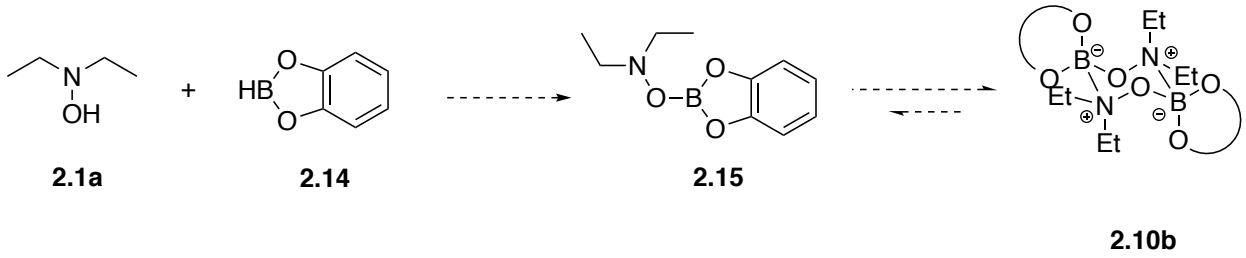
A completely different approach towards *O*-borylhydroxylamine compound synthesis was tested. It was suggested that intramolecular coordination of lone pair of nitrogen atom in the molecule with boron would occur faster than its intermolecular dimerization reaction. This way *O*-borylhydroxylamine **2.13** compound will be stabilized and has different reactivity towards further possible aminoboration reaction. A lone pair from pyridine would allow to form tetra-coordinated boron species and at the same time a thermodynamically favourable six-membered intermediate (*Scheme 2.11*). As a reactive boron reagent pinacolborane **2.12** was used. It was believed that gas evolution instead of the formation of water (as attempted previously) could lead to a different outcome. 1-Octyne was added to the system for further trapping of *O*-borylhydroxylamine **2.13** intermediate. Even though the reaction was run in inert atmosphere and intense bubbling was observed, the hydrolysis of pinacolborane nor any reactivity of the alkyne could observed by NMR spectroscopy.



Scheme 2.11: Intramolecular stabilization of tri-coordinated boron

In further studies, pinacolborane **2.12** was switched to catecholborane **2.14**, as the impact of varying the Lewis acidity of boron was explored. First, as a nitrogen component a commercially available *N,N*-diethylhydroxylamine **2.1a** was chosen. Although the obtained results suggested that a dimer could be formed (*Scheme 2.12*), the right conditions for recrystallization to obtain pure compound were not found. Again, proceeding to the next aminoboration step with

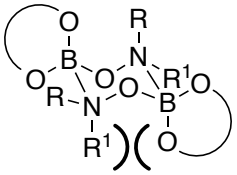
cyclohexenone, unfortunately, did not show any reactivity. After heating at 50 ºC in CF_3CH_2OH for 20 h, only staring material cyclohexenone was observed



2.1a **2.14** **2.15** **2.10b**

Scheme 2.12: Catecholborane reactivity towards secondary hydroxylamine

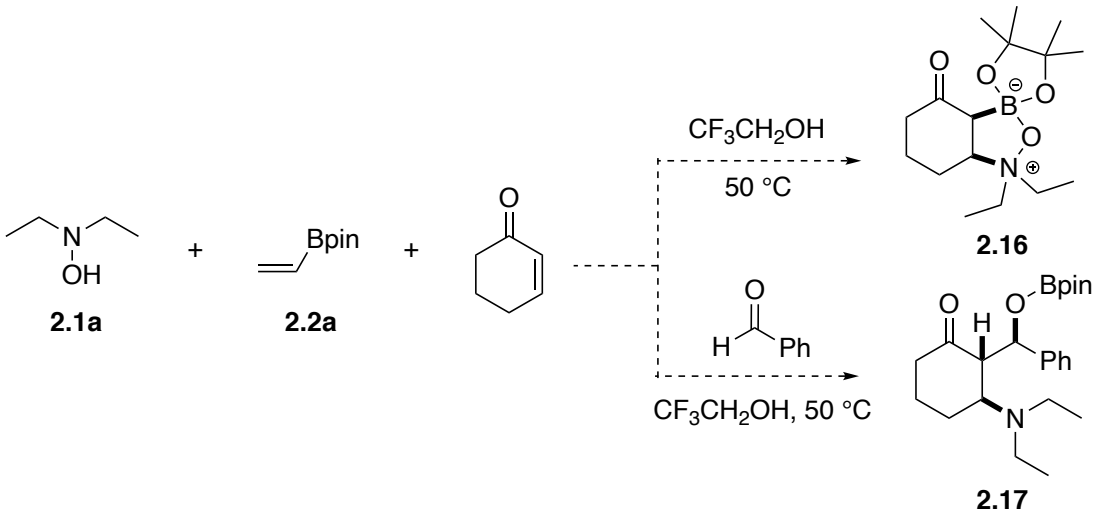
It was then taken into consideration that 1,3-diaxial interactions can prevent efficient formation of dimer **2.10c** (*Figure 2.6*). Switching secondary to a primary hydroxylamine would allow to obtain more stable compound. Unfortunately, after reaction of catecholborane with primary *N*-cyclohexyl-hydroxylamine it was also not possible to conduct a recrystallization.



2.10c

Figure 2.6: Unfavourable steric interactions

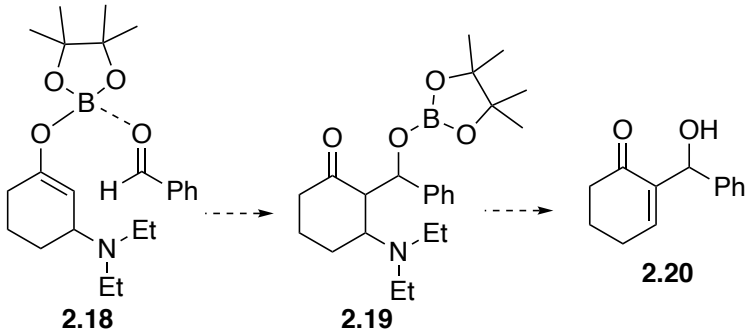
Another experiment which was conducted to trap *O*-borylhydroxylamine is a reaction which was discussed before with vinylboronate derivative. The ethylene peak was observed in spectra after holding compound for a long time on high vacuum, it was assumed that some unstable *O*-borylhydroxylamine can be formed. Direct trapping of *O*-borylhydroxylamine intermediate as one-pot reaction was tested with cyclohexenone in presence or absence of aldehyde (*Scheme 2.13*). Although no reaction with neither ketones no aldehydes occurred.



Scheme 2.13: Reactivity of oxazaborolidines with ketones

An aldehyde was added to the system to perform reaction in a similar manner to Morita-Baylis-Hillman reaction.[81] We expect that an electron-deficient alkene could react with benzaldehyde catalysed by nucleophilic amine (*Scheme 2.14*). Presence of boron also impact the reactivity of species **2.18**. Some aldol reactions of boron enolates (formed by using a trans-metalation sequence) with aldehydes are reported[82] in excellent yields and high diastereoselectivity (d.r. 99:1 – 94:6).[82b] Unfortunately, we were not able to find the right conditions for this reaction to occur.

[81] McDougal, N. T.; Schaus, S. E. *J. Am. Chem. Soc.* **2003**, *125*, 12094.
[82] (a) Lipshutz, B.H.; Papa, P. *Angew. Chem. Int. Ed.* **2002**, *41*, 4580; (b) Beltran, F.; Bergamaschi, E.; Funes-Ardoiz, I.; Teskey, C. J. *Angew. Chem.* **2020**, *132*, 21362.



Scheme 2.14: Attempts of trapping O-borylhydroxylamine species with ketone and aldehyde

2.3.2 Possibility of reaction with other boron esters

Based on the experiments above, it was hypothesized that the efficiency of forming stable tetra-coordinated *O*-borylhydroxylamine compound (both dimers and oxazaborolidines) and their further reactivity depends also on Lewis acidity of the boron. Thus, a larger range of boron derivatives were tested.

It is established that the Lewis acidity of boron is dependent on diol component and the substituents attached to diol, as well as the ring of the size. The relative stability of boronic acid esters was described in 2007 by the Brown group.[83] Boronic acid trans-esterification with various diols was conducted in NMR tubes under inert atmosphere. Experimentally it was found that six-membered boronic esters are thermodynamically more stable than their five-membered analogues (*Figure 2.7*). The Musgrave group proposed that the five-membered ring has more potential energy due to their angle strain, which results in higher difference of energies upon forming tetra-coordinated species.[84] Also, using α-alkyl substituted diols transesterification rate is slower, and thus more stable products are formed. In catechol **2.21** the interactions between oxygen lone pair

[83] Roy, C. D.; Brown, H. C. *J. Organomet. Chem.* **2007**, *692*, 784.
[84] Bowie, R. A.; Musgrave, O. C. *J. Chem. Soc.* **1963**, 3945.

and boron p-empty orbital overlaps with the benzene ring. For boronate **2.25** its high stability can be explained by the steric shielding present.

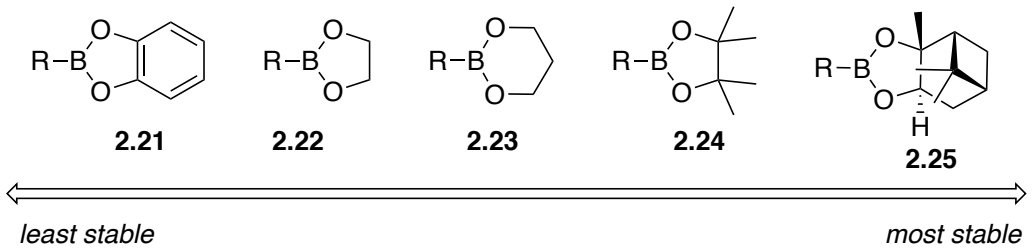


Figure 2.7: Relative stability of boronates

This unique boron feature helps to differentiate between species and could help identify the appropriate stability / reactivity profile. Given this, several attempts to synthesize a broad range of boron derivatives for further screening were conducted (*Figure 2.8*). Although, due to high air sensitivity compound **2.2b**[85] it could not be obtained. In contrast, compound **2.2c** was obtained in small amounts and some reactivity towards hydroxylamine was registered. Further attempts to purify obtained compound **2.2c** via distillation were not successful and we decided not to proceed in this direction due to this challenge, as more synthetically attractive methods exist in parallel. However, it was possible to successfully obtain boronate **2.2d**.

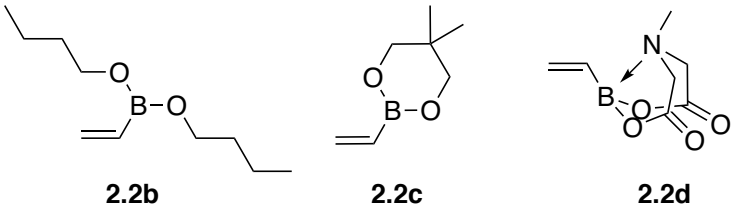


Figure 2.8: Various boron substituted esters

A reaction of hydroxylamine with vinylboronic acid MIDA ester **2.2d** was conducted using the developed conditions for vinylboronic acid pinacol ester (*Figure 2.9*). The obtained ^{1}H NMR

[85] Matteson, D. S. *J. Am. Chem. Soc*. **1959**, *81*, 5004.

yield of the product was 37%. No optimization of this reaction was attempted to allow comparison with the results discussed in section **2.1**. Current reaction strongly suggests that despite dative bonding of boron with nitrogen from MIDA ester, forming of oxygen-boron bonding is more favourable thermodynamically and Cope-type hydroamination can still proceed under mild reaction conditions.

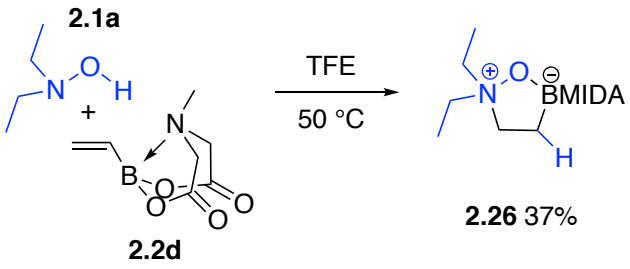
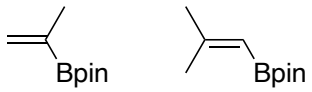


Figure 2.9: Possibility of Cope-type hydroamination with BMIDA substituted species

At this stage, we decided to proceed with commercially available boronates to facilitate the development and use of this reactivity. Some other studies of this reaction are described further in this chapter with catechol species.

2.3.3 Reaction with substituted vinylboronates

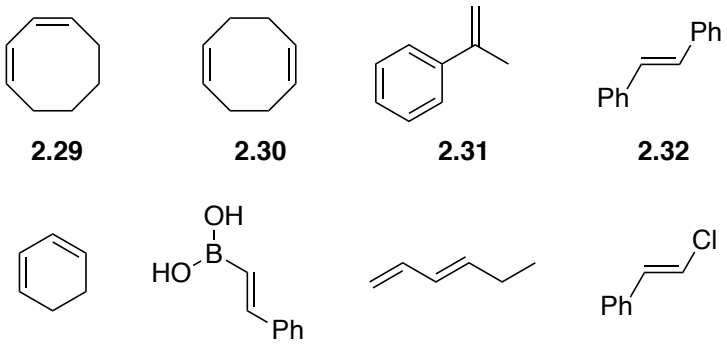
The scope of Cope-type hydroamination was explored with other alkenyl boronates **2.27-2.28** (*Figure 2.10*). Instead of expected oxazaborolidine products, a degradation of starting materials was observed. Increasing the steric bulk and replacing H with methyl did not provide the expected oxazaborolidine. Increasing the reactive ratio to 5 equivalents of hydroxylamine to 1 equivalent of boron substrate versus 1.5:1 did not show any impact on the reaction. Unfortunately, increasing the reaction temperature was not beneficial.



2.27 **2.28**

Figure 2.10: Tested substituted vinylboronates

The results described above are not unexpected, as they are consistent with other results of Cope-type hydroamination of unfunctionalized alkenes.[86] Cope-type hydroamination of alkenes is limited to selected vinylarenes and strained alkenes. A broad range of substituted alkenes do not show any reactivity (*Figure 2.11*). Interestingly, the reaction with boronic acid **2.34** was tested earlier by PhD student Joseph Moran and it was reported that no reaction occurred, likely as this substrate species is not soluble in *i*-PrOH.



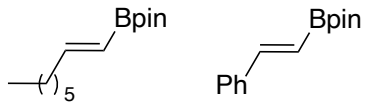
2.29 **2.30** **2.31** **2.32**

2.33 **2.34** **2.35** **2.36**

Figure 2.11: Previously tested unreactive or incompatible substituted alkenes

As those, considering the possibility of bora-Cope type elimination, we decided to test vinylboronates with longer carbon chain **2.37-2.38** to be able to work with more stable alkenes once they are eliminated (*Figure 2.12*). In both cases, only a product of elimination was observed. Based on ^{1}H NMR the yield of obtained 1-octene with primarily tested conditions is 11%, while for styrene it is 4%.

[86] Moran, J. 2009, PhD Thesis, University of Ottawa, Ottawa.

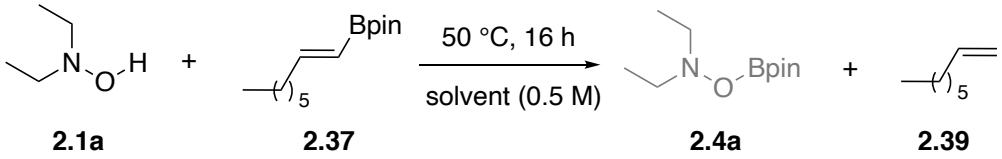


2.37 **2.38**

Figure 2.12: Tested vinylboronates with longer carbon chain

A solvent scan was conducted (*Table 2.8*). Interestingly, the bora-Cope elimination reaction product was only observed in CF_3CH_2OH as solvent. Significant degradation of starting vinylboronate **2.37** was observed in most of the solvents. In MeCN and toluene, the reagent was less prone to degradation. Unfortunately, we were not able to confirm formation of *O*-borylhydroxylamine. Given these shortcomings, no further investigation of this reaction was conducted.

Table 2.8: A solvent scan for bora-Cope elimination[a]

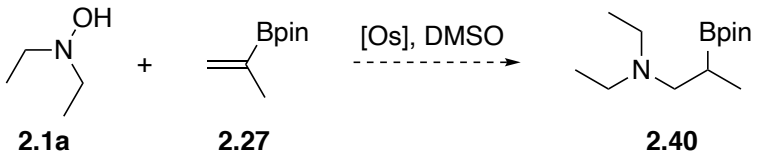


2.1a **2.37** **2.4a** **2.39**

Solvent	Conversion of **2.37**, %[b]	Yield of **2.39**, %[b]
CF_3CH_2OH	59	**11**
EtOH	71	0
t-BuOH	52	0
MeCN	33	0
pentane	62	0
toluene	36	0
THF	78	0
CH_2Cl_2	26	0

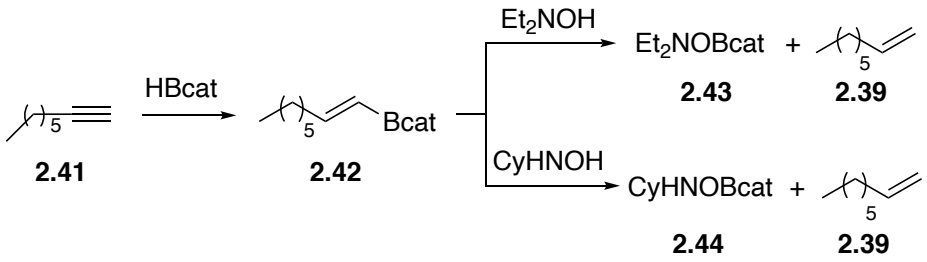
(a) Conditions: boronate **2.37** in solvent (0.5 M), Et_2NOH added, 50 °C, sealed tube, 16 h; (b) ^1H NMR yields using 1,3,5-trimetoxybenzene as internal standard

At this stage we decided to attempt a different approach to shift reaction equilibrium towards the desired product. It was assumed that forming of oxazaborolidine compound followed by immediate reduction in one-pot of generated *N*-oxide can be beneficial. The conditions developed by PhD student in our lab Huy Ly were tested. Indeed, an osmium catalyst can selectively reduce *N*-oxide, while DMSO is used as an reductant in the system (*Scheme 2.15*). Unfortunately, no expected product **2.40** was registered on a spectrum, and only partial degradation of both starting materials **2.1a** and **2.27** was observed.



Scheme 2.15: Aminoboration reaction with further reduction

In further studies, the pinacol subunit **2.37** was switched to catechol **2.42**. An impact of different boron substituent on the reaction was tested. The starting alkene derivative **2.42** for current reaction was obtained from commercially available catecholborane solution (1.0 M in THF) and alkyne **2.41** using conditions described by Zhang group.[87] Using this approach the alkenyl boronate **2.42** was formed in a 65% yield. In a subsequent step, we tested its reactivity towards primary and secondary hydroxylamines (*Scheme 2.16*). In both cases, an elimination of alkene **2.39** was observed. Interestingly, in comparison to the pinacol derived substrate, the alkenyl catecholborane showed more reactivity towards bora-Cope elimination. Product **2.43** was obtained as a precipitate, although optimal conditions for its recrystallization were not found. Appearance of *O*-borylhydroxylamine **2.44** was also very likely based on ^{11}B NMR. Based on ^{1}H NMR alkene **2.39** yield is 24% in both cases. The same yield for alkene was obtained after changing alkyne **2.41** to phenylacetylene.

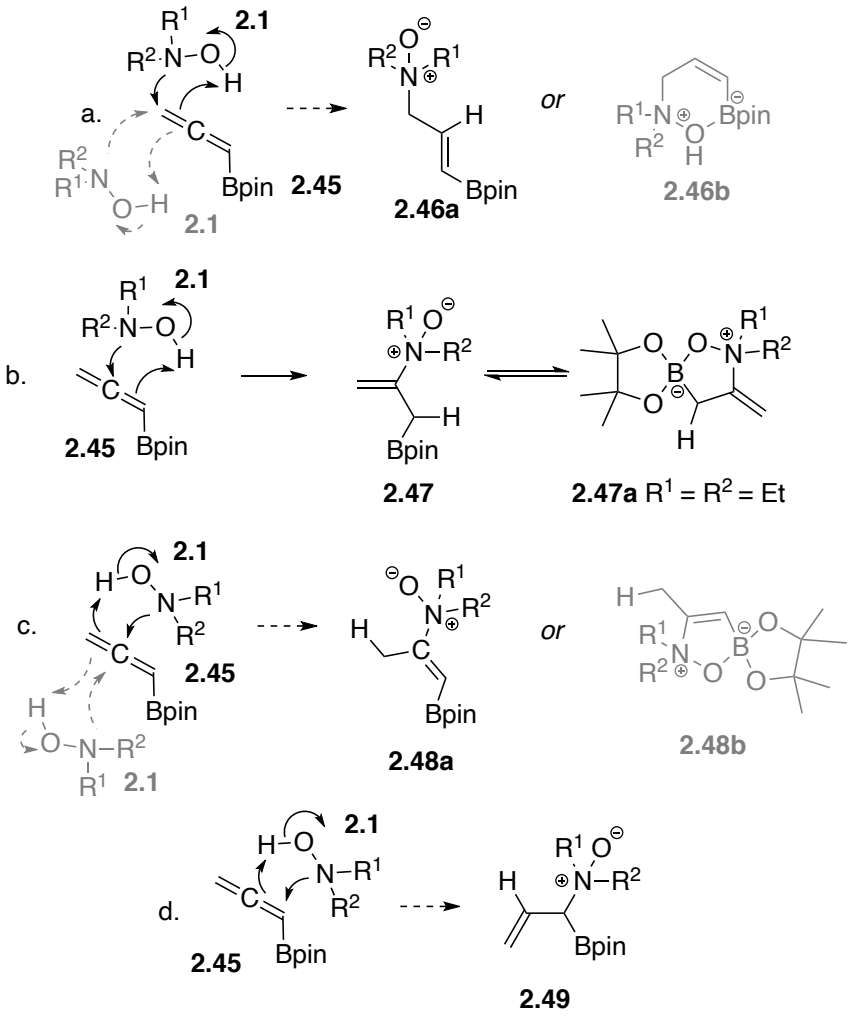


Scheme 2.16: Reactivity of catecholboranes with hydroxylamines

[87] Liao, S.; Porta, A.; Cheng, X.; Ma, X.; Zanoni, G.; Zhang, L. *Angew. Chem. Int. Ed.* **2018**, *57*, 8250.

2.3.4 Reaction with allene

Intermolecular reaction of hydroxylamine was tested with allenylboronic acid pinacol ester. Allenes have two cumulated reactive double bonds which suggests the possibility of six products (*Scheme 2.17*).



Scheme 2.17: Suggested products for hydroamination of allenylboronates

Experimentally, only the formation of **2.47** was observed, reaction shows complete regioselectivity. At the same time, the allenylboronate substrate exhibited lower reactivity in comparison to vinylboronate. Using the optimized conditions for vinylboronates, Cope-type hydroamination with allenylboronate **2.45** result in a modest 30% yield for **2.47a** with *N,N*-

diethylhydroxylamine (*Scheme 2.17*). Also, only traces of products were registered by ^{11}B NMR with primary *N*-cyclohexylhydroxylamine under same conditions. The reaction requires milder temperatures compared to unfunctionalized allenes (room temperature - 50 °C versus 90 - 140 °C).[88] Interestingly, the reaction yield with *N,N*-diethylhydroxylamine **2.1a** at room temperature increased by 5% (*Figure 2.13*). The isolated yield is 17%. No product was observed when CF_3CH_2OH solvent was switched to MeOH. Compatibility of this reaction with other alkyl-substituted allenes were not tested. So, at this stage, no further optimization was conducted. Beyond reaction optimization, further development should include looking for potential synthetical use of such functionalized allylborane reagent.

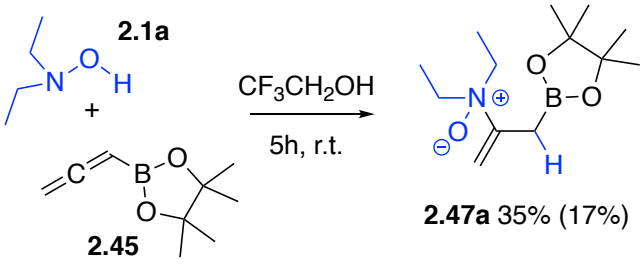


Figure 2.13: Possibility of Cope-type hydroamination with allenes

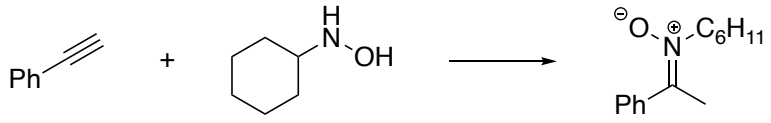
2.4 COPE-TYPE HYDROAMINATION IN FLUORINATED SOLVENT

As was mentioned before, in Chapter **2.1**, a significant different outcome after conducting a solvent scan for hydroamination was noticed. In our early works,[54Error! Bookmark not defined.] it was shown that Cope-type hydroamination proceeds better in alcohol solvents, specifically *i*-PrOH. Herein, the developed Cope-type hydroamination with alkenyl boron species proceeds more efficiently using CF_3CH_2OH solvent (93% yield compared to 59% in *i*-PrOH for substrate **2.3a**).

[88] Moran, J.; Pfeiffer, J. Y.; Gorelsky, S. I.; Beauchemin, A. M. *Org. Lett.* **2009**, *11*, 1895.

At this stage, the conditions described in our paper from 2008[54] were reviewed (*Table 2.9*). No reactivity was observed while the newly developed conditions for boronates were transferred to substrates **2.50** and **2.51** (*Table 2.9, entry 2*). Increasing reaction temperature resulted in product degradation (*Table 2.9, entry 3*). Unfortunately, the same yield was obtained when *i*-PrOH was switched to CF_3CH_2OH. It is worth mentioning that reaction occurs with same outcome at milder temperature (*Table 2.9, entry 4*).

Table 2.9: Reviewing conditions for alkyne hydroamination[a]



2.50 **2.51** **2.52**

entry	equiv **2.50**	equiv **2.51**	solvent	temperature, °C	yield (%)[b]
1[c]	**4.8**	**1**	***i*-PrOH**	**110**	**52**
2	1	1.5	CF_3CH_2OH	50	0
3[d]	4.8	1	CF_3CH_2OH	110	16
4	**4.8**	**1**	**CF_3CH_2OH**	**50**	**52**

(a) Conditions: phenylacetylene **2.50** in solvent (1.0 M), $C_6H_{11}NHOH$ added, sealed tube, 16 h; (b) ^1H NMR yields using 1,3,5-trimetoxybenzene as internal standard; (c) previous conditions;[54] (d) 0.5 M reaction instead of 1.0 M.

No further investigation of reactivity was conducted, as no significant difference was observed.

2.5 CONCLUSION AND FUTURE WORK

Overall, the work in this chapter demonstrates a new route towards oxazaborolidine heterocycles, allowing to obtain several β-aminoboronic acids and their derivatives via a Cope-type hydroamination reaction.

In comparison to unsubstituted alkene species, intermolecular Cope-type hydroamination with boron reagents occurs under mild reaction conditions (temperature 50 °C versus above 90 °C for unsubstituted species) with yields up to 95%.

However, important challenges remain associated with isolation of the reaction products. Even though different methods for isolation of products were conducted, no general procedure was found. Probably, it can be credited to the unique structure of oxazaborolidines and some further isolation problems associated with boron species. More importantly, new reactivity towards bora-Cope type elimination was discovered and accounts for the currently limited scope of the reaction.

Future work includes studying intramolecular Cope-type hydroamination reactivity with boron containing reagents. This possibly should streamline the scope of more synthetically stable Cope-type hydroamination products, and the relative ease observed for the elimination reaction suggests that intramolecular reactivity should be possible under mild reaction conditions.

CHAPTER 3: HYDROXYLAMINE SYNTHESIS

To obtain a broad range of NOB-heterocycles, different hydroxylamines were required as a starting materials. In this Chapter, known methods of hydroxylamine synthesis and their limitations are first described. Then, a new practical strategy to obtain secondary hydroxylamine is presented. Finally, scope and purification problems of this new method are discussed.

3.1 BACKGROUND ON SYNTHESIS OF HYDROXYLAMINES

Synthetic methods to obtain hydroxylamines can be divided to two main categories (*Figure 3.1*). The first category includes substitution (alkylation, arylation), hydrolysis and addition reaction.[89] Hydroxylamines have an ambident nucleophile nature and can react to form *N*- or *O*-alkylated/arylated products (*Figure 3.1a*). Hydrolysis is usually used as a final step of reaction with nitrones, oximes or hydroxamic acid (*Figure 3.1b*). Addition reaction on C=C bond are Cope-type hydroamination reaction, which was discussed earlier, and C=N and N=O bond reaction with an organometallic (*Figure 3.1c*).

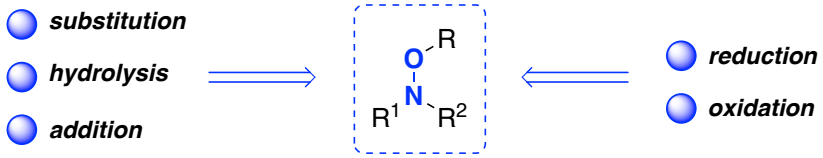
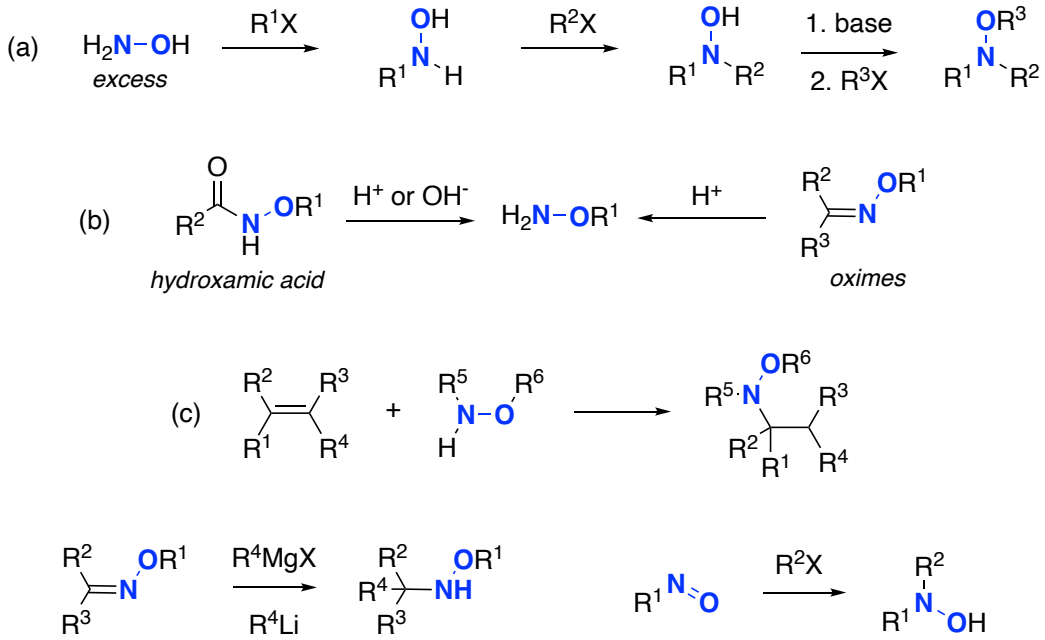


Figure 3.1: Different type of reactions for hydroxylamine synthesis

[89] Melman, A. *The Chemistry of Hydroxylamines, Oximes and Hydroxamic Acids*; John Wiley & Sons, Ltd.: Southern Gate, **2008**, 117.

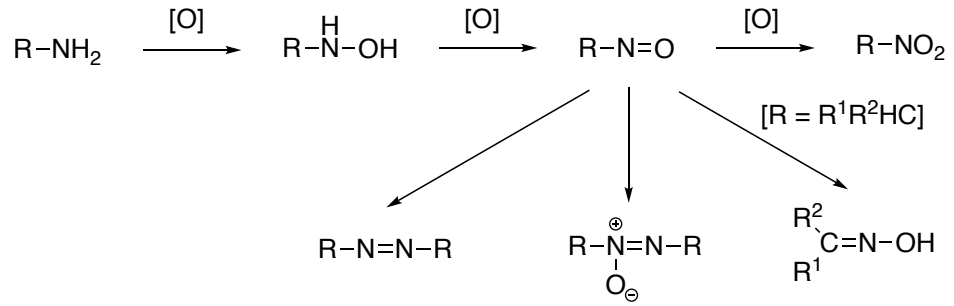
Other category is oxidation and reduction reactions. By working at a different oxidation state, the hydroxylamine group can be synthesised from different functional groups such as amines or nitro groups for example.



Scheme 3.1: Summary of common hydroxylamine synthesises

In this Chapter, a practical oxidative method is reported. Consequently, herein the attention will be focused on oxidation reactions forming hydroxylamines.

Oxidation of an amino group is synthetically a very attractive method due to relatively cheap and broad commercial availability of amines. The main challenges associated with reaction are overoxidation and low yields of the product. For primary amines overoxidation is even more a problem as it can easily go further to nitroso and nitro compounds (*Scheme 3.2*).

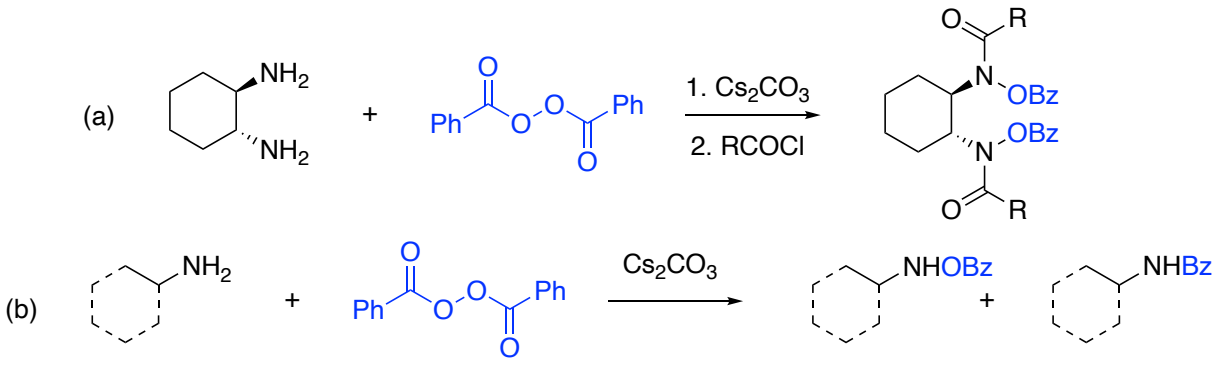


Scheme 3.2: Some plausible overoxidation products

In early studies, first attempts of amines oxidation were performed with peroxides or peroxide derivatives: hydrogen peroxide,[90] benzoyl peroxide[91] and *m*CPBA.[92] Interestingly, the reported products for the first two reagents were dialkylated amines[90] and oximes,[91] respectively. *m*CPBA reagent worked better,[9292] however the isolated yield was fair (below 50%).

Nowadays, all these three reagents are used for amine oxidation. After improving the primary conditions, an adduct of hydrogen peroxide with urea in presence of sodium tungstate can oxidize primary amines to their parent hydroxylamines with yields from 65% to 80%.[93] Reaction with benzoyl peroxide showed good reactivity on 1,2-diamines and then was extended to primary amines (*Scheme 3.3*).[94] However, this reaction conditions require mild benzoyl deprotection conditions. There are some additional examples where *O*-protection is used to prevent overoxidation of hydroxylamines. However, in such cases the hydroxylamine acts as intermediate and is not isolated.[95]

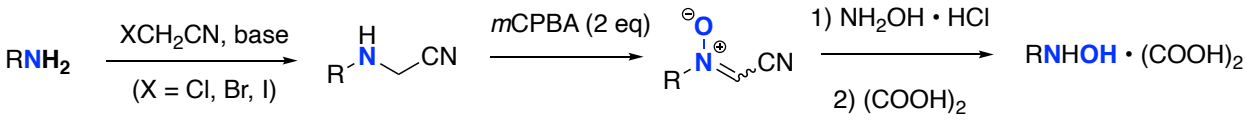
[90] Mammlock. L.; Wolffensteion. R. *Ber. Dtsch. Chim. Ges*. **1901**, *34*, 2500.
[91] Denney, D. B.; Denney D. Z. *J. Am. Chem. Soc.* **1960**, *82*, 1389.
[92] Beckett, A. H.; Salami, M. A. *J. Pharm. Pharmacol*. **1972**, *24*, 900.
[93] Heydari, A.; Ashanzadeh, S. *Adv. Synth. Catal*. **2005**, *347*, 1223.
[94] Benarjee, A.; Yamamoto, H. *Chem. Sci.* **2019**, *10,* 2124.
[95] Phanstiel, O.; Wang, Q. X.; Powell, D. H.; Ospina, M. P.; Leeson, B. A. *J. Org. Chem.* **1999**, *64*, 803.



Scheme 3.3: Oxidation of amines with benzoyl peroxide

The most common approach for the oxidation of amines is using *m*CPBA as reagent. The reaction proceeds with secondary amines and results in the corresponding hydroxylamines. If *m*CPBA reagent is in excess, then nitroxyl radical is formed.[96]

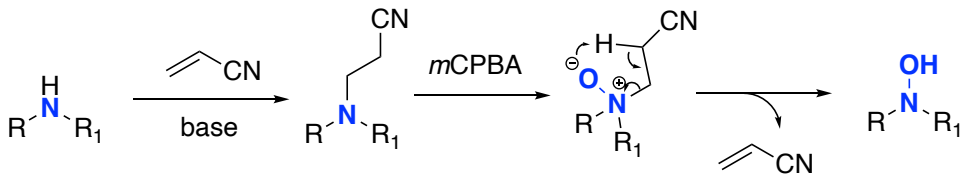
Synthesis of *N*-monoalkylhydroxylamines using *m*CPBA is more challenging. Direct oxidation with *m*CPBA leads to nitro and nitroso compounds. These species can be further reduced, although this can cause a loss of stereochemical information. Using 2 equivalents of *m*CPBA leads to oximes with conversion >90%.[97] In 2000, Fukuyama group published a new approach to solve this problem.[98] The primary amine can be converted to a secondary amine by monocyanomethylation reaction (*Scheme 3.4*). Oxidation and removing the cyanomethyl unit to primary hydroxylamine leads affords products which can be isolated in good yields (55% - 89% over three steps).



Scheme 3.4: Three-step protocol for primary hydroxylamine synthesis

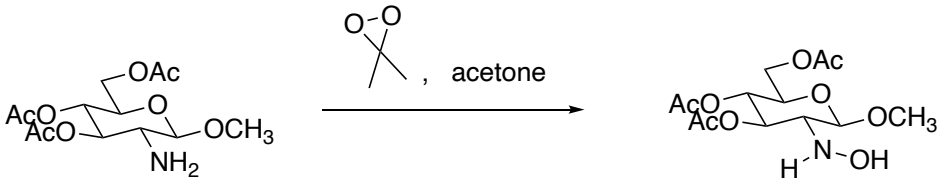
[96] Rauckman, E. J.; Rosen, G. M.; Rosen, G. M.; Abou-donia, M. B. *Synt. Commun.* **1975**, *5*, 409.
[97] Patil, V. V.; Gayakwad, E. M.; Shankarling, G. S. *J. Org. Chem.* **2016**, *81*, 781.
[98] Tokuyama, H.; Kuboyama, T.; Amano, A.; Yamashita, T.; Fukuyama, T. *Synthesis*, **2000**, *9*, 1299.

Another approach was reported by the O'Neil group.[62] In this approach, secondary hydroxylamines can be obtained through selective Cope elimination of tertiary amine *N*-oxides. This reaction works with cyclic and acyclic systems and reported yields vary from 72% to 96%. These reaction conditions show one of the bests results. Although, from work in our group it is important to note that it is usually difficult completely remove the acrylonitrile by-product.



Scheme 3.5: Obtaining secondary hydroxylamines via Cope-elimination reaction

Oxidation of secondary amines also can be performed with dimethyl-dioxirane with high yields (66-96%).[99] Similar conditions are also applicable to oxidation of sugars (*Scheme 3.6)*.[100] The main downside of this reaction is the safety aspects inherent to the synthesis of DMDO and its further high reactivity.



Scheme 3.6: Oxidation of sugars with an amino group

Later, the oxidation of primary and secondary amines with precursor to dimethyl-dioxirane – OXONE over silica gel was performed.[101] The authors proposed a surface mediated reaction (*Figure 3.2a*) and the overoxidation is prevented by absorption of hydroxylamine to the associate

[99] Murray, R. W.; Singh, M. *Synth. Commun.* **1989**, *19*, 3509.
[100] Wittman, M. D.; Halcomb, R. L.; Danishefsky, S. J. *J. Org. Chem*. **1990**, *55*, 1981.
[101] Kropp, P. J.; Fields, J. D. *J. Org. Chem*. **2000**, *65*, 5937.

sites (*Figure 3.2b*). The reaction scope is limited to only seven substrates, although one of them is selective treatment of Boc-protected L-lysine.

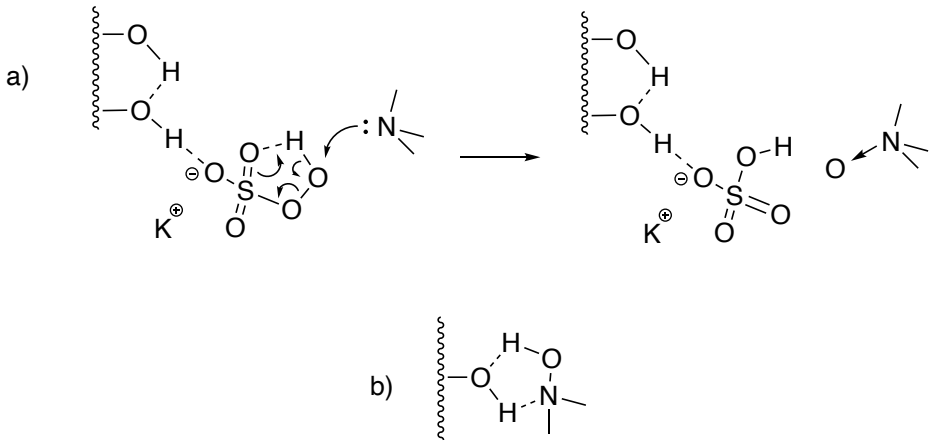
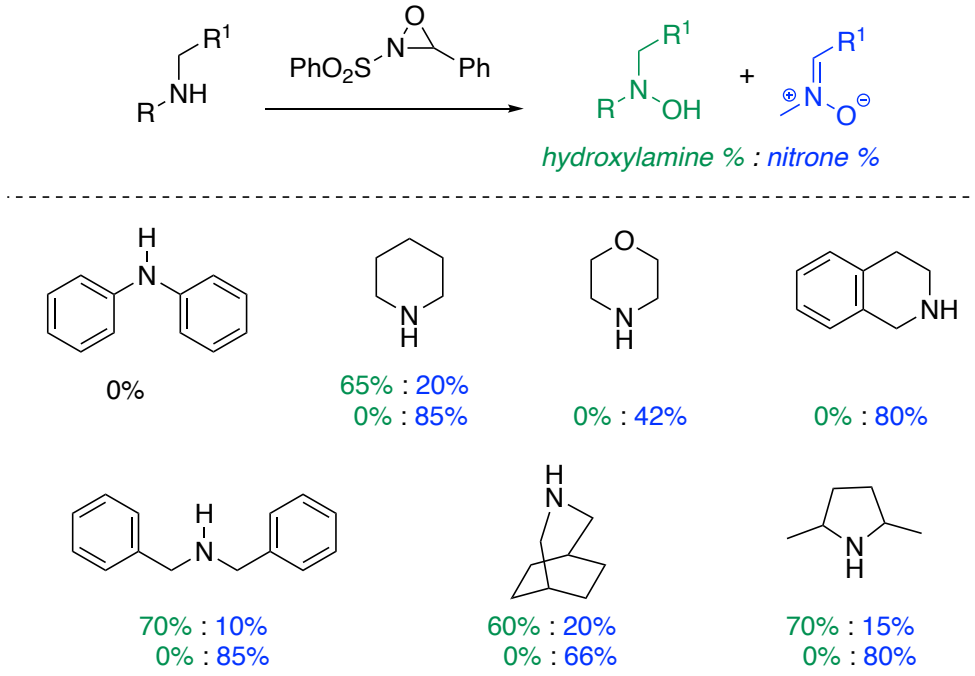


Figure 3.2: Binding to the associated sites of silica gel

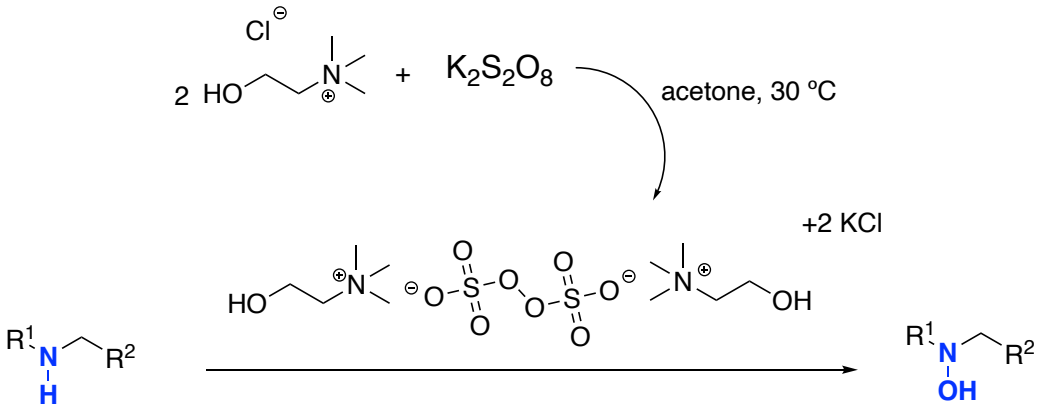
Davis' Reagent is a lesser used oxidant for oxidation of secondary amines to hydroxylamines and in some cases a significant amount of nitrone if formed (*Table 3.1*).

Table 3.1: Scope of amine oxidation with Davis' Reagent[a]



[a] top row 1:1 amine : oxidant ratio; bottom row 1:2 amine : oxidant ratio

The preparation of *N,N*-disubstituted hydroxylamine from amine can be conducted with oxidizing task-specific ionic-liquid.[102] The authors were inspired by Shankarling's group work, where alcohols were selectively oxidized to aldehydes without overoxidation to acid.[103] Choline peroxydisulfate shows to be a good alternative to other oxidants and can be used for transforming amines to hydroxylamines (*Scheme 3.7*). Reaction yields for this green reaction vary from 64% to 96%.



Scheme 3.7: Preparation of secondary hydroxylamines by choline peroxydisulfate

In general, oxidation methods of amine to hydroxylamine are very limited due to overoxidation of the product. Because of this, a new practical method which would allow to synthesise hydroxylamines was developed.

3.2 NEW ROUTE TO SYNTHESIS OF HYDROXYLAMINES

In this part of project, I was working with PhD candidate Meredith Allen. She developed the conditions for oxidation of secondary amines to hydroxylamines. I was working on oxidation of primary amines.

[102] Banan, A.; Valizadeh, H.; Heydari, A.; Moghimi, A. *Synlett*, **2017**, *28*, 2315.
[103] Gadilohar, B. L.; Kumbhar, H. S.; Shankarling, G. S. *Ind. Eng. Chem. Res*. **2014**, *53*, 19019.

We were challenged to come up with new practical oxidative method of amines to hydroxylamines, as known methods generally lack efficiency and require further development to be practical.

As an oxidant, the more stable form of hydrogen peroxide, a complex with urea (UHP, urea - hydrogen peroxide) was tested. This is a mild, inexpensive green oxidant that is also a solid. In some works, it is suggested that the electrophilic activation of hydrogen peroxide occurs in fluorinated alcohols (*Figure 3.3*) and these solvents facilitate other oxidation reactions such as alkene epoxidation and sulfide oxidation to sulfoxides.[104] As such, 2,2,2-trifluoroethanol (TFE) and hexafluoroisopropanol (HFIP) solvents were preliminary selected for reaction development.

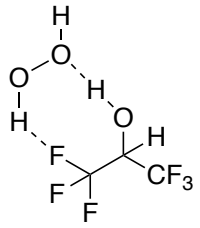
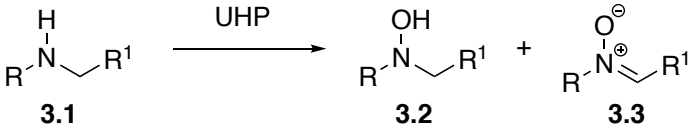


Figure 3.3: Electrophilically activated hydrogen peroxide

First attempts to oxidize different secondary amines **3.1** with UHP looked promising. Besides a fair amount of hydroxylamine **3.2**, a significant amount of nitrone **3.3** was formed (*Scheme 3.8*).



Scheme 3.8: Oxidation of secondary hydroxylamines with UHP

During the initial optimization of the reaction several key issues were important to address:

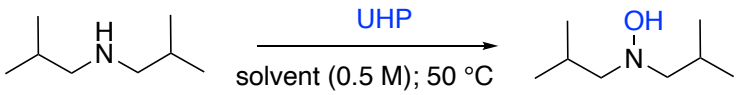
[104] (a) Neimann, K. and Neumann, R. *Org. Lett.,* **2000**, *2*, 2861; (b) Llopis, N.; Gisbert, P.; Baeza, A. J. *Org. Chem*. **2020**, *85*, 11072; (c) Legros, J.; Crousse, B.; Bonnet-Delpon, D.; Bégué, J. -P. *Eur. J. Org. Chem*. **2002**, *19*, 3290.

1. preventing overoxidation;
2. mild conditions to enable functional group tolerance;
3. simple isolation method.

Using diisobutylamine **3.1a** as a model amine and UHP as a source of oxygen, we started by evaluating the optimal reagents ratio. Results obtained with 1:1.2 and 1:3 *oxidant : amine* ratio suggested that a larger excess of amine is required.[105] Gratifyingly, changing the ratio to 5 equivalents of amine reduces the overoxidation product even more and at the same time increases hydroxylamine yield *(Table 3.2, entry 3)*. Important solvent effects were observed. The reaction showed to be less efficient under room temperature (*Table 3.2, entry 6*). Also, hydrogen peroxide showed to be less efficient then UHP.

[105] Allen, M. M. PhD thesis, 2022, University of Ottawa.

Table 3.2: Optimization of secondary hydroxylamine synthesis[a]



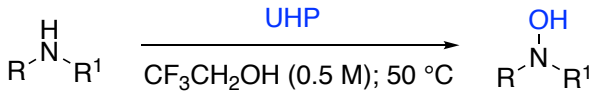
3.1a **3.2a**

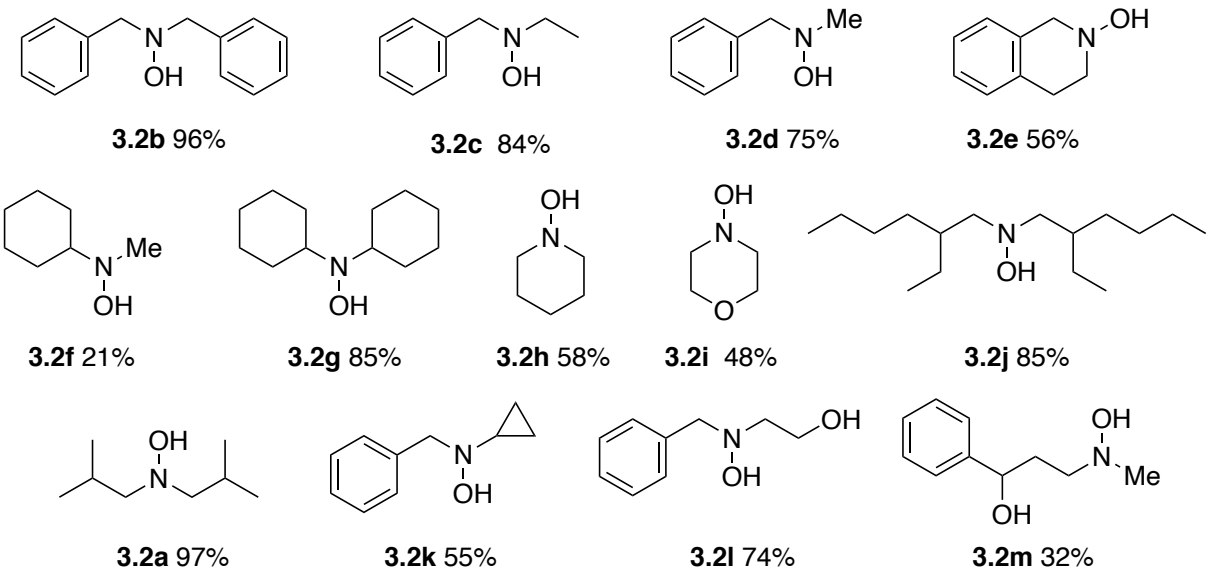
entry	equiv UHP	equiv 3.1a	solvent	yield (%)[a]
1	1.0	3.0	CF_3CH_2OH	86
2	1.0	3.0	$(CF_3)_2CHOH$	36
3	**1.0**	**5.0**	**CF_3CH_2OH**	**99**
4	1.0	5.0	$(CF_3)_2CHOH$	56
5	1.0	5.0	CH_3OH	38
6[b]	1.0	5.0	CF_3CH_2OH	74
7[c]	1.0	5.0	CF_3CH_2OH	86

(a) Conditions: UHP in solvent (0.5 M), amine added, stir at 50 °C, sealed tube, 16 h; (b) ^{1}H NMR yields using 1,3,5-trimetoxybenzene as internal standard; (c) reaction stirred at rt instead of 50 ºC; (d) 1.0 equiv of 30% H_2O_2 in H_2O used instead of UHP.

With a high yielding oxidation method, showing minimal by-product formation for the model hydroxylamines, a reaction scope and group tolerance for secondary hydroxylamine was evaluated. A secondary hydroxylamine scope is presented in *Table 3.3*.

Table 3.3: Secondary hydroxylamine scope[ab]





3.2b 96% **3.2c** 84% **3.2d** 75% **3.2e** 56%

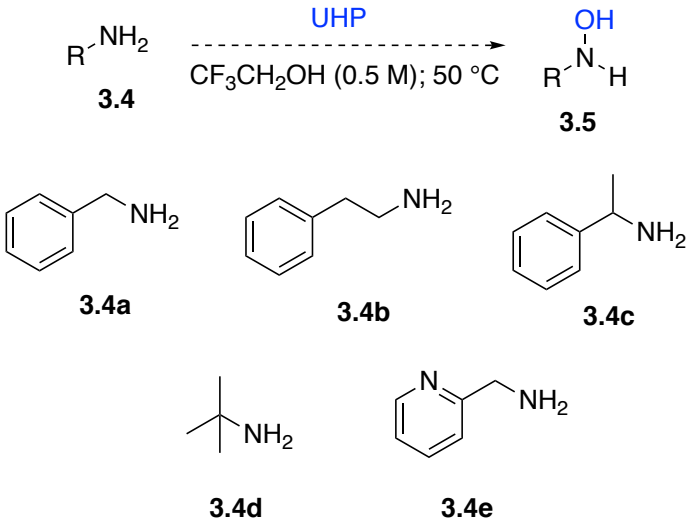
3.2f 21% **3.2g** 85% **3.2h** 58% **3.2i** 48% **3.2j** 85%

3.2a 97% **3.2k** 55% **3.2l** 74% **3.2m** 32%

(a) Conditions: 1 equiv UHP in CF_3CH_2OH(0.5 M), 5 equiv amine added, stir at 50 °C, sealed tube, 16 h; (b) ^{1}H NMR yields using 1,3,5-trimethoxybenzene as an internal standard.

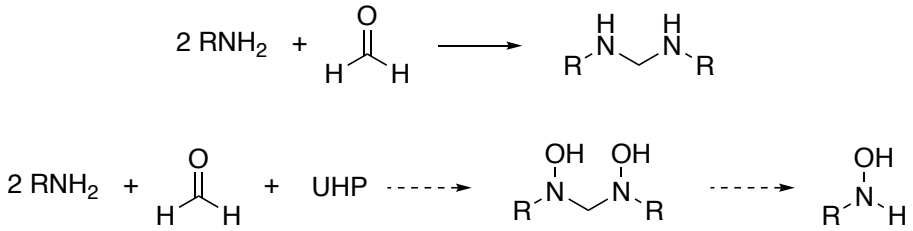
After these studies, optimized conditions were tested for the synthesis of primary hydroxylamines. The compounds which were investigated are shown in *Table 3.4*. Unfortunately, no hydroxylamine was observed. Instead, oxime, azo-compounds and other overoxidation products were formed. A solvent scan was conducted for amine **3.4e** as a model substrate using DCM, EtOAc, acetone and THF solvents, but no desired product was observed. No further modifications of reaction conditions were conducted, as primary amines are known to be more problematic to oxidize to hydroxylamines when compared to secondary amines.[89]

Table 3.4: Primary hydroxylamine testing[a]



(a) Conditions: 1 equiv UHP in CF_3CH_2OH (0.5 M), 5 equiv amine added, stir at 50 °C, sealed tube, 16 h.

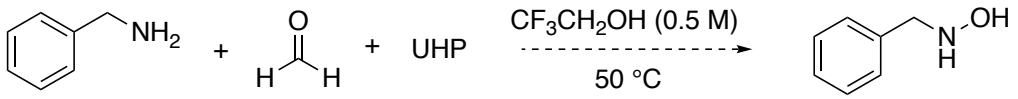
Furthermore, a different approach was tried for the transformation of primary amines into hydroxylamine. Inspired by the work of Fukuyama[98] previously mentioned, we thought that formation of secondary amine from the correspondent primary amine would allow us to oxidize it to the hydroxylamine and turn it into the primary hydroxylamine. For example, methylenebishydroxylamine shown in *Scheme 3.9* could be formed by adding of formaldehyde to amine followed by UHP oxidation.



Scheme 3.9: An approach for oxidation of primary amines with UHP oxidant

A reaction outcome was tested on amine **3.4a** used as a model substrate. A diamine was expected to be formed by using 2 equiv. of amine with 1 equiv. of formaldehyde in aquas solution (*Table 3.6, entry 2-3*). To oxidize the newly formed diamine, the same amount of oxidant as for oxidation of secondary amine was added. However, as the formed amine contains two amino groups, the ratio of biamine was tested: oxidant is 1.5:1 and 2.5:1 (*Table 3.6, entry 1-3*). Unfortunately, this strategy was not successful. Current method did not show any promise and no further modifications were conducted.

Table 3.5: Formation of primary hydroxylamine from amine



3.4a *aldehyde* **3.5a**

entry	equiv **3.4a**	equiv aldehyde	equiv UHP	yield in 16 h, (%)[b]	yield in 48 h, (%)[b]
1	3	1.5 [c]	1	0	0
2	3	1.5	1	0	0
3	5	2.5	1	0	0

(a) Conditions: amine **3.4a** in CF_3CH_2OH (0.5 M), formaldehyde, UHP added, sealed tube; (b) ^1H NMR yields using 1,3,5-trimetoxybenzene as internal standard; (c) paraformaldehyde (comes as precipitate)

3.3 EFFORTS TOWARDS ISOLATION OF THE PRODUCT

On developing of conditions for purification I was working with Honors student from our lab – Daniel Barriault. Early attempts to investigate the necessary conditions are discussed in this part. The final conditions and all supported results could be found in Daniel's thesis.[106]

Once the optimal reaction conditions for the oxidation to form secondary hydroxylamines were identified, we were challenged to isolate pure hydroxylamine from the reaction mixture. Urea, the excess amount of amine present and traces amounts of nitrone needed to be removed. Initial attempts suggested that hydroxylamines and amines form strong hydrogen bonds, and that consequently the isolation would not be as simple as initially envisioned.

Firstly, the reaction mixture was transferred to a round bottom flask and evaporated. After addition of diethyl ether to the flask, a significant amount of precipitate was formed. Urea is known to be insoluble in diethyl ether. So, it was expected that all urea was removed from the mixture at this step. Precipitate was filtered and dissolved in ethanol for further testing it with TLC and conformation that no other compounds except urea had been removed. Indeed, TLC analysis confirmed that amine, hydroxylamine and nitrone were all still in the mixture, while the urea was removed.

The easiest way to remove the amine would be to selectively convert it to an amine salt. The pK_a difference between secondary amine and hydroxylamine is around 4-5 units (pK_a(*i*-Pr$_2$N$^+$H$_2$) = 11.05 vs pK_a(HON$^+$H$_3$) = 5.96 in water) and this effectively allows to protonate only the amine in the presence of hydroxylamines. Several approaches were investigated to identify the most promising separation strategy. (*Figure 3.4*).

[106] Barriault, D. 2022, Honors Thesis, University of Ottawa.

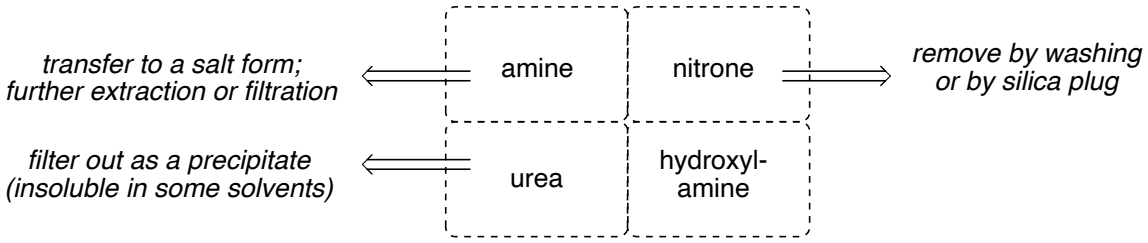


Figure 3.4: Possible way to remove by-products

The first idea tested was to extract an amine salt from a mixture by liquid-liquid extraction (dissolve a salt in an aqueous phase, while hydroxylamine stays in the organic phase).

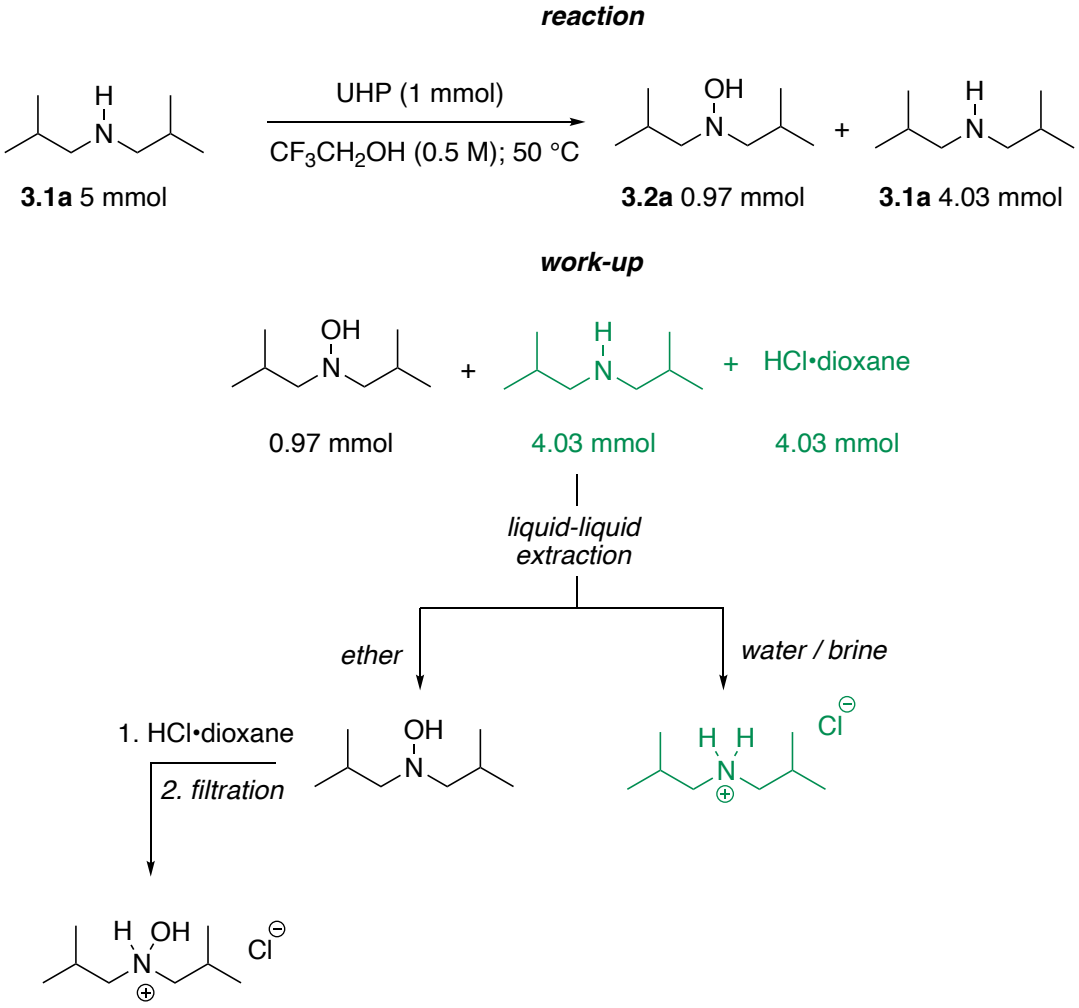
To protonate the amine, an HCl•dioxane solution was used. The reason for choosing this acid was a broad range of reported amine hydrochloride salts.

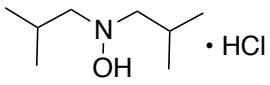
The primary procedure for an isolation of the hydroxylamine was:

1. Concentrate a sample
2. Addition of ether (to remove urea)
3. Addition of *x* eq of HCl·dioxane solution, where *x* stands for = 5 – reaction yield (to protonate all amine which did not react)
4. Stirring for 15 minutes (to protonate all amine)
5. Diluting solution with ether
6. Extraction with brine
7. Drying of a sample using Na_2SO_4, filtering, further evaporation
8. Dilute a sample with hexane
9. Addition of *x* eq of HCl·dioxane (to protonate all hydroxylamine)
10. Filter and wash precipitate with hexane
11. Collect solids

As model substrate diisobutylamine **3.1a** was tested (*Table 3.6*).

Table 3.6: Efficiency of removing an amine salt by liquid-liquid extraction



Compound	^{1}H NMR yield, %[a]	Isolated yield, %	Impurities, %
	99	31	17

[a] using 1,3,5-trimetoxybenzene as internal standard

Unfortunately, the isolated yields of hydroxylamine salt were lower than ^{1}H NMR yield by 68%. What is more, the final isolated product was not clean and contained some traces of amine salt, as judged by ^{1}H NMR analysis. An estimation of purity of the product is shown in *Table* 3.6.

The high boiling points of the amine **3.1a**, 140 ° C, excluded the possibility that partial amount of amine is lost during a solvent evaporation, and it may lead to undesirable hydroxylamine

3.2a protonation. As an extra precaution, steps 1 and 3 were reversed to protonate the excess amine before evaporating the solvent. However, it was not beneficial, and same results were obtained.

The results obtained suggested that current amine isolation procedure was not efficient enough.

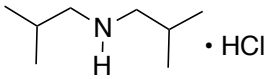
At this stage, the possibility of removing the amine salt via liquid-liquid extraction was further tested. The solubility of hydroxylamine and amine hydrochloride in various solvents was investigated.

Amine salts are known to be polar compounds. Their solubility in solvents can be explained by presence of negatively and positively charged ions. Cations and anions impact the formation of hydrogen or donor-acceptor bonds in a solution. In solvents of low polarity, amine salts are present primarily in an undissociated state and the solubility should generally be poor. However, it is also stated that some organic solvents lead to increase of solubility of a salt.[107] Thus, selecting a suitable solvent combination in which amine salts are fully soluble selectively in one of the phases was conducted.

As a model substrate, diisobutylamine hydrochloride salt **3.6a** was chosen. Firstly, the salt's solubility in different organic solvent was scanned (*Table 3.7*). Four different solutions of salt with equal concentrations (0.5 M) were prepared. A salt was formed in-situ by mixing 1 equiv. of amine with 1 equiv. of HCl. After stirring for an hour, formed amine salts were soluble in ethyl acetate. These solvents showed to be inappropriate for further liquid-liquid extraction, as no solubility of amine salt in the organic phase was desired.

[107] Shmidt, V. S.; Shesterikov, V. N.; Mezhov, E. A. *Russ. Chem. Rev.* **1967**, *36*, 946.

Table 3.7: Solubility of amine salt in various organic solvents[a]

	MTBE	EtOAc	Petr. ether	Diethyl ether
 **3.6a**	low	good	low	low

[a] only qualitative evaluation using TLC was conducted

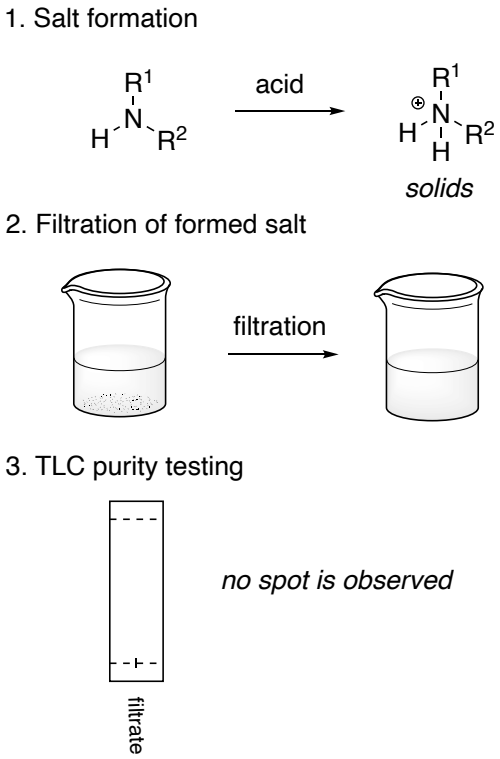
Further, in liquid-liquid extraction only MTBE, diethyl ether and petroleum ether were tested as organic phases, while distilled water, buffers Na_2HPO_4/NaH_2PO_4 with pH around 5.8 and 7.0 were used as aqueous phases. A respective hydroxylamine was added to the system. Unfortunately, none of the experiments worked. Multiple washes with the aqueous phases were not efficient to fully remove all amine salt. Neither was multiple washes with the organic phase. After separation via liquid-liquid extraction and spotting every fraction by TLC in every case both spots appeared (one from hydroxylamine and one from amine salt), even though it looked like almost no salt was dissolved in organic phase for diethyl ether and petroleum ether. No yield comparison was conducted, and current experiments were limited to TLC observation.

These preliminary results suggested that liquid-liquid separation is not efficient. Some amount of formed hydroxylamine is partially soluble in water and in aqueous buffer solutions with pH 5.8 and 7.0. What is more, removing of amine salt is also not efficient.

Further an idea to screen solubility of various amine salts in ether solvent was implemented. Previous results suggested that efficient formation of an insoluble amine salt in an organic solvent can be beneficial. Further removal by filtration would simplify the mixture and would allow to prevent partial loss of hydroxylamine during extraction.

Dissolving of an amine salt in organic solvent is also known to depend on the polarity of the molecule. The polarity of the molecule can be controlled by changing the negatively charged anion to form a different salt.[107]

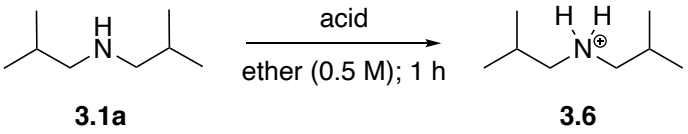
Thus, different acids were scanned on the same model substrate, diisobutylamine. This time no hydroxylamine was added. The efficiency of removing a salt by further filtration was investigated (*Scheme 3.10*).



Scheme 3.10: Overview of general strategy to remove amine

To perform this, 1 equiv. of an amine **3.1a** was dissolved in ether, followed by adding of 1 equiv. of acid. After stirring for one hour, a significant amount of precipitate was formed in a flask with hydrochloric and sulfuric acid. All precipitates were filtered, and a filtrate was checked by TLC analysis (*Table 3.8*).

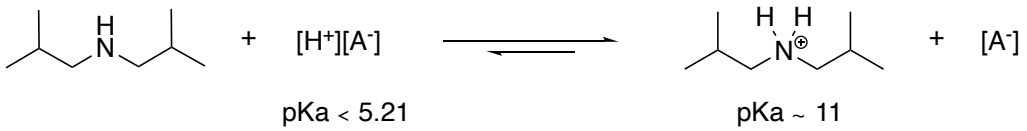
Table 3.8: Comparison of solubility of different salts



3.1a **3.6**

Acid	***pK*$_a$ (water)**	**Solubility of salt X in Et_2O**
hydrochloric	-8.0	quite insoluble
sulfuric	-3.0	quite insoluble
p-toluenesulfonic	-2.8	quite insoluble
oxalic	1.25; 4.16	slightly soluble
citric	3.13; 4.76; 6.39	slightly soluble
mandelic	3.37	slightly soluble
PPTS	5.21	quite insoluble

Although *pK*$_a$ difference should allow fully protonation of an amine, the respective equilibrium is shown in *Scheme 3.11*, after 1 hour of stirring, unprotonated amine was partially present in all solutions. However, as judged by TLC analysis, the concentration of unreacted free amine in hydrochloric and sulfuric acid solutions was significantly lower. During weighting of starting materials, it was assumed that the amount of an added acid can be slightly bigger, although should not vary significantly from the targeted 1:1 ratio. Using an excess of acid would not be desirable, as this would reduce the yield of hydroxylamine product once it also presents in tested solution. Also, no experiment was attempted with a longer time than 1 hour for practical considerations.



Scheme 3.11: Formation of salt based on pKa difference

Later efficiency of forming oxalic amine salts in *different* solvents was reinvestigated by Honours student in our lab Daniel Barriault.[106] Brief results are presented in the end of this Chapter.

At this stage, HCl (used as a solution in dioxane) showed to be the most suitable for further usage. This acid can be considered as the most synthetically attractive reagent as it comes in solution and by mixing it with an amine solution, a precipitation of salt is easy to achieve.

It was decided to stick to forming an amine salt and its subsequent removal by filtration. This approach can be also considered greener, as the excess amine recovered could in theory be easily regenerated with a base and this would not require use of water.

Also, the step of hydroxylamine protonation in the end to obtain pure salt and removal of the nitrone by filtration was replaced by a purification using a short silica gel plug. The relatively non-polar nature of the nitrone would allow to remove it easily, while traces of amine salt remaining would stick to the top of a column upon filtration.

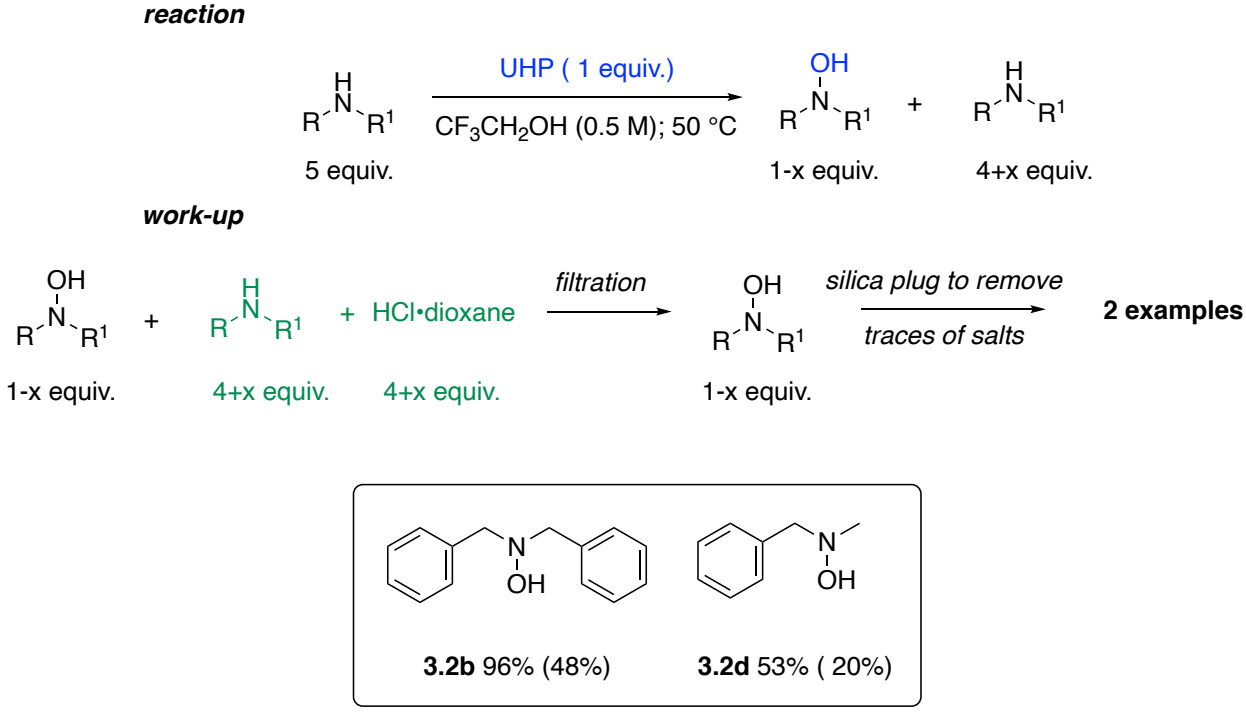
Modified procedure was:

1. Concentrate a sample
2. Addition of ether (to remove urea)
3. Addition of x eq of HCl·dioxane solution, where x stands for = 5 – reaction yield (to protonate all amine, which did not react)
4. Stirring for 15 minutes (to make sure that all amine is protonated)
5. Filtration, multiple washes with ether (to make sure that all hydroxylamine is in filtrate, test last fraction by TLC)

6. Short silica plug

Current conditions gave promising results only for two screened hydroxylamines shown in *Table 3.9*. Though no excellent yield was obtained.

Table 3.9: Isolated yield for selected hydroxylamines[a]



[a] isolated yields are shown in parentheses; ^{1}H NMR yields determined using 1,3,5-trimethoxybenzene as internal standard.

With unsatisfied isolated yield and presence of impurities, a screening of acids was continued. Inspired by some other documented amine salts[108] (*Figure 3.5*), additional acids were tested: HNO_3, HBr, H_2SO_4 and tartaric acid with diisobutylamine sample. Although, no good results were obtained.

[108] Stahl, P. H.; Wermuth, C. G. *Handbook of Pharmaceutical Salts. Properties, Selection and Use*; VHCA and WILEY-VCH; Zurich, **2002**, 374.

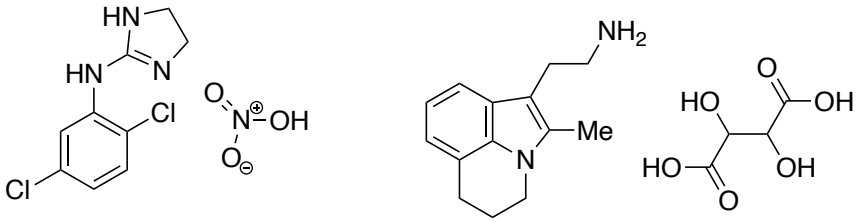


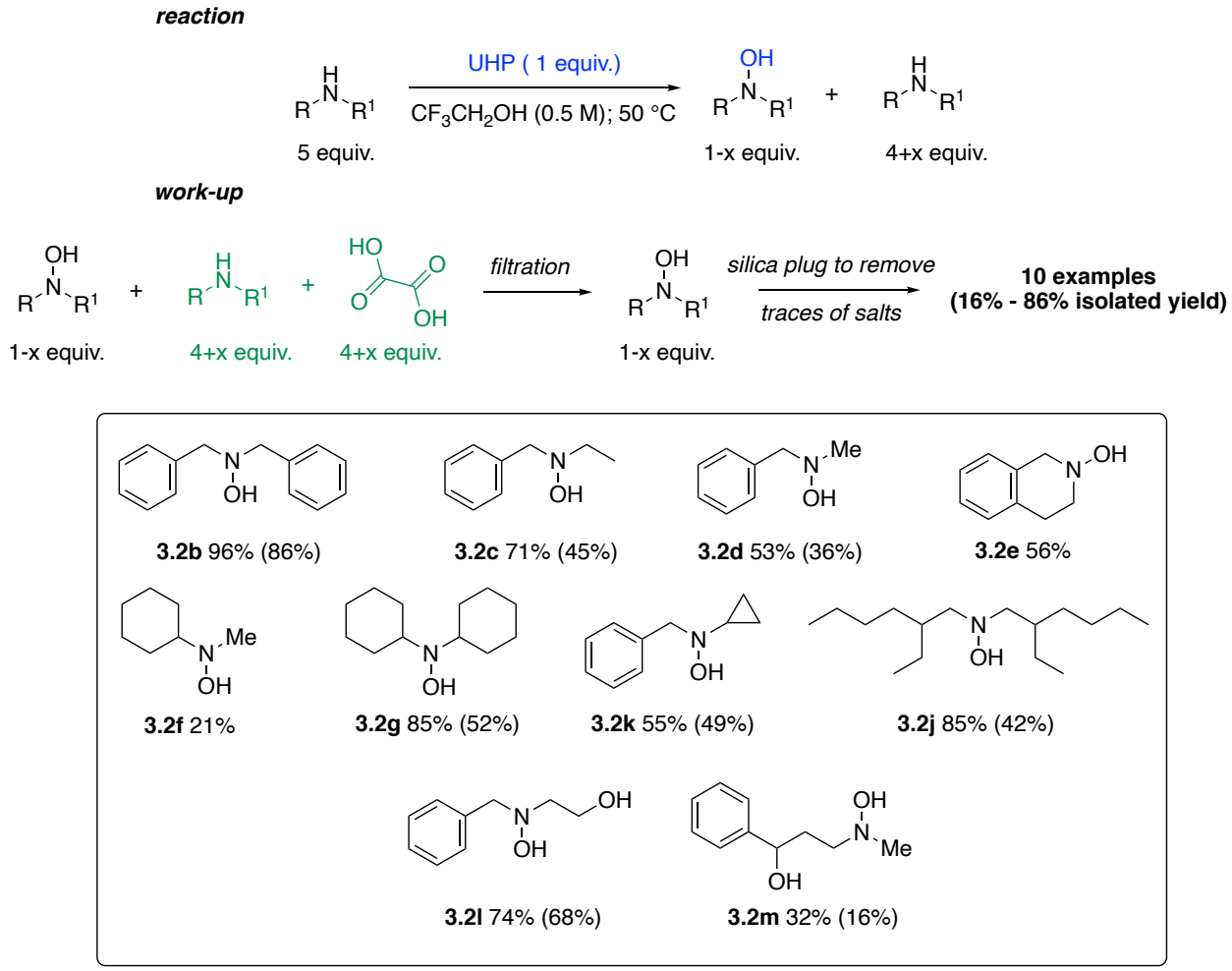
Figure 3.5: Some untypical commercially available amine salts

With an idea of one general purification procedure, we kept scanning isolation conditions. The size of the column was changed, silica gel was replaced with neutral or basic alumina, using reversed phase column chromatography C18, but unfortunately none of these changes proved efficient enough to obtain pure hydroxylamine.

At this stage, it looked like the separation of amine salt and hydroxylamine via column chromatography would be challenging. Thus, the conclusion was that the filtration method should be improved.

The further work on this project was conducted by Daniel Barriault. Final results with fair to excellent yields (16% to 86%) can be found in *Table 3.10*. The most significant improvement was the observation that a fritted glass filter is not efficient for filtration. Thus, three of Fisherbrand™ filter papers P8 grade were added on top of the frit. Also, the use of HCl as acid was replaced by oxalic acid, as those amine salts were easier to remove by filtration. It can probably be explained due to the bigger size of the crystals formed.

Table 3.10: Scope of the reaction and purification procedure for hydroxylamines[a]



[a] isolated yields are shown in parentheses, ^{1}H NMR yields determined using 1,3,5-trimethoxybenzene as internal standard.

It is worth mentioning, that purification conditions for cyclic hydroxylamine, for example such as morpholine or tetrahydroisoquinoline, are still under development. One of the hypothesis of poor isolation yield of these compounds is the impact of the dimension and shape of the molecule on the dissolving of an amine salt and its further state in solution. Unfortunately, this area of studying still remains very empirical, as properties of formed salts vary significantly. This significantly impacts further isolation of clean hydroxylamine.

3.4 CONCLUSION AND FUTURE WORK

The goal of the purification part of the project was achieved in collaboration work with D. Barriault. Secondary hydroxylamines obtained via novel oxidation reaction were isolated in fair to excellent yields (16% - 86%). However, obtained results suggest that a specific isolation procedure should be developed for some species, especially for cyclic hydroxylamines. Based on observations, it can be assumed that the crucial step for the isolation procedure is the formation of the salt, and therefore a larger screen of acids will be conducted.

CHAPTER 4: CONCLUSIONS AND FUTURE WORK

Overall, the work in this thesis shows that Cope-type hydroamination is efficient for the amination of vinylboronate species. Moreover, the presence of boron allows using milder hydroamination conditions in comparison to unsubstituted alkene species. Structures of obtained oxazaborolidine products have not been reported before. The X-ray analysis for a heterocyclic product allowed structural confirmation. The intermolecular reaction was studied with primary and secondary hydroxylamines. However, important challenges are associated with the product stability in particular with further bora-Cope type elimination. This undesired reaction is currently limiting the application of the reaction to more substituted alkenylboronates, since more stable alkenes can be formed.

Future work includes studying intramolecular reactivity with boron substituted species. More stable Cope-type hydroamination products could be obtained. The relative ease observed for the elimination reaction suggests that intramolecular reactivity should be possible under mild reaction conditions.

In Chapter 3, the main goal of the project was also achieved since an oxidation reaction was improved to become a practical method to synthesize hydroxylamines. The goal was to identify a purification method overcoming the propensity of the unreacted amine and hydroxylamine product to interact together. After some experimentation, conditions selectively forming oxalate salts of amines in the presence of hydroxylamines, followed by filtration over filter paper and then, through a silica gel plug allowed isolation of a variety of hydroxylamines products without the need for an extraction, or silica gel chromatography.

The future work includes an investigation of appropriate isolation conditions for cyclic hydroxylamines. Based on observations, it can be assumed that the crucial step for the isolation procedure is the formation of the salt, and therefore a larger screen of acids should be conducted.

PUBLICATIONS AND PRESENTATIONS FROM THIS WORK

1. Allen, M.A.; Volosheniuk, M.; Nicol, E.; Schwan, A. L.; Beauchemin, A. M. Cope-type hydroamination of vinylboronates - *Manuscript in preparation*

2. Allen, M.A.; Barriault, D.; Volosheniuk, M.; Beauchemin, A. M. Synthesis of *N,N*-dialkylhydroxylamines - *Manuscript in preparation*

3. Ottawa-Carleton Chemistry Institute (06/2021, online, oral presentation): Intermolecular Cope-type hydroamination with boron-containing reagents – *Award for the 5 min slot*.

4. Canadian Society for Chemistry Conference and Exhibition (08/2021, online, poster presentation): Intermolecular Cope-type hydroamination with boron-containing reagents

5. Québec-Ontario Mini-Symposium on Bioorganic and Organic Chemistry (12/2021, online, poster presentation): Intermolecular Cope-type hydroamination with boron-containing reagents – *Poster award*

6. Ottawa-Carleton Chemistry Institute (06/2022, Ottawa, oral presentation): The impact of Boron-substitution on the Cope-type hydroamination of alkenes

7.Canadian Society for Chemistry Conference and Exhibition (06/2022, Calgary, oral presentation): The impact of Boron-substitution on the Cope-type hydroamination of alkenes

SUPPORTING INFORMATION

GENERAL INFORMATION

Purification of reaction products was conducted by flash column chromatography using 40-63 μm silica gel. Analytical thin layer chromatography (TLC) was performed on aluminum plates, cut to size. Visualization was attained with UV light followed by staining in a potassium permanganate, cerium molybdate (both universal), ninhydrin (for amines and hydroxylamines) solutions and further heating.

^{1}H spectra were recorded on Bruker AVANCE 300 MHz, 400 MHz and 500 MHz spectrometers at room temperature and are reported in ppm using solvent as the internal standard ($CDCl_3$ at 7.26 ppm, DMSO-d_6 at 2.50 ppm or acetone-d_6 at 2.05 ppm). Data are reported as: multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration and coupling constant(s) in Hz. ^{13}C NMR spectra were recorded at 100 MHz or 125 MHz. Chemical shifts are reported in ppm from the residual solvent resonance employed as the internal standard ($CDCl_3$ at 77.16 ppm, DMSO-d_6 at 39.52 ppm or acetone-d6 at 29.84 ppm). ^{11}B NMR spectra were recorded at 95 MHz or 160 MHz. ^{19}F NMR spectra were recorded at 471 MHz. Consistent with other works,[41,67a] no references were used for ^{11}B NMR and ^{19}F NMR. High-resolution mass spectroscopy (HRMS) was performed on a Kratos Concept IIH mass spectrometer with an electron beam of 70 eV. High Performance Liquid Chromatography (HPLC) was performed on an Agilent 1200 series

MATERIALS

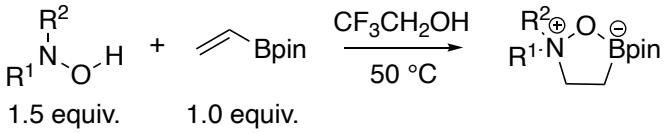
Unless otherwise noted, all commercially available materials were used without further purification. Solvents were either distilled according to standard techniques or degassed prior to use.

NMR YIELDS

NMR yields were determined using 1,3,5-trimethoxybenzene as an internal standard. These results are subject to the uncertainty of NMR integrations and the error resulting from the measurement of 1,3,5-trimethoxybenzene. As a rule, this data normally ranges anywhere from 5-10% and only reactivity trends are drawn as conclusions.

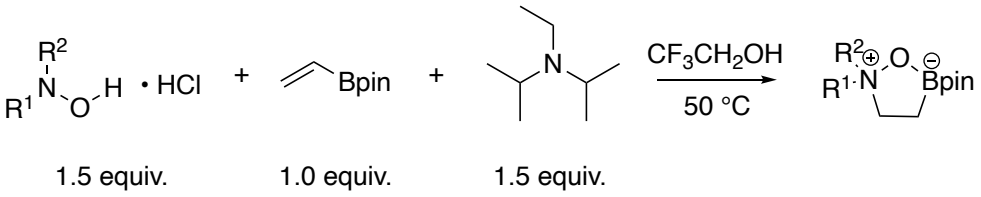
GENERAL PROCEDURES

GENERAL PROCEDURE **A**: FORMING OF OXAZOBOROLIDINES



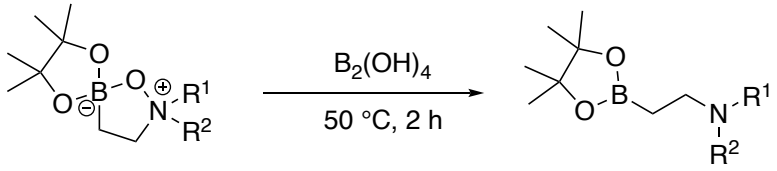
To a 5 mL microwave vial charged with a stir bar was added the vinylboronic acid pinacol ester (1.0 equiv.) then CF_3CH_2OH (0.5 M), followed by addition of hydroxylamine (1.5 equiv.). The vial was sealed with microwave cap and heated for 16 h at 50 °C (oil bath). Solvent was removed under reduced pressure and generally the product was further purified using silica gel chromatography.

GENERAL PROCEDURE **B**: FORMING OF OXAZOBOROLIDINES FROM HYDROXYLAMINE SALTS



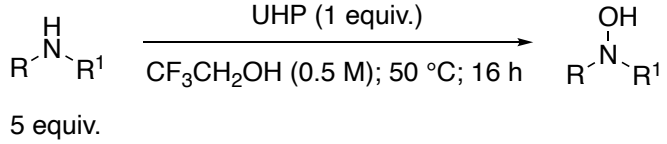
To a 5 mL microwave vial charged with a stir bar was added the vinylboronic acid pinacol ester (1.0 equiv.) then CF_3CH_2OH (0.5 M), followed by addition of hydroxylamine (1.5 equiv.) and *N,N*-diisopropylethylamine (1.5 equiv.) was added. The vial was sealed with microwave cap and heated for 16 h at 50 °C (oil bath). Solvent was removed under reduced pressure and generally product was further purified using silica gel chromatography.

GENERAL PROCEDURE **C**: REDUCING OF OXAZABOROLIDINES TO AMINOBORONIC ACID DERIVATIVES



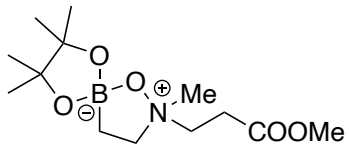
To oxazaborolidine crude (1.0 equiv.) in CF_3CH_2OH (0.5 M), $B_2(OH)_4$ (2 equiv.) was added. The vial was sealed with microwave cap and heated for 2 hours at 50 °C (oil bath). Solvent was removed under reduced pressure and product was further purified using silica gel chromatography.

GENERAL PROCEDURE **D**: SYNTHESIS OF HYDROXYLAMINES (UNOPTIMIZED)



To a 5 mL microwave vial charged with a stir bar was added the secondary amine (1.0 equiv.) then CF_3CH_2OH (0.5 M) followed by addition of urea-hydrogen peroxide complex (5.0 equiv.) was added. The vial was sealed with microwave cap and heated for 16 hours at 50 °C via oil bath heating. Upon completion, the reaction mixture was concentrated under reduced pressure. Ether was added, which induced the formation of a white precipitate (urea). The work-up was followed by addition of HCl·dioxane (4.0 M) in 1:1 ratio with the remaining amine, which induced more precipitate (forming of an amine salt). The resulting solution was stirred for 15 minutes. The precipitate was filtered by multiple washes with an ether and the filtrate was collected. The filtrate was concentrated via rotary evaporation and isolated using silica plug.

SYNTHESIS AND CHARACTERIZATIONS



2-(3-Methoxy-3-oxopropyl)-2,7,7,8,8-pentamethyl-1,6,9-trioxa-2-aza-5-boraspiro[4.4]nonan-2-ium-5-uide (2.3b):

The title compound was synthesized according to general procedure **A** using methyl 3-(hydroxy(methyl)amino)propanoate (0.0399 g, 0.300 mmol) and vinylboronic acid pinacol ester (0.034 mL, 0.20 mmol) in CF_3CH_2OH (0.4 mL, 0.5 M). The crude product was isolated using flash chromatography to yield the mixture of two compounds: title compound as a yellow oil (0.0183 g, 32%) and respective hydroxylamine as undesired contamination (32% hydroxylamine impurities appeared after holding 1 day on high vacuum).

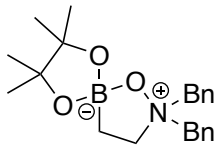
TLC R_f: 0.30 in 30% MeOH/EtOAc.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.73 (s, 3H), 3.61-3.45 (m, 4 H), 3.09 (s, 3H), 3.02-2.98 (m, 2H), 1.12 (s, 12H), 0.97 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.9, 88.6, 83.1, 70.6, 57.1, 51.8(2), 48.6, 32.3, 24.6(4).

^{11}B NMR (95 MHz, $CDCl_3$): δ 12.8.

HRMS (ESI): Exact mass calcd for $C_{13}H_{27}BNO_5^+$ $[M+H]^+$: 288.1982. Found: 288.1985.



2,2-Dibenzyl-7,7,8,8-tetramethyl-1,6,9-trioxa-2-aza-5-boraspiro[4.4]nonan-2-ium-5-uide (2.3d):

The title compound was synthesized according to general procedure **A** using *N,N*-dibenzylhydroxylamine (0.0639 g, 0.300 mmol) and vinylboronic acid pinacol ester (0.034 mL, 0.20 mmol) in CF_3CH_2OH (0.4 mL, 0.5 M). The crude product isolated using flash chromatography to yield the mixture of two compounds: title compound as a yellow oil (0.0081 g, 11%) and (58% hydroxylamine impurities appeared after holding 1 day on high vacuum).

Structural composition of title compound is also proved by its further derivatization.

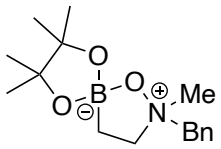
TLC R_f: 0.25 in 10% MeOH/EtOAc.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59-7.66 (m, 4H), 7.47-7.35 (m, 6H), 4.47 (d, J = 13.3 Hz, 2H), 4.27 (d, J = 13.3 Hz, 2H), 3.50 (t, 3H), 1.20 (s, 12H), 0.98 (t, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 129.7(2), 128.9(4), 128.4(4), 127.7(2), 83.0, 77.2, 75.9, 63.8, 24.6(4).[a]

^{11}B NMR (95 MHz, $CDCl_3$): δ 13.8.

[a] tertiary carbon was not observed in the ^{13}C NMR



2-Benzyl-2,7,7,8,8-pentamethyl-1,6,9-trioxa-2-aza-5-boraspiro[4.4]nonan-2-ium-5-uide (2.3e):

The title compound was synthesized according to general procedure **A** using *N*-benzyl-*N*-methylhydroxylamine (0.0414 g, 0.300 mmol) and vinylboronic acid pinacol ester (0.0308 g, 0.200 mmol) in CF_3CH_2OH (0.4 mL, 0.5 M). The crude product isolated using flash chromatography to yield the mixture of two compounds: title compound as a white solid (0.0157 g, 27%) and 23% hydroxylamine impurities appeared after holding 1 day on high vacuum).

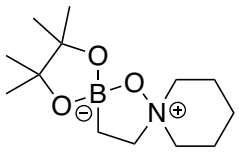
TLC R_f: 0.10 in 10% MeOH/EtOAc.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54-7.29 (m, 5H), 4.58 (d, *J* = 12.9 Hz, 1H), 4.23 (d, *J* = 12.9 Hz, 1H), 3.79-3.66 (m, 1H), 3.46-3.36 (m, 1H), 2.95 (s, 3H), 1.16 (s, 12H), 1.03 (t, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 132.1, 130.2(2), 128.8(2), 128.7, 83.0, 78.6, 70.2, 69.0, 51.9(2), 24.7(4).

^{11}B NMR (95 MHz, $CDCl_3$): δ 12.7.

HRMS (ESI): Exact mass calcd for $C_{16}H_{26}BNNaO_3^+$ $[M+Na]^+$: 314.1907. Found: 314.1903.



2,2,3,3-Tetramethyl-1,4,6-trioxa-7-aza-5-boradispiro[4.1.57.25]tetradecan-7-ium-5-uide (2.3f):

The title compound was synthesized according to general procedure **B** using *N*-hydroxypiperidine hydrochloride (0.0544 g, 0.400 mmol), vinylboronic acid pinacol ester (0.0410 g, 0.260 mmol) and *N,N*-diisopropylethylamine (0.056 mL, 0.40 mmol) in CF_3CH_2OH (0.52 mL, 0.5 M). The crude product was isolated using flash column chromatography to yield the title compound as a white solid (0.0484 g, 73%).

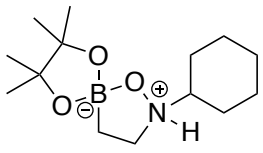
TLC R_f: 0.40 in 15% MeOH/EtOAc.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.54 (d, 2H), 3.38 (t, 2H), 2.94 (dt, 2H), 2.24-2.05 (m, 2H), 1.77-1.71 (m, 1H), 1.67-1.61 (m, 2H), 1.41-1.32 (m, 1H), 1.09 (s, 12H), 0.89 (t, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 78.3, 69.9, 63.2(2), 50.2(2), 25.0(4), 21.8, 21.2(2).

^{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 (2.6e):

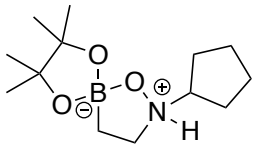
The title compound was synthesized using according to general procedure **A** using *N*-cyclohexylhydroxylamine (0.0345 g, 0.300 mmol) and vinylboronic acid pinacol ester (0.0308 g, 0.200 mmol) in CF_3CH_2OH (0.4 mL, 0.5 M). The reaction mixture was concentrated under reduced pressure and recrystallized in diethyl ether/methylene chloride mixture yielding white crystals (0.0301 g, 56%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 11.26 (br s, 1H), 3.51 (m, 1H), 3.15 (q, 1H), 2.92 (m, 1H), 2.27 (d, 1H), 2.05 (d, 1H), 1.84 (m, 2H), 1.65 (m, 1H), 1.54 (qt, 2H), 1.23 (m, 2H), 1.08 (s, 12 H), 0.85 (m, 1H), 0.98 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 78.4, 66.3, 54.6(2), 27.8, 26.7, 25.4, 25.3, 25.0(4), 24.9, 24.6.

^{11}B NMR (160 MHz, $CDCl_3$): δ 11.8.

HRMS (ESI): Exact mass calcd for $C_{14}H_{28}BNNaO_3^+$ $[M+Na]^+$: 291.2070. Found: 291.2096.



2-Cyclopentyl-7,7,8,8-tetramethyl-1,6,9-trioxa-2-aza-5-boraspiro[4.4]nonan-2-ium-5-uide (2.6f):

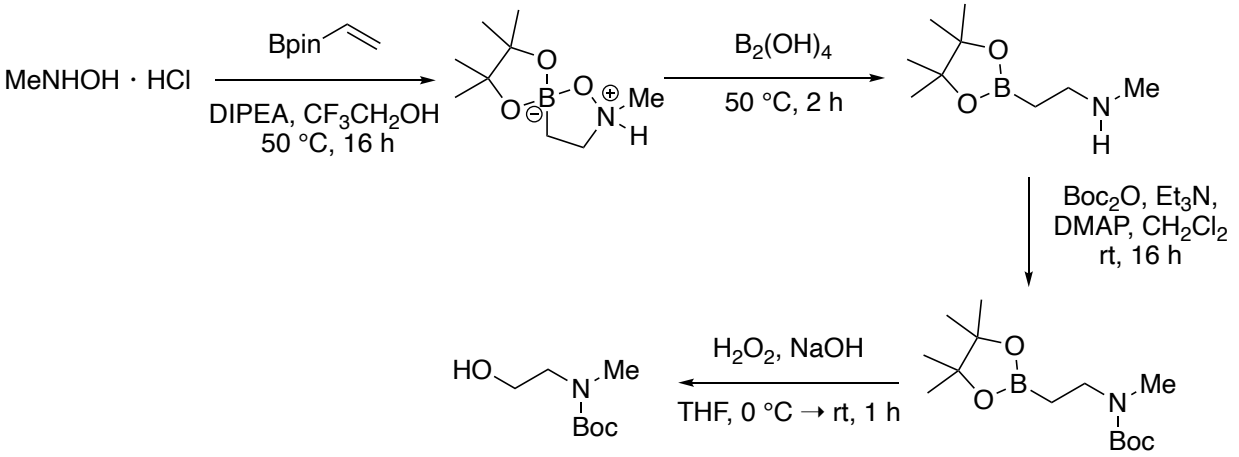
The title compound was synthesized using according to general procedure **A** using *N*-cyclopentylhydroxylamine (0.0303 g, 0.300 mmol) and vinylboronic acid pinacol ester (0.0308 g, 0.200 mmol) in CF_3CH_2OH (0.4 mL, 0.5 M). The reaction mixture was concentrated under reduced pressure and recrystallized in diethyl ether/methylene chloride mixture yielding white crystals (0.0188 g, 34%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 11.60 (br s, 1H), 3.56-3.45 (m, 2H), 3.07 (d, 1H), 2.20-2.13 (m, 1H), 1.98-1.73 (m, 3H), 1.59-1.48 (m, 2H), 1.08 (s, 12H), 0.89 (m, 1H), 0.71 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 67.2, 56.4(2), 28.9(2), 26.5, 25.3, 25.1(4), 24.8(2).

^{11}B NMR (160 MHz, $CDCl_3$): δ 12.5.

HRMS (ESI): Exact mass calcd for $C_{13}H_{26}BNNaO_3^+$ $[M+Na]^+$: 277.1922. Found: 277.1940.



***tert*-Butyl (2-hydroxyethyl)(methyl)carbamate (2.6a.4):**

The title compound was synthesized according to general procedure **B** using *N*-methylhydroxylamine hydrochloride (0.0626 g, 0.750 mmol), vinylboronic acid pinacol ester (0.0770 g, 0.500 mmol) and *N,N*-diisopropylethylamine (0.13 mL, 0.75 mmol) in CF_3CH_2OH (1 mL, 0.5 M).

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 $B_2(OH)_4$ (0.0897 g, 1.00 mmol). After 2 hours the reaction mixture was stopped and allowed to warm to room temperature. The crude reaction was evaporated. The compound 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 CH_2Cl_2 (0.33 mL, 1.5 M). To this solution Et_3N (0.11 mL, 0.75 mmol) and catalytic amount of DMAP (0.006 g, 0.05 mmol) was added. It was followed immediately by dropwise addition of Boc_2O (0.17 mL, 0.75 mmol). After stirring for 16 hours at room temperature the solvent was removed and diluted with CH_2Cl_2. The crude reaction was extracted with water (3 mL x3). The organic phase was collected and dried with Na_2SO_4. This procedure was performed in accordance to known literature method.[70b]

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) and cooled to 0 °C. A premixture of H_2O_2 (30% in H_2O, 1.25 mL) and aquas NaOH (2.0 M, 2.5 mL) was added. The reaction mixture was stirred for 1 hour at room temperature. Upon completion, the reaction mixture was evaporated and diluted further with water (5 mL). The organic phase was extracted with CH_2Cl_2 (5 mL x3). The organic phase was collected and dried with Na_2SO_4. The solids were filtrated over a cotton plug, and the filtrate was evaporated under reduced pressure. This procedure was performed in accordance to known literature method.[23c] The crude product was isolated using flash column chromatography to yield the title compound as a colorless oil (0.0368 g, 42% over 4 steps).

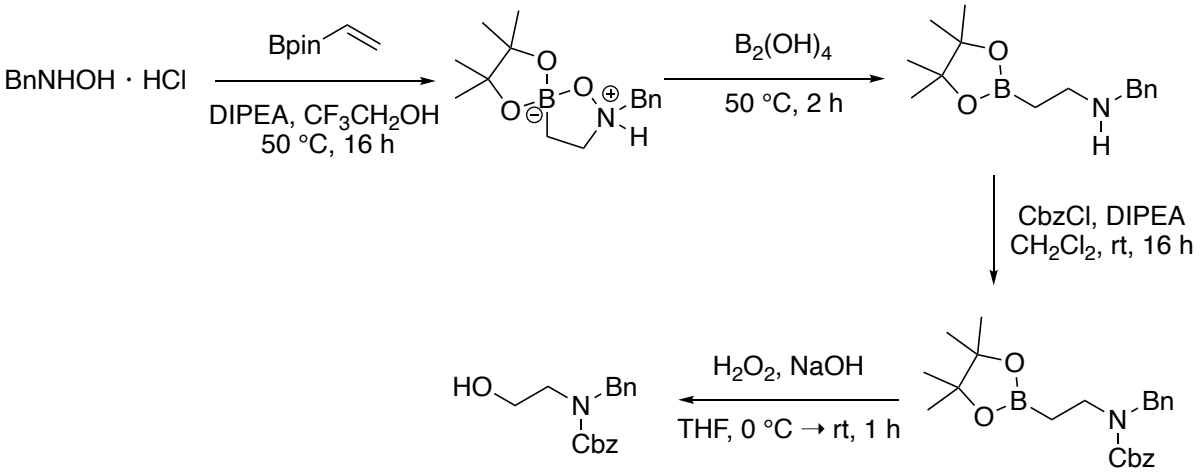
The characterization data below is in good agreement with previously reported data.[109]

TLC R_f: 0.20 in 80% EtOAc/Hexanes.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.74 (q, 2 H), 3.38 (t, 2H), 2.91 (s, 3H), 1.45 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 157.6, 80.0, 61.8, 51.5, 35.6, 28.4(3).

[109] 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 (2.6c.6):

The title compound was synthesized according to general procedure **B** using *N*-benzylhydroxylamine hydrochloride (0.1197 g, 0.750 mmol), vinylboronic acid pinacol ester (0.0770 g, 0.500 mmol) and *N,N*-diisopropylethylamine (0.13 mL, 0.75 mmol) in CF_3CH_2OH (1 mL, 0.5 M).

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 $B_2(OH)_4$ (0.0897 g, 1.00 mmol). After 2 hours the reaction mixture was stopped and allowed to warm to room temperature. The crude reaction was evaporated. The compound 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 CH_2Cl_2 (0.33 mL, 1.5 M). To this solution DIPEA (0.13 mL, 0.75 mmol) was added, and followed immediately by dropwise addition of CbzCl (0.011 mL, 0.75 mmol). The reaction was stirred overnight. Upon completion, reaction was diluted with CH_2Cl_2. The crude reaction was extracted with $NaHCO_3$ (3 mL x3). The organic phase was collected and dried with Na_2SO_4. This procedure was performed in accordance to known literature method. [70a]

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) and cooled to 0 °C. A premixture of H_2O_2 (30% in H_2O, 1.25 mL) and aquas NaOH (2.0 M, 2.5 mL) was added. The reaction mixture was stirred for 1 hour at room temperature. Upon completion, the reaction mixture was evaporated and diluted further with water (5 mL). The organic phase was extracted with CH_2Cl_2 (5 mL x3). The organic phase was collected and dried with Na_2SO_4. The solids were filtrated over a cotton plug, and the filtrate was evaporated under reduced pressure. This procedure was performed in accordance to known literature method.[23c] The crude product was isolated using flash column chromatography to yield the title compound as a colorless oil (0.0498 g, 35% over 4 steps).

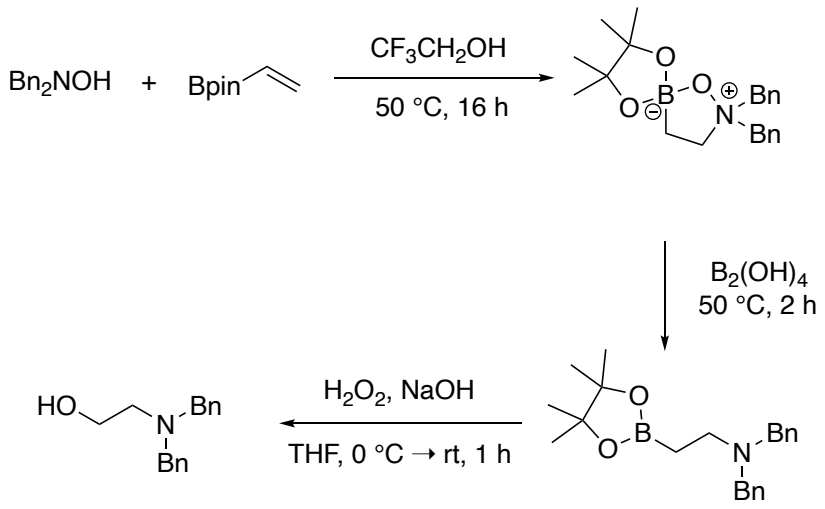
Characterization data is in good agreement with previously reported data.[110]

TLC R_f: 0.10 in 70% EtOAc/Hexanes.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42-7.23 (m, 10H), 5.24 (s, 2H), 4.63 (s, 2H), 3.75 (m, 2H), 3.48 (m, 2H), 2.94 (br s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 157.7, 137.6, 136.4, 128.7, 128.6, 128.2, 128.0, 127.5, 127.4, 67.7, 61.6, 51.7, 50.1.

[110] Pal, R.; O'Brien, S. C.; Willis, M. C. *Chem. Eur. J.* **2020**, *26*, 11710.



2-(Dibenzylamino)ethan-1-ol (2.3d.1):

The title compound was synthesized according to general procedure **A** using *N,N*-dibenzylhydroxylamine (0.0960 g, 0.450 mmol) and vinylboronic acid pinacol ester (0.0462 g, 0.300 mmol) in CF_3CH_2OH (1.2 mL, 0.25 M). The reaction was heated at 50 °C for 48 hours. The formed crude product was used in further step without purification.

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 $B_2(OH)_4$ (0.0538 g, 0.600 mmol). After 2 hours the reaction mixture was stopped and allowed to warm to room temperature. The crude reaction was evaporated. The compound was used in next step without purification.

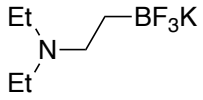
To the crude *N,N*-dibenzyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethan-1-amine was added THF (0.3 mL, 0.1 M) and cooled to 0 °C. A premixture of H_2O_2 (30% in H_2O, 0.75 mL) and NaOH (2.0 M, 1.5 mL) was added. The reaction mixture was stirred for 1 hour at room temperature. Upon completion, the reaction mixture was evaporated and diluted further with water (3 mL). The organic phase was extracted with CH_2Cl_2 (3 mL x3). The organic phase was collected and dried with Na_2SO_4. The solids were filtrated over a cotton plug, and the filtrate was evaporated

under reduced pressure. This procedure was performed in accordance to known literature method.[23c] The crude product was isolated using flash column chromatography to yield the title compound as a white solid (0.0274 g, 39% over 3 steps). Characterization data is in good agreement with previously reported data.[111]

TLC R_f: 0.30 in 33% EtOAc/Hexanes.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40-7.29 (m, 10H), 3.69 (s, 4H), 3.64 (t, 2H), 2.73 (t, 2H), 2.60 (br s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 138.3(2), 129.1(4), 128.5(4), 127.3(2), 58.6(2), 58.4, 54.8.



***N*,*N*-Diethyl-2-(trifluoro-λ^4-boraneyl)ethan-1-amine, potassium salt (2.3a.1):**

The title compound was synthesized according to general procedure **A** using *N,N*-diethylhydroxylamine (0.031 mL, 0.30 mmol) and vinylboronic acid pinacol ester (0.0308 g, 0.200 mmol) in CF_3CH_2OH (0.4 mL, 0.5 M). The formed crude product was used in further step without purification.

With the crude solution of 2,2-diethyl-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 $B_2(OH)_4$ (0.0359 g, 0.4 mmol) was added. After 2 hours the reaction mixture was stopped and allowed to warm to room

[111] Zimmermann, B. M.; Ngoc, T. T.; Tzaras, D.-I.; Kaicharla, T.; Teichert, J. F. *J. Am. Chem. Soc.* **2021**, *143*, 16865.

temperature. The crude reaction was evaporated. The compound was used in next step without purification.

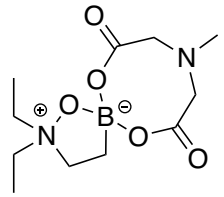
The next step was performed in accordance to known literature method. [67a] The crude *N,N*-diethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethan-1-amine was dissolved in MeOH (1.33 mL, 0.15 M). An aqueous solution of KHF_2 (0.0703 g, 0.900 mmol, 4.5 M) was added dropwise. The reaction mixture was stirred for 3 hours at room temperature. Upon completion, the reaction mixture was evaporated under reduced pressure. To remove pinacol three extra portions of methanol (5 mL x3) were added and evaporated after. The solid was triturated with acetone (3 mL x3) and filtered through a filter. The filtrate was evaporated and formed compound was washed with Et_2O. The trifluoroborate salt was obtained as yellow solid (0.0145 g, 35% over 3 steps). Characterization data is in good agreement with previously reported data. [67a,112]

^{1}H NMR (500 MHz, acetone-d_6): δ 3.30 (q, 4H), 3.18 (t, 2H), 1.35 (t, 6H), 0.47 (br t, 2H).

^{13}C NMR (125 MHz, acetone-d_6): δ 52.8(2), 46.9, 46.1, 8.6(2).

^{11}B NMR (160 MHz, acetone-d_6): δ 3.8.

^{19}F NMR (471 MHz, acetone-d_6): δ -139.5.



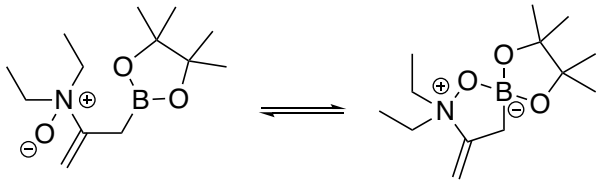
2,2-Diethyl-9-methyl-7,11-dioxo-1,6,12-trioxa-2,9-diaza-5-boraspiro[4.7]dodecan-2-ium-5-uide (2.26):

[112] Jones, M. R.; Fast, C.D.; Schley, N. D.; *J. Am. Chem. Soc.* **2020**, *142*, 6488.

To a 5 mL microwave vial charged with a stir bar was added the vinylboronic acid MIDA ester (0.0366 g, 0.200 mmol) then CF_3CH_2OH (0.4 mL, 0.5 M), followed by addition of hydroxylamine (0.031 mL, 0.30 mmol) was added. The vial was sealed with microwave cap and heated for 16 hours at 50 °C (oil bath). Solvent was removed under reduced pressure and product was further purified using silica gel chromatography. The title compound degraded on silica column. The ^1H NMR spectra obtained for the unpurified reaction mixture can be found in appendix.

^1H NMR (500 MHz, $CDCl_3$): δ 3.43-3.40 (t, 2H), 3.31-3.23 (m, 2H), 3.19-3.08 (m, 4H), 2.65 (s, 3H), 1.17 (t, 6H), 0.82 (m, 2H).

^{11}B NMR (160 MHz, $CDCl_3$): δ 10.8.



***N,N*-Diethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-1-en-2-amine oxide (2.47a):**

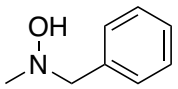
To a 5 mL microwave vial charged with a stir bar was added allenylboronic acid pinacol ester (0.0332 g, 0.200 mmol) then CF_3CH_2OH (0.4 mL, 0.5 M), followed by addition of hydroxylamine (0.031 mL, 0.30 mmol) was added. The vial was sealed with microwave cap and heated for 16 hours at 50 °C (oil bath). Solvent was removed under reduced pressure and product was further purified using silica gel chromatography. The title compound was isolated a white solid (0.0086 g, 17%)

TLC R_f: 0.15 in 10% MeOH/EtOAc.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.12 (dt, 1H), 4.85 (dt, 1H), 3.48 (q, 4H), 1.56 (t, 2H), 1.35 (t, 6H), 1.15 (s, 6H), 1.08 (s, 6H)

^{13}C NMR (125 MHz, $CDCl_3$): δ 161.1, 102.5, 78.5, 61.5(2), 53.4(2), 25.3(2), 25.1(2), 8.6(2).

^{11}B NMR (160 MHz, $CDCl_3$): δ 11.3.



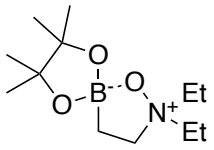
***N*-Benzyl-*N*-methylhydroxylamine (3.2d):** Synthesized according to general procedure **D** using *N*-benzyl-*N*-methylamine (0.64 mL, 5.0 mmol) and urea-hydrogen peroxide complex (0.0941 g, 1.00 mmol) in CF_3CH_2OH (0.5 M). The title compound was isolated a white solid (0.0274 g, 20%). Characterization data is in good agreement with previously reported data.[113]

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35-2.28 (m, 5H), 3.79 (s, 2H), 2.66 (s, 3H).

^{13}C NMR (500 MHz, $CDCl_3$): δ 129.6, 128.4(2), 127.6(2), 66.6, 47.9.

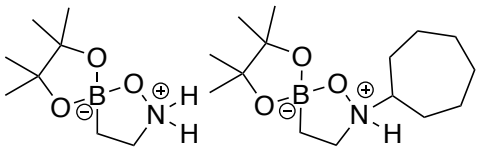
NOTE

Another compound from oxazaborolidine scope **2.3a** was purified by Meredith Allen. Obtained spectra are presented in her PhD thesis.



[113] Dhanju, S.; Crich, D. *Org. Lett.* **2016**, *18*, 1820.

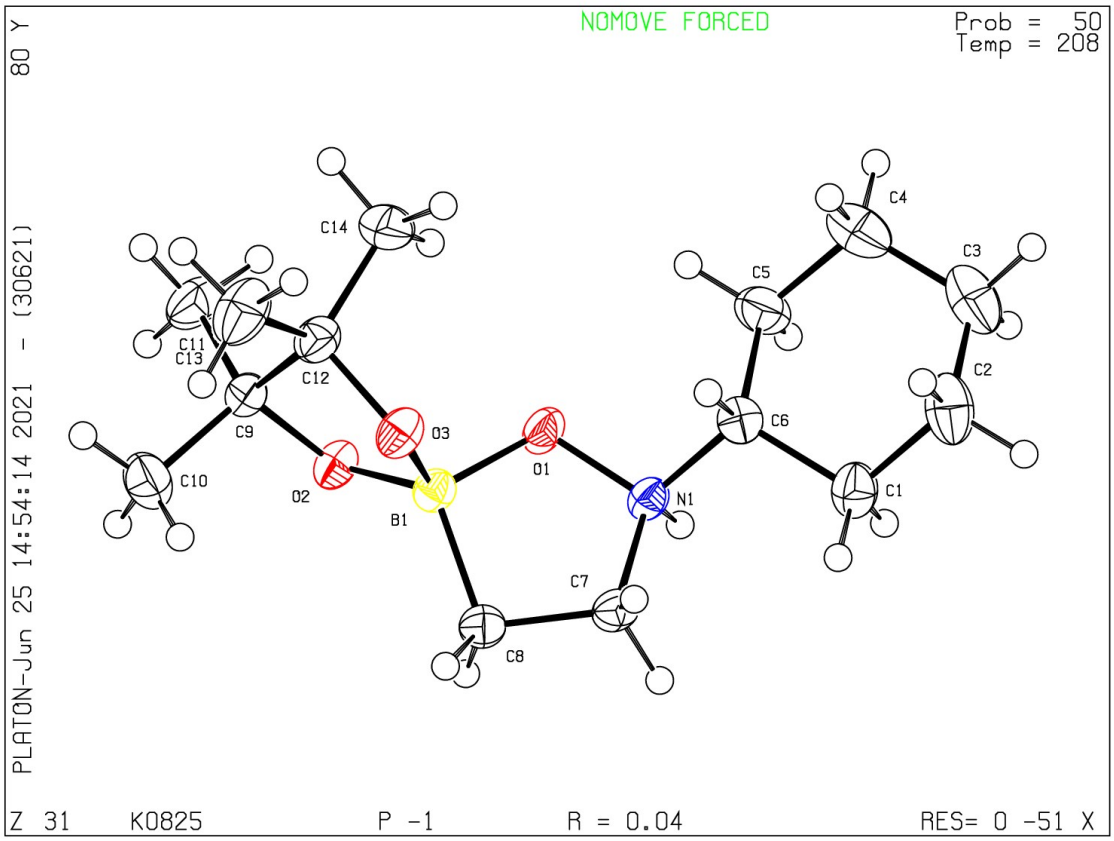
Due to challenges associated with the significant instability of oxazaborolidines, conditions for purifying **2.6d** and **2.6g** were not found. Crude ^{1}H NMR spectra could be included in current thesis if needed.



Only one example from the hydroxylamine scope is included in the current thesis, as obtained hydroxylamine was used for an experiment described in Chapter 2. Other pure hydroxylamines were obtained by an optimized isolation procedure developed by Daniel Barriault and can be found in his Honours thesis.

X-RAY STRUCTURE

Structure **2.6f** determination via X-ray analysis



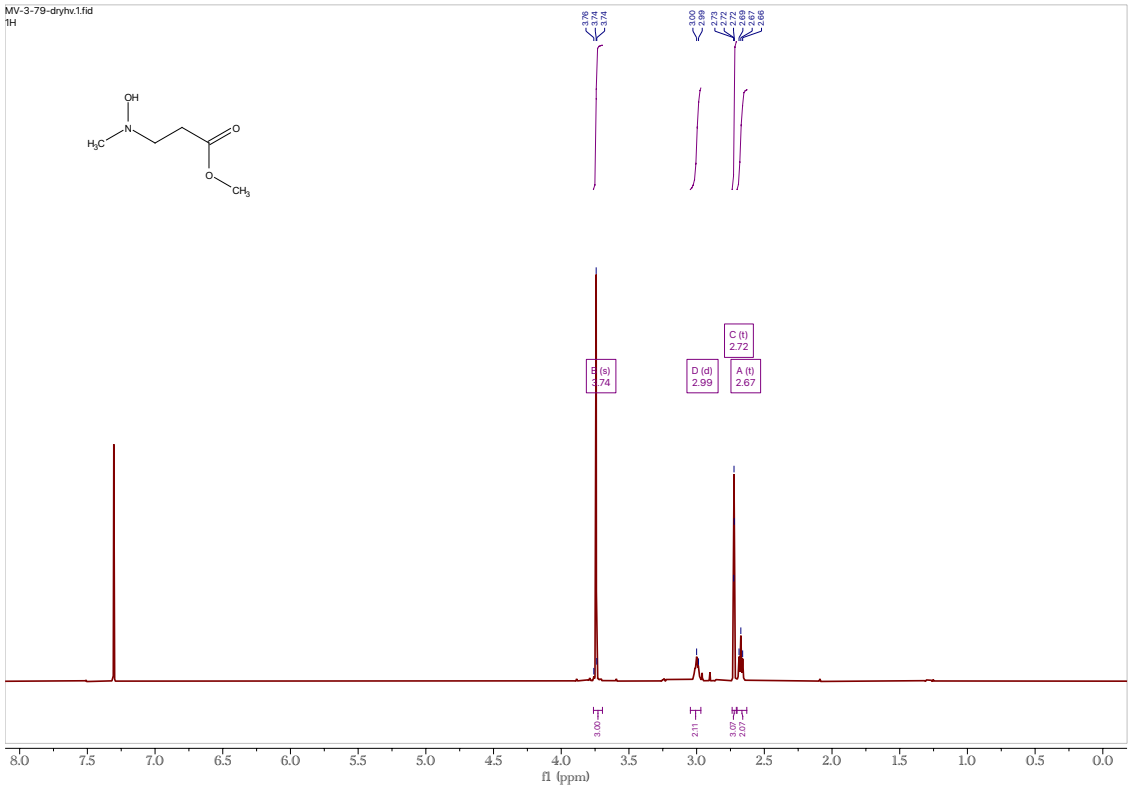
Bond precision: C-C = 0.0016 A Wavelength=0.71073

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

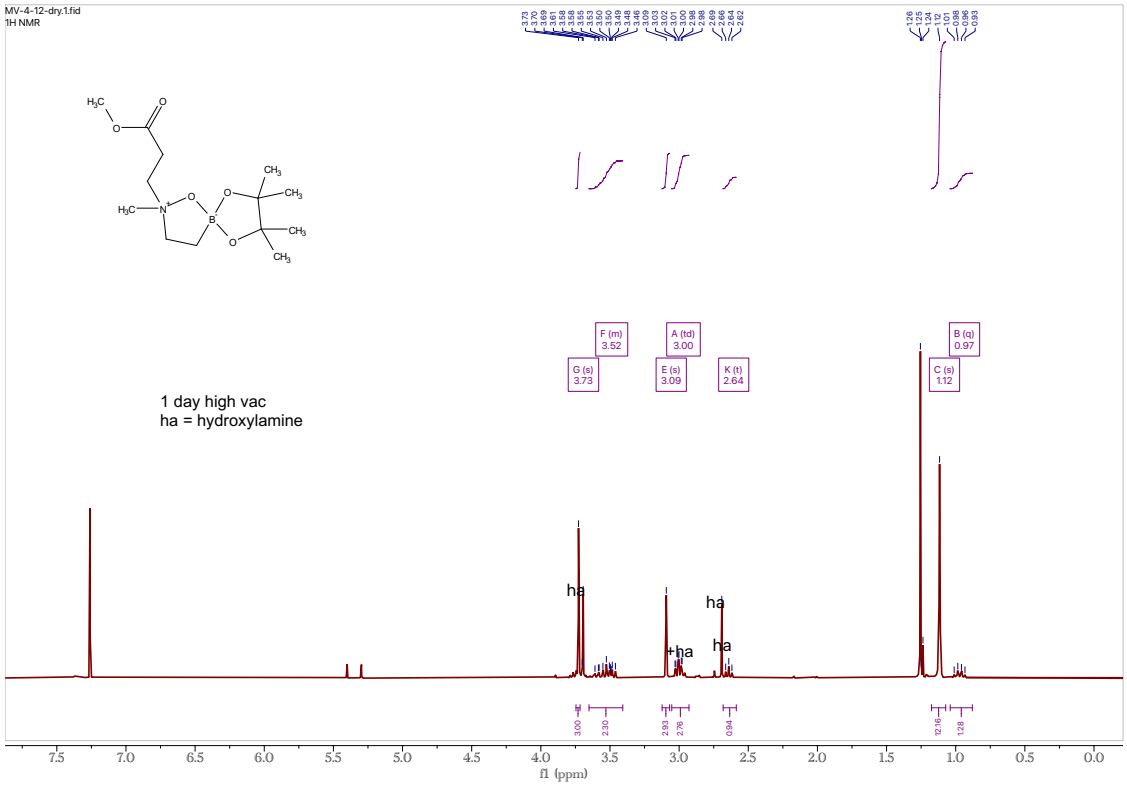
	Calculated	Reported
Volume	774.29(5)	774.29(5)
Space group	P -1	P -1
Hall group	-P 1	-P 1
Moiety formula	C14 H28 B N O3	C14 H28 B N O3
Sum formula	C14 H28 B N O3	C14 H28 B N O3
Mr	269.18	269.18
Dx,g cm-3	1.155	1.155
Z	2	2
Mu (mm-1)	0.078	0.078
F000	296.0	296.0

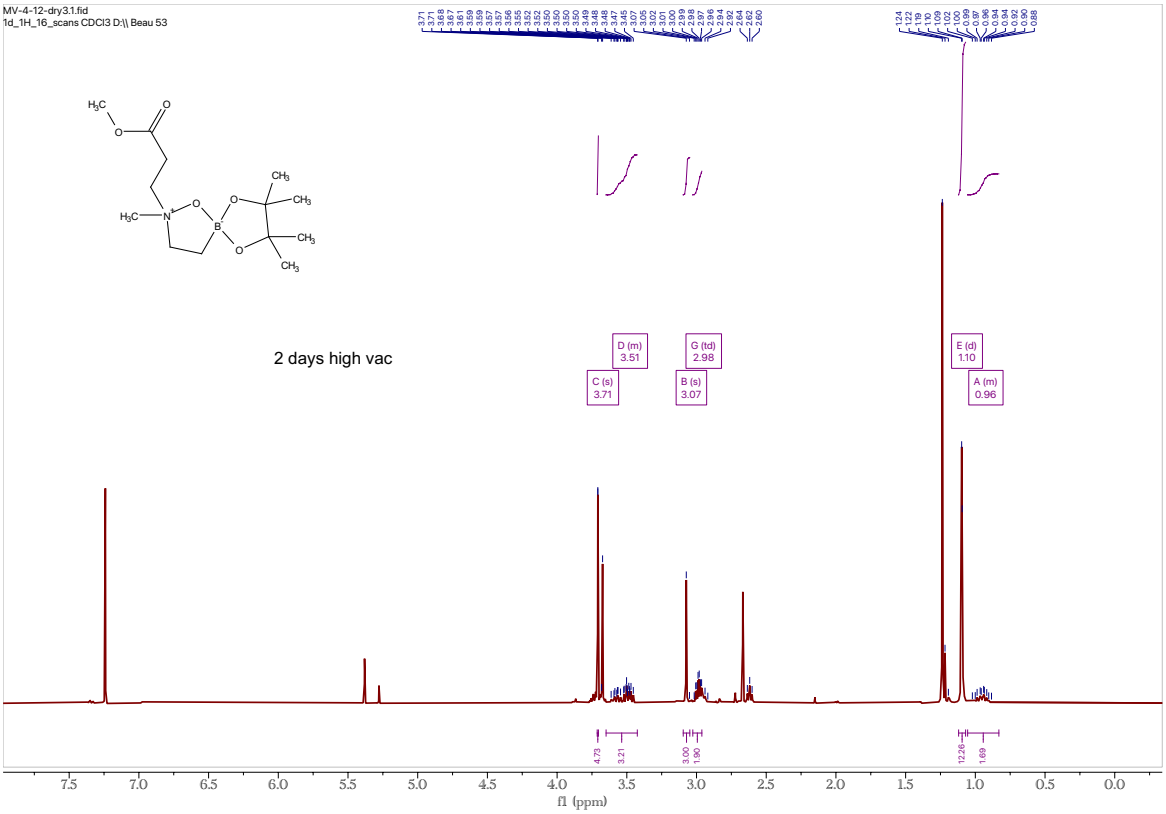
```
F000'          296.13
h,k,lmax       12,12,16                12,12,16
Nref           5525                    5518
Tmin,Tmax      0.975,0.991             0.720,0.746
Tmin'          0.958
Correction method= # Reported T Limits: Tmin=0.720 Tmax=0.746
AbsCorr = MULTI-SCAN

Data completeness= 0.999       Theta(max)= 32.335

R(reflections)= 0.0441( 4139)  wR2(reflections)= 0.1280( 5518)

S = 1.020               Npar= 176
```

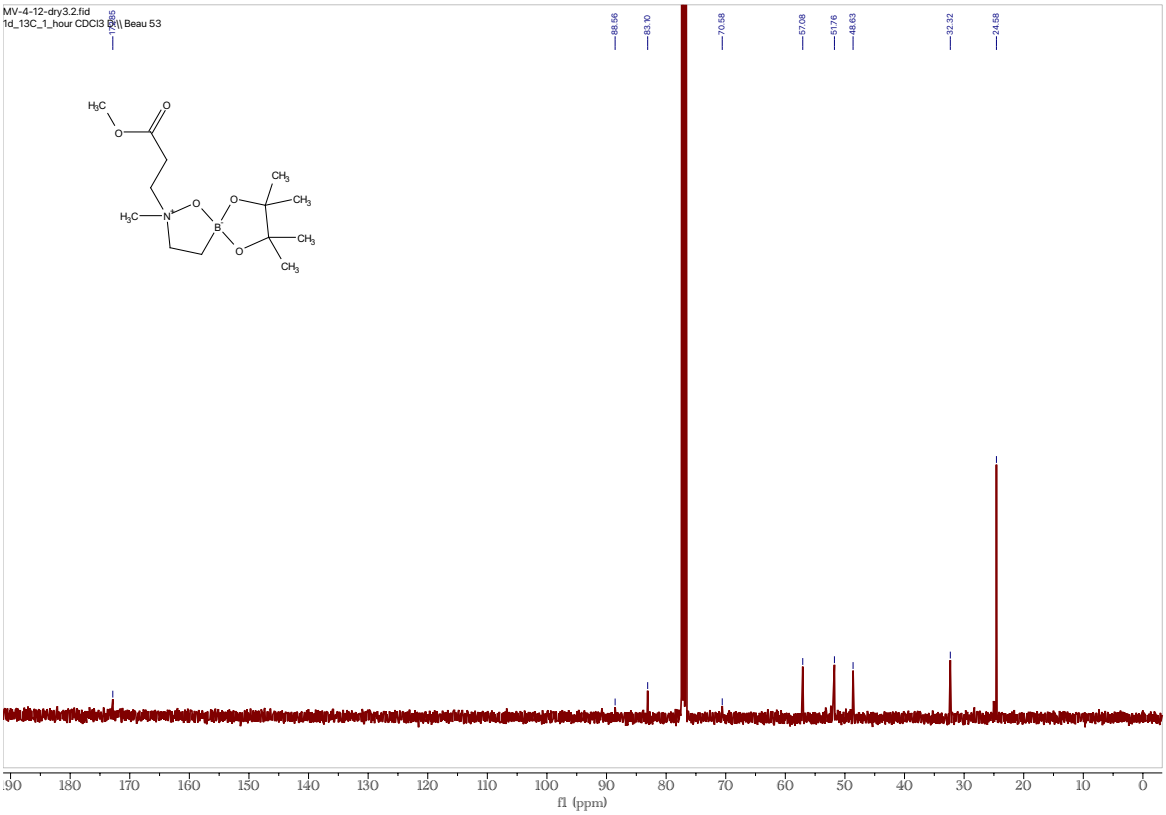
SPECTRA

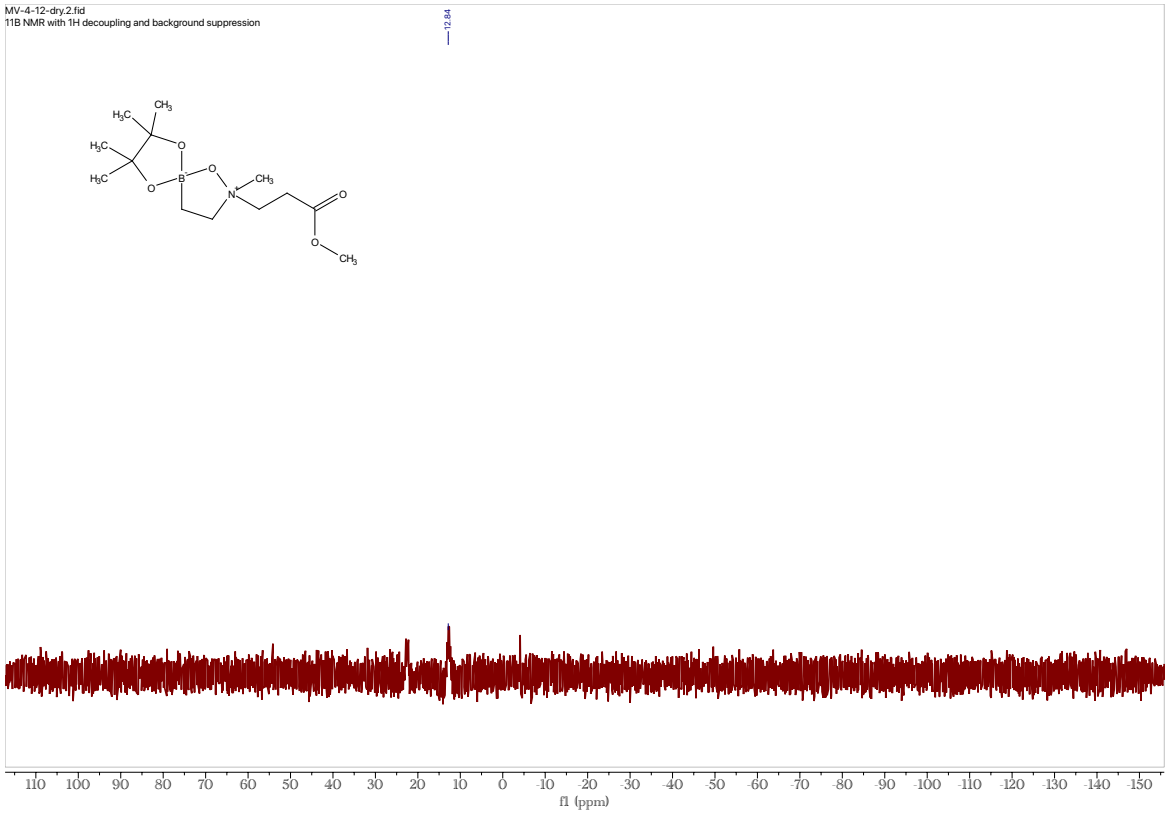

MV-3-79-dryhv.1.fid
1H
B (s) 3.74
D (d) 2.99
C (t) 2.72
A (t) 2.67
f1 (ppm)

2.3b

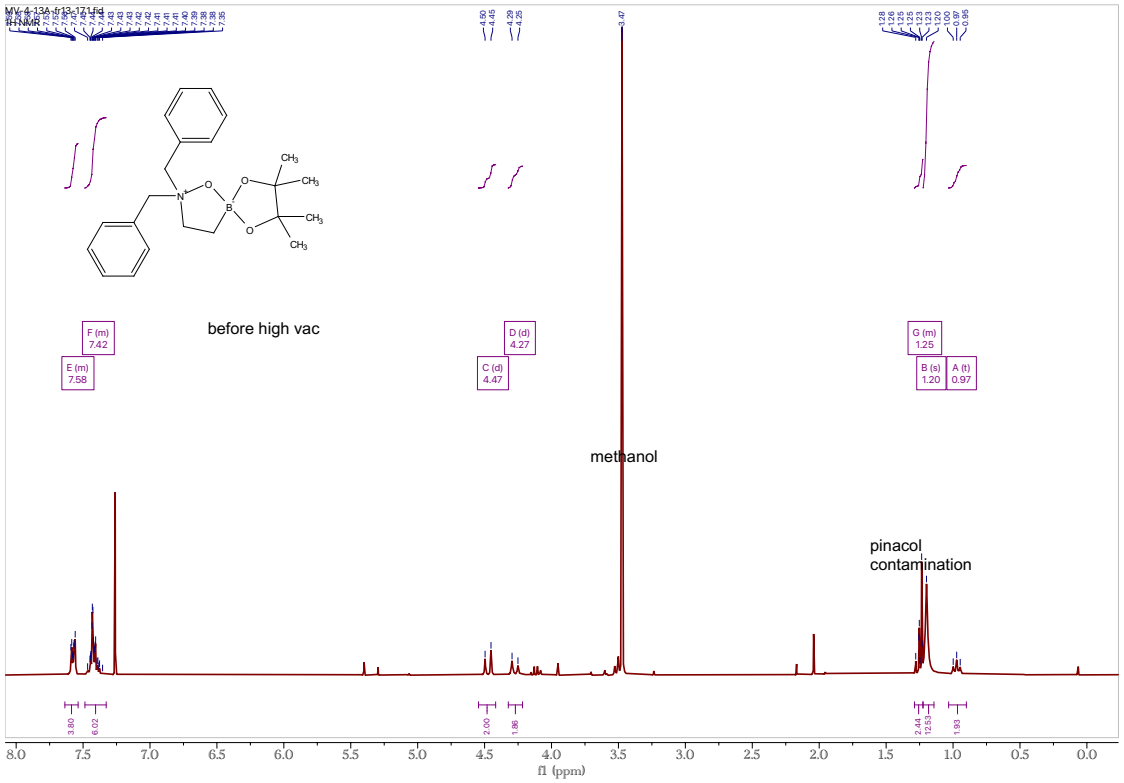

MV-4-12-dry.1.fid
1H NMR
F (m) 3.52
A (td) 3.00
B (q) 0.97
G (s) 3.73
E (s) 3.09
K (t) 2.64
C (s) 1.12
1 day high vac
ha = hydroxylamine
ha
ha
+ha
ha
f1 (ppm)

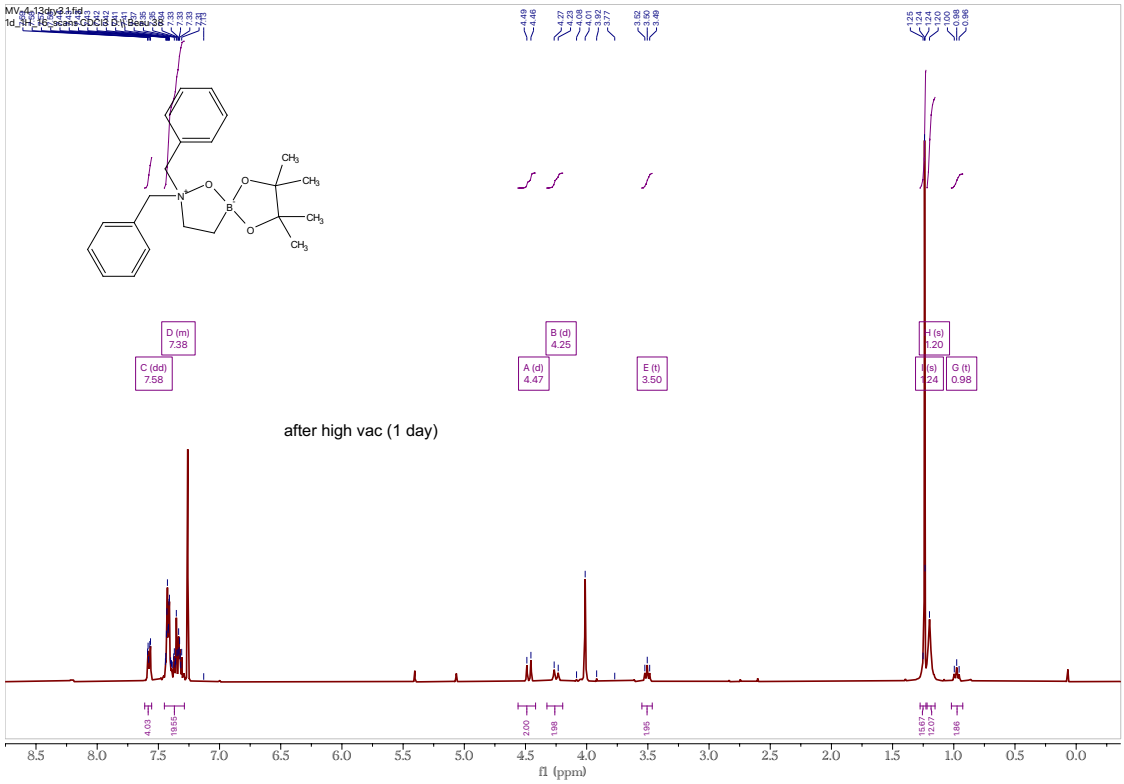

MV-4-12-dry3.1.fid
1d_1H_16_scans CDCl3 D:\\ Beau 53
2 days high vac
D (m) 3.51
G (td) 2.98
E (d) 1.10
C (s) 3.71
B (s) 3.07
A (m) 0.96
4.73
3.21
3.00
1.90
12.26
1.69
f1 (ppm)

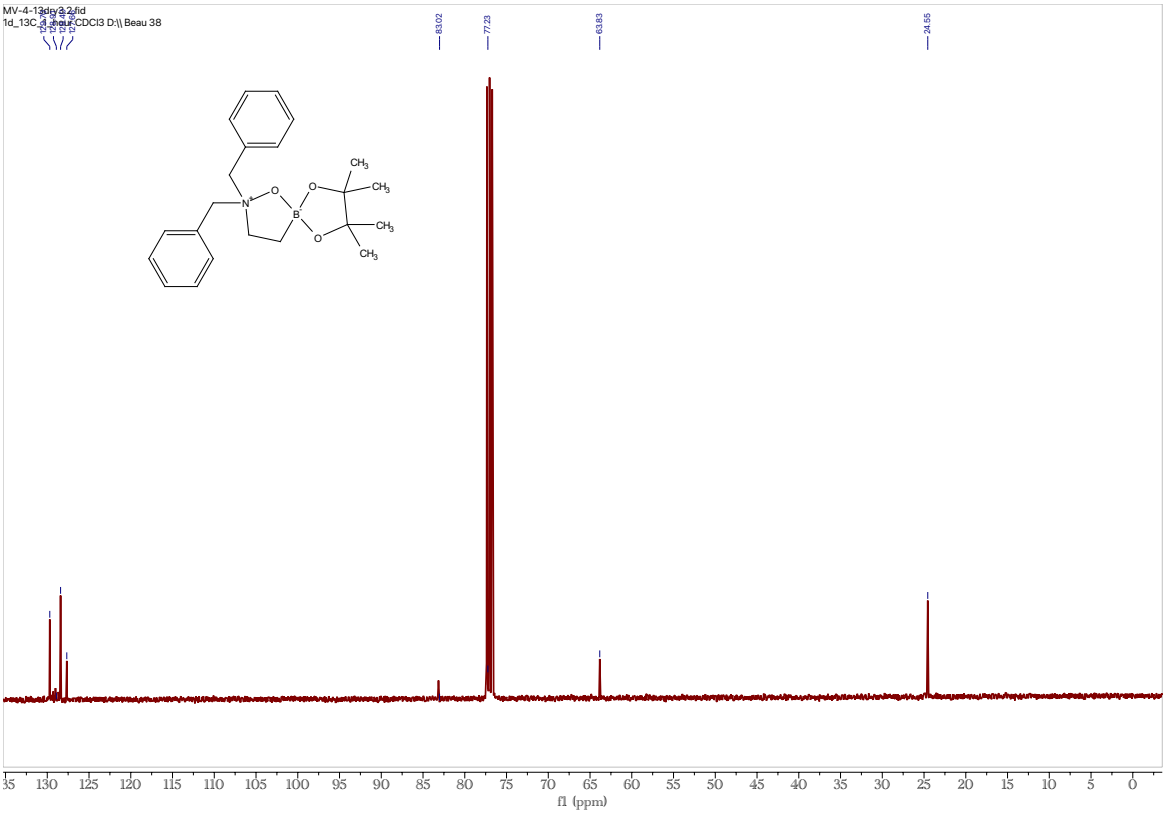

MV-4-12-dry3.2.fid
1d_13C_1_hour CDCl3 D:\\ Beau 53
88.56
83.10
70.88
57.08
51.76
48.63
32.32
24.58
f1 (ppm)

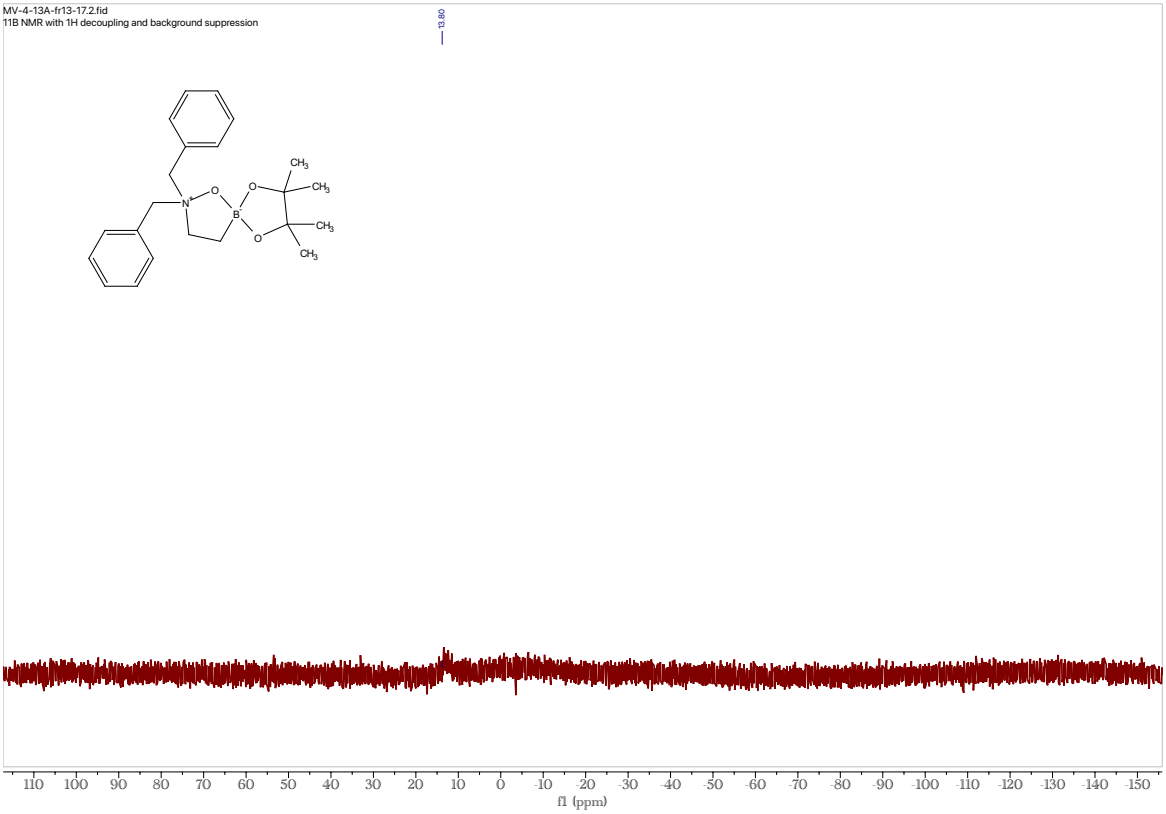

MV-4-12-dry.2.fid
11B NMR with 1H decoupling and background suppression
12.84
110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150
f1 (ppm)

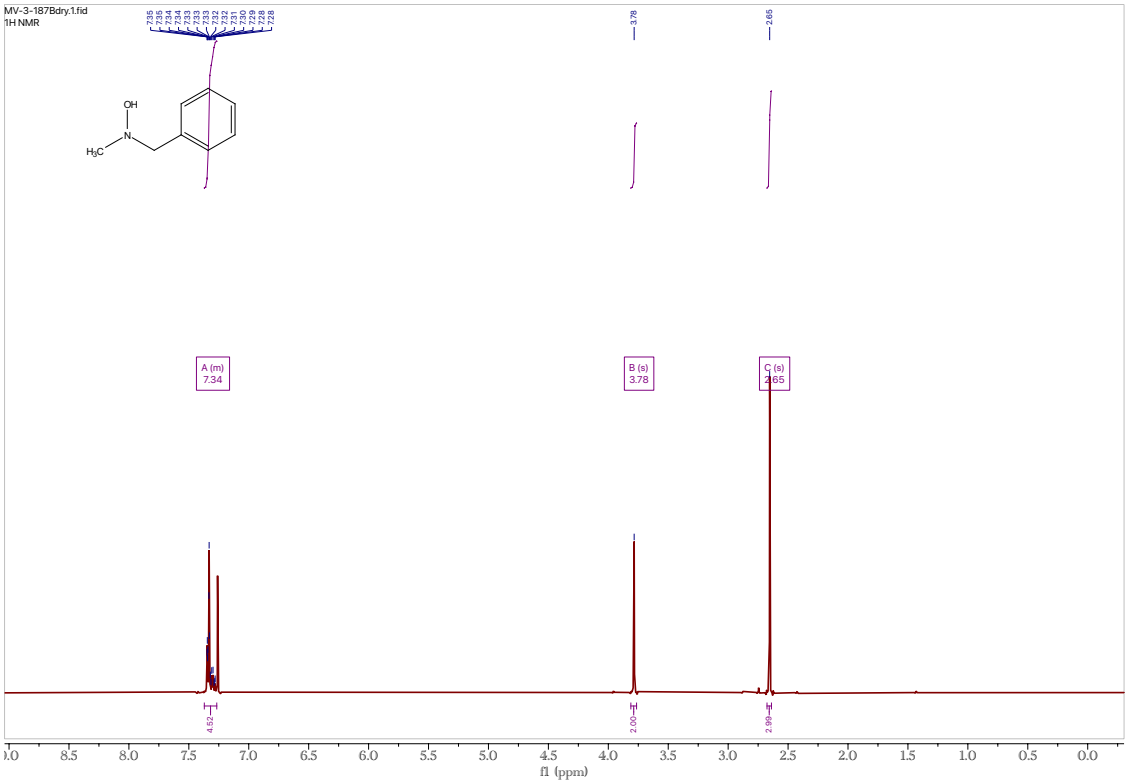
2.3d


before high vac
methanol
pinacol
contamination
f1 (ppm)

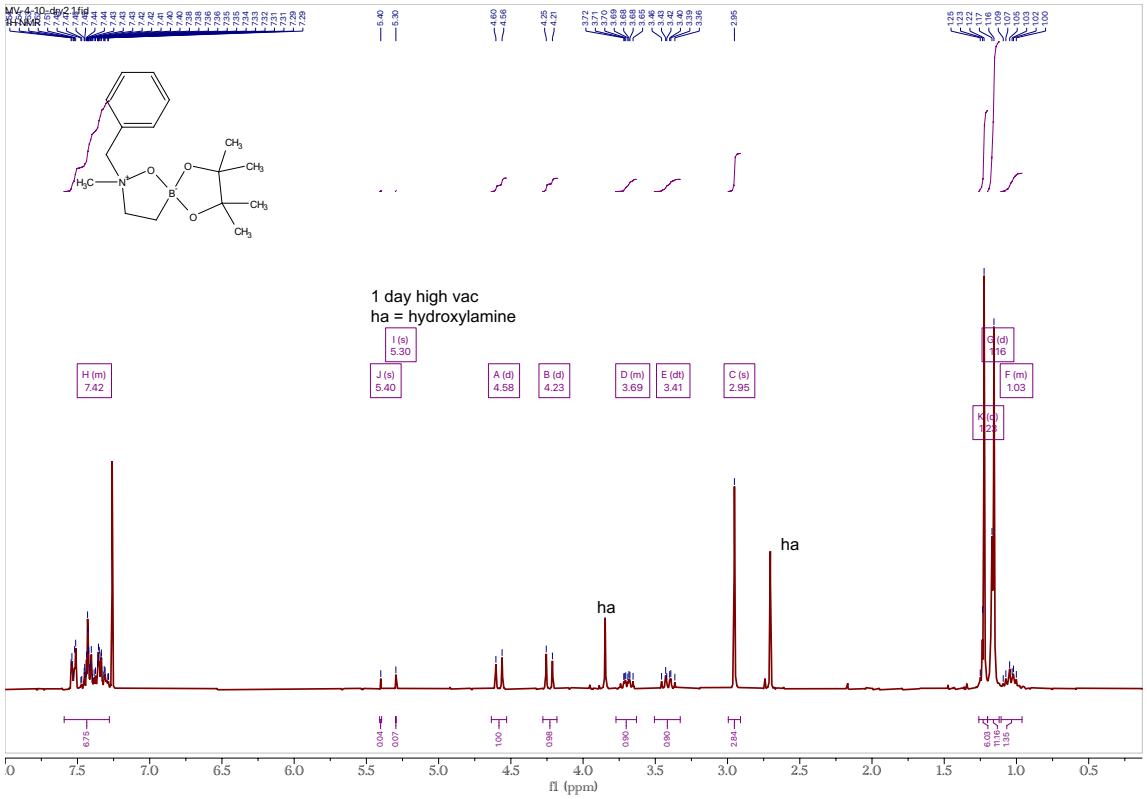

after high vac (1 day)
f1 (ppm)

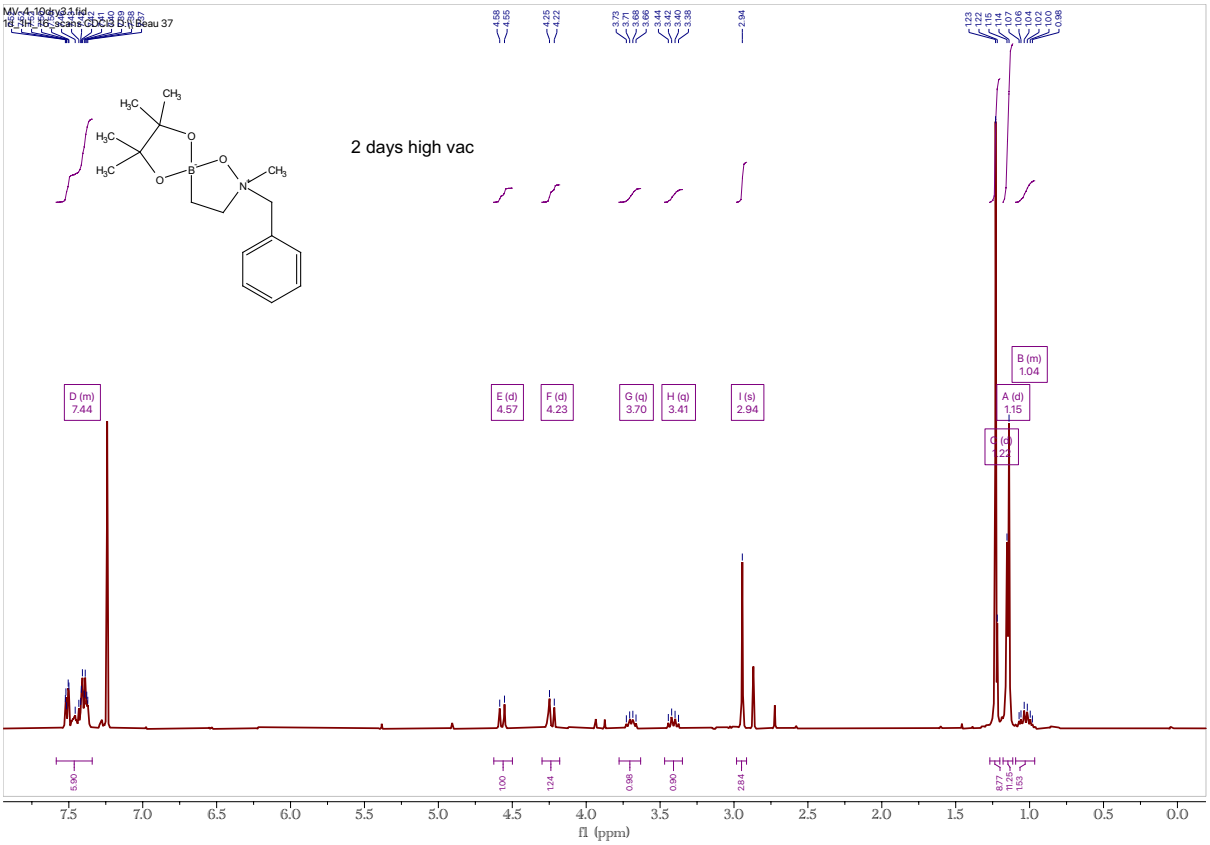

MV-4-13dy-2-2.fid
1d_13C_4 Beau CDCl3 D:\\ Beau 38
83.02
77.23
63.83
24.55
f1 (ppm)

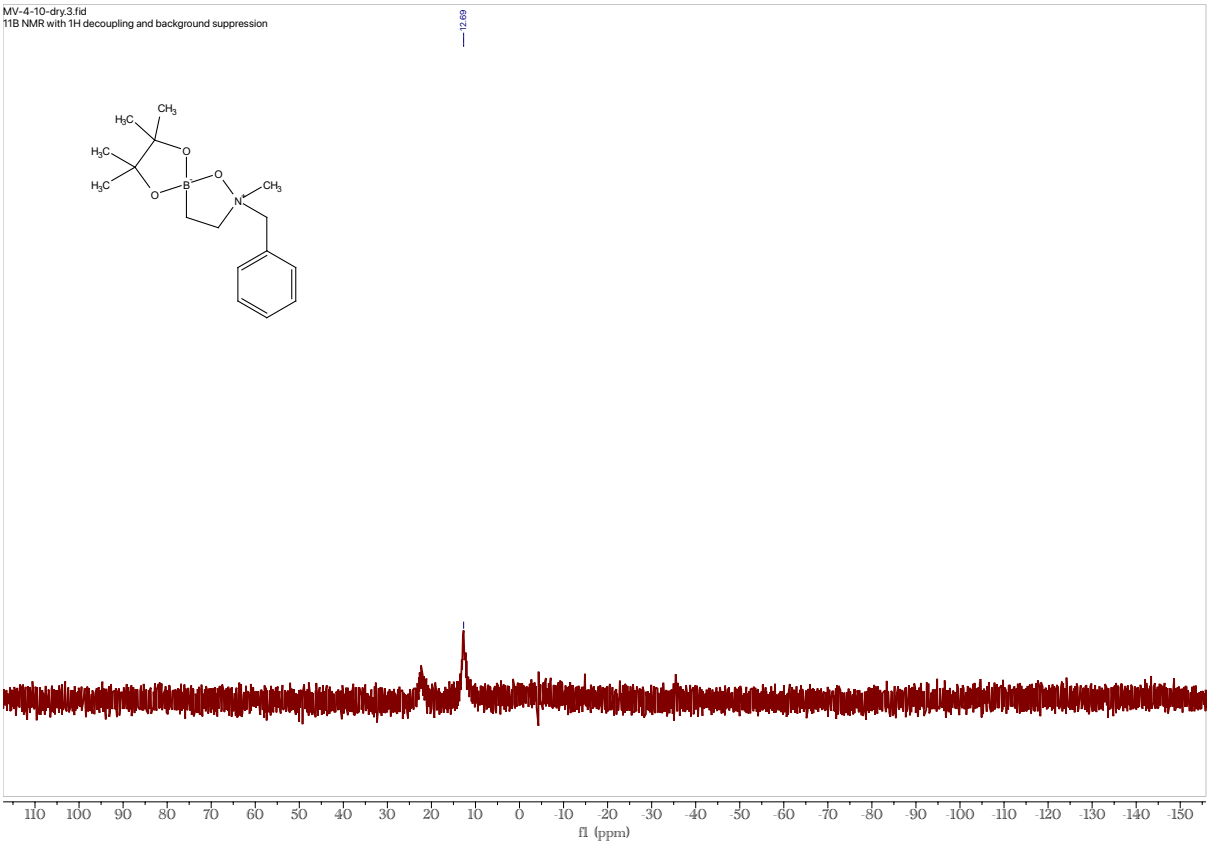

MV-4-13A-fr13-17.2.fid
11B NMR with 1H decoupling and background suppression
13.80
f1 (ppm)

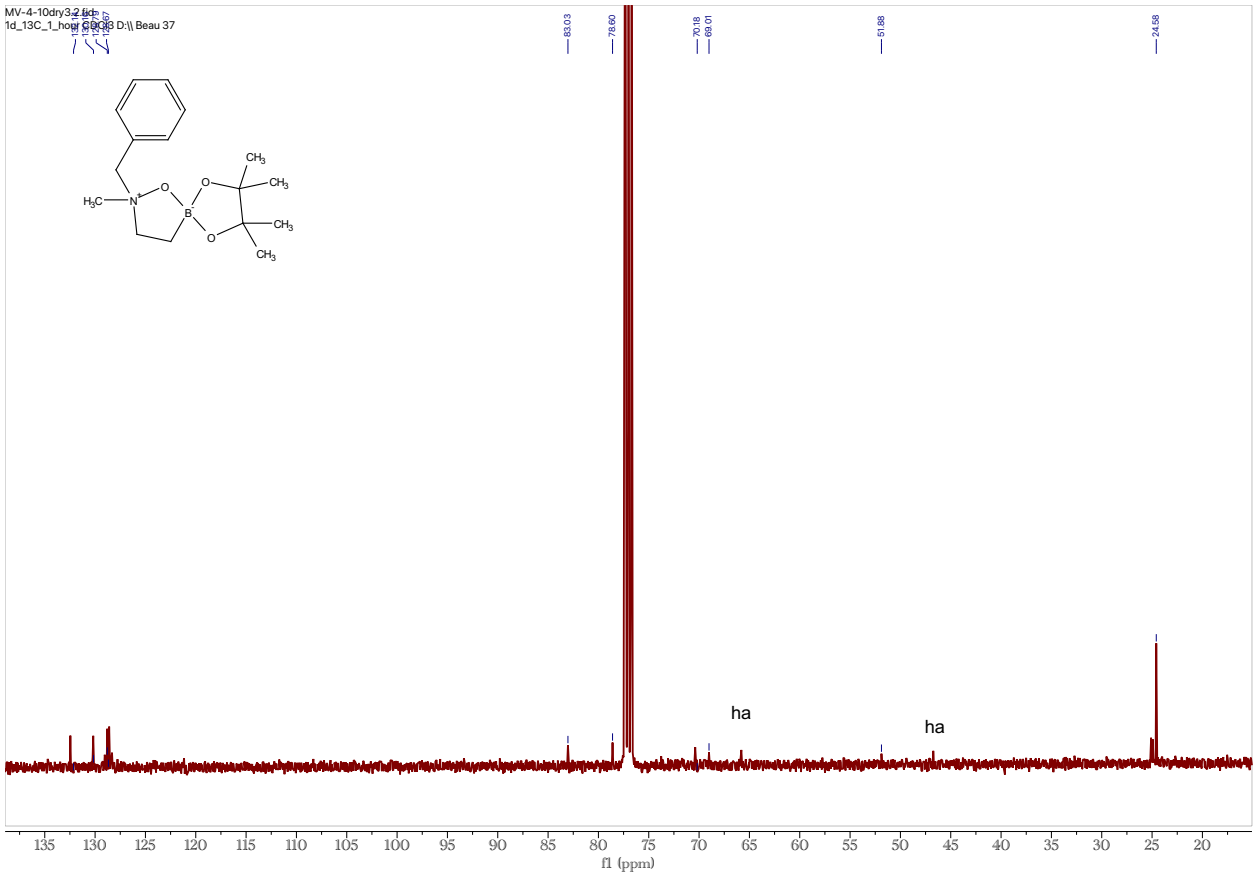

MV-3-187Bdry.1.fid
1H NMR
OH
N
H3C
A (m)
7.34
B (s)
3.78
C (s)
2.65
f1 (ppm)

2.3e

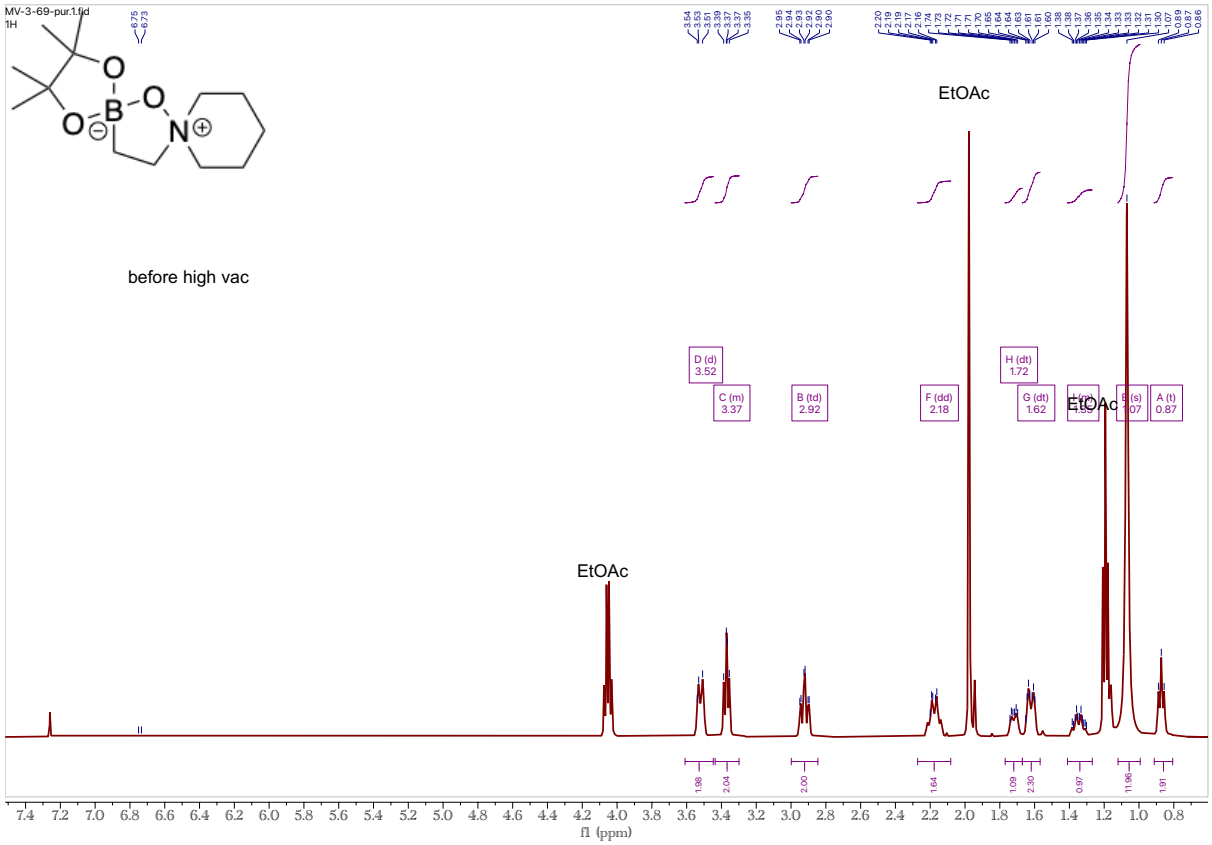

1 day high vac
ha = hydroxylamine
I (s)
5.30
J (s)
5.40
H (m)
7.42
A (d)
4.58
B (d)
4.23
D (m)
3.69
E (dt)
3.41
C (s)
2.95
G (d)
1.16
F (m)
1.03
K (d)
1.23
ha
ha
f1 (ppm)

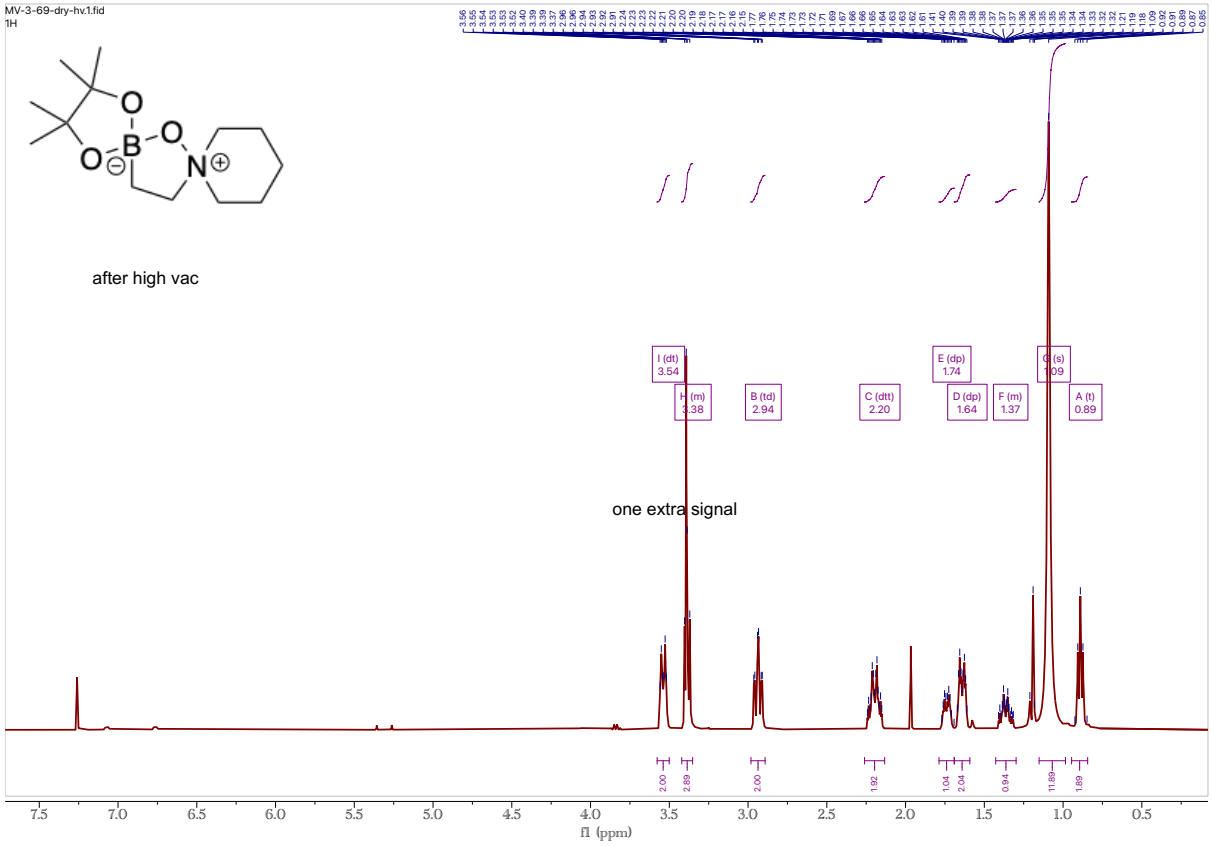

2 days high vac
D (m) 7.44
E (d) 4.57
F (d) 4.23
G (q) 3.70
H (q) 3.41
I (s) 2.94
A (d) 1.15
B (m) 1.04
f1 (ppm)

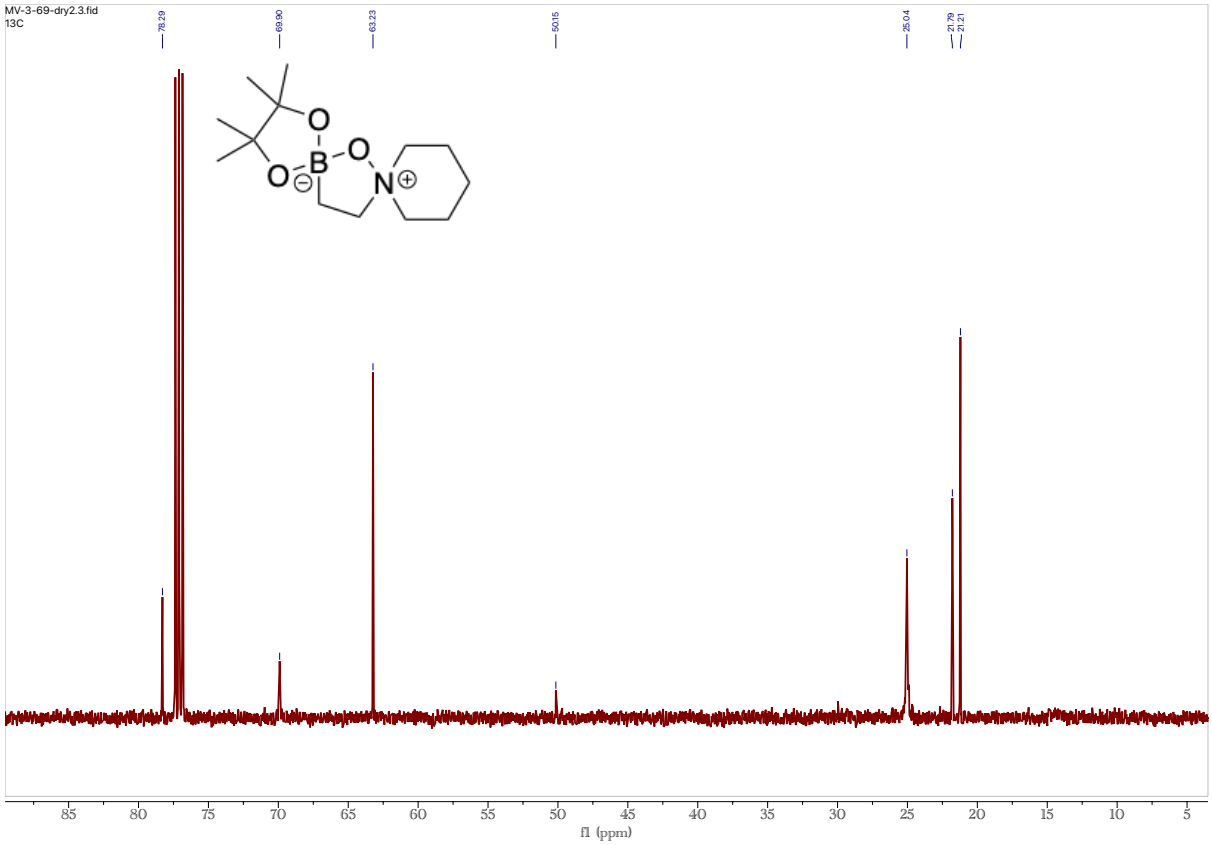

MV-4-10-dry.3.fid
11B NMR with 1H decoupling and background suppression
12.69
f1 (ppm)

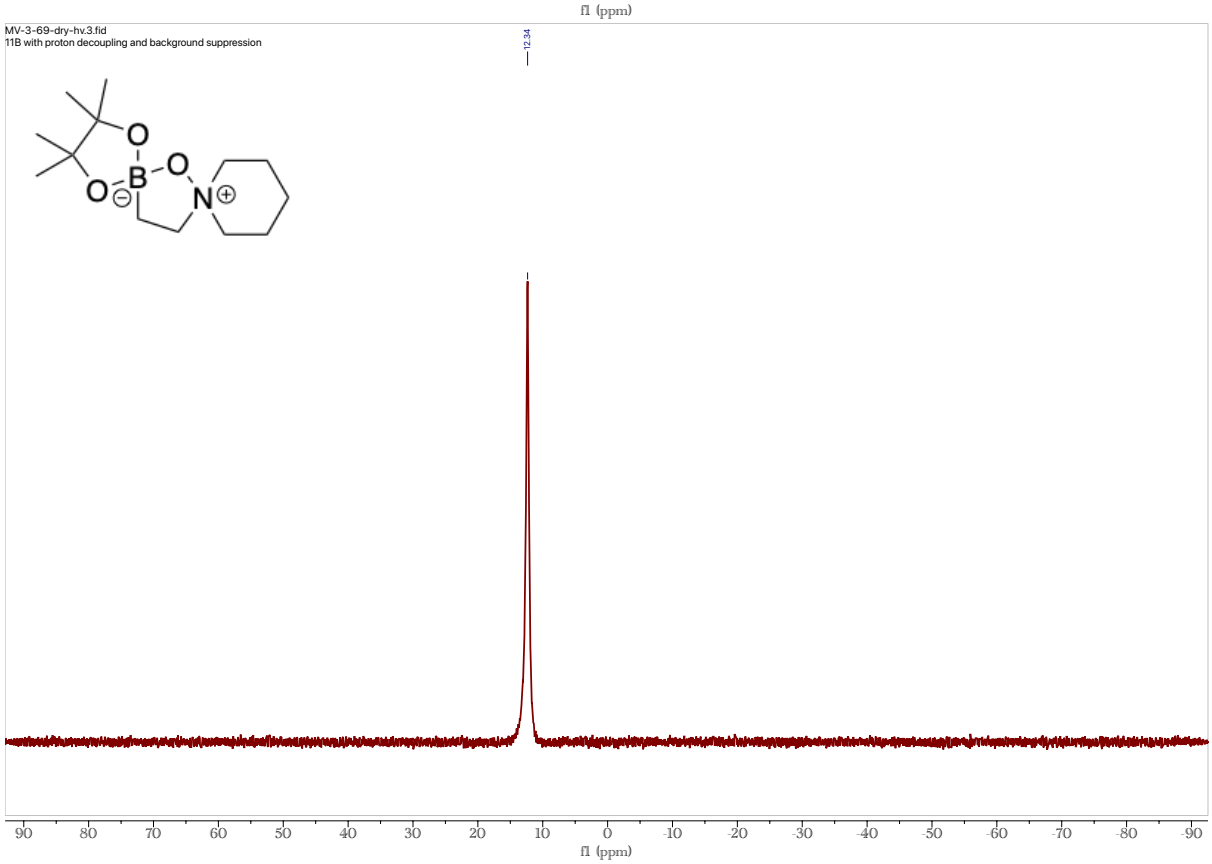

MV-4-10dry3-2.fid
1d_13C_1_hour CDCl3 D:\\ Beau 37
83.03
78.60
70.18
69.01
51.88
24.58
ha
ha
135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20
f1 (ppm)

2.3f

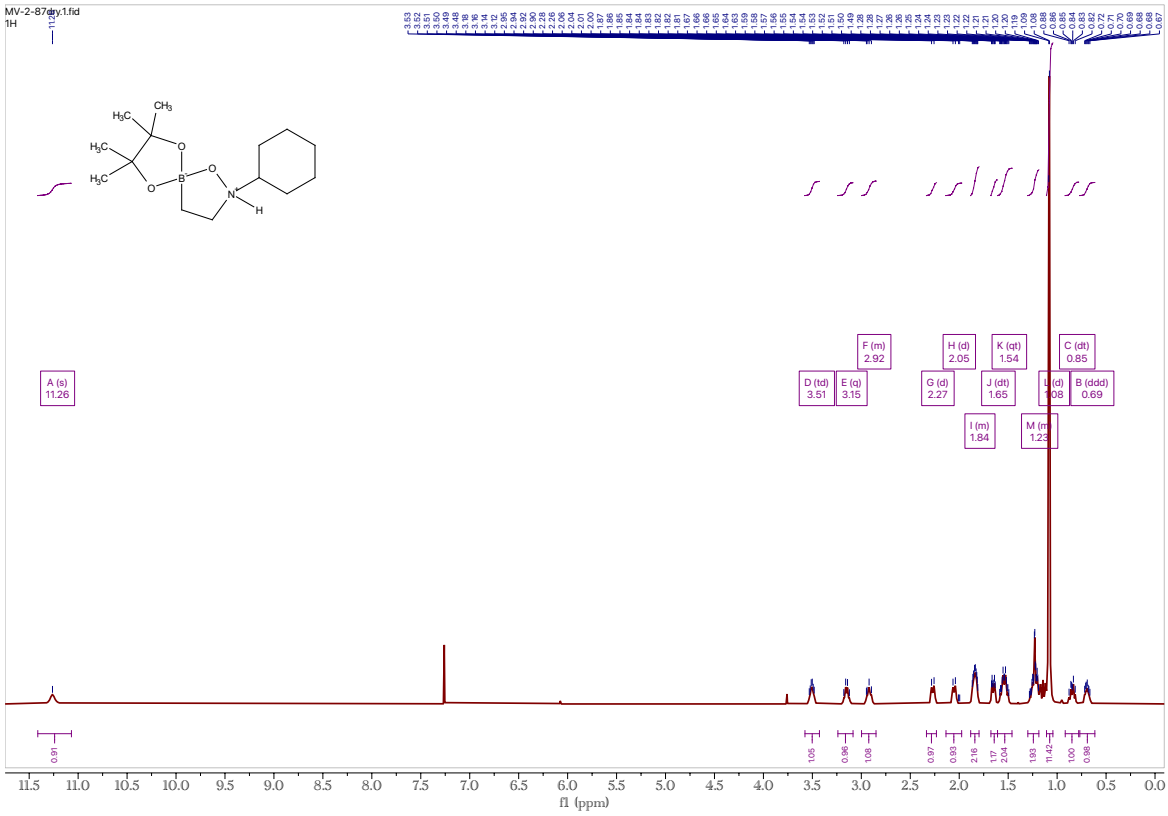

MV-3-69-pur.1.fid
1H
before high vac
EtOAc
EtOAc
EtOAc
D (d) 3.52
C (m) 3.37
B (td) 2.92
F (dd) 2.18
H (dt) 1.72
G (dt) 1.62
A (t) 0.87
f1 (ppm)

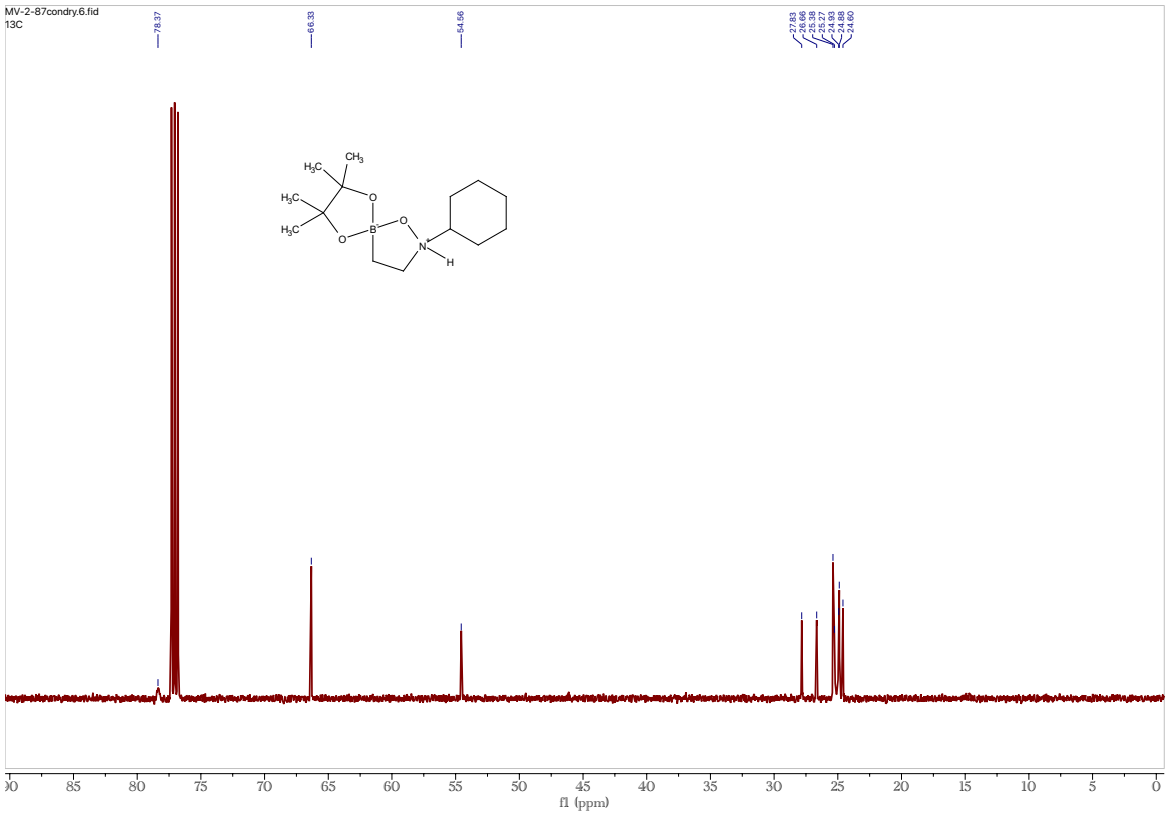

MV-3-69-dry-hv.1.fid
1H
after high vac
one extra signal
I (dt) 3.54
H (m) 3.38
B (td) 2.94
C (dtt) 2.20
E (dp) 1.74
D (dp) 1.64
F (m) 1.37
A (t) 0.89
f1 (ppm)

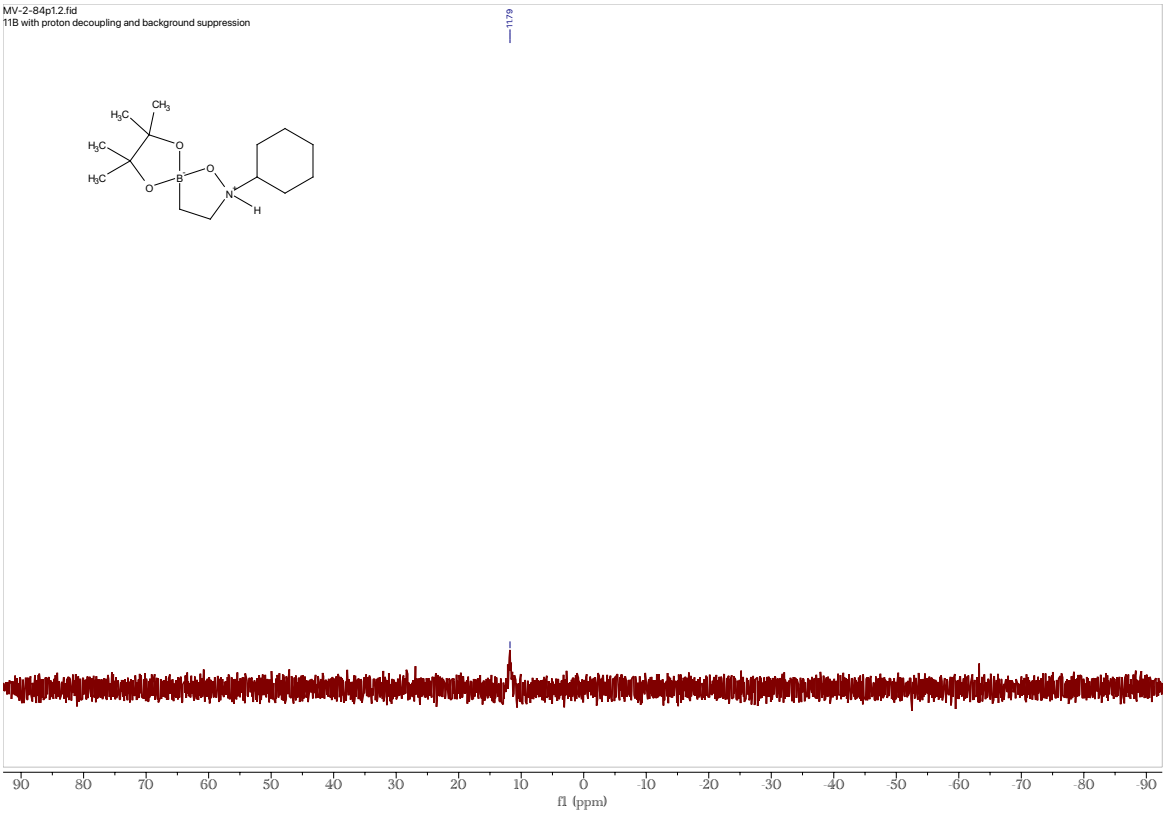

MV-3-69-dry2.3.fid
13C
78.29
69.90
63.23
50.15
25.04
21.79
21.21
O
B
O
O
N
85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5
f1 (ppm)


MV-3-69-dry-hv.3.fid
11B with proton decoupling and background suppression
12.34
O
B
O
O
N
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90
f1 (ppm)

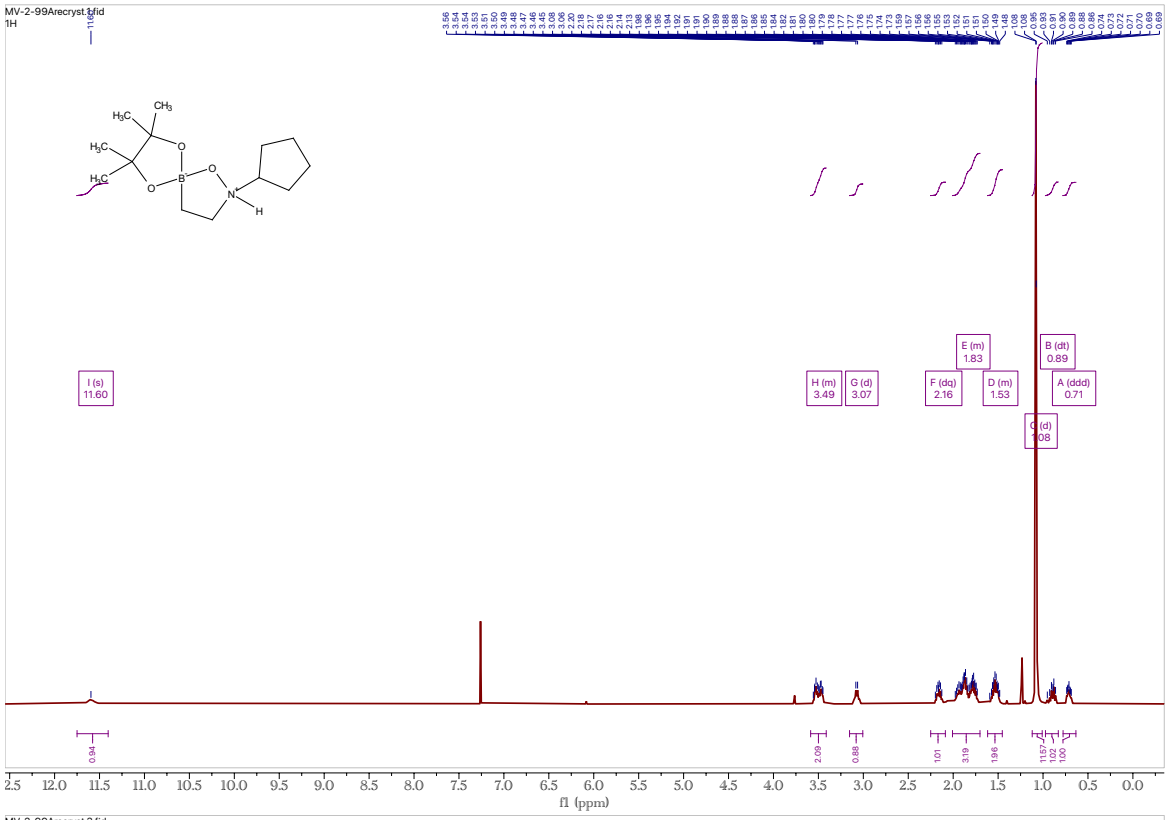
2.6e

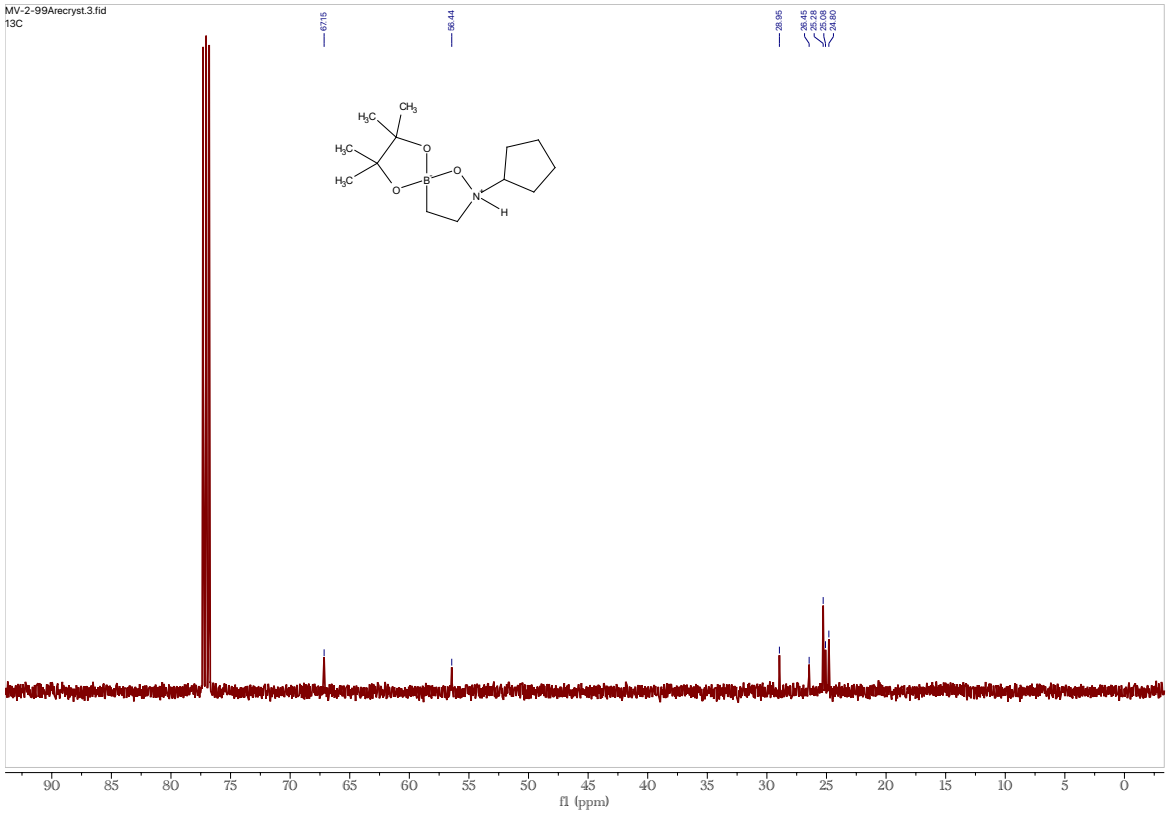

MV-2-87dry.1.fid
1H
A (s) 11.26
D (td) 3.51
E (q) 3.15
F (m) 2.92
G (d) 2.27
H (d) 2.05
I (m) 1.84
J (dt) 1.65
K (qt) 1.54
C (dt) 0.85
B (ddd) 0.69
f1 (ppm)

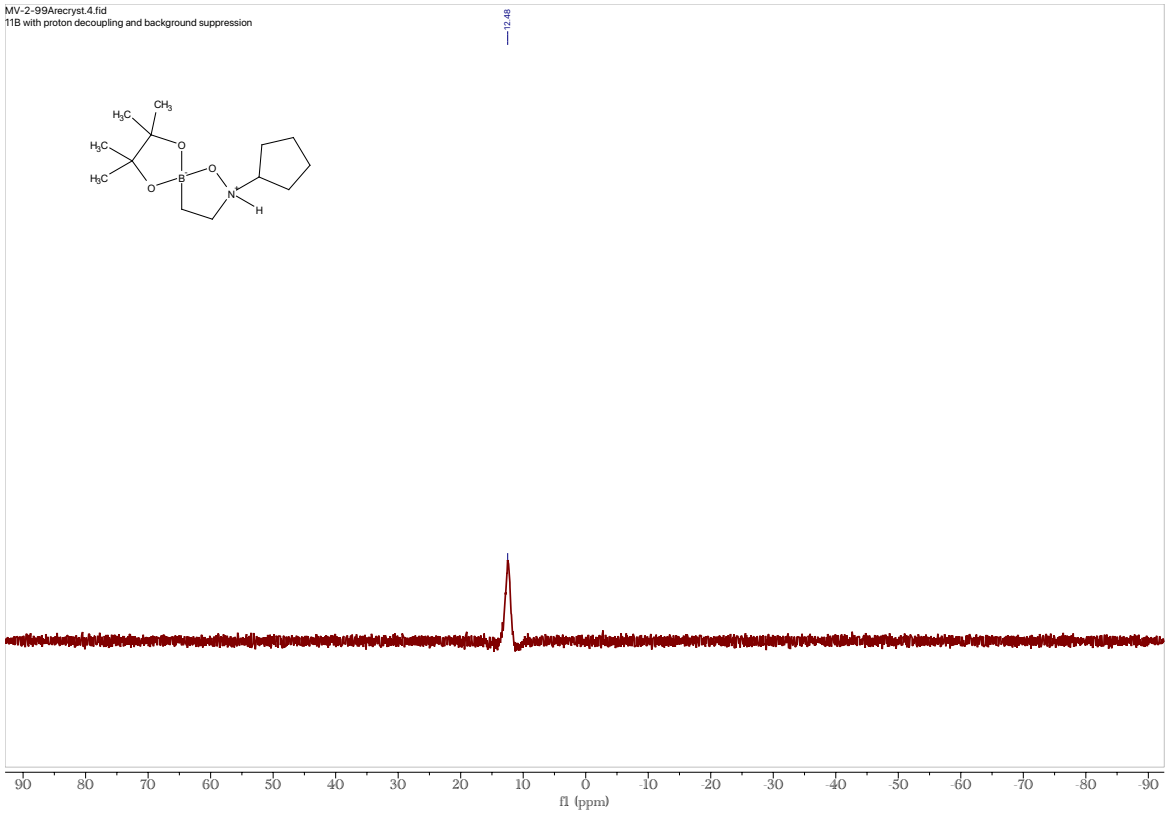

MV-2-87condry.6.fid
13C
78.37
66.33
54.56
27.83
26.66
25.38
25.27
24.93
24.88
24.60
f1 (ppm)


MV-2-84p1.2.fid
11B with proton decoupling and background suppression
11.79
H3C
CH3
H3C
H3C
O
O
O
B
N+
H
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
f1 (ppm)

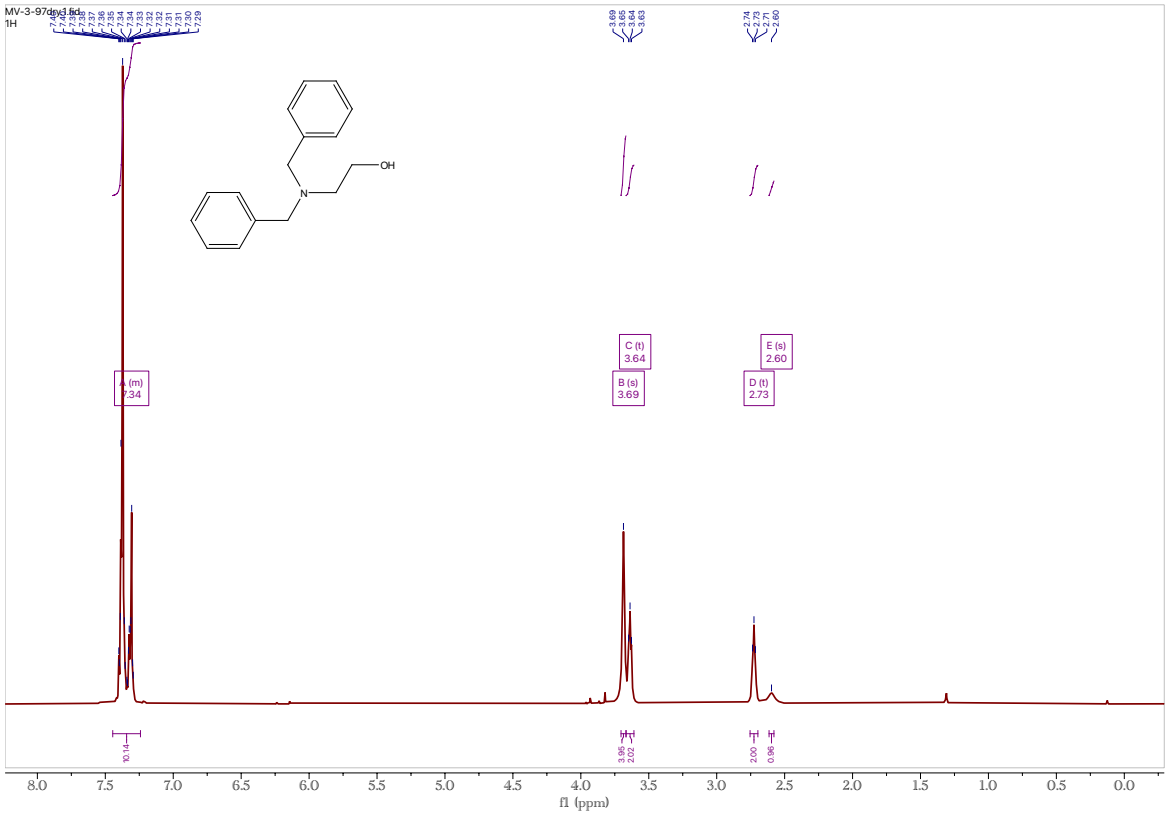
2.6f

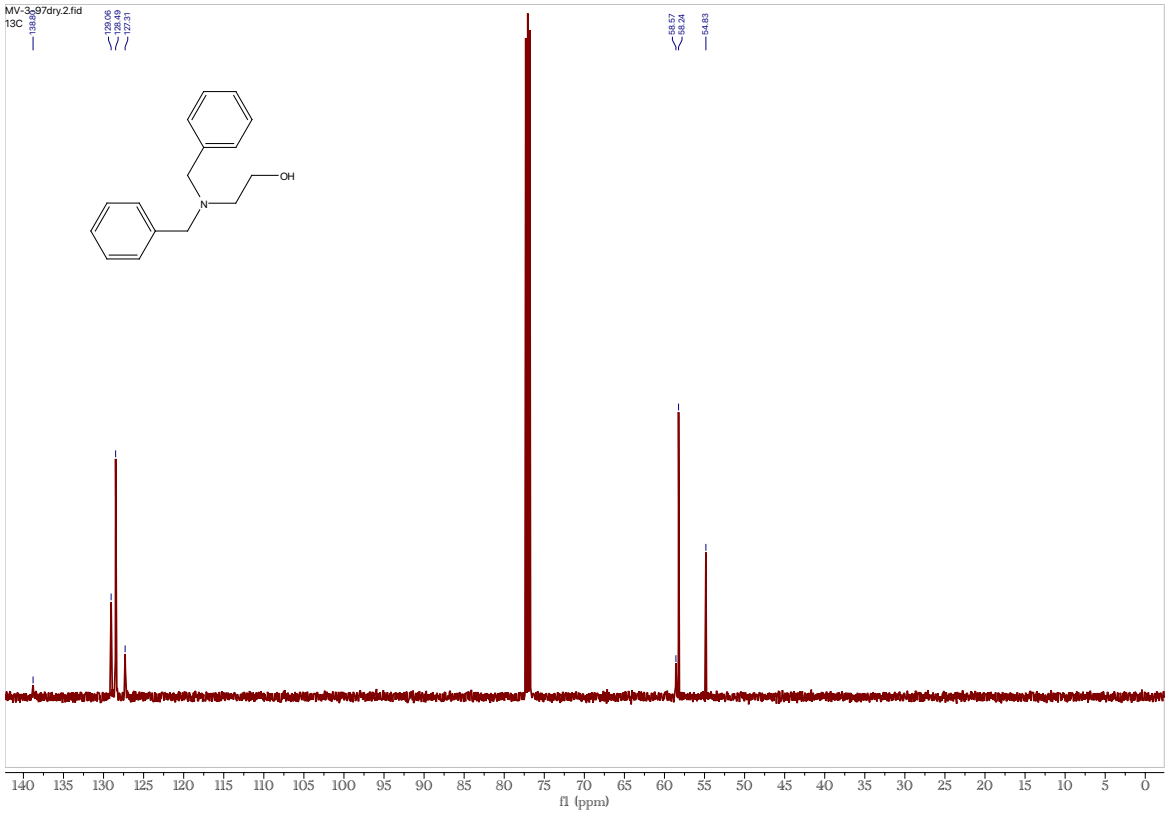

MV-2-99Arecryst.1.fid
1H
I (s)
11.60
H (m)
3.49
G (d)
3.07
E (m)
1.83
F (dq)
2.16
D (m)
1.53
B (dt)
0.89
A (ddd)
0.71
C (d)
1.08
f1 (ppm)


MV-2-99Arecryst.3.fid
13C
67.15
56.44
28.95
26.45
25.28
25.08
24.60
f1 (ppm)

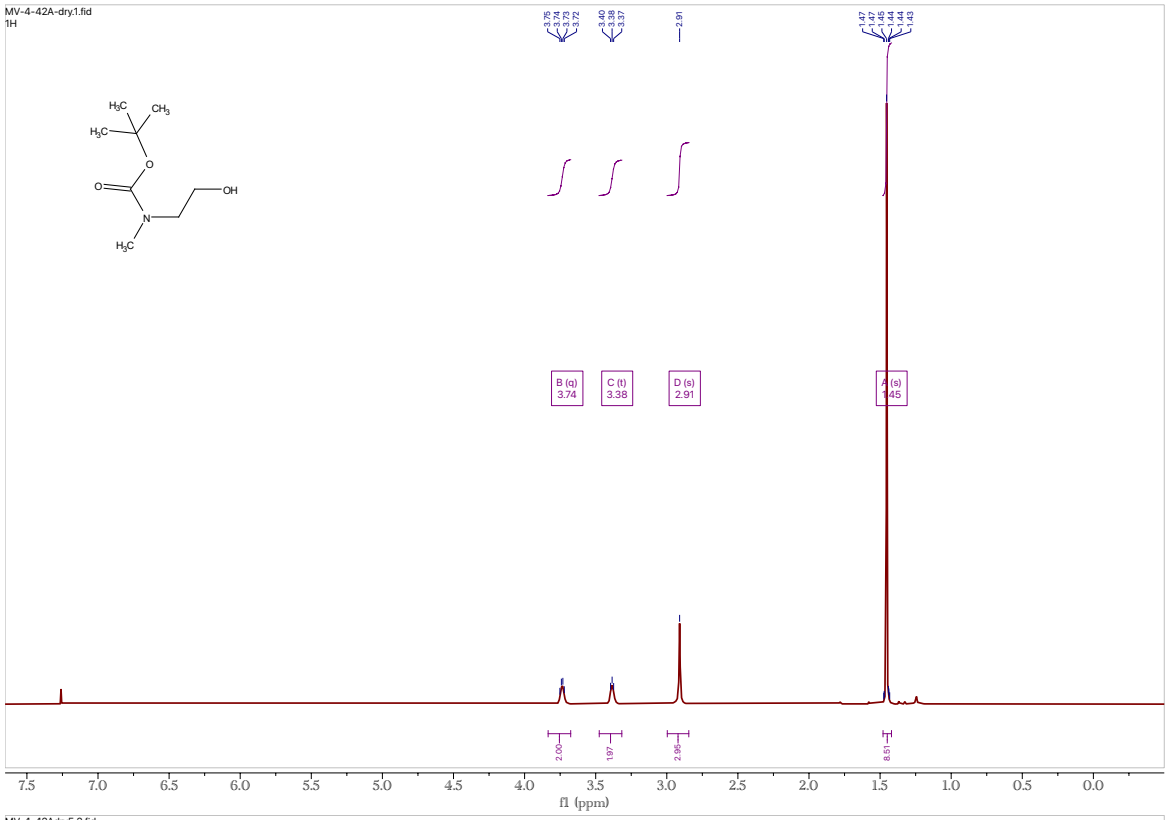

MV-2-99Arecryst.4.fid
11B with proton decoupling and background suppression
12.48
H3C
CH3
H3C
H3C
O
O
O
B
N+
H
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
f1 (ppm)

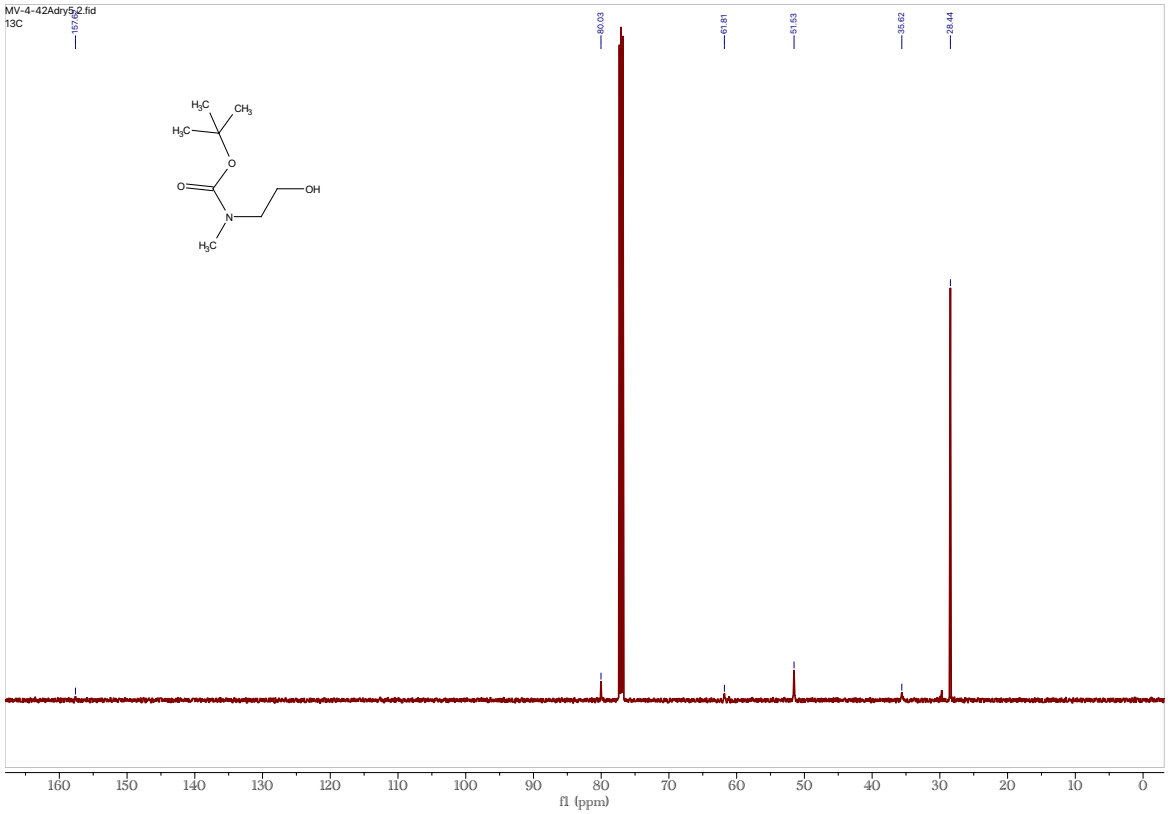
2.3d.1


MV-3-97dry.1.fid
1H
OH
N
A (m)
7.34
B (s)
3.69
C (t)
3.64
D (t)
2.73
E (s)
2.60
f1 (ppm)


MV-3-97dry.2.fid
13C
OH
N
f1 (ppm)

2.6a.4

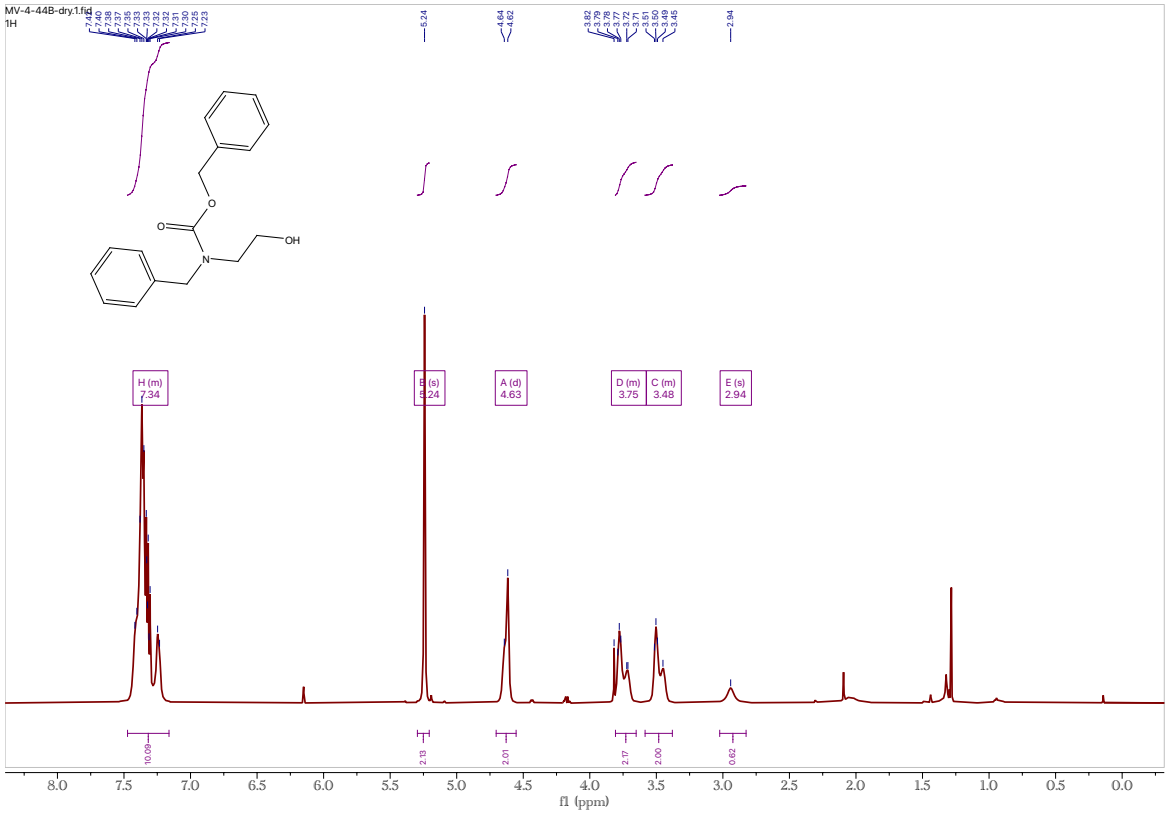

MV-4-42A-dry.1.fid
1H
3.75
3.74
3.73
3.72
3.40
3.38
3.37
2.91
1.47
1.47
1.45
1.44
1.44
1.43
B (q)
3.74
C (t)
3.38
D (s)
2.91
A (s)
1.45
2.00
1.97
2.96
8.51
f1 (ppm)

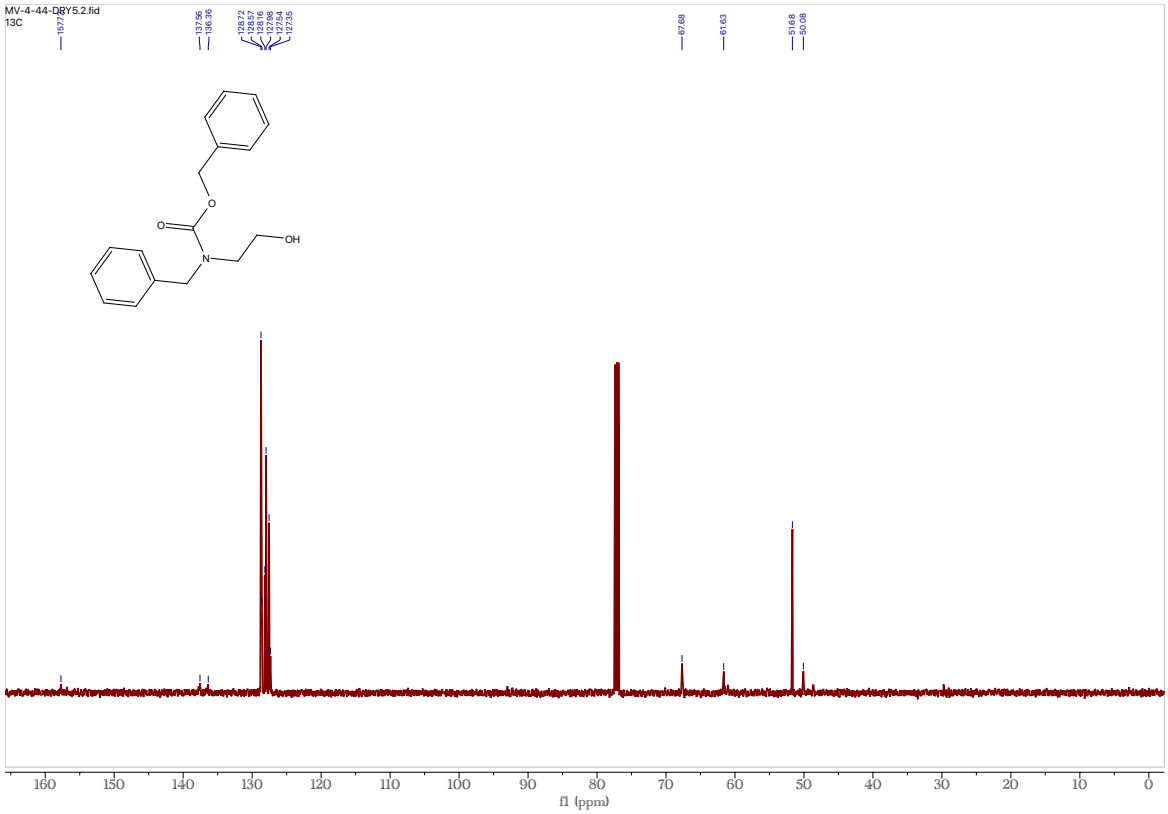

MV-4-42Adry5_2.fid
13C
157.16
80.03
61.81
51.53
35.62
28.44
f1 (ppm)

2.3e

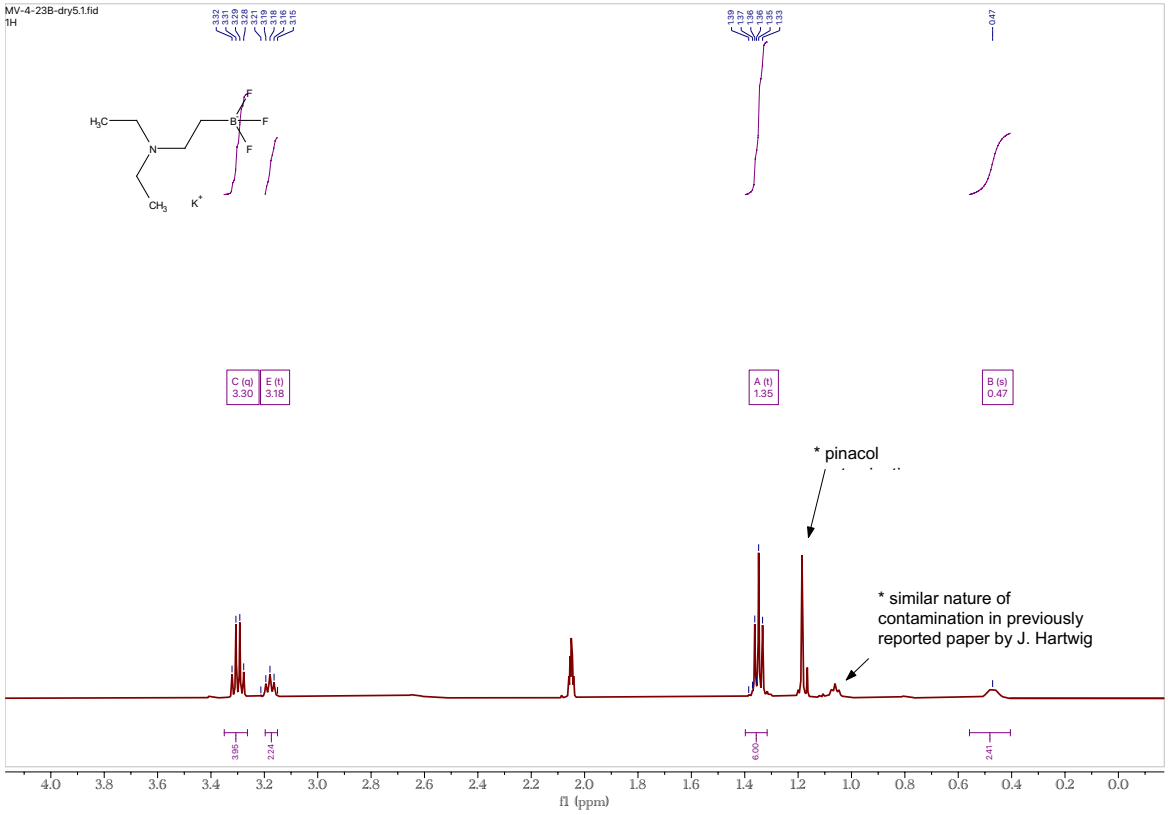
2.6c.6

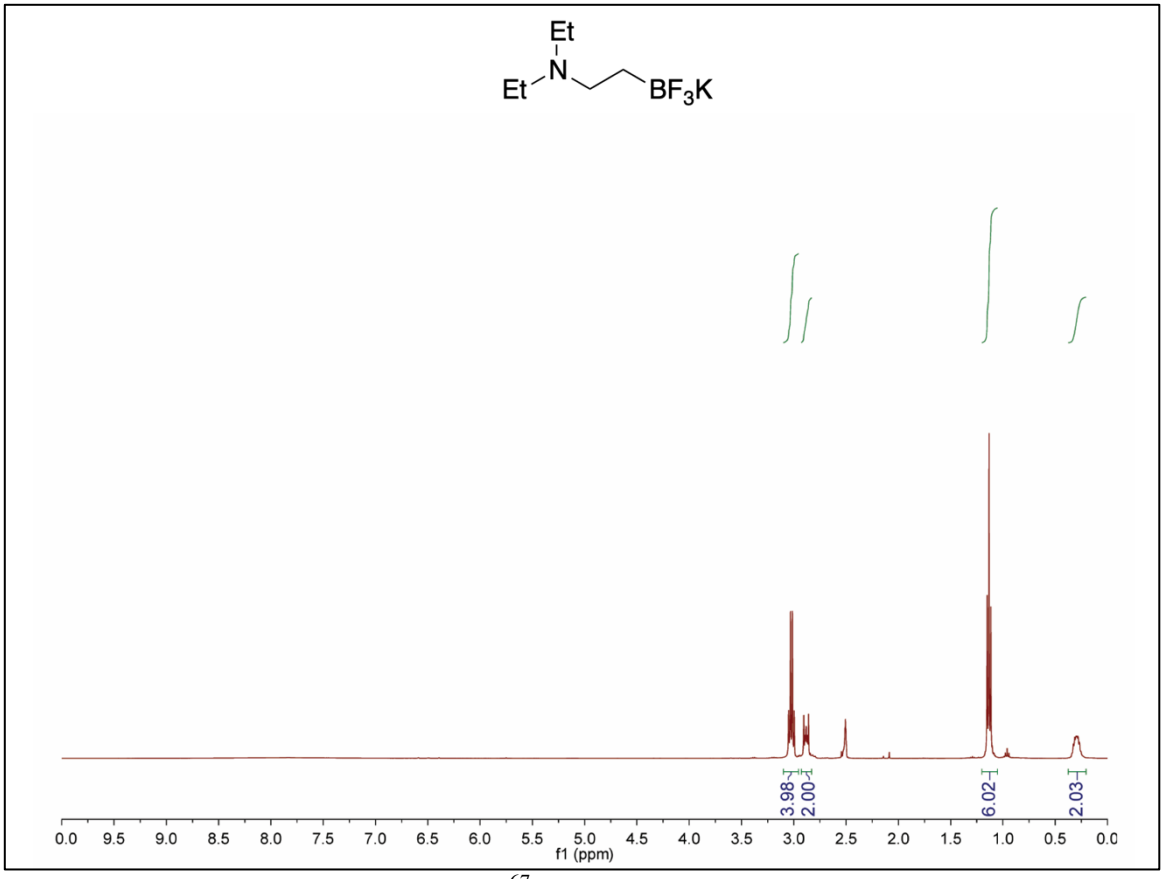

MV-4-14A-flr.1.fid
1H NMR
C (m) 7.32
G (s) 5.14
E (s) 4.52
D (d) 4.39
B (s) 1.22
A (t) 1.12
f1 (ppm)


MV-4-44B-dry.1.fid
1H
H (m) 7.34
B (s) 5.24
A (d) 4.63
D (m) 3.75
C (m) 3.48
E (s) 2.94
f1 (ppm)

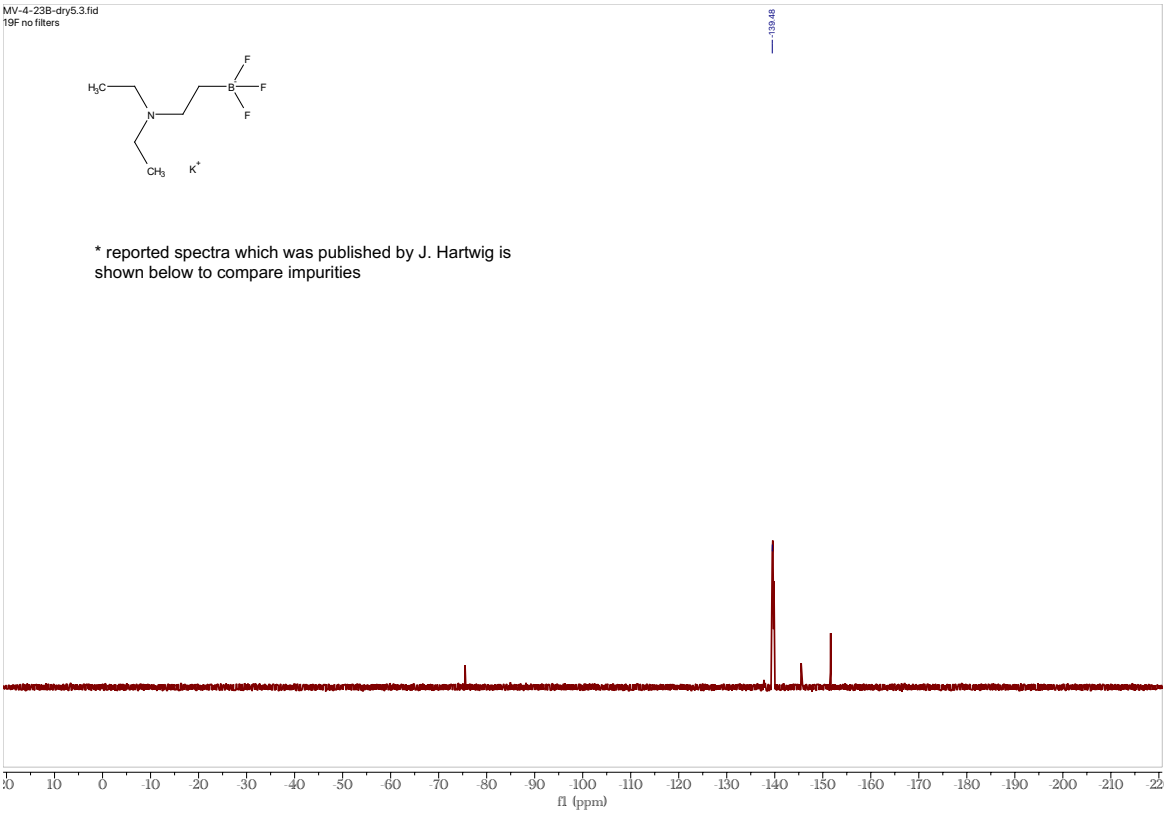

MV-4-44-DRY5.2.fid
13C
157.7
137.56
136.36
128.72
128.57
128.18
127.98
127.54
127.35
67.68
61.63
51.68
50.08
O
O
N
OH
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

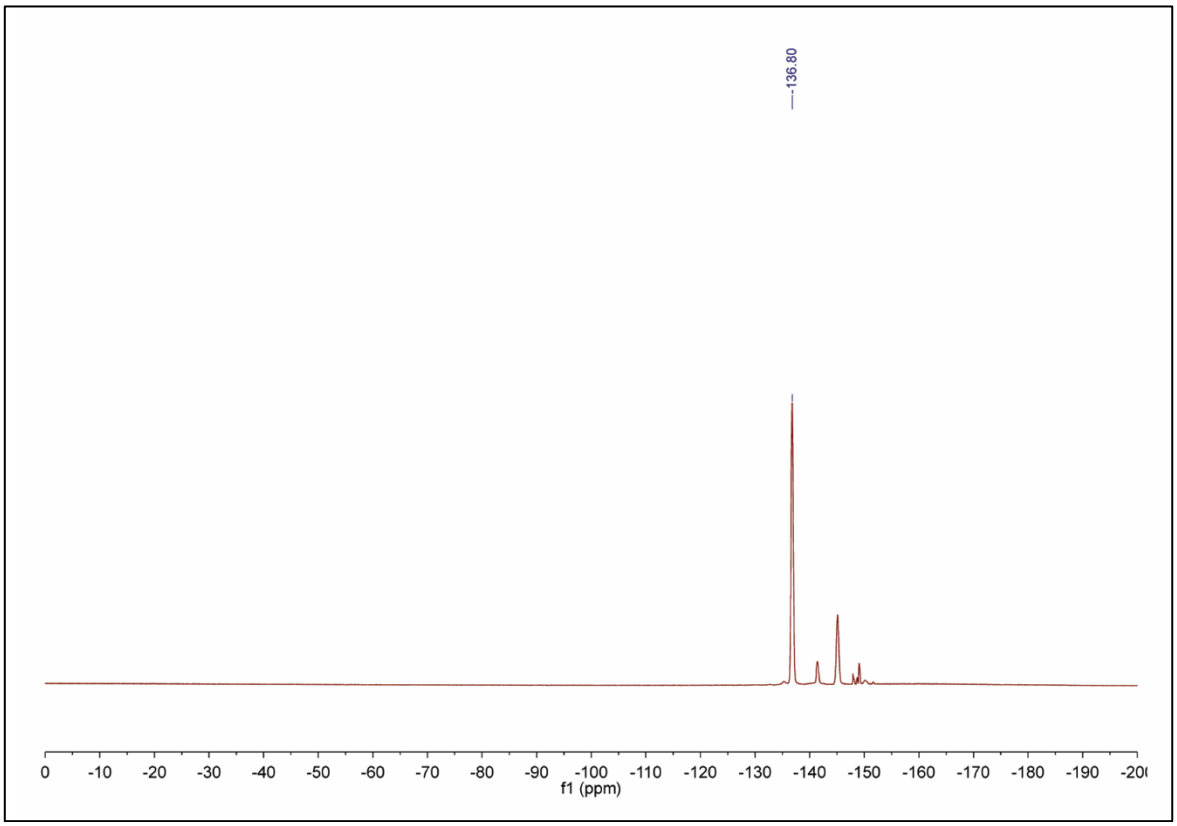
2.3a.1


MV-4-23B-dry5.1.fid
1H
C (q) 3.30
E (t) 3.18
A (t) 1.35
B (s) 0.47
* pinacol
* similar nature of contamination in previously reported paper by J. Hartwig
f1 (ppm)

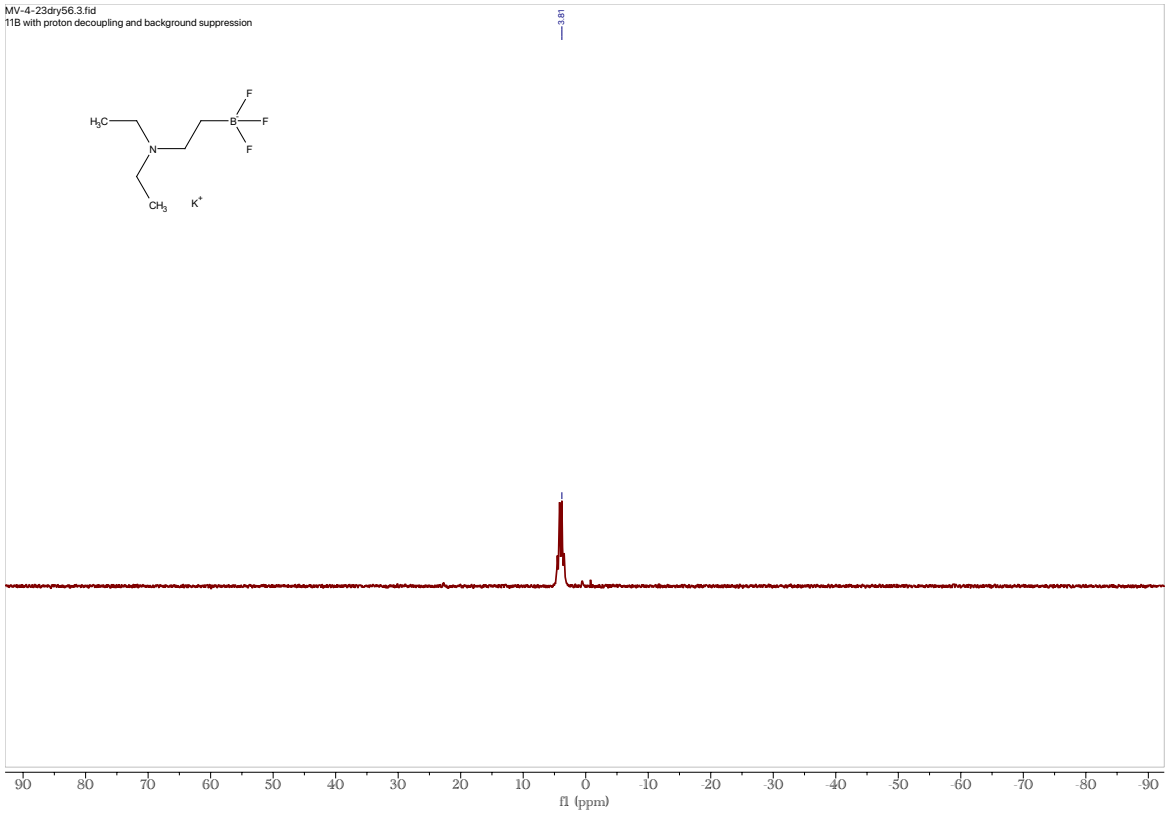


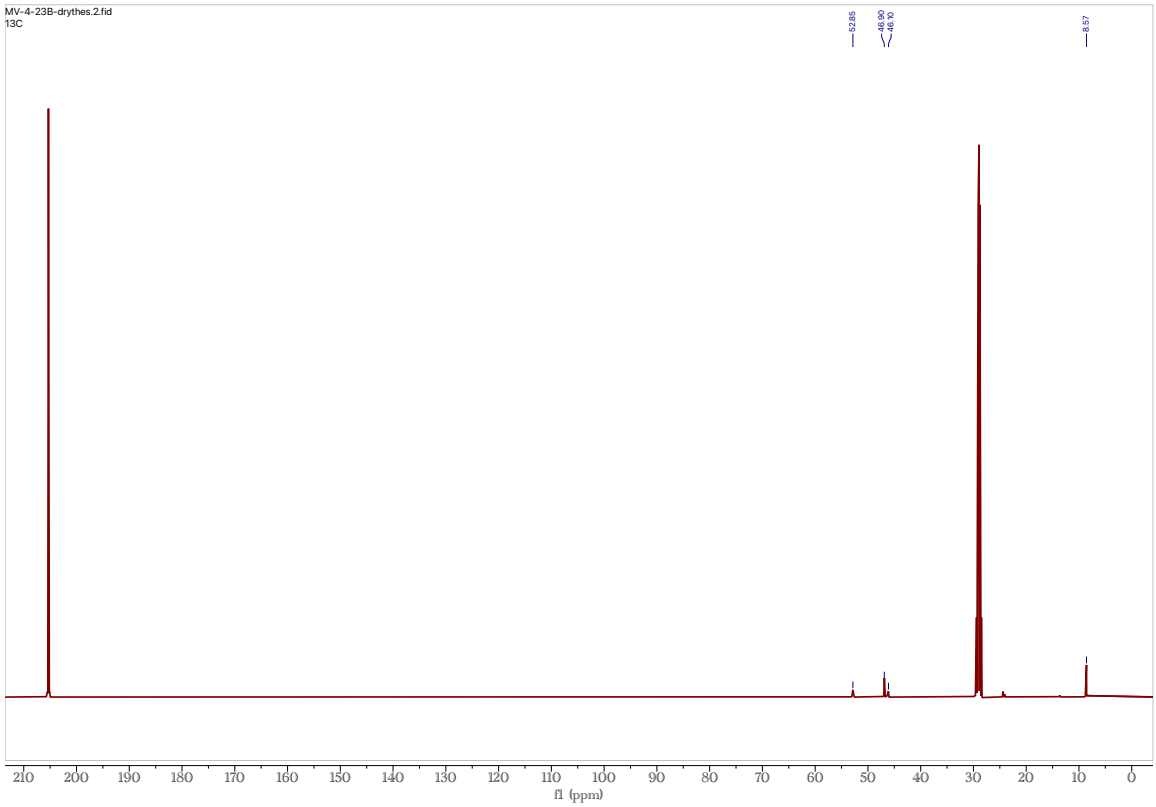
** Spectrum observed by the Hartwig group[67a] for compound **2.3a.1**. Reproduced with permission of the ACS.*



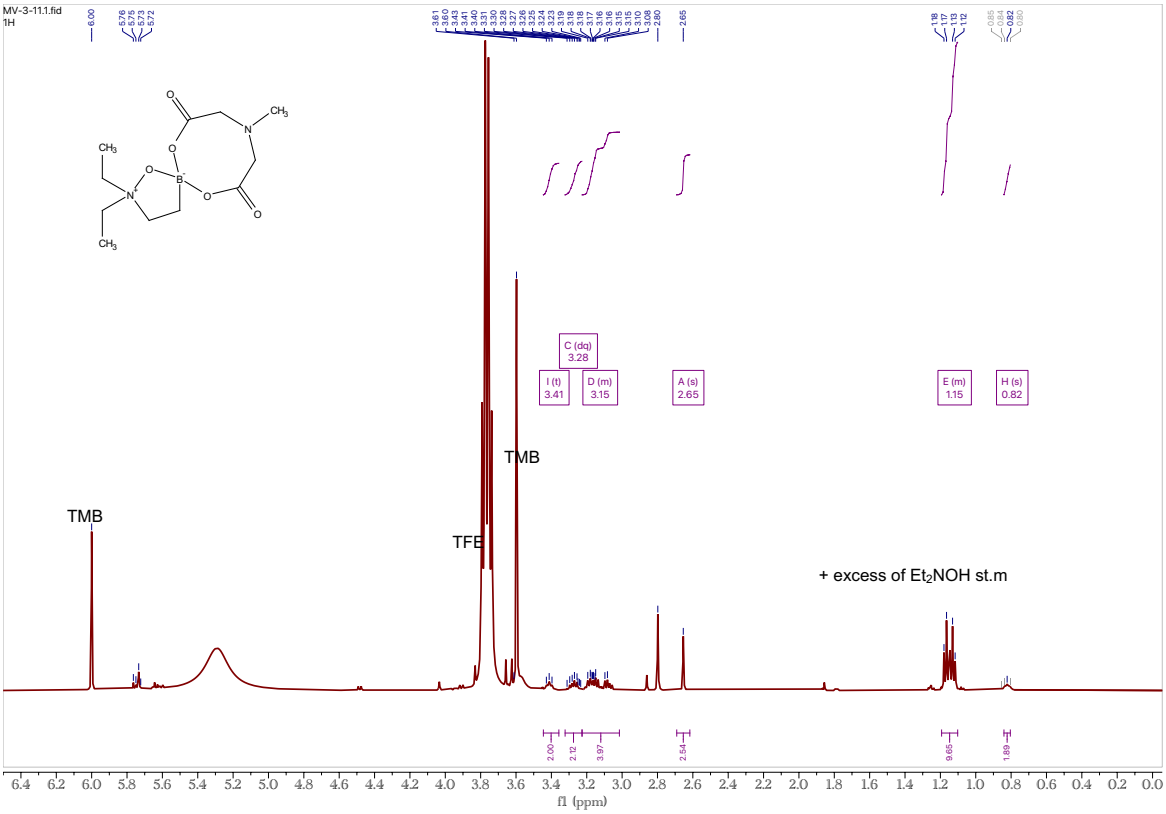


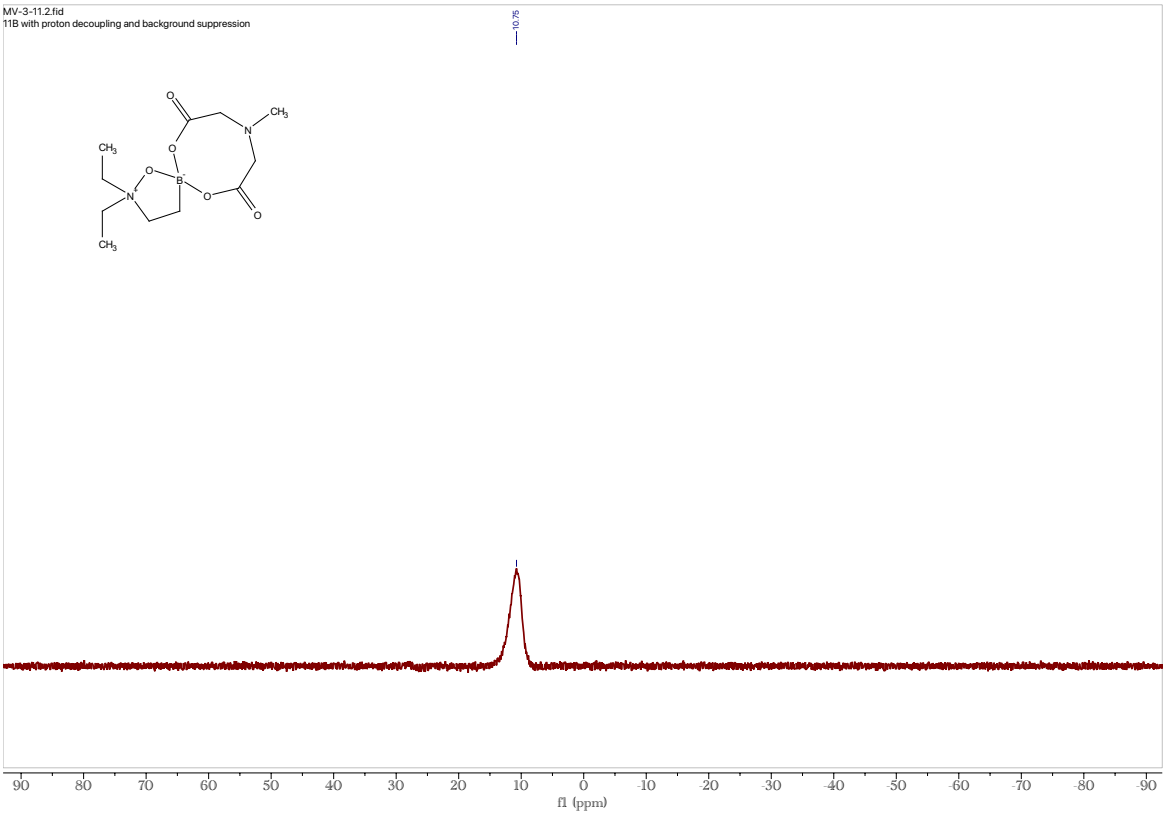
Spectrum observed by the Hartwig group[67a] for compound **2.3a.1. Reproduced with permission of the ACS.*


MV-4-23dry56.3.fid
11B with proton decoupling and background suppression
3.81
F
H3C
B
F
N
F
CH3
K+
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90
f1 (ppm)

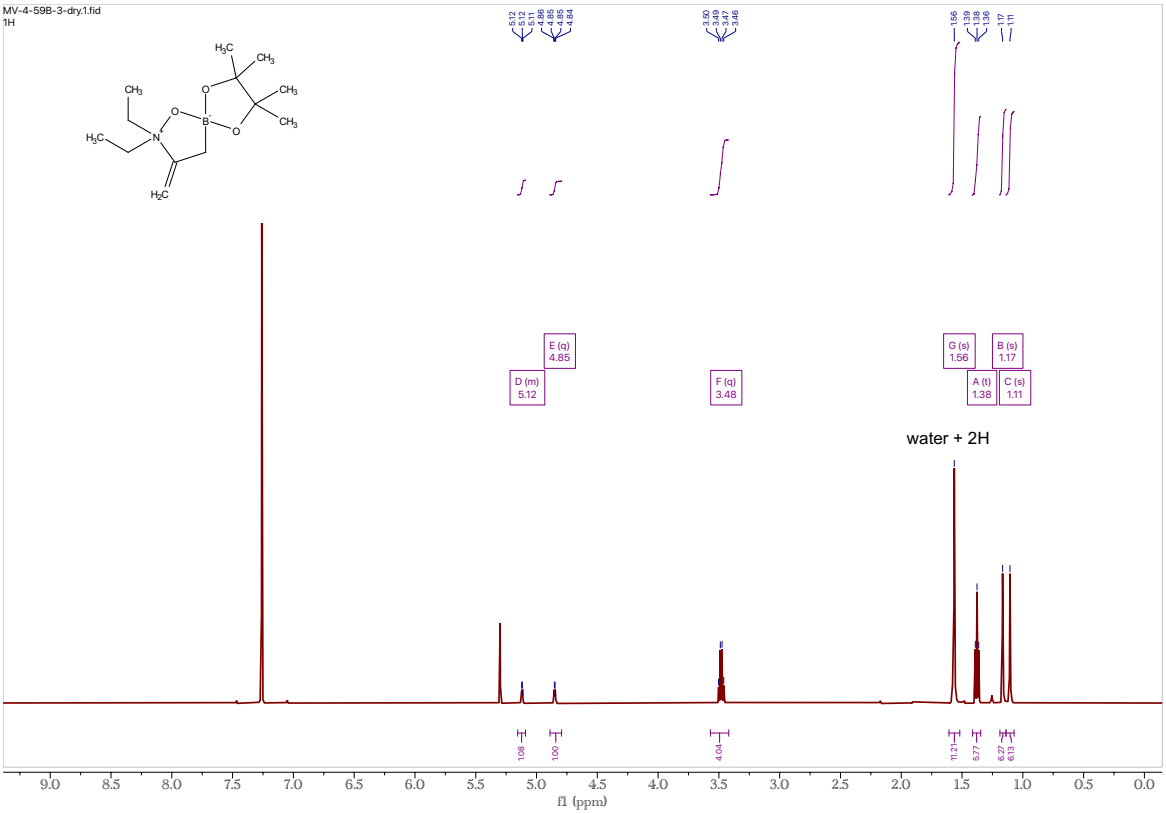

MV-4-23B-drythes.2.fid
13C
52.85
46.90
46.10
8.57
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

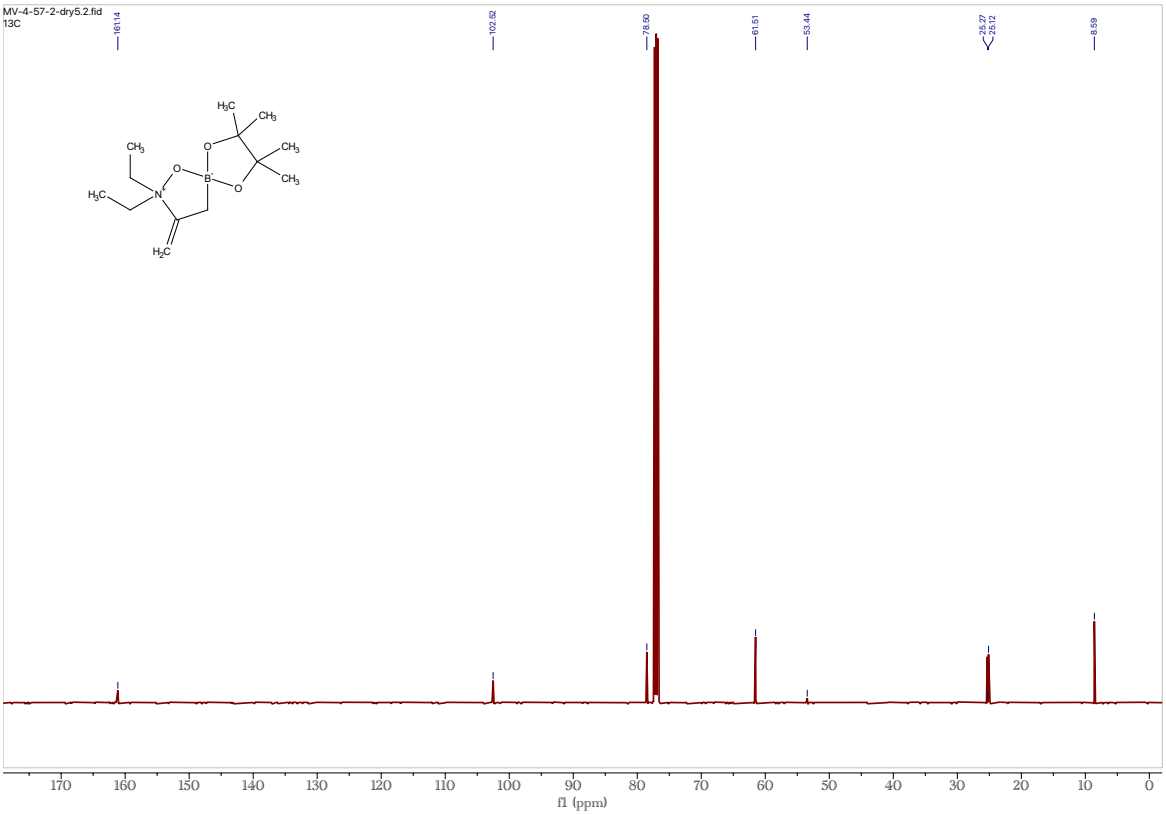
2.26

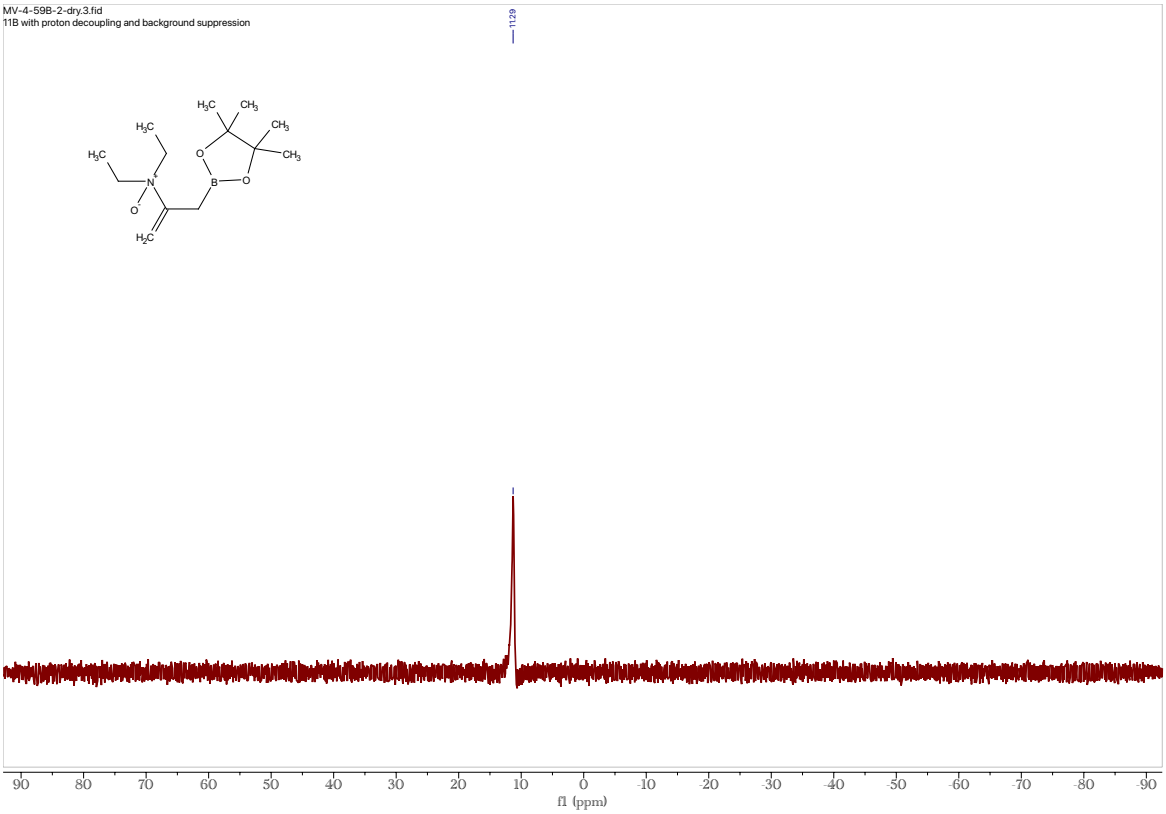

MV-3-11.1.fid
1H
TMB
TFE
TMB
+ excess of Et2NOH st.m
f1 (ppm)


MV-3-11.2.fid
11B with proton decoupling and background suppression
f1 (ppm)

2.3e
2.47a

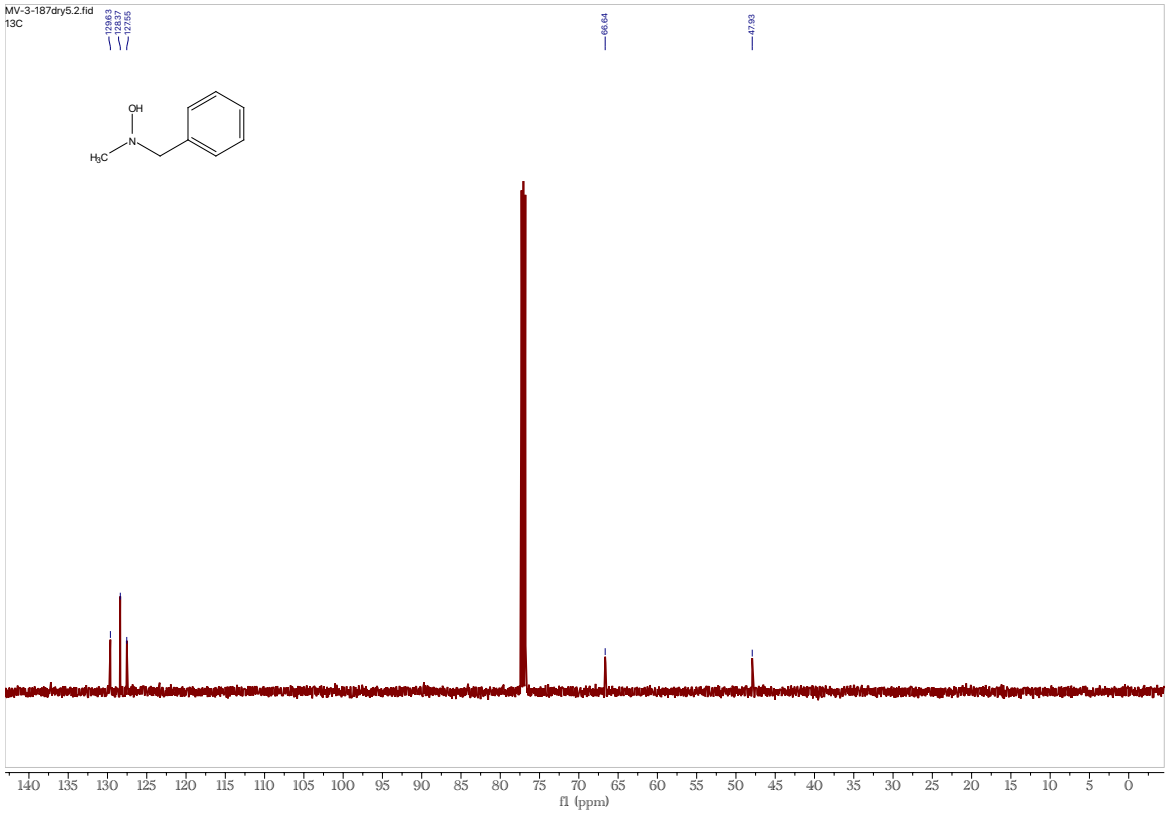

MV-4-59B-3-dry.1.fid
1H
D (m)
5.12
E (q)
4.85
F (q)
3.48
G (s)
1.56
A (t)
1.38
B (s)
1.17
C (s)
1.11
water + 2H
f1 (ppm)


MV-4-57-2-dry5.2.fid
13C
161.14
102.62
78.50
61.51
53.44
25.27
25.12
8.59
f1 (ppm)


MV-4-59B-2-dry.3.fid
11B with proton decoupling and background suppression
11.29
H3C
CH3
CH3
CH3
H3C
H3C
O
N
O
B
O
H2C
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
f1 (ppm)

3.2d


MV-3-187Bdry.1.fid
1H NMR
7.36
7.35
7.34
7.33
7.33
7.33
7.32
7.31
7.30
7.29
7.29
7.28
3.79
2.66
OH
N
H3C
C (m)
7.34
A (s)
3.79
B (s)
2.66
4.62
2.00
3.01
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


MV-3-187dry5.2.fid
13C
129.03
128.77
128.37
127.55
66.64
47.93
OH
N
H3C
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
f1 (ppm)