Chemoselective Transformations of Amphoteric Aziridine Aldehydes and α-Boryl Aldehydes

by

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A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy
Department of Chemistry
University of Toronto

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2014

Abstract

The development of novel chemical strategies aimed at the synthesis of complex chemical entities comprises a central part of organic chemistry. An important area of this research is the development of reagents and/or building blocks that possess multiple handles with orthogonal reactivity. In this area, amphoteric molecules represent a platform for uncovering novel transformations previously inaccessible with conventional reagents. This thesis reports on the development of chemoselective transformations with amphoteric molecules developed in the Yudin lab. Following the introduction, Chapter 2 describes the development of an aldehyde-amine-alkyne (A₃-coupling) reaction. Chapter 3 describes the development of an alkyl-MIDA boronate Suzuki-Miyaura cross-coupling reaction with direct application to the introduction of heterocycles to aryl substrates.¹ The remainder of the thesis concentrates on amphoteric α-MIDA boryl aldehydes and the identification of unusual boron-containing products and intermediates. Chapter 4 describes a method for the synthesis of cyclic-amino boronates and highlights the influence of the MIDA boronate substituent on C-H activation. Chapter 5 delves into the chemoselective enolization of α-boryl aldehydes to form a C,O-bis enolate.² This intermediate was subsequently utilized in a Tsuji–Trost allylic alkylation reaction affording quaternary alkyl boronate products. Finally, Chapter 6 describes the condensation of α-boryl aldehydes with

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amines, yielding α-boryl enamines and α-boryl enamides. These densely functionalized nitrogen-containing substrates were then applied to the synthesis of boron-containing heterocycles and other biologically relevant products.

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Outline of Thesis

The research described in this thesis is presented with a single overarching concept of chemoselective transformations involving amphoteric molecules. In Chapter 1, the development of a divergent multicomponent aldehyde-amine-alkyne ($A_3^-$-coupling) reaction based upon the $\alpha$-aziridine aldehyde dimer scaffold. Preliminary work on this project was performed by Mr. Nick Afagh (Yudin lab, M.Sc. 2007-2010). In addition, a collaboration with Mr. Sean Liew (Yudin lab) allowed for the development of the stereochemical model of both the Petasis-boron-Mannich and $A_3^-$-coupling reactions. Chapter 2 describes the development of a primary alkyl MIDA boronate and aryl bromide Suzuki-Miyaura cross-coupling (SMCC) reaction. This project was designed by the author of this thesis and Professor Andrei Yudin. Mr. C. Frank Lee (Yudin lab) assisted with the preparation of an alkyl MIDA boronate compound and the corresponding SMCC reaction product and Dr. Conor Scully (Yudin lab) attempted computational modeling on the proposed intermediates. Chapter 3 pertains to the development of an $\alpha$-amination reaction of alkyl boronates. The invaluable assistance of Mr. C. Frank Lee was crucial for the preparation of several alkyl sulfamate esters and their cyclized products. Chapter 5 involves the development of a [Pd]-catalyzed allylation reaction of boryl aldehydes. Lastly, Chapter 6 describes the development of both enamine and enamide chemistry pertaining to boryl aldehydes. While independently designed, the parent boryl aldehyde was provided by Mr. Adam Zajdlik (Yudin lab) and Dr. Piera Trinchera (Yudin lab). Additionally, Ms. Joanne Tan (Yudin lab) performed the synthesis of a number of indolone structures and the isoindolone boronic acid. All work described within has been presented at academic conferences and/or published in the chemical literature. Unless explicitly stated all work described in this thesis was performed during the tenure of its author (September 2010 - September 2014) in the laboratory of Prof. Andrei Yudin.
Acknowledgments

I would like to express my sincere gratitude to Professor Andrei Yudin for his guidance, excitement and most of all *patience* throughout my tenure at University of Toronto. His incredible and relentless pursuit of ‘enabling’ chemistry has changed not only changed the course of my Ph.D. but also deeply affected the way I approach the field. I hope to further develop this skill in my future endeavors.

I am grateful to my supervisory and thesis defense committee members: Professor Mark Lautens, Professor Mark Taylor, and Professor Rob Batey. I would also like to thank my external examiner, Professor James McNulty for taking the time to review my thesis and attend my examination.

In the Department of Chemistry, I would like to thank the incredible NMR staff, including Dr. Tim Burrow, Dr. Darcy Burns, and Mr. Dmitry Pichugin for maintaining the instrumentation and being available for consultations at a moment’s notice. Dr. Alan Lough is also gratefully acknowledge for performing single crystal X-ray analysis and structure determination on all compounds within this thesis. I would also like to thank Dr. Matthew Forbes and Mr. Chung Fung in the AIMS lab for performing mass determination on all compounds in this thesis. Lastly, to the wonderful office staff, Anna Liza Villavelez, Stefanie Steele, and formerly Denise Ing who have been inexhaustible sources of assistance with filling out paper work.

During my tenure at University of Toronto I was fortunate to have received NSERC PGS-D and OGS QEI scholarship. These two scholarships allowed me to concentrate on my education for the entire course of my Ph.D. I was also fortunate to be awarded the Merck-Frosst Travel Grant in 2013 and 2014 that allowed me to present my research at ESOC in Marseille, France and Tetrahedron Conference in London, England, respectively. I was also awarded the Leslie Cook Memorial scholarship in 2014.

I would like to thank a previous members of the Yudin group; Dr. Zhi He for providing valuable advice and insights with several projects in my first two years at University of Toronto. I would also like to extend my deepest gratitude to Dr. Conor Scully, Dr. Shinya Adachi, Mr. C. Frank Lee, Mr. Adam Zajdlik, Ms. Joanne Tan and Mr. Sean Liew for assistance with a number of projects as well as Mr. Diego Diaz for editorial assistance with Chapter 1 of this thesis. Mr.
Benjamin Chung is also acknowledged for his willing assistance over the past four years. Dr. Rodrigo Mendoza-Sanchez is warmly acknowledged for his friendship and expertise over the past six years and two provinces. Thank you to everyone else who has come and gone through the Yudin lab for providing me with inspiration on how to carry myself in an organic chemistry lab. Thank you to my friends outside of chemistry for balance and normalcy in which I can turn off and relax.

To my parents, David and Elizabeth, and my brother Andrew, thank you for the encouragement and support in this extended educational experience.

Finally, my wife Megan has provided me with unconditional support, motivation and a fresh set of eyes in which to tackle all of life’s problems. I could not have done it without my much better half. Love you Doodle, this is all for you. Now we are off to the next adventure.
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List of Abbreviations

Å  angstrom
Ac  acetyl
AcOH  acetic acid
aq  aqueous
Ar  aryl
Assay yield  product yield versus internal standard
B:  base
BINAP  2,2’-bis(diphenylphosphino)-1,1’-binaphthalene
B[MIDA]/[B]  N-methyliminodiacetylboron
Bn  benzyl
Boc  tert-butoxycarbonyl
Bz  benzoyl
tBu  tert-butyl
δ  chemical shift
°C  degrees Celsius
calc.  calculated
Cat.  Catalyst/catalytic
CHCl₃  chloroform
COD  cyclooctadiene
conv  conversion

cHex  cyclohexyl

CR  component reaction

d  doublet

d  deuterio

dd  doublet of doublets

dt  doublet of triplets

DABCO  1,4-diazabicyclo[2.2.2]octane

DBU  1,8-diazabicyclo[5.4.0]undec-7-ene

DCM  dichloromethane

DEAD  diethylazodicarboxylate

DIAD  diisopropylazodicarboxylate

DIBAL  diisobutyaluminium hydride

DIPEA/iPr₂NEt  diisopropylethylamine

dppf  1,1'-ferrocenediy1-bis(diphenylphosphine)

DMF  dimethyl formamide

DMSO  dimethyl sulfoxide

d.r.  diastereomeric ratio

E  electrophile

E:Z  entgegen:zusammen
E1cB: elimination unimolecular conjugate base

equiv: equivalents

ESI: electrospray ionization

EDCI: 3-(3-dimethylaminopropyl)carbodiimide hydrogen chloride salt

ESI: electron spray ionization (mass spectroscopy)

Esp: α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid

Et₂O: diethyl ether

Et: ethyl

Et₃N: triethylamine

EtOAc: ethyl acetate

g: gram

GC: gas chromatography

h: hours

Hex: hexanes

HFIP: 1,1,1,3,3,3-hexafluoro-2-propanol

HMPA: hexamethylphosphoramide

HPLC: high-performance liquid chromatography

HWE: Horner-Wadsworth-Emmons (reaction)

HRMS: high resolution mass spectrometry

Hz: hertz
$J$  
coupling constant

L  
ligand or litre

LC  
liquid chromatography

LDA  
lithium diisopropylamide

lit.  
literature

m  
mili

µ  
micro

M  
moles per litre (molar)

M  
mega

$M^+$  
parent molecular ion

$M+H^+$  
parent molecular ion plus proton

$M+Na^+$  
parent molecular ion plus sodium

Me  
methyl

MeCN  
acetonitrile

MeOH  
methanol

MIDA  
$N$-methyliminodiacetic acid

mmol  
millimole

mL  
millilitre

mg  
milligram

mHz  
megahertz
<table>
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<tr>
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<tr>
<td>MS</td>
<td>mass spectroscopy</td>
</tr>
<tr>
<td>m/z</td>
<td>mass-to-charge ratio</td>
</tr>
<tr>
<td>n-</td>
<td>normal</td>
</tr>
<tr>
<td>NBS</td>
<td>N-bromosuccinimide</td>
</tr>
<tr>
<td>NCS</td>
<td>N-chlorosuccinimide</td>
</tr>
<tr>
<td>NMM</td>
<td>N-methylmorpholine</td>
</tr>
<tr>
<td>NEt3</td>
<td>triethylamine</td>
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<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
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<tr>
<td>Nu</td>
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<td>ppm</td>
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<tr>
<td>Pyr</td>
<td>pyridine</td>
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<td>quartet</td>
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R  generic substituent
R_f  retention factor
R_T  retention time
rt  room temperature
Ruphos  2-dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl
SMCC  Suzuki–Miyaura cross-coupling
TBS  tert-butyldimethylsilyl
t-Bu  tert-butyl
TFA  trifluoroacetic acid
TFE  2,2,2-trifluoroethanol
TES  triethylsilyl
THF  tetrahydrofuran
TIPS  triisopropylsilyl
TIPSOTf  triisopropylsilyl triflate
TMS  trimethylsilyl
TLC  thin-layer chromatography
Ts  tosyl
Tol  toluene
Tolyl  p-toluenesulfonyl
[M]  ligated metal catalyst
Chapter 1

Introduction
1 Introduction

1.1 Amphoteric Molecules

The term “amphoteric” is originated from the Greek “amphoteroi” meaning “both of two”. In acid/base chemistry, an amphoteric reagent has the capability to react both as a Brønsted acid and a Brønsted base. Amino acids, and even water, are amphoteric in nature. Reversible proton transfer exemplifies the thermodynamic amphotericism of both reagents.

In the realm of synthetic organic chemistry, a molecule containing both nucleophilic and electrophilic sites can be considered kinetically amphoteric. The textbook example of an amphoteric functional group is the isocyanide (e.g. R-NC). This moiety possesses a terminal carbon that behaves as both nucleophile and electrophile in substitution reactions. As reaction occurs at the same site, isocyanide containing compounds are classified as [1,1]-amphoteric reagents.

The most common use of isocyanides is in multicomponent transformations, such as the Passerini three-component (Passerini 3-CR) or Ugi 4-CR. Both of these venerable reactions have been used to generate heterocycles, peptides, highly functionalized polymers (Figure 1.1). In addition to their utility in MCR reactions, isocyanides have been used as C1-transfer reagents or carbon monoxide surrogates. The orthogonal reactivity between the nucleophilic and electrophilic components affords the potential for the formation of multiple bonds in a single...
chemoselective transformation. The construction of complex molecules with high atom- and step-economy encourages the development of amphoteric small molecules.

1.2 Aziridine Aldehydes

1.2.1 Unprotected α-Amino Aldehydes

Amines and carbonyl compounds undergo a rapid condensation to yield enamines and imines which are important functionalities in Nature’s aldolases and target-oriented organic synthesis.\(^4\) In particular, the field of enamine and iminium catalysis has exploited this enabling reactivity for \(\alpha\)-functionalization reactions.\(^5\) However, when attempting to perform transformations on substrates that possess unprotected amine and carbonyl functional groups, the favourable condensation process can be regarded as a limitation (Scheme 1.1).

![Scheme 1.1. Imine and enamine formation between amines and aldehydes](image)

Scheme 1.1. Imine and enamine formation between amines and aldehydes

Aldehyde and amine functionalities are utilized in a wide range of organic transformations. Incorporation of both functional groups into a small molecule, specifically the generation of \(\alpha\)-amino aldehydes, is of particular interest given the potential for chemoselective transformations adjacent to a nitrogen stereocentre. This potential has been exploited with the use of protected \(\alpha\)-amino aldehydes as intermediates in synthetic sequences, as well as several industrial processes.\(^6\) Unprotected \(\alpha\)-amino aldehydes cannot exist for a prolonged period of time without undergoing inter- or intramolecular condensation, polymerization or decomposition. This presents a considerable limitation not only the preparation but also the isolation of unprotected \(\alpha\)-amino aldehydes.
Reports concerning the synthesis and/or isolation of unprotected amino aldehydes are exceedingly rare. The first unprotected amino aldehyde; glucosamine (1.2.01), was discovered by Fischer in 1902 (Figure 1.2). The stability of glucosamine is attributed to the formation of the hemiacetal and the attenuation of nitrogen reactivity by formation of the ammonium salt. Further studies into amino aldehydes by Fischer included attempts at isolation of the simplest amino aldehyde glycinal (1.2.02). Characterization of 1.2.02 was largely unsuccessful due to self-condensation/polymerization therefore degradation studies were employed to determine connectivity.8

Myers and co-workers have reported the in situ protection of some amino aldehydes affording bench stable products. In this example, exposure of unprotected α-amino aldehydes to TFA and methanol results in the formation of the hemiacetal ammonium salts (Figure 1.3, 1.2.03).9 These amphoteric molecules were found to be stable under strongly acidic conditions; however, self-condensation occurs above pH 5. In a separate study, Maruoka and co-workers found that the installation of a quaternary α-stereocentre inhibits the self-condensation process (1.2.04).10

Attenuation of the nucleophilic nitrogen by protonation, in concert with hemiacetal formation is the most common strategy to access unprotected amino aldehydes. Although this method is effective, only a limited number of substrates are compatible with the acidic conditions. The lack of widely applicable methods to access the unprotected amino aldehyde scaffold has limited synthetic application to their respective C- or N-protected derivatives.11 Protection of the reactive
functionalities prevents destructive condensation/polymerization while adding two extra synthetic steps and, in the case of N-protection, the potential for α-stereocentre racemization.

1.2.2 Stability of Aziridines and Aldehydes

Aziridines (1.2.05), nitrogen-containing three-membered rings, do not form exocyclic double bonds (e.g. aziridinium cations 1.2.07). This behaviour suggests stability in the presence of aldehyde moieties. Experimentally, the intermolecular reaction of aziridines and aldehydes results in the exclusive formation of the hemiaminal product (Figure 1.4, 1.2.06). The barrier to formation of the aziridinium cation significantly reduces the driving force that would normally allow amines and aldehydes to condense, polymerize and further decompose. From these results it was hypothesized that the incorporation of aziridine and aldehyde functionalities within the same molecule might afford access to unprotected amino aldehydes.

\[
\text{NH} + \text{O} \xrightarrow{\text{1.2.06}} \text{OH} \xrightarrow{\text{1.2.07}} \text{N}^- \xrightarrow{\text{1.2.05}} \text{O}
\]

Figure 1.4. Formation of hemiaminal (1.2.06) from aziridines (1.2.05) and aldehydes

1.2.3 Preparation of Unprotected Aziridine Aldehydes

The quantitative formation of a hemiaminal product from the reaction of an aziridine and an aldehyde reaction led our group to investigate a new class of bench-stable unprotected amino aldehydes – α-aziridine aldehydes. Prior to the entry of the Yudin lab into the area of amino aldehydes, there was a single report relating to the formation and in situ characterization of an unprotected NH-aziridine aldehyde (1.2.08). Treatment of 1.2.09 with NaOMe resulted in acetate displacement and concomitant aziridine ring formation. The aziridine aldehyde 1.2.08 was not isolated as aziridine ring opening by the adjacent amide was found to be a facile process.
In 2006, the Yudin lab reported the synthesis of bench-stable \( NH-\alpha \)-aziridine aldehydes. Unprotected aziridine aldehydes can be accessed via traditional organic transformations from readily available starting materials (Scheme 1.3).\(^\text{13}\) The synthesis of the common intermediate \( NH \)-aziridine ester (1.2.10); is accomplished via three different synthetic routes:

**Route A:** Regio- and diastereoselective \( \alpha \)-lithiation of \( N \)-Boc aziridines (1.2.11) results in the \( N \rightarrow C \) Boc-transfer affording \( \text{trans} \)-aziridine ester (1.2.10).\(^\text{15}\) The NBoc aziridines can be obtained from the Boc-amino acid following a reduction/ring closing sequence.

**Route B:** 1,2-amino alcohol esters (1.2.12) are appropriate starting materials for the synthesis of aziridine esters. After esterification of the \( \alpha \)-amino acid, a Mitsunobu reaction can be carried out to generate the aziridine ring. The most common substrates for Route B are the amino acids L-serine and L-threonine.

**Route C:** Sodium azide ring opening of epoxy esters affords the 1,2 azido-alcohol. This is then followed by the Staudinger ring closure to yield the \( NH \)-aziridine.
Scheme 1.3. Synthetic routes to the common aziridine ester intermediate 1.2.10

The solid state characterization of aziridine aldehydes was important to understand any interactions of the dimeric species. Single crystal X-ray analysis of trans-phenyl α-aziridine aldehyde (Figure 1.5, 1.2.14) revealed an intramolecular hydrogen bond between the pendant NH-aziridine and hemiacetal. This hydrogen bonding interaction is an important factor contributing to the overall stability of the homochiral [3,5]-aziridine aldehyde dimeric assembly which allows 1.2.13 to persist in the solidstate.16

Figure 1.5. X-ray structure of trans-phenyl aziridine aldehyde (1.2.14)

The stability and behaviour of aziridine aldehyde dimers in the solution phase has also been investigated. By NMR and mass spectroscopy, there was no evidence of monomers, symmetrical dimers (1.2.16), or heterochiral dimers in solution (Figure 1.6). Notably, when mixing two different aziridine aldehyde dimers there is an observed cross-over product. The crossover
between dimeric species is attributed to the dynamic and reversible hemiaminal functional groups.

![Figure 1.6. Dimerization of aziridine aldehydes](image)

1.2.4 Reactivity of Unprotected α-Aziridine Aldehydes

The crystal structure of 1.2.14 illustrates a [3,5]-bicyclic assembly; however the reversible, covalent nature of the hemiaminal and hemi-acetal bonds should permit reactivity under carefully controlled reaction conditions. One of the first examples of aziridine aldehyde reactivity was the successful reduction to the corresponding NH-aziridine alcohol (Figure 1.7, 1.2.17). This confirmed the dynamic nature of aziridine aldehydes and afforded products corresponding to monomeric amino aldehydes.

![Figure 1.7. Reduction of 1.2.14](image)

Aziridine aldehyde reactivity was further investigated with amines. It was found that primary amines readily condense with aziridine aldehyde dimers (Figure 1.8). The condensation products were subjected to reductive amination conditions to afford the amino aziridine (1.2.19). This method was useful for the incorporation of α-amino acid esters or peptide derivatives to yield
peptidomimetics with reduced amide bonds (1.2.20).\textsuperscript{17} Notably, epimerization of the α-stereocentre was not observed under the reaction conditions. The synthesis of aziridine amines demonstrates that the aziridine and aldehyde are orthogonal functionalities permitting chemoselective reactivity.

![Chemical structure](image1)

**Figure 1.8.** Reductive amination of aziridine aldehydes affording diamines (1.2.19) and peptidomimetic compounds (1.2.20)

The addition of organometallic carbon nucleophiles to aldehydes is an important transformation for the synthesis of alcohol stereocentres.\textsuperscript{18} In this regard, the reactivity of the aldehyde functionality of aziridine aldehyde dimers was evaluated. The \textsuperscript{In} \textsuperscript{0}-mediated allylation reaction of 1.2.13 proved successful, whereas the organolithium and Grignard reagents did not form the desired alcohol product (Scheme 1.4).\textsuperscript{19} The allylation reaction was applicable to a variety of allyl bromides delivering the homoallylic alcohol (1.2.21) in high yields (85-96%) and high diastereoselectivity (>20:1 \textit{syn:anti}). Electron-poor allyl bromides resulted in \textit{N}-allylation products.

![Chemical structure](image2)

**Scheme 1.4.** \textsuperscript{In} \textsuperscript{0}-mediated allylation of aziridine aldehyde dimers\textsuperscript{19}
The products of the allylation can also be used to access elaborate scaffolds. The NH-aziridine can be ring-opened with thiophenol to afford three adjacent stereocentres (Scheme 1.4, 1.2.22). Intramolecular amino-bromination of the pendant alkene was also performed with NBS. 5-exo-trig cyclization resulted in the fused aziridinyl-pyrrolidine bicycle (1.2.23). Both of these scaffolds are densely functionalized and rich in stereochemistry.

![Figure 1.9. Synthesis and application of ethynyl aziridines (1.2.25)](image)

Aziridine aldehydes are also amenable to a number of other chemoselective aldehyde transformations. The Ohira-Bestmann reagent (1.2.24) was found to be effective for the ethynylation of aziridine aldehydes (Figure 1.9, 1.2.25).20 A detailed investigation into the synthetic application of these alkynyl aziridines was performed. First, the terminal alkynes could be elaborated via Sonogashira coupling reaction to yield the internal alkyne (1.2.26). Subsequent treatment of the internal alkynes with 9-BBN resulted in the stereoselective addition of hydride affording geometrically pure amino allenenes.21 Oxidation of the aziridine ring under conditions reported by Swern affords the azirine alkyne product 1.2.28.22 Finally, engagement of both functionalities can be accomplished by annulation with acetone to yield the fused bicyclic structure 1.2.29.

![Scheme 1.5. Unprotected vinyl aziridine 1.2.30 by H-W-E reaction of aziridine aldehydes](image)
The synthesis of vinyl aziridines can also be accomplished by application of the Horner-Wadsworth-Emmons reaction (Scheme 1.5). Treatment of aziridine aldehyde with the stabilized ylides in 2,2,2-trifluoroethanol (TFE) resulted in the corresponding vinyl aziridines in good yield and high trans-selectivity (1.2.30). Use of the weakly acidic, non-nucleophilic TFE was crucial as it is conducive for aziridine aldehyde dissociation. The vinyl aziridines products can then be subjected to DMAD to afford biologically relevant cyclic azepines via engagement of the aziridine component.

Scheme 1.6. Intercepted Pictet-Spengler reaction of aziridine aldehydes

Aziridines are important functional groups and display reactivity that is different from other cyclic secondary amines. Notably, aziridine basicity is attenuated due to the increased $s$-character of the lone pair while nucleophilicity is relatively unaffected due to the steric accessibility and barrier to lone pair inversion. The seminal report of stable aziridine aldehydes found that the aziridine ring can be engaged following aldehyde reaction with external nucleophiles. In this case, the Pictet-Spengler reaction was found to be the proving grounds. The reaction of $N$-benzyl tryptamine (1.2.32) and aziridine aldehyde resulted in the pentacyclic (1.2.31) aziridine product through an aziridine addition process (1.2.33).

Scheme 1.7. Reaction between aziridine aldehyde dimers and isocyanates
Cascade reactions of aziridine aldehydes that engage both functional group handles do not require initial attack at the aldehyde (Scheme 1.7). Exposure of aziridine aldehyde dimers to isocyanates in diethyl ether resulted in the quantitative formation of the dimeric-carbamate adduct (1.2.34). Notably, exchanging the solvent for an 8:2 HFIP:H₂O mixture resulted in the exclusive formation of the reduced hydantoin bicycle (1.2.35). The use of HFIP was found to be crucial as it promotes aziridine aldehyde dimer dissociation, and subsequent collapse on to the aldehyde. Further proof came from subjecting 1.2.34, isolated from the reaction in diethyl ether, to the HFIP/H₂O mixture. This experiment resulted in the formation of the corresponding hydantoin 1.2.35.

![Scheme 1.8. Reactions between aziridine aldehyde dimers and α,β-unsaturated aldehydes](image)

In order to engage the aziridine nitrogen prior to aldehyde moiety aprotic solvents are required. In the presence of α,β-unsaturated aldehydes, benzoic acid and pyrrolidine, the products of a formal Baylis-Hillman addition were obtained in high diastereoselectivity (Scheme 1.8, 1.2.36). The highly diastereoselective addition is attributed to the proposed 8-membered ring transition state that is rigidified by hydrogen bonding (1.2.37).

The varied and atypical mode of reactivity described within this section demonstrates the synthetic application of aziridine aldehydes. The dimeric assembly of this class of amino aldehydes does not inhibit reactivity; in fact it provides opportunities for chemoselective engagement via control of the reaction medium. The ability of aziridine aldehydes to access complex final products via interception of common reaction intermediates further attests to the value of amphoteric small molecules.
1.3 Amphoteric α-Metallocarbonyl Compounds

Aziridine aldehydes are a versatile class of amphoteric small molecules containing a nucleophilic nitrogen and an electrophilic aldehyde in a [1,3]-relationship. This prompted further studies into novel classes of amphoteric small molecules with both nucleophilic and electrophilic components in close proximity. It was envisioned that α-metallo carbonyl species (C-enolates), which possess a [1,2]-relationship of nucleophile and electrophile, would provide the opportunity for development (Figure 1.10).

![Figure 1.10. Amphoteric α-aziridine aldehyde and α-metallo carbonyls](image)

Transition metal enolates, particularly late transition metals, commonly exist in the C-bound form and examples of isolable α-metallo carbonyl complexes are well-known.\(^30\) In contrast, C-bound alkali enolates (e.g. Li\(^+\), Na\(^+\)) are thermodynamically unstable and cannot be isolated (Figure 1.11).\(^31\) Attempts to bridge the divide have resulted in the development of stannyl enolates, which equilibrate to a ratio of C-[Sn] and O-[Sn] tautomers,\(^32\) and the relatively stable α-silyl carbonyls.\(^33\) In light of the scarce reports, the development of stable main-group α-metallo carbonyls, in particular second-row elements, is still a challenge.

![Figure 1.11. Equilibrium between C- and O-enolates](image)
1.4 α-Boryl Carbonyl Compounds

Generally, the behaviour of organoboron compounds is similar to that of the corresponding silyl derivatives.\textsuperscript{34} Isolation of stable α-silyl and α-stannyl carbonyls infer the potential for the corresponding α-boryl carbonyl species. However, boryl enolates favour the thermodynamically more stable $O$-bound enolate tautomer, with a typical energy difference of ~20 kcal/mol. The stability of the $O$-bound boryl enolate is due to the strong B-O bond (Figure 1.12).\textsuperscript{31} As such, reports pertaining to the isolation and full characterisation of α-boryl carbonyl species are decidedly rare, even though they are commonly proposed reaction intermediates.\textsuperscript{35}

![Figure 1.12. Facile $C\rightarrow O$ boron migration](image)

1.4.1 Fleeting α-Boryl Carbonyl Species

The alkylation of α-bromo ketones with organoboranes in the presence of strong base was reported by Brown and co-workers.\textsuperscript{36} Without spectroscopic or structural evidence, the authors proposed a possible mechanism for the rapid bromide displacement. The ‘-ate’ complex 1.4.01, resulting from the addition of the potassium enolate addition to the empty p-orbital of the borane, transfers the alkyl group displacing the bromide anion. The α-boryl ketone 1.4.02 is a fleeting intermediate as rapid $C\rightarrow O$ boryl transfer occurs to yield the $O$-enolate (1.4.03). Hydrolysis of 1.4.03 yields the disubstituted carbonyl product.
Scheme 1.9. Alkylation of α-bromo ketones via proposed α-boryl carbonyl intermediate (1.4.02)

The instability and facile C→O boryl migration has limited structural characterization studies pertaining to α-boryl carbonyls. In the recent years, a small number of reports have identified reactive α-boryl carbonyl intermediates via spectroscopic techniques. The first evidence for α-boryl carbonyl compounds was provided in 2002 by Abiko and co-workers (Scheme 1.11, 1.4.04). The authors observed that 2,6-diisopropylphenyl acetate formed a mixture of C/O-enolates when treated with dicyclohexylboryl triflate and triethylamine. The relatively high abundance of C-boron enolate tautomer is attributed to the sterically demanding 2,6-diisopropylbenzene substituent.

Scheme 1.10. 1H NMR identification of 1.4.04

Following the report by Abiko, the platinum-catalyzed addition of B₂pin₂ to α,β-unsaturated esters was found to proceed through the α,β-bis-boryl pinacol ester intermediate (Scheme 1.11, 1.4.06). This intermediate, identified by in situ 1H NMR, hydrolyzed in the presence of moisture to yield the β-boryl esters. The stability and exclusive formation of the β-boryl ester product is attributed to the intramolecular coordination between the sp²-boron centre and carbonyl moiety.
**Scheme 1.11.** α-Boryl carbonyl compounds identified by NMR spectroscopy

Intramolecular complexation of \( \textit{sp}^2 \)-hybridized boron atoms has been used to stabilize the \( \alpha \)-boryl carbonyl intermediate and inhibit the \( C\rightarrow O \) boryl migration. The BH\(_3\)-catalyzed oligomerization of ethyl diazoacetate has been described to proceed through a stabilized \( C \)-bound boryl enolate (Scheme 1.12, 1.4.07).\(^{41}\) The intermediate diethyl 2-borylsuccinate (1.4.07) was fully characterized by \( ^1\text{H}, ^{13}\text{C} \) and \( ^{11}\text{B} \) NMR. Results from the \( ^{13}\text{C} \) NMR study found the downfield shift of an ester group to 190.6 ppm. In addition, the \( ^{11}\text{B} \) NMR study found the boron signal was shifted upfield to 11.7 ppm. The data from the NMR studies suggest the formation of a five-membered structure resultant from the strong intramolecular coordination between the carbonyl oxygen and the boron centre.

**Scheme 1.12.** Stabilized \( \alpha \)-boryl intermediate (1.4.07) in the oligomerization of ethyl diazoacetate

### 1.4.2 Stable \( \alpha \)-Boryl Carbonyl Compounds

The facile \( C\rightarrow O \) migration of \( \textit{sp}^2 \)-hybridized boron centres adjacent to carbonyl moieties limits the identification, isolation and chemical investigations. Stabilization of \( \alpha \)-boryl carbonyl intermediates can be accomplished via strong interaction with Lewis bases. The increased electron density of the ‘-ate’ complex is proposed to inhibit the migration process. Therefore, employment of electron-rich boron centers, such as \( \textit{sp}^3 \)-hybridized boronates, should inhibit the \( C\rightarrow O \) migration by preventing carbonyl interaction with the boron centre.
Prior to the entry of the Yudin lab into the field, there were only four examples of stable and isolable \( \alpha \)-boryl carbonyl compounds. The first synthesis of these amphoteric molecules was reported by Sucrow and co-workers.\(^{42}\) Regioselective hydroboration of enoates with diborane resulted in the synthesis of \( \alpha \)-boryl esters (Scheme 1.13, 1.4.08). The pendant hydrazone was found to be crucial for stabilization of the C-boron enolate via intramolecular dative bonding.

![Scheme 1.13. Hydrazone stabilization of \( \alpha \)-boryl esters](image)

Dimeric \( \alpha \)-boryl amides have been synthesized by Paetzold and co-workers.\(^{43}\) The four-membered ring of the dimeric structure is a result of the reaction between bis(dialkylamino)haloboranes (1.4.09) and ketenes (Scheme 1.14). The proposed mechanism begins with the addition of amine to the ketene to afford the O-boron enolate (1.4.10). This enolate undergoes dimerization with another equivalent of 1.4.10 to form the four-membered ring structure (1.4.11). The electron-rich boronate then undergoes \( O \rightarrow C \) migration resulting in the \( \alpha \)-boryl amide (1.4.12). It must be stressed that this is a proposed mechanism; however, if further investigation proves this pathway to be operative then this would be the first example of a \( O \rightarrow C \) boryl migration.

![Scheme 1.14. Synthesis of dimeric \( \alpha \)-boryl amides from ketene and halo-diaminoboranes](image)
Another entry to stable α-boryl carbonyls has been reported by Bürger and co-workers (Scheme 1.15). In the presence of dimethylaminobis(trifluoromethyl) borane (1.4.13), carbonyl substrates undergo an ene-type rearrangement yielding the boryl carbonyl 1.4.14. Analysis of the boryl carbonyls by $^{11}$B NMR found that the signal had shifted upfield (δ -8 to -10 ppm) revealing an exceptionally electron-rich boron atom. The stability of these products is attributed to the strong Lewis base interaction of the dimethyl amine substituent with the boron centre. This rearrangement was also observed with alkyl nitriles to afford α-boryl nitriles.

Lastly, heterocyclic boron structures are a class of stable α-boryl carbonyl species. First prepared by Danion-Bougot in 1995, the heterocyclic structure (Scheme 1.16, 1.4.16) results from the hydroboration of the enamide ester (Scheme 1.16, 1.4.15). This molecule was isolated as the potassium salt for ease of handling and characterization purposes.
1.4.3 α-MIDA Boryl Aldehydes

The previous examples of amphoteric boryl carbonyls have limited synthetic value due to issues surrounding preparation and handling. The stabilizing ligands of these α-boryl carbonyls are easily displaced by external nucleophiles resulting in decomposition. In 2011, the Yudin group discovered a new class of α-boryl aldehydes (1.4.17) that is stabilized by a conformationally rigid trivalent ligand (Figure 1.13, 1.4.18). The ligand, N-methyliminodiacetic acid (MIDA), not only inhibits C→O boryl migration but also prevents interaction of external nucleophiles with the boron centre.

![Figure 1.13. General structure of α-MIDA boryl aldehydes 1.4.17](image)

1.4.4 Preparation of α-MIDA Boryl Aldehydes

The preparation of α-MIDA boryl aldehydes is relatively straightforward and utilizes inexpensive (mostly) starting materials (Scheme 1.17). To start, the vinyl boronic acid is subjected to dehydration conditions in the presence of MIDA to form the vinyl MIDA boronate. Epoxidation of the vinyl boronate with m-CPBA followed by rearrangement with BF₃·OEt₂ yields the corresponding α-boryl aldehyde via [1,2]-boryl migration. The aldehydes were isolated as white solids and were found to be stable to aqueous work-up, silica gel chromatography and ambient conditions.
Scheme 1.17. General preparation of α-MIDA boryl aldehydes 1.4.17

The unprecedented [1,2]-boryl shift was investigated by deuterium labeling experiments (Scheme 1.18). Rearrangement of $d_1$-epoxy MIDA boronates (1.4.19 and 1.4.20) confirmed that [1,2]-boryl migration was occurring and not [1,2]-alkyl shift. Concurrent with the work performed in the Yudin lab, Burke and co-workers found that the pinene-derived iminodiacetyl (PIDA) epoxy boronates (1.4.21) rearranged in a similar fashion in the presence of MgClO$_4$ with complete stereoretention.$^{48}$

Scheme 1.18. Results of the BF$_3$-promoted rearrangement of deuterium labeled epoxy MIDA boronates
1.4.5 Synthetic Applications of α-MIDA Boryl Aldehydes

In the initial report, the synthetic potential of α-MIDA boryl aldehydes was thoroughly investigated. The electrophilic aldehyde was exploited in a number of reactions (Figure 1.14). These transformations include: vinylation, gem-dibromoalkenylation, In\(^0\)-mediated allylation, halogenation, enol ether formation, and enamine/enamide condensation. All of these transformations preserve the C-B bond for further elaboration.

![Figure 1.14. Synthetic transformations of α-boryl aldehydes](image)

Engagement of the C-B bond can be effected by first forming the vinyl boronic pinacol ester (1.4.22). The latent nucleophile 1.4.22 can then be subjected to the Petasis reaction with glycolic acid and a variety of primary or secondary amines (Scheme 1.19). This method enabled the synthesis of several unnatural amino acids (1.4.23). The chemoselective engagement of both nucleophilic C-B bond and electrophilic aldehyde components represents an important advance of α-boryl carbonyl chemistry and amphoteric molecules in general.
Scheme 1.19. Petasis reaction of vinyl boronic acids (1.4.22) derived from α-boryl aldehydes

The stability of α-boryl aldehydes to common reagents has advanced the production of complex boron-containing small molecules. This encouraged the Yudin lab to investigate the synthesis of α-MIDA boryl carboxylic acids. Under Pinnick oxidation conditions, a number of substituted acids were obtained as stable white solids (Scheme 1.20, 1.4.24). Aside from standard amide bond coupling reactions, these boryl carboxylic acids were amenable to Curtius rearrangement conditions to afford a novel class of bench stable α-boryl isocyanates (Scheme 1.20, 1.4.25).

Scheme 1.20. Preparation of α-boryl carboxylic acids (1.4.24) and α-boryl isocyanates (1.4.25)

The α-boryl isocyanates (1.4.25) are a versatile class of amphoteric molecules with a nucleophilic C-B bond and electrophilic isocyanate carbon in a [1,3]-relationship (Scheme 1.21). Exploitation of isocyanate reactivity with nucleophiles provides access to a range of ureas, carbamates, isocyanides, and their corresponding sulfur analogues. In addition, the α-boryl isocyanide (1.4.26) can be utilized in the Ugi-4-CR to afford a range of peptides containing boron, including Velcade® (1.4.27, bortezomib), an FDA-approved treatment for multiple myeloma.
Scheme 1.21. Application of α-boryl isocyanates and α-boryl isocyanides for the synthesis of α-amino boronates and boro-peptides

1.5 Summary

Amphoteric molecules contain both nucleophilic and electrophilic components that exist in an orthogonal manner. Specifically, dimeric α-aziridine aldehydes have been utilized in a range of chemical transformations that engage both aziridine and aldehyde functional groups in a chemoselective manner. The ability to produce highly functionalized nitrogen-containing products attests to the synthetic potential of this class of reagents. Expansion of the synthetic utility directed at diamines will be discussed.

Identification of α-MIDA boryl aldehydes as a class of [1,2]-amphoteric molecules has been a major advance in α-metallo carbonyl chemistry. Not only does the aldehyde moiety offer a handle for the introduction of complexity, but engagement of the C-B bond can now be realized under controlled conditions. The ability to generate highly-functionalized boron-containing small molecules has been enabled by the trivalent MIDA ligand. Development of novel chemistry surrounding the amphoteric α-boryl aldehyde and related structures will be described in this thesis.
1.6 References

1 The term “ambiphilic” has also been used to describe molecules that contain both electrophilic and nucleophilic components.


35 For examples of transformations involving C-boron enolate intermediates, see: (a) Bell, N. J.; Cox, A. J.; Cameron, N. R.; Evans, J. S. O.; Marder, T. B.; Duin, M. A.; Elsevier, C. J.;


Chapter Two

\[ \text{Zn}^{\text{II}}\text{-Acetylide Reactivity with Reversibly Formed Dimeric Aziridine Aldehyde Assemblies} \]
2 Zn\textsuperscript{II}-Acetylide Reactivity with Reversibly Formed Dimeric Aziridine Aldehyde Assemblies

2.1 Introduction

Diethylzinc (Et\textsubscript{2}Zn) was successfully isolated and characterized in 1849 by Edward Franklin.\textsuperscript{1} This moment is considered the start of organometallic chemistry. Today, organozinc compounds are common synthetic reagents and exhibit similar behaviour to that of organolithium (RLi) and Grignard (RMgX) reagents. The nonpolar nature of the Zn\textsuperscript{II}-alkyl bond results in lowered reactivity and high-functional group tolerance as compared to the corresponding alkyl lithiums or Grignard reagents.\textsuperscript{2}

\[
\begin{align*}
R^+\text{ZnX} & \quad + \quad X\text{FG} \quad \xrightarrow{\text{[Ni]} \text{or [Pd]}} \quad R^\text{+}\text{FG}
\end{align*}
\]

**Scheme 2.1.** Generic Negishi cross-coupling of organozinc and aryl halides

Monomeric dialkylzinc reagents undergo facile transmetallation with transition metal salts ([Cu], [Ni], [Ti], [Pd]).\textsuperscript{3} The resulting complex undergoes further reactivity with electrophiles that are normally inert to organozinc compounds.\textsuperscript{4} A common example is the [Pd]-/[Ni]-catalyzed cross-coupling reaction (Negishi cross-coupling) of organozinc and aryl halides (Scheme 2.1).\textsuperscript{5} The utility of the Negishi cross-coupling in organic synthesis has been demonstrated in a number of total syntheses (Scheme 2.2).\textsuperscript{6} In conjunction with Prof. Suzuki and Prof. Heck, Prof. Negishi earned the Nobel Prize in 2010 for its introduction and subsequent development.

\[
\begin{align*}
\text{N(Li)} \quad + \quad \text{Br}^\text{N(Pri)}_2 \quad \xrightarrow{\text{ZnCl}_2} \quad \text{Pd}_2\text{dba}_{3} \quad \text{PPh}_3 & \quad \xrightarrow{\text{THF, RT, 80\% yield}} \quad \text{caerulomycin C}
\end{align*}
\]

**Scheme 2.2.** Total synthesis of caerulomycin C via Negishi cross-coupling

Dialkylzinc compounds possess both a nucleophilic carbon substituent and a Lewis acid metal centre which constitutes an amphiphilic reagent.\textsuperscript{7} These organometallic reagents are non-polar due to the linear geometry of the alkyl substituents and do not readily participate in polar
reactions (Figure 2.1, 2.1.01). Replacement of an alkyl group with electron-withdrawing substituents, including Lewis basic ligands, polarizes the alkyl-Zn bond which increases reactivity. The addition of a Lewis basic ligand to dialkylzinc reagents results in the formation of an organozinc-Lewis base adduct (Figure 2.1). The tetracoordinate ‘-ate’ complex renders the alkyl-substituent of 2.1.02 nucleophilic and therefore participates in addition reactions to electrophiles.

![Figure 2.1. C-Zn-C bond angles of dimethylzinc (2.1.01) and tetrazine adduct (2.1.02)](image)

### 2.1.1 1,2-Amino Alcohol Catalyzed Reactions

Amino alcohols are an important class of ligands that catalyze the nucleophilic addition of organozinc reagents to electrophilic partners, namely aldehydes. The chiral pool affords a large number of readily available 1,2-amino alcohol ligands or precursors, including amino acids, pseudoephedrine, and terpenes (Figure 2.2). Ready access to both antipodes is also an enabling feature of the amino alcohol scaffold.

![Figure 2.2. Common chiral 1,2-amino alcohol ligands](image)

In 1984, Oguni and Omi reported the first 1,2-amino alcohol catalyzed organozinc addition to aldehydes. A small number of chiral amino alcohols derived from the corresponding L-amino acids were utilized in the report. The addition of Et₂Zn to aldehydes in the presence of 2 mol % (S)-leucinol (2.1.03) resulted in the secondary alcohol in 96% yield and a modest 49% ee. Other chiral amino alcohols were screened and gave poor enantioinduction (Scheme 2.3). The small
sample size of chiral ligands opened the door for further investigations into the design of effective catalysts.

![Chemical reaction diagram](image)

<table>
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<tr>
<th>ligand</th>
<th>yield (%)</th>
<th>ee (%)</th>
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<td>26</td>
</tr>
<tr>
<td>(S)-valinol</td>
<td>95</td>
<td>47</td>
</tr>
<tr>
<td>(S)-leucinol (2.103)</td>
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<td>49</td>
</tr>
<tr>
<td>(S)-phenylalaninol</td>
<td>98</td>
<td>39</td>
</tr>
<tr>
<td>(S)-prolinol</td>
<td>100</td>
<td>28</td>
</tr>
</tbody>
</table>

**Scheme 2.3.** Enantioselective addition of diethylzinc to benzaldehyde

Shortly after the report by Oguni and Omi, a highly asymmetric dialkylzinc addition to aldehyde was described by Noyori and co-workers. In this example, the 1,2-amino alcohol (-)-3-exo-(dimethylamino)isoborneol (DIAB, 2.1.04), enabled the highly enantioselective addition of diethylzinc to aryl aldehydes (Figure 2.3). The addition of Et₂Zn in the presence of 2 mol % 2.1.04 afforded the chiral alcohol in 98% ee. Similar results were obtained with other dialkylzinc reagents.

![Chemical reaction diagram](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>yield%</th>
<th>ee%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>86</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
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<tr>
<td>5</td>
<td></td>
<td>81</td>
<td>61</td>
</tr>
</tbody>
</table>

**Figure 2.3.** DIAB (2.1.04) catalyzed asymmetric addition of Et₂Zn to aldehyde
2.1.2 1,2-Aziridine Alcohol Catalyzed Organozinc Additions

Aziridines are readily available from the chiral pool or asymmetric synthesis. A common starting material for the production of chiral aziridines is the amino acid L-serine (Scheme 2.4, 2.1.05). Access to the serine-derived aziridine alcohol (2.1.06) is a three step process that involves esterification of the carboxylic acid, followed by Mitsunobu ring closure then reduction to afford the 1,2-amino-alcohol moiety. This sequence can be extended to other chiral amino acids such as threonine and allo-threonine.\(^\text{15}\) Not only are aziridines useful in synthesis as amine containing building blocks but also as ligands for metal cations.\(^\text{16}\)

![Scheme 2.4. Mitsunobu of \(L\)-serine ester (2.1.05) to form chiral aziridine alcohol (2.1.06)](image)

Chiral, non-racemic 1,2-aziridine alcohols readily complex \(Zn^{II}\)-cations and have been used to induce chemoselective and enantioselective transformations, including organozinc additions to electrophiles.\(^\text{17}\) The enabling feature of the 1,2-aziridine alcohol ligand is attributed to the barrier to inversion of the aziridine lone pair which rigidifies the transition state and introduces a stereogenic centre at nitrogen.\(^\text{16}\)

![Figure 2.4. Select chiral, non-racemic 1,2-aziridine alcohol ligands](image)

Tanner and co-workers found that 1,2-aziridine alcohol ligands promote the addition of dialkylzinc reagents to aldehydes with low catalytic loadings.\(^\text{18}\) A number of chiral, non-racemic 1,2-aziridine alcohols were screened for the zinc addition to benzaldehyde and it was found that the \(C_2\)-symmetrical ligand (Figure 2.5, entry 5, 2.1.10a) was the most effective at promoting high reactivity (92% yield) and high enantioselectivity (94% ee).
Further screening of the ligand 2.1.10a with other aldehydes was performed to gauge the scope of the addition reaction (Figure 2.6). Analysis of the reaction of aromatic aldehydes showed no evidence for any electronic effect of ring substituents. Changing to aliphatic aldehydes afforded low yields and disappointing enantioselectivity. The decreased reactivity of aliphatic substrates is attributed to tautomerization to the enamine form.

**Figure 2.5.** 1,2-Aziridine alcohol catalyzed addition
Asymmetric organozinc addition to aldehydes catalyzed by 1,2-aziridine alcohol ligand (2.1.10a)

Ferrocene-substituted aziridine alcohols have been developed by Dogan for the asymmetric addition of dialkylzincs to aldehydes. The ferrocene containing 1,2-aziridine alcohol (2.1.10) catalyzes the highly enantioselective addition of dialkyl zincs to a variety of aldehydes in greater than 90% ee for most substrates and up to 99% ee in some cases. The authors noted that the (R)-stereocentre on the aziridine ring gave products with the (R)-configuration. Likewise, the (S)-stereocentre affords the (S)-configuration of product. The mild conditions and crystallinity of the 1,2-aziridine alcohol ligand are enabling benefits for this methodology.

Figure 2.6. Asymmetric organozinc addition to aldehydes catalyzed by 1,2-aziridine alcohol ligand (2.1.10a)

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>yield (%)</th>
<th>ee (%)</th>
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<td>91</td>
</tr>
<tr>
<td>2</td>
<td>MeO</td>
<td>95</td>
<td>97</td>
</tr>
<tr>
<td>3</td>
<td>MeO</td>
<td>95</td>
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<td>4</td>
<td>Me</td>
<td>70</td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>95</td>
<td>10</td>
</tr>
</tbody>
</table>
2.1.3 Zn^{II}-Catalyzed Alkyne Addition to Aldehydes

Chiral, propargyl alcohols are versatile intermediates in organic synthesis. Carreira and co-workers reported access to enantioenriched propargyl alcohols via a stoichiometric Zn(OTf)₂/(+)-N-methylephedrine (2.1.13)-mediated addition of terminal alkynes to aldehydes (Scheme 2.5). For most substrates, the addition reaction proceeded with high enantioinduction (95-99% ee). Interestingly, the reaction is amenable to ambient conditions without care for inert atmosphere or exclusion of water. This is in contrast to previous reports of dialkylzinc reagents that require the absolute exclusion of water and oxygen for an effective transformation. The ease of setup and highly enantioselective nature of the reactions provides direct and convenient access to chiral propargyl amines without a separate metalation step.
The same authors reported the catalytic variant of the same reaction later the same year.\textsuperscript{23} The addition of terminal alkynes in the presence of 20 mol % Zn(OTf)\textsubscript{2} and 22 mol % \textit{2.1.13} was found to proceed with comparable enantioinduction and yield as the stoichiometric version (Scheme 2.6, \textit{2.1.14}). A solvent free reaction was also reported with no change in enantioselectivity or yield. This represents the first example of a reaction in which an alkyl-zinc has been added to aldehyde in a catalytic fashion.

\textbf{Scheme 2.5. Asymmetric Zn(OTf)\textsubscript{2}-mediated alkyne addition to aldehydes catalyzed by \textit{2.1.13}}

Acetylene (ethyne) is a commodity chemical that is rarely used in enantioselective, let alone catalytic bond forming transformations.\textsuperscript{24} The challenges associated with the addition of acetylene (H-C≡C-H) to aldehyde substrates include metal acetylide disproportionation and a double functionalization reaction.\textsuperscript{25} The Carreira group has circumvented these challenges with the use of 2-methylbut-3-yn-2-ol (\textit{2.1.15}) as the acetylene surrogate (Scheme 2.7).\textsuperscript{26} Addition of the terminal alkyne proceeds as expected to yield the propargyl alcohol in high yield. The propargyl alcohol (\textit{2.1.16}) is then subjected to base-mediated fragmentation and results in the formation of the terminal alkyne product (\textit{2.1.17}) and one equivalent of acetone. Ir\textsuperscript{I}-catalyzed addition of trimethylsilyl-acetylene (TMS-acetylene) to aldehydes followed by TMS removal is also an effective method to access chiral propargyl alcohols (e.g. \textit{2.1.17}).\textsuperscript{27}
Scheme 2.7. Indirect synthesis of propargyl alcohol 2.1.17 via fragmentation of 2.1.16

In stark contrast with Cu$^{II}$/Ag$^+$-acetylides, zinc-acetylides react readily with carbonyl-containing compounds. A number of spectroscopic techniques were utilized to uncover the process by which the zinc-acetylide is formed. It was determined that treatment of terminal alkynes with zinc salts, notably Zn(OTf)$_2$, in combination with trialkylamine base (Et$_3$N) leads to a complete disappearance of the acidic C-H bond within 5 minutes (Scheme 2.8). This process is reversible, whereby treatment with acid leads to the reconstitution of the terminal alkyne signal.

Scheme 2.8. Proposed mechanism for zinc-acetylide 2.1.20 formation

Based on this data, a mechanistic proposal for the addition of Zn$^{II}$-acetylides to aldehydes has been developed (Scheme 2.8). First, the Zn$^{II}$-cation coordinates to the $\pi$-system to form the metal-$\pi$ complex (2.1.18). The coordination of the alkyne to the Zn$^{II}$ acidifies the terminal C-H bond which permits proton abstraction by weak trialkylamine base (2.1.19). Subsequent deprotonation forms the Zn$^{II}$-acetylide (2.1.20). The Zn$^{II}$-acetylide is a competent nucleophile for a number of transformations and has been extended to C=N electrophiles (Scheme 2.9).
2.1.4 Catalytic [M]-Alkyne Addition to C=N Electrophiles

A common method for the synthesis of substituted propargylamines is through the addition of a metal-acetylide to the C=N bond, of which nitrones and imines are viable substrates (Scheme 2.10). The metal acetylide is formed from the deprotonation of the relatively acidic C≡C-H by strong bases, such as LDA or n-BuLi. These lithiated alkynes are highly moisture sensitive, stoichiometric in nature and require strict control of the reaction conditions.

Scheme 2.10. Lithium-acetylide addition to nitrone

A transition metal catalyzed addition reaction that was tolerant of air and moisture would lead to a practical method for the synthesis of propargyl nitrones. Carreira and co-workers reported that the stoichiometric Zn(OTf)₂ and DIPEA allowed for the rapid addition of the terminal alkynes to nitrones (Scheme 2.11). The authors further optimized the reaction conditions and found that the addition proceeds in the presence of 10 mol % Zn(OTf)₂ to afford the propargyl N-hydroxylamine (2.1.21) in excellent yields, up to 99%. A range of nitrones and terminal alkynes
were found to be suitable substrates for the addition reaction. A limitation of the methodology is that the nitrone component required preparation prior to the reaction.

\[
\text{O}^+\text{N}^+\text{R}^+ \quad \text{cat. } \text{Zn(OTf)}_2 \quad \text{cat. DIPEA} \quad \text{DCM} \quad \text{HO}^{-}\text{N}^{-}\text{R}^+ \quad \text{43-99\% yield}
\]

**Scheme 2.11.** Zn(OTf)$_2$-catalyzed addition of terminal alkynes to nitrones

This methodology was applied to the development of a one-pot multi-component reaction that utilizes aldehyde-amine-alkyne partners ($A^3$-coupling). In 2002, C.J. Li and co-workers reported the three-component copper-catalyzed alkyne addition to $N$-aryl imines (Scheme 2.12). The reactive copper-acetylide is formed *in situ* and adds to the iminium cation in preference to the aldehyde. In addition to the observed chemoselectivity, high yields and high enantioselectivities were obtained under vastly different reaction conditions, including: water, toluene and neat conditions. Again, the scope was limited to aryl aldehydes.

\[
\text{R}^+\text{N}^+\text{R}^+ \quad \text{10 mol\% Cu(OTf)} \quad \text{10 mol\% Ph-Pybox} \quad \text{H}_2\text{O or toluene} \quad \text{RT} \quad \text{R}^+\text{N}^+\text{R}^+ \quad \text{56-93\% yield} \quad \text{87-96\% ee}
\]

**Scheme 2.12.** Asymmetric $A^3$-coupling reaction

The application of Zn$^{II}$-alkynes in the $A^3$-coupling reaction was not realized until 2007 by the group of Adapa. A large screen of Zn$^{II}$-salts found that Zn(OAc)$_2$·2H$_2$O was the most effective catalyst for propargylamine synthesis (Scheme 2.13). Thus, the chemoselective addition of [Zn]-acetylides to iminium cations, without the aldehyde addition product was demonstrated.

\[
\text{R}^+\text{N}^+\text{R}^+ \quad \text{10 mol\% Zn(OAc)$_2$·2H}_2\text{O} \quad \text{toluene, reflux} \quad \text{R}^+\text{N}^+\text{R}^+ \quad \text{62-99\% yield}
\]

**Scheme 2.13.** Zn(OAc)$_2$-catalyzed $A^3$-coupling
2.1.5 $\text{A}^3$-Coupling Mechanism

The mechanism of the $\text{A}^3$-coupling reaction involves a number of elementary steps that are similar to the addition of $\text{Zn}^{II}$-acetylides to aldehyde electrophiles (Figure 2.8). The first step in the $\text{A}^3$-coupling is the reaction of the secondary amine component with the aldehyde. The condensation reaction of secondary amines with aldehydes results in the formation of an iminium cation and one equivalent of water. Concurrently, the transition metal catalyst is proposed to coordinate with the alkyne to result in a $\pi$-metal alkyne complex (2.1.22). The formation of this complex results in the acidification of the $\text{R-C≡C-H}$ and subsequent proton abstraction by base (2.1.23). The intermediate iminium cation is electrophilic enough to react with metal-acetylide complexes without Lewis acid activation. Therefore, direct addition of the metal acetylide to the iminium cation forms the propargyl amines (2.1.24) with concomitant catalyst regeneration. This mechanism is not dependent on the formation of the dinuclear zinc species that is common for the addition to carbonyl moieties.\(^{35}\)

![Proposed mechanism for the A$^3$-coupling reaction](image)

**Figure 2.8.** Proposed mechanism for the A$^3$-coupling reaction
2.2 Catalytic Alkynylzinc Addition to Aziridine Aldehydes

2.2.1 Proposal

Catalytic transformations are a cornerstone of modern organic synthesis.\(^{36}\) In contrast, starting material feedback mechanisms, which involve a reaction cycle based on starting materials, are rare in organic synthesis.\(^{37}\) The atypical reactivity of feedback mechanisms served as an inspiration in our pursuit of novel chemical processes driven by dimeric assemblies based upon aziridine aldehyde dimers (Figure 2.10).\(^{38}\) There are several requirements that need to be met in order to realize this type of system. Firstly, the reaction should involve an efficient monomer re-dimerization in order to provide substantial feedback into the starting material pool. The reactive dimeric intermediate must be held together by reversible covalent bonds to facilitate dissociation and subsequent re-dimerization.\(^{39}\)

![Figure 2.9. General model of starting material feedback mechanism](image)

Our recent inroads in the area of unprotected aziridine aldehyde transformations offered an opportunity to assess product feedback into the starting material pool with concurrent activation of a nucleophilic Zn\(^{II}\)-bound species.\(^{40}\) In the dimeric state, unprotected aziridine aldehydes (Figure 2.10, 2.2.01) possess a dense array of heteroatoms that can participate in hydrogen-bonding or Lewis acid complexation.\(^{41}\) We sought to utilize the reversible nature of the hemiaminal functional group for carbon-carbon bond formation.
The dynamic nature of aziridine aldehydes is described in Figure 2.10. The reactivity of 2.2.02 hinges on hemiacetal ring-opening, resulting in isomer 2.2.05. Upon nucleophilic addition to the aldehyde, the hemiaminal-stabilized assembly is weakened as a result of the absence of the intramolecular hydrogen bond. Decomposition of the hemiaminal assembly provides the newly formed product 2.2.04 and aziridine aldehyde 2.2.03. Dimerization occurs rapidly with another equivalent and re-enters the reaction cycle. Herein, we report our study aimed at activation of organozinc reagents via reversibly formed aziridine aldehyde assembly.

2.2.2 Effect of Zn$^{II}$-cation on $^1$H NMR spectra of 2.2.06

As described in the introduction of this chapter, organozinc reagents are commonly ligated with 1,2-aziridine alcohols. These ligands have also been used for the enantioselective addition of organozinc reagents to electrophilic species. The dynamic nature of the aziridine aldehydes affords the intermediate 2.2.05 which possesses the hemiaminal stabilized 1,2-aziridine alcohol binding motif (Figure 2.10). This constitutes a unique coordination environment in which to probe organozinc reactivity.
Figure 2.11. $^1$H NMR spectra of 2.2.06 in TFE-$d_3$. Inset: appearance of aldehyde hydrogen.

The polar, non-nucleophilic solvent 2,2,2-trifluoroethanol (TFE) has been shown to promote the formation of the open dimer form. $^{44}$ To investigate the formation of the open dimer, the aziridine aldehyde 2.2.06 was dissolved in TFE-$d_3$ and the $^1$H NMR spectrum was recorded (Figure 2.11). At room temperature a broad peak at 9.32 ppm was apparent and was attributed to the formation of the free aldehyde 2.2.06a. In comparison, measurement of the $^1$H NMR spectrum of 2.2.06 in CDCl$_3$ found no aldehyde peak (Figure 2.12). This data suggests that dissolution of 2.2.06 in TFE increases the population of the open-dimer form and concomitant formation of the 1,2-aziridine alcohol motif.
**Figure 2.12.** $^1$H NMR spectra of **2.2.06** in CDCl$_3$ peaks are clearly defined. *Inset:* no aldehyde signal

To evaluate the ability of dimeric aziridine aldehydes to coordinate Zn$^{ll}$-species we mixed phenethyl-substituted aziridine aldehyde dimer **2.2.06** and 1.0 equiv Zn(OTf)$_2$ in trifluoroethanol-$d_3$ (TFE-$d_3$). The addition of Zn(OTf)$_2$ to **2.2.06** resulted in substantial peak broadening. Notably, the aldehyde signal had become more prominent and shifted downfield by 0.15 ppm. These results suggest the complexation and stabilization of the open-dimer form by complexation of the Zn$^{ll}$-cation to the 1,2-aziridine alcohol binding site.$^{45}$ There was no evidence for the formation of the monomeric species under these conditions. This led us to explore the development of a mild reaction between organozinc reagents and aziridine aldehydes dimers driven by monomer feedback and zinc-complexation.$^{46}$
Figure 2.13. $^1$H NMR of 2.2.06 + 1.0 equiv Zn(OTf)$_2$ in TFE-$d_3$. Note the broadening of the upfield signals.

2.2.3 Reaction Development

The observed stabilization of the open-dimer conformation by Zn$^{II}$-cation led us propose the chemoselective engagement of the aldehyde moiety (Scheme 2.14). The addition of a secondary amine should readily condense to form a non-enolizable iminium cation. This charged iminium cation is an excellent electrophile and has been shown to participate in other acetylide addition reactions, including with Zn$^{II}$-acyetylides.
Scheme 2.14. Zn$^{II}$-stabilization of open-dimer species

In an effort to elucidate the appropriate reaction conditions, we screened a number of zinc-salts with common A$^3$-coupling partners (phenylacetylene, piperidine) in toluene (Table 2.1, entry1). These conditions failed to promote the alkyne addition to dimer 2.2.09. We postulated that the iminium cation was not forming in situ due to the negligible population of open-dimer tautomer in toluene.

Scheme 2.15. Formation of piperidine adduct 2.2.10 and iminium cation 2.2.11

As observed in the $^1$H NMR study, there is an increase in aldehyde population in polar protic solvents. It is assumed that in the presence of a secondary amine, the same conditions would also increase the population of iminium cation. The polar protic TFE(HFIP):H$_2$O solvent mixtures have been utilized in other reactions with aziridine aldehyde dimers.$^{47}$ However these conditions failed to promote iminium cation formation in this instance. Surprisingly, TFE as a single component resulted in the rapid consumption of 2.2.09 to afford the iminium/hemiaminal adduct 2.2.10/2.2.11 (Scheme 2.15). From this observation we found that Zn(OAc)$_2$ in TFE afforded the propargylamine product 2.2.12 in 93% yield and 1:1 d.r (Table 2.1, entry 3). The use of other zinc and silver catalysts, as well as different solvents did not improve the outcome of the reaction (Table 2.1).
Table 2.1. Optimization of reaction conditions\textsuperscript{48}

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst (20 mol%)</th>
<th>temperature (°C)</th>
<th>solvent</th>
<th>conversion (%)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Zn(OAc\textsubscript{2})</td>
<td>100</td>
<td>toluene</td>
<td>decomp</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Zn(OAc\textsubscript{2})</td>
<td>RT</td>
<td>MeOH</td>
<td>0</td>
<td>ND</td>
</tr>
<tr>
<td>3</td>
<td>Zn(OAc\textsubscript{2})</td>
<td>RT</td>
<td>2,2,2-trifluoroethanol (TFE)</td>
<td>100</td>
<td>93</td>
</tr>
<tr>
<td>4</td>
<td>Zn(OAc\textsubscript{2})</td>
<td>RT</td>
<td>9:1 TFE:H\textsubscript{2}O</td>
<td>0</td>
<td>ND</td>
</tr>
<tr>
<td>5</td>
<td>Zn(OAc\textsubscript{2})</td>
<td>RT</td>
<td>1:1 TFE:H\textsubscript{2}O</td>
<td>0</td>
<td>ND</td>
</tr>
<tr>
<td>6\textsuperscript{b}</td>
<td>Zn(OAc\textsubscript{2})</td>
<td>RT</td>
<td>TFE</td>
<td>0</td>
<td>ND</td>
</tr>
<tr>
<td>7</td>
<td>ZnCl\textsubscript{2}</td>
<td>RT</td>
<td>TFE</td>
<td>trace</td>
<td>ND</td>
</tr>
<tr>
<td>8</td>
<td>ZnBr\textsubscript{2}</td>
<td>RT</td>
<td>TFE</td>
<td>trace</td>
<td>ND</td>
</tr>
<tr>
<td>9</td>
<td>AgX, X=Cl, Br, I</td>
<td>100</td>
<td>toluene</td>
<td>0</td>
<td>ND</td>
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<td>AgX, X=Cl, Br, I</td>
<td>RT</td>
<td>TFE</td>
<td>0</td>
<td>ND</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Conversion measured by ESI-MS in positive ion mode, \textsuperscript{b} N\textsubscript{a}isopropylamine used in place of piperidine. ND = not determined

Figure 2.14. Aziridine aldehydes used in study

The dimeric form of aziridine aldehydes is required for the successful addition reaction as demonstrated by the bisulfite adduct results. Therefore, we sought to apply the A\textsuperscript{3}-coupling reaction to other dimeric aziridine aldehydes (Figure 2.14). For most substrates the desired propargylamine was obtained in moderate to good yield. In an isolated example, we found that 3-
phenyl aziridine aldehyde produced an intractable mixture of products (Scheme 2.16, 2.2.14). Facile ring opening at the benzylic carbon is proposed to be the predominant reaction pathway which results in aziridine aldehyde decomposition. 49 2-Substituted aziridine aldehydes 2.2.13 and 2.2.15 afforded the propargylamine in >20:1 diastereomeric ratio in favour of the anti-1,2-diamine.

Scheme 2.16. Scope of aziridine aldehydes

Next, we sought to investigate the secondary amine and terminal alkyne coupling partners for any influence on product formation and diastereoselectivity. First, a number of acyclic and cyclic secondary amines were screened with phenylacetylene in the $\text{A}_3^3$-coupling reaction. As illustrated in Scheme 2.17, diastereoselectivity was not affected by amine coupling partner. The nature of the alkyne also had no observable effect on the efficiency of the reaction (Scheme 2.17). These results suggest that the diastereoselectivity of the reaction is dependent on the dimeric aziridine aldehyde.
2.2.4 Proposed Feedback Mechanism

A proposed feedback loop involving the aziridine aldehyde is described in Figure 2.15. First, the rapid condensation of a secondary amine onto the aziridine aldehyde affords the iminium cation 2.2.37. Concurrently, deprotonation of the Zn\(^{II}\)-alkyne π-complex results in the formation of the
XZn$^\text{II}$-acetylde. The iminium cation (2.2.38) then coordinates the XZn$^\text{II}$-acetylde through the 1,2-aziridine alcohol binding site to afford the adduct 2.2.39, which is followed by alkyne transfer to the iminium cation. Decomposition of the hemiaminal 2.2.40 results in the propargylamine product and monomeric aziridine aldehyde. Lastly, the monomeric aziridine then undergoes rapid re-dimerization and re-enters the reaction cycle.

Figure 2.15. Proposed feedback loop for the addition of organozinc reagents to the iminium adducts of dimeric aziridine aldehydes.

Based upon the diastereoselectivity results obtained with different aziridine aldehydes, we sought to propose a stereochemical model for the addition reaction. In the case of $\alpha$-unsubstituted aziridine aldehydes (Figure 2.16, 2.2.39a, R = H), the iminium cation can adopt a cis- or trans-geometry, which results in the observed 1:1 d.r. In contrast, the condensation of secondary amines and $\alpha$-substituted aziridine aldehyde dimers results in the potential A$^{1,3}$-interaction between the iminium and $\alpha$-substituents. Minimization of the unfavourable A$^{1,3}$-interaction results in a single iminium cation conformation, and the observed d.r. (Figure 2.16, 2.2.41b, R $\neq$ H).
The 1,2-aziridine alcohol binding motif can also complex other Lewis acids. The Petasis-borono-Mannich (P-B-M) reaction of dimeric aziridine aldehydes affords allyl amines in moderate yields and high diastereomeric ratio.\textsuperscript{51} In this example, the \textit{in situ} coordination of the boronic acid to the aziridine nitrogen and alkoxy moieties results in the formation of a boronate complex (Figure 2.17, \textbf{2.2.42}). The high diastereoselectivity of the P-B-M is proposed to be due to the steric interaction between the vinyl and iminium substituents (\textbf{2.2.42a} vs \textbf{2.2.42b}). The aziridine alcohol coordination to the Lewis acidic RB(OR)\textsubscript{2} and the steric interactions results in the highly diastereoselective migration of the vinyl moiety.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure216}
\caption{A\textsuperscript{1,3}-interaction controls iminium cation geometry}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure217}
\caption{Stereochemical model for the Petasis-borono-Mannich reaction}
\end{figure}

\textbf{2.2.5 Summary}

In summary, an organozinc-based feedback mechanism of aziridine aldehyde dimers has been developed. The reversibly formed dimeric assemblies enables the 1,2-aziridine alcohol complexation to organozinc reagents which directs the alkyne transfer to the electrophilic iminium cation. The importance of the dimeric assembly is further established by the lack of
reactivity with the corresponding bisulfite adduct. In addition a stereochemical model and feedback mechanism has been proposed.

2.2.6 Other Synthetic Investigations with Aziridine Aldehydes

Early into aziridine aldehyde chemistry it was proposed that an aldol reaction would afford complex, densely functionalized substrates for downstream synthetic applications. The first attempt was by Dr. Ryan Hili using previously reported conditions that were effective for the intercepted Michael reaction. Mixing aziridine aldehyde dimer and aldehyde in the presence of benzoic acid and pyrrolidine did not induce aldol reactivity, but afforded the novel heterocycles, referred to as mixed adducts (2.2.43). Further development of this condensation chemistry was performed by Ms. Shannon Decker (Yudin Lab, M.Sc). It was found that these heterocycles are generally unreactive to most nucleophilic ring opening reactions.

Scheme 2.18. Synthesis of mixed-adducts

Shortly after this study on aldehyde reactivity was concluded we attempted a similar Mannich reaction with aziridine aldehyde dimers, isovaleraldehyde and piperidine. In this single example it was found that the attempted Mannich reaction did not afford the desired product. However the formation of a mixed aminal adduct (2.2.44) was formed in moderate yields (Scheme 2.19). This class of heterocycles has not yet been reported to date.

Scheme 2.19. Mixed aminal adduct formation
2.3 Supporting Information

2.3.1 General Information

Tetrahydrofuran (THF) was purified by distillation from sodium/benzophenone ketyl radical under an atmosphere of nitrogen. Acetonitrile (MeCN) was purified by distillation from 3Å molecular sieves (3Å MS). Dichloromethane, methanol (MeOH) and triethylamine (Et3N) were purified by distillation from CaH2 respectively. Diethyl ether (Et2O), toluene, dimethyl formamide (DMF), was purified through a solvent purification system. All other reagents were purchased from commercial sources used as received. Compound 2.2.09 was synthesized by Mr. Nick Afagh (M.Sc. 2010). All aziridine aldehyde dimers were synthesized according to Hili, R.; Yudin, A. K. J. Am. Chem. Soc. 2006, 128, 14772–14773.

Chromatography

Flash column chromatography was carried out using Silicycle 230-400 mesh silica gel. Thin-layer chromatography (TLC) was performed on Macherey Nagel pre-coated glass backed TLC plates (SIL G/UV254, 0.25 mm) and visualized using a UV lamp (254 nm), KMnO4, ninhydrin, or I2 stain in case of no UV activity.

Nuclear Magnetic Resonance Spectroscopy

Proton (1H-NMR), carbon (13C-NMR) and 2D NMR experiments were performed on Bruker 400 MHz or Varian 300, 400, or 500 MHz spectrometers. NMR spectra chemical shifts (δ) are reported in parts per million (ppm) referenced to residual protonated solvent peak (CDCl3, δ = 7.26, DMSO-d6, δ = 2.49, acetone-d6 δ = 2.05, acetonitrile-d3 δ = 1.94). Spectral data is reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, ddt = doublet of doublet of triplets, dtd= doublet of triplet of doublets, m = multiplet, br = broad), coupling constant (J) in Hertz (Hz), and integration. 13C NMR spectra chemical shifts (δ) are reported in parts per million (ppm) were referenced to carbon resonances in the NMR solvent (CDCl3, δ = 77.0; DMSO-d6, δ = 39.5, center line, acetone-d6, δ= 206.2, 29.8 (centre line), acetonitrile-d3, δ = 118.2, 1.3 (centre line)).
High-Resolution Mass Spectra was obtained at the University of Toronto mass spectrometry centre.

**Infrared Spectroscopy**

IR spectra were recorded on a Perkin-Elmer 100 instrument equipped with a single-reflection diamond/ZnSe ATR accessory. Performed on an NaCl disc as a thin layer.

**Mass Spectrometry**

High resolution mass spectra were obtained on a VG 70-250S (double focusing) mass spectrometer at 70 eV or on an ABI/Sciex Qstar mass spectrometer with ESI source, MS/MS and accurate mass capabilities.

### 2.3.2 Representative Procedure for Aziridine Aldehyde Synthesis

To a pre-cooled (–78 °C) solution of tert-butyl (2S,3R)-3-phenethylaziridine-2-carboxylate (2.34 g, 9.5 mmol) in toluene (80 mL), was added DIBAL in toluene (1.5 M, 13.2 mL, 19.8 mmol) slowly along the wall of a flask maintained at –78 °C. Then the mixture was stirred for additional 2 hours at –78 °C. The reaction mixture was then subjected to standard Fieser workup conditions for DIBAL reagents (dilute with 1 vol Et₂O, add 0.7 mL dH₂O, then add 0.7 mL 1.0 M NaOH, then add 1.9 mL dH₂O, stir warming to RT for 15 min, add anhydrous Na₂SO₄, stir 30 min). The mixture was then filtered and then the filter cake was washed with dichloromethane (2 x 25 mL). To the combined organic filtrate was dried with anhydrous Na₂SO₄, concentrated to dryness, affording the title compound (1.01 g) as a white solid, yield 61%, which can be used as is in subsequent transformations. If required, purification of the title compound can be performed on SiO₂ with CHCl₃:MeOH (100:0 → 90:10).

![Chemical Structure](image)

**Chemical Formula:** C₂₂H₂₆N₂O₂

Phenethyl aziridine aldehyde (2.2.06)

61% yield, white solid
1H NMR (399 MHz, Chloroform-d)

δ 7.33 – 7.26 (m, 4H), 7.24 – 7.13 (m, 6H), 5.18 (s, 1H), 4.74 (s, 1H), 2.85 – 2.65 (m, 4H), 2.37 (d, J = 2.9 Hz, 1H), 2.00 (br s, 2H), 1.90 – 1.79 (m, 1H), 1.78 – 1.65 (m, 3H), 1.37 (m, 1H)

13C NMR (100 MHz, Chloroform-d)

δ 141.3, 140.9, 128.6, 128.5, 128.4, 126.3, 126.1, 96.3, 94.3, 50.4, 38.7, 38.5, 35.6, 34.0, 33.9, 33.4, 32.8

HRMS [DART-MS] (M+H+)

m/z calculated for C_{22}H_{27}N_{2}O_{2} = 351.2080

m/z found = 351.2072

TLC (CHCl_{3}:MeOH 95:5)

R_{f} = 0.5

2.3.2.1 Synthesis of 5-methyl-2-(2-methylaziridin-2-yl)-3-oxa-1-azabicyclo[3.1.0]hexan-4-ol (2.2.14)

To an oven dried two necked flask, equipped with magnetic stir bar, was added ethyl 2-methylaziridine-2-carboxylate (1.0 g, 7.74 mmol)\textsuperscript{53} followed by toluene (30 mL) and then cooled to –78°C. A solution of DIBAL in toluene (11.3 mL, 17.0 mmol, 1.5 M in toluene) was taken up in a syringe and the needle was then immersed in the reaction solvent (approx 5 cm). The solution of DIBAL was then added via syringe pump over 45 min. After addition the syringe was removed and the reaction continued to stir for 4-5 hours with monitoring via TLC and/or ESI-MS for disappearance of SM at which point Et_{2}O (90 mL) was added and stirring was continued at –78 °C for 5 minutes. The reaction was then afforded the standard Fieser workup at which time the aluminium precipitate was filtered off. The solid filtrate was then washed with 90 mL of DCM and concentrated in vacuo at room temperature. The residue was purified via silica gel chromatography using hexanes:acetone as eluent to produce the desired aziridine aldehyde dimer as a white solid.
rac-(2R,4R,5S)-5-methyl-2-((S)-2-methylaziridin-2-yl)-3-oxa-1-azabicyclo[3.1.0]hexan-4-ol (2.2.14)\textsuperscript{54}

69\% yield, white solid (purity 95\%)

H NMR (500 MHz, Chloroform-d)

\begin{align*}
\delta & 5.13 (s, 1H), 4.60 (s, 1H), 1.93 (d, J = 4.5 \text{ Hz}, 1H), 1.68 (s, 1H), 1.67 – 1.63 (m, 1H), \\
& 1.57 (s, 1H), 1.50 (s, 3H), 1.41 (s, 1H), 1.38 (s, 3H), 1.30 – 1.26 (m, 1H)
\end{align*}

C NMR (126 MHz, Chloroform-d)

\begin{align*}
\delta & 97.9, 97.5, 48.3, 36.5, 35.0, 29.7, 20.7, 15.1
\end{align*}

HRMS [ESI-MS] (M+H\textsuperscript{+})

\begin{align*}
m/z \text{ calculated for } & C_8H_{15}N_2O_2 = 171.1128 \\
& m/z \text{ found } = 171.1121
\end{align*}

TLC (hexanes:acetone 1:1)

R\textsubscript{f} = 0.28

2.3.3 General Procedure for the $A^3$-Coupling Reaction

To an oven dried 2 dram vial was added a magnetic stir bar and $\alpha$-aziridine aldehyde dimer and 2,2,2-trifluoroethanol (TFE). The reaction flask was sequentially charged with alkyne (4.0 equivalents to dimer), secondary amine (3.0 equivalents to dimer) and Zn(OAc)\textsubscript{2} (20 mol\% to dimer). The reactions were stirred at room temperature for 8-24 hours with monitoring by ESI-MS. At which time the solvent was removed and purified via column chromatography using hexanes:ethyl acetate, hexanes:acetone or DCM:MeOH as eluent.
1-((S)-1-((2S,3R)-3-isobutylaziridin-2-yl)-3-phenylprop-2-yn-1-yl)piperidine (syn-2.2.10)\(^4\)

47% yield, clear oil

\(^1\)H NMR (400 MHz, Chloroform-\(d\))

\(\delta\) 7.46 – 7.38 (m, 2H), 7.35 – 7.27 (m, 3H), 4.20 – 3.98 (m, 1H), 2.78 (d, \(J = 4.5\) Hz, 2H), 2.53 (d, \(J = 4.7\) Hz, 2H), 1.96 (s, 1H), 1.90 (td, \(J = 6.3, 3.1\) Hz, 1H), 1.78 (tt, \(J = 13.3, 6.6\) Hz, 1H), 1.69 – 1.56 (m, 4H), 1.49 – 1.36 (m, 3H), 1.30 – 1.18 (m, 1H), 1.01 – 0.92 (m, 6H)

\(^{13}\)C NMR (100 MHz, Chloroform-\(d\))

\(\delta\) 132.0, 128.5, 128.4, 122.7, 105.0, 88.6, 61.3, 51.3, 42.4, 38.6, 27.5, 26.3, 24.4, 23.1, 22.7

HRMS [DART-MS] (M+H\(^+\))

\(m/\text{z}\) calculated for C\(_{20}\)H\(_{29}\)N\(_2\) = 297.2330

\(m/\text{z}\) found = 297.2323

TLC (hexanes:EtOAc 1:1)

\(R_f = 0.5\)

\[\text{anti-2.2.17}\]

1-((R)-1-((2S,3R)-3-isobutylaziridin-2-yl)-3-phenylprop-2-yn-1-yl)piperidine (anti-2.2.10)

46% yield, clear oil

\(^1\)H NMR (400 MHz, Chloroform-\(d\))

\(\delta\) 7.45 – 7.40 (m, 2H), 7.33 – 7.28 (m, 3H), 3.65 (s, 1H), 2.80 – 2.70 (m, 2H), 2.57 (d, \(J = 4.9\) Hz, 2H), 2.04 (d, \(J = 4.6\) Hz, 1H), 1.97 (s, 1H), 1.82 (m, 1H), 1.64 (m, 4H), 1.47 (m, 2H), 1.34 (t, \(J = 6.4\) Hz, 2H), 0.98 (dd, \(J = 6.6, 1.2\) Hz, 6H)

\(^{13}\)C NMR (100 MHz, Chloroform-\(d\))

\(\delta\) 132.0, 128.5, 128.4, 123.0, 87.4, 84.1, 62.0, 51.4, 42.7, 38.0, 27.5, 26.2, 24.5, 23.0, 22.8

HRMS [DART-MS] (M+H\(^+\))

\(m/\text{z}\) calculated for C\(_{20}\)H\(_{29}\)N\(_2\) = 297.2330

---

\(^4\) Nick Afagh (Yudin Lab, M.Sc) synthesized this compound
m/z found = 297.2323

TLC (hexanes:EtOAc 1:1)
R_f = 0.42

rac-1-((S)-1-((S)-2-methylaziridin-2-yl)-3-phenylprop-2-yn-1-yl)piperidine (2.2.19)
74% yield, slightly orange oil

^1^H NMR (500 MHz, Chloroform-d)
δ 7.41 m 2H), 7.33 – 7.26 (m, 3H), 3.90 – 3.74 (m, 1H), 2.68 (m, 2H), 2.51 – 2.39 (m, 2H), 2.04 (s, 1H), 1.61 (m, 4H), 1.52 (s, 1H), 1.44 (m, 2H), 1.33 (s, 3H)

^13^C NMR (126 MHz, Chloroform-d)
δ 131.8, 128.2, 128.2, 122.6, 64.8, 51.2, 33.8, 30.4, 26.1, 24.4, 21.0

HRMS [DART-MS] (M+H^+) 
m/z calculated for C_{17}H_{23}N_{2} = 255.1861
m/z found = 255.1863

TLC (acetone)
R_f = 0.58

rac-1-((S)-3-phenyl-1-((S)-2-phenylaziridin-2-yl)prop-2-yn-1-yl)piperidine (2.2.21)
82% yield, clear oil

^1^H NMR (399 MHz, Chloroform-d)
δ 7.54 – 7.48 (m, 2H), 7.48 – 7.42 (m, 2H), 7.36 – 7.29 (m, 5H), 7.29 – 7.22 (m, 1H), 4.17 (s, 1H), 2.79 (m, 2H), 2.44 (m, 2H), 2.37 (s, 1H), 1.97 (s, 1H), 1.52 (m, 4H), 1.41 (m, 2H)

^13^C NMR (100 MHz, Chloroform-d)
δ 141.1, 128.6, 127.4, 126.8, 98.6, 92.4, 65.1, 51.1, 29.6, 25.8, 24.2, 0.0
HRMS [ESI-MS] (M+H⁺)

\[ m/z \text{ calculated for } C_{22}H_{25}N_2 = 317.2002 \]
\[ m/z \text{ found } = 317.2012 \]

TLC (hexanes:acetone 3:1)

\[ R_f = 0.3 \]

![Image of compound 2.222]

1-(1-((2S,3S)-3-methylaziridin-2-yl)-3-phenylprop-2-yn-1-yl)piperidine (2.2.22)

d.r. = 1.2:1

46% yield, clear oil, inseparable diastereomers

\(^1\)H NMR (500 MHz, Chloroform-\(d\))

\[ \delta 7.45 - 7.40 (m, 4H), 7.33 - 7.27 (m, 6H), 4.07 (s, 1H), 3.90 (s, 1H), 2.81 - 2.71 (m, 6H), 2.55 - 2.52 (m, 4H), 2.15 - 2.11 (m, 1H), 1.98 - 1.90 (m, 3H), 1.71 - 1.58 (m, 8H), 1.47 - 1.45 (m, 4H), 1.24 m, 3H), 1.21 (m, 3H) \]

\(^{13}\)C NMR (126 MHz, Chloroform-\(d\))

\[ \delta 131.8, 131.8, 131.8, 128.3, 128.2, 128.2, 128.2, 128.1, 128.1, 61.2, 61.0, 51.1 \text{ (2 carbons), 39.1, 38.4, 30.9, 30.2, 26.1, 26.1, 26.0, 24.4, 24.3, 24.2} \]

HRMS [DART-MS] (M+H⁺)

\[ m/z \text{ calculated for } C_{17}H_{23}N_2 = 255.1861 \]
\[ m/z \text{ found } = 255.1861 \]

TLC (hexanes:acetone 1:3)

\[ R_f = 0.17 \]

![Image of compound 2.2.23]

rac-1-((S)-1-((S)-2-methylaziridin-2-yl)-3-phenylprop-2-yn-1-yl)pyrrolidine (2.2.23)

65% yield, orange oil

\(^1\)H NMR (500 MHz, Chloroform-\(d\))
δ 7.42 – 7.38 (m, 2H), 7.30 – 7.27 (m, 3H), 3.85 (br s, 1H), 2.76 – 2.72 (m, 2H), 2.68 – 2.64 (m, 2H), 1.94 (s, 1H), 1.81 – 1.76 (m, 4H), 1.50 (s, 1H), 1.37 (s, 3H)

13C NMR (126 MHz, Chloroform-\textit{d})
δ 131.8, 128.2, 128.1, 122.6, 61.8, 50.4, 35.2, 29.8, 23.4, 20.8

HRMS [ESI-MS] (M+H\textsuperscript{+})

\[ m/z \text{ calculated for } C_{16}H_{21}N_2 = 241.1704 \]
\[ m/z \text{ found } = 241.1711 \]

TLC (acetone)
\[ R_f = 0.38 \]

\[ \text{ rac-4-((S)-1-((S)-2-methylaziridin-2-yl)-3-phenylprop-2-yn-1-yl)morpholine (2.2.24) } \]
54\% yield, orange oil

1H NMR (500 MHz, Chloroform-\textit{d})
δ 7.44 – 7.40 (m, 2H), 7.33 – 7.29 (m, 3H), 3.77 (m, 5H), 2.76 (m, 2H), 2.61 – 2.53 (m, 2H), 2.02 (s, 1H), 1.54 (m, 1H), 1.36 (s, 3H)

13C NMR (126 MHz, Chloroform-\textit{d})
δ 131.8, 128.4, 128.3, 122.3, 87.7, 82.1, 67.0, 64.6, 50.5, 33.6, 30.0, 20.9

HRMS [DART-MS] (M+H\textsuperscript{+})

\[ m/z \text{ calculated for } C_{16}H_{21}N_2O = 257.1653 \]
\[ m/z \text{ found } = 257.1663 \]

TLC (acetone)
\[ R_f = 0.48 \]

\[ \text{ rac-1-((S)-1-((S)-2-phenylaziridin-2-yl)hept-2-yn-1-yl)pyrrolidine (2.2.25) } \]
75\% yield, yellow oil
\(^1\)H NMR (300 MHz, Methylene Chloride-\(d_2\))
\[\delta 7.43 - 7.30 (m, 2H), 7.27 - 7.08 (m, 3H), 4.09 (s, 1H), 2.66 - 2.58 (m, 2H), 2.57 - 2.42 (m, 2H), 2.18 - 2.13 (m, 2H), 2.09 (br s, 1H), 1.70 (br s, 1H), 1.64 - 1.58 (m, 4H), 1.54 - 1.27 (m, 4H), 0.84 (t, \(J = 7.1\) Hz, 3H)

\(^1^3\)C NMR (75 MHz, Methylene Chloride-\(d_2\))
\[\delta 142.3, 128.9, 127.9, 127.0, 61.5, 50.1, 31.2, 28.9, 23.6, 22.1, 18.37, 13.5\]

HRMS [DART-MS] (M+H\(^+\))
\[m/z\] calculated for C\(_{19}\)H\(_{27}\)N\(_2\) = 283.2174
\[m/z\] found = 283.2182

TLC (DCM:MeOH 95:5)
\[R_f = 0.64\]

rac-1-((S)-1-((S)-2-phenylaziridin-2-yl)-3-(trimethylsilyl)prop-2-yn-1-yl)piperidine (2.2.27)
67% yield, yellow oil

\(^1\)H NMR (399 MHz, Chloroform-\(d\))
\[\delta 7.41 - 7.36 (m, 2H), 7.25 - 7.14 (m, 3H), 3.88 (s, 1H), 2.68 - 2.62 (m, 2H), 2.30 - 2.21 (m, 2H), 2.20 (s, 1H), 1.83 (s, 1H), 1.51 - 1.43 (m, 4H), 1.38 - 1.34 (m, 2H), 0.13 (s, 9H)

\(^1^3\)C NMR (100 MHz, Chloroform-\(d\))
\[\delta 141.4, 128.9, 127.7, 122.7, 98.8, 92.4, 65.4, 51.4, 39.9, 29.9, 26.1, 24.5, 0.2\]

HRMS [DART-MS] (M+H\(^+\))
\[m/z\] calculated for C\(_{19}\)H\(_{29}\)N\(_2\)Si = 313.2104
\[m/z\] found = 313.2100

TLC (hexanes:EtOAc 1:1)
\[R_f = 0.48\]
rac-1-((S)-4-((tert-butyldimethylsilyl)oxy)-1-((S)-2-phenylaziridin-2-yl)but-2-yn-1-yl)piperidine (2.2.28)

67% yield, clear oil

$^1$H NMR (300 MHz, Chloroform-$d$)

$\delta$ 7.36 – 7.28 (m, 2H), 7.20 – 7.06 (m, 3H), 4.24 (br s, 2H), 3.84 (s, 1H), 2.63 – 2.50 (m, 2H), 2.28 – 2.15 (m, 2H), 2.12 (s, 1H), 1.77 (s, 1H), 1.38 – 1.30 (m, 4H), 1.29 – 1.18 (m, 2H), 0.79 (s, 9H), 0.00 (s, 6H)

$^{13}$C NMR (75 MHz, Chloroform-$d$)

$\delta$ 146.4, 133.8, 132.7, 132.0, 91.5, 82.9, 69.8, 56.7, 56.4, 45.0, 35.0, 31.0, 30.8, 29.4, 23.3, 0.0

HRMS [DART-MS] (M+H$^+$)

$m/z$ calculated for C$_{23}$H$_{37}$N$_2$OSi = 385.2682

$m/z$ found = 385.2675

TLC (hexanes:acetone 1:1)

$R_f$ = 0.5

rac-(S)-2-methyl-5-((S)-2-phenylaziridin-2-yl)-5-(pyrrolidin-1-yl)pent-3-yn-2-ol (2.2.29)

X-ray quality crystals of 2.2.29 were grown from the slow diffusion of hexanes into EtOAc

54% yield, off-white solid

$^1$H NMR (300 MHz, Chloroform-$d$)

$\delta$ 7.48 – 7.41 (m, 2H), 7.33 – 7.20 (m, 3H), 4.14 (s, 1H), 2.70 – 2.63 (m, 2H), 2.60 – 2.55 (m, 2H), 2.18 (s, 1H), 1.91 (s, 1H), 1.70 – 1.63 (m, 4H), 1.52 (s, 6H)

$^{13}$C NMR (75 MHz, Chloroform-$d$)

$\delta$ 141.4, 128.7, 128.0, 127.4, 65.0, 61.0, 50.3, 32.0, 31.9, 29.4, 23.8, 23.7

HRMS [ESI-MS] (M+H$^+$)
m/z calculated for C_{18}H_{25}N_{2}O = 285.1970

m/z found = 285.1961

TLC (hexanes:EtOAc 1:4)

R_f = 0.24

![Structure](image)

rac-4-((S)-3-phenyl-1-((S)-2-phenylaziridin-2-yl)prop-2-yn-1-yl)morpholine (2.2.30)

72% yield, clear oil

^1^H NMR (400 MHz, Chloroform-^d^, 90% pure)

δ 7.52 – 7.42 (m, 4H), 7.40 – 7.26 (m, 6H), 4.16 (s, 1H), 3.84 – 3.80 (m, 1H), 3.70 – 3.64 (m, 3H), 2.87 – 2.82 (m, 2H), 2.58 – 2.53 (m, 2H), 2.35 (s, 1H), 2.01 (s, 1H)

^1^3^C NMR (101 MHz, Chloroform-^d^)

δ 140.9, 131.9, 128.7, 128.5, 128.3, 127.9, 127.3, 126.8, 88.5, 81.8, 66.96, 65.0, 59.6, 50.6, 29.6

HRMS [ESI-MS] (M+H^+^)

m/z calculated for C_{21}H_{23}N_{2}O = 319.1804

m/z found = 319.1801

TLC (DCM:MeOH 95:5)

R_f = 0.5

![Structure](image)

rac-(S)-N,N-diethyl-3-phenyl-1-((S)-2-phenylaziridin-2-yl)prop-2-yn-1-amine (2.2.31)

81% yield, clear oil

^1^H NMR (399 MHz, Chloroform-^d^)

δ 7.43 – 7.39 (m, 2H), 7.37 – 7.34 (m, 2H), 7.28 – 7.24 (m, 5H), 7.22 – 7.16 (m, 1H), 4.35 (s, 1H), 2.72 – 2.63 (m, 2H), 2.45 – 2.36 (m, 2H), 2.34 (s, 1H), 1.99 (br s, 1H), 0.89 (app t, J = 7.1 Hz, 6H)
\( ^{13}C \) NMR (100 MHz, Chloroform-\( d \))
\[
\delta 141.6, 132.0, 129.1, 128.5, 128.4, 127.9, 127.3, 123.0, 60.1, 45.0, 29.8, 13.2
\]

IR (thin film)
\[
\nu 3061, 2968, 2931, 2359, 2341, 1624, 1448, 1271
\]

HRMS [DART-MS] (M+H\(^+\))
\[
m/z \text{ calculated for } C_{21}H_{25}N_2 = 305.2017
\]
\[
m/z \text{ found } = 305.2017
\]

TLC (hexanes:acetone 2:1)
\[
R_f = 0.34
\]

rac-1-((S)-1-((S)-2-phenylaziridin-2-yl)-3-(trimethylsilyl)prop-2-yn-1-yl)pyrrolidine (2.2.32)
54% yield, clear oil

\( ^{1}H \) NMR (399 MHz, Chloroform-\( d \))
\[
\delta 7.51 - 7.44 (m, 2H), 7.32 - 7.22 (m, 3H), 4.13 (s, 1H), 2.72 - 2.62 (m, 2H), 2.64 - 2.54 (m, 2H), 2.21 (s, 1H), 1.87 (s, 1H), 1.75 - 1.65 (m, 4H), , 0.19 (s, 9H)
\]

\( ^{13}C \) NMR (100 MHz, Chloroform-\( d \))
\[
\delta 141.1, 128.5, 127.6, 127.0, 61.7, 49.9, 29.2, 23.4, 0.0
\]

HRMS [DART-MS] (M+H\(^+\))
\[
m/z \text{ calculated for } C_{18}H_{27}N_2Si = 299.1943
\]
\[
m/z \text{ found } = 299.1943
\]

TLC (hexanes:EtOAc 1:1)
\[
R_f = 0.34
\]

rac-1-((S)-3-phenyl-1-((S)-2-phenylaziridin-2-yl)prop-2-yn-1-yl)pyrrolidine (2.2.33)
87% yield, yellow oil
$^1$H NMR (300 MHz, Chloroform-$d$)
\[ \delta 7.57 - 7.49 \text{ (m, 2H)}, 7.48 - 7.39 \text{ (m, 2H)}, 7.37 - 7.27 \text{ (m, 6H)}, 4.35 \text{ (s, 1H)}, 2.78 \text{ (m, 2H)}, 2.74 - 2.63 \text{ (m, 2H)}, 2.31 \text{ (s, 1H)}, 1.94 \text{ (s, 1H)}, 1.73 \text{ (m, 4H)} \]

$^{13}$C NMR (100 MHz, Chloroform-$d$)
\[ \delta 141.5, 132.1 \text{ (2 carbons)}, 128.8, 128.5, 128.1, 127.4, 122.8, 62.0, 50.5, 29.7, 23.8 \]

HRMS [DART-MS] (M+H$^+$
\[ m/z \text{ calculated for } C_{21}H_{23}N_2 = 303.1861 \]
\[ m/z \text{ found } = 303.1859 \]

TLC (hexanes:EtOAc 1:2)
\[ R_f = 0.28 \]

rac-1-((S)-4-((tert-butyldimethylsilyl)oxy)-1-((S)-2-phenylaziridin-2-yl)but-2-yn-1-yl)pyrrolidine (2.2.34)

70% yield, yellow oil

$^1$H NMR (300 MHz, Chloroform-$d$)
\[ \delta 7.40 - 7.32 \text{ (m, 2H)}, 7.22 - 7.08 \text{ (m, 3H)}, 4.24 \text{ (m, 2H)}, 4.06 \text{ (s, 1H)}, 2.57 \text{ (m, 2H)}, 2.47 \text{ (m, 2H)}, 2.08 \text{ (s, 1H)}, 1.75 \text{ (s, 1H)}, 1.57 \text{ (m, 4H)}, 0.79 \text{ (s, 9H)}, 0.00 \text{ (s, 6H)} \]

$^{13}$C NMR (100 MHz, Chloroform-$d$)
\[ \delta 146.4, 133.6, 132.9, 132.2, 66.3, 56.7, 55.2, 34.6, 30.8, 28.6, 23.3, 0.0 \]

HRMS [ESI-MS] (M+H$^+$)
\[ m/z \text{ calculated for } C_{22}H_{35}N_2OSi = 371.2513 \]
\[ m/z \text{ found } = 371.2527 \]

TLC (hexanes:acetone 1:1)
\[ R_f = 0.35 \]

1-(1-((2S,3S)-3-methylaziridin-2-yl)-3-phenylprop-2-yn-1-yl)pyrrolidine (2.2.36a)
Slightly orange oil, less polar diastereomer

$^1$H NMR (500 MHz, Chloroform-$d$)

$\delta$ 7.42 – 7.40 (m, 2H), 7.33 – 7.26 (m, 3H), 4.05 (br s, 1H), 2.85 – 2.79 (m, 2H), 2.75 – 2.71 (m, 2H), 2.1 – 2.10 (m, 1H), 2.04 – 1.94 (m, 1H), 1.85 – 1.81 (m, 4H), 1.29 – 1.23 (m, 3H)

$^{13}$C NMR (126 MHz, Chloroform-$d$) two observable conformations in solution approx 3:1

$\delta$ 131.8, 128.2, 128.2, 122.5, 57.5 major, 57.5 minor, 50.5 minor, 50.1 major, 40.1 major, 39.4 minor, 29.5, 23.4 major, 23.4 minor, 18.3

HRMS [ESI-MS] (M+H$^+$)

$m/z$ calculated for C$_{16}$H$_{21}$N$_2$ = 241.1699

$m/z$ found = 241.1709

TLC (hexanes:acetone 1:3)

$R_f$ = 0.21

1-(1-((2S,3S)-3-methylaziridin-2-yl)-3-phenylprop-2-yn-1-yl)pyrrolidine (2.2.36b)

41% combined yield, clear oil,

more polar diastereomer

$^1$H NMR (500 MHz, Chloroform-$d$)

$\delta$ 7.44 – 7.38 (m, 2H), 7.32 – 7.28 (m, 3H), 4.06 (s, 1H), 2.81 – 2.78 (m, 2H), 2.76 – 2.72 (m, 2H), 2.14 – 2.10 (m, 1H), 1.98 – 1.96 (m, 1H), 1.87 – 1.80 (m, 4H), 1.25 (m, 3H)

$^{13}$C NMR (126 MHz, Chloroform-$d$)

$\delta$ 131.8, 128.3, 128.2, 122.5, 57.5, 50.1, 39.4, 29.6, 23.4, 18.2

HRMS [ESI-MS] (M+H$^+$)

$m/z$ calculated for C$_{16}$H$_{21}$N$_2$ = 241.1699

$m/z$ found = 241.1709

TLC (hexanes:acetone 1:3)

$R_f$ = 0.1
2.3.4 Procedure for the Ring Opening of 2.2.18 and 2.2.35

![Chemical structure](image)

To the crude reaction mixture of aziridine amino alkyne was added THF (2 mL) and H$_2$O (2 mL) and then thiophenol (0.1 mL, 0.978 mmol, 1.1 equiv). The crude reaction mixture was warmed to 50°C and stirred at this temperature for one hour. At the one hour mark, ESI-MS analysis showed consumption of starting material and the reaction was removed from the heat source. After cooling to room temperature, the mixture was extracted with EtOAc (3 x 2 mL), dried over Na$_2$SO$_4$ (anhydrous) and removed in vacuo. The residue was purified via silica gel chromatography using hexanes/ethyl acetate as eluent to provide separable diastereomers.

(2R)-5-phenyl-1-(phenylthio)-3-(piperidin-1-yl)pent-4-yn-2-amine (2.2.18)

Combined yield of 30% over two steps

Major diastereomer, yellow oil

$^1$H NMR (300 MHz, Chloroform-$d$)

δ 7.47 – 7.39 (m, 4H), 7.34 – 7.27 (m, 5H), 7.21 – 7.12 (m, 1H), 3.69 – 3.54 (m, 1H), 3.40 – 3.37 (m, 1H), 3.16 (m, 1H), 2.91 (dd, $J = 13.6, 7.9$ Hz, 1H), 2.66 – 2.51 (m, 2H), 2.52 – 2.35 (m, 2H), 1.87 (m, 1H), 1.61 – 1.54 (m, 4H), 1.47 – 1.41 (m, 1H), 1.26 (br s, 2H)

$^{13}$C NMR (75 MHz, Chloroform-$d$)

δ 136.7, 132.0, 129.4, 129.0, 128.4, 128.3, 126.1, 123.1, 87.7, 85.5, 64.7, 51.7, 38.9, 29.9, 26.4, 24.6

TLC (hexanes:EtOAc 5:1)

$R_f = 0.2$

Minor diastereomer (95% pure)

$^1$H NMR (300 MHz, Chloroform-$d$)
\[ \delta \ 7.48 - 7.37 \text{ (m, 4H)}, \ 7.35 - 7.31 \text{ (m, 3H)}, \ 7.29 - 7.21 \text{ (m, 2H)}, \ 7.17 - 7.13 \text{ (m, 1H)}, \ 3.70 - 3.60 \text{ (m, 1H)}, \ 3.40 - 3.38 \text{ (m, 1H)}, \ 3.33 - 3.23 \text{ (m, 1H)}, \ 2.99 - 2.92 \text{ (m, 1H)}, \ 2.69 - 2.30 \text{ (m, 6H)}, \ 1.67 - 1.49 \text{ (m, 4H)}, \ 1.45 \text{ (br s, 2H)} \]

\[ ^{13}C \text{ NMR (100 MHz, Chloroform-}d) \]
\[ \delta \ 136.6, 131.9, 129.1, 129.1, 128.5, 128.4, 126.0, 123.1, 88.2, 85.0, 63.8, 51.4, 39.3, 29.9, 26.4, 24.6 \]

HRMS [DART-MS] (M+H\(^+\))
\[ \text{m/z calculated for } \text{C}_{22}\text{H}_{27}\text{N}_{2}\text{S} = 351.1894 \]
\[ \text{m/z found} = 351.1906 \]

TLC (hexanes:EtOAc 5:1)
\[ R_f = 0.25 \]

(2R)-5-phenyl-1-(phenylthio)-3-(pyrrolidin-1-yl)pent-4-yn-2-amine (2.2.35)

Combined Yield of 42% over 2 steps, yellow oil

Inseparable diastereomers

\[ ^{1}H \text{ NMR (300 MHz, Chloroform-}d) \]
\[ \delta \ 7.46 - 7.39 \text{ (m, 8H)}, \ 7.31 \text{ (m, 8H)}, \ 7.27 - 7.22 \text{ (m, 2H)}, \ 7.21 - 7.12 \text{ (m, 2H)}, \ 3.69 - 3.61 \text{ (m, 4H)}, \ 3.19 - 3.07 \text{ (m, 2H)}, \ 2.96 \text{ (m, 2H)}, \ 2.72 - 2.61 \text{ (m, 8H)}, \ 1.82 \text{ (m, 12H)} \]

\[ ^{13}C \text{ NMR (75 MHz, Chloroform-}d) \]
\[ \delta \ 136.8, \ 136.6, \ 132.0, \ 131.9, \ 129.7, \ 129.2, \ 129.1, \ 129.1, \ 128.5, \ 128.5, \ 128.4, \ 128.3, \ 126.2, \ 126.0, \ 123.1 \text{ (2C)}, \ 87.7, \ 87.1, \ 85.8, \ 85.5, \ 61.4, \ 60.5, \ 53.3, \ 53.3, \ 50.7, \ 49.6, \ 39.4, \ 39.1, \ 23.8, \ 23.7 \]

HRMS [DART-MS] (M+H\(^+\))
\[ \text{m/z calculated for } \text{C}_{21}\text{H}_{25}\text{N}_{2}\text{S} = 337.1738 \]
\[ \text{m/z found} = 337.1738 \]

TLC (hexanes:EtOAc 3:1)
\[ R_f = 0.32 \]
rac-(2S,4R,5S,6R)-2-isopropyl-6-phenyl-4-(piperidin-1-yl)-3-oxa-1-azabicyclo[3.1.0]hexane (2.2.44)

52% yield, clear oil

$^1$H NMR (300 MHz, Chloroform-$d$)

$\delta$ 7.38 – 7.09 (m, 5H), 4.91 (s, 1H), 4.51 (d, $J = 8.4$ Hz, 1H), 2.93 (m, 2H), 2.63 (m, 4H), 1.58 (m, 6H), 1.48 (m, 1H), 1.04 (dd, $J = 6.7, 5.4$ Hz, 6H)

$^{13}$C NMR (75 MHz, Chloroform-$d$)

$\delta$ 138.4, 128.5, 127.3, 126.7, 102.6, 95.8, 49.3, 37.9, 32.2, 26.4, 24.6, 19.9, 19.5
2.4 References


Preliminary optimization of reaction conditions was performed by Nick Afagh, M.Sc 2010.


Chapter Three

*Suzuki-Miyaura Cross-Coupling of Primary Alkyl MIDA Boronates*
3 Suzuki-Miyaura Cross-Coupling of Primary Alkyl MIDA Boronates

3.1 Introduction

A paradigm shift has taken place in the fundamental strategy for the creation of C-C (or C-X) bonds, in particular $sp^2$-$sp^2$($sp$) bonds. These transformations are based on catalytic transition metal cross-coupling reactions.$^1$ Extensive mechanistic investigation and method development has been an enabling factor for the employment of cross-coupling reactions for the synthesis of bioactive small molecules, natural products and organic polymers (Figure 3.1).$^2$ These highly chemoselective cross-coupling reactions permit application towards complex molecule synthesis.$^3$

![Figure 3.1. Access to natural products (3.1.01 and 3.1.03)$^4$ and biologically active small molecules (3.1.02)$^5$ via SMCC reaction (bonds in bold are formed from SMCC)](image)

The Suzuki-Miyaura cross-coupling reaction (SMCC)$^{12}$ is among the most important developments in the realm of transition metal catalyzed cross-coupling reactions, which include; Stille (C-Sn),$^6$ Hiyama (C-Si),$^7$ Sonogashira (C-Cu),$^8$ Negishi (C-Zn),$^9$ and Kumada-Tamao (C-Mg)$^{10}$. In 1979, the catalytic SMCC was developed to address the harsh reaction conditions and low chemoselectivity associated with nucleophilic aromatic substitution ($S_N$Ar) and Ullmann coupling$^{11}$ for the creation of C$sp^2$-C$sp^2$ bonds.$^{12}$ Today, the SMCC reaction can be applied to $sp^3$-$sp^2$, $sp$-$sp^2$, even $sp^3$-$sp^3$ C-C bond formation. The development and application of the SMCC and the related Negishi and Heck reactions resulted in the award of the Nobel Prize to Professor Akira Suzuki, along with Professors Ei-ichi Negishi and Richard Heck in 2010.$^{13}$
3.1.1 Seminal Report

The SMCC reaction (C-B) is closely associated with the Stille (C-Sn) and Negishi (C-Zn) reactions.\textsuperscript{14} In the development of the Negishi coupling, alkenyl boranes were found to be inert to Pd\textsuperscript{0}-catalysis.\textsuperscript{15} The inherent stability of the organoborane is due to the low-polarity of the C-B bond which inhibits transmetallation. The seminal report by Suzuki and Miyaura described the successful cross-coupling reaction between alkenyl-boronic esters and aryl halides, but only in the presence of strong base (e.g. NaOH, NaOEt).\textsuperscript{16} Other \textit{sp}\textsuperscript{2}-hybridized organoboron reagents (e.g. 9-BBN, pinacol, propanediol) are amenable to the SMCC reaction; however, in the context of this thesis, organoboronic acids and their \textit{closely} associated derivatives shall be discussed.

\begin{center}
\begin{tikzpicture}

\node (a) [draw, rounded corners, minimum width=3cm, minimum height=1cm] at (0,0) {R = alkyl or aryl};
\node (b) [draw, rounded corners, minimum width=2cm, minimum height=1cm] at (1.5,0) {X = Br, I};
\node (c) [draw, rounded corners, minimum width=2cm, minimum height=1cm] at (3,0) {R' = CO\textsubscript{2}Et, OMe};
\node (d) [draw, rounded corners, minimum width=2cm, minimum height=1cm] at (4.5,0) {1-5mol\% Pd(PPh\textsubscript{3})\textsubscript{4}};
\node (e) [draw, rounded corners, minimum width=2cm, minimum height=1cm] at (6,0) {Base};
\node (f) [draw, rounded corners, minimum width=3cm, minimum height=1cm] at (7.5,0) {R = alkyl or aryl};
\node (g) [draw, rounded corners, minimum width=2cm, minimum height=1cm] at (9,0) {X = Br, I};
\node (h) [draw, rounded corners, minimum width=2cm, minimum height=1cm] at (10.5,0) {R' = CO\textsubscript{2}Et, OMe};
\node (i) [draw, rounded corners, minimum width=2cm, minimum height=1cm] at (12,0) {41-100\% yield};
\draw [->] (a) -- (b) -- (c) -- (d) -- (e) -- (f) -- (g) -- (h) -- (i);
\end{tikzpicture}
\end{center}

\textbf{Scheme 3.1.} Seminal report describing the SMCC reaction

3.1.2 Mechanism of the SMCC

The mechanism of the SMCC reaction is analogous to similar Pd\textsuperscript{0}-catalyzed reactions and consists of several distinct steps (Figure 3.2):

\textbf{Formation of a coordinatively unsaturated Pd\textsuperscript{0}-centre} – Ligand dissociation from the Pd\textsuperscript{0}-catalyst, exemplified by the square planar, 18-electron Pd(PPh\textsubscript{3})\textsubscript{4}, must proceed prior to participation in the SMCC. Loss of two ligands forms the 14-electron-Pd\textsuperscript{0}-centre Pd(PPh\textsubscript{3})\textsubscript{2}.

\textbf{Oxidative addition} – The oxidative addition of the Pd\textsuperscript{0}-catalyst to C-X (X = I, Br, Cl, pseudohalides) results in the formation of a organyl-Pd\textsuperscript{II} (pseudo)halide intermediate (3.1.04).\textsuperscript{17}

\textbf{Transmetallation} –
Transmetallation of organoboron species has yet to be fully elucidated. However, there are two proposals that are currently under investigation:¹⁸

**Boronate pathway:** The addition of base results in the formation of the ‘-ate’ species (3.1.05) which coordinates with the Pd\(^{\text{II}}\) -centre (3.1.04) to form the \(\mu\)-hydroxo-bridged species (3.1.06). Transfer of the organo moiety to the Pd\(^{\text{II}}\)-centre forms the di-organyl-Pd\(^{\text{II}}\)-complex.

**Oxo-Palladium Pathway:** The oxidative addition R\(\text{Pd}^{\text{II}}\)X (3.1.04) is hydrolyzed to R\(\text{Pd}^{\text{III}}\)OH. This species then complexes with the organoboron species to afford 3.1.06.

**Reductive Elimination** – Upon formation of the di-organyl-Pd\(^{\text{II}}\)-complex (3.1.07), rapid and irreversible C-C bond formation occurs and the Pd\(^{\text{II}}\)-catalyst is reformed.

![Figure 3.2. General catalytic cycle of the SMCC reaction](image)

3.1.3 **SMCC of Alkylboronic Acids**

Since its introduction, the SMCC has developed into one of the most important transformations for the functionalization of organic molecules.¹⁹ Important contributions to ligand design and mechanistic understanding have widened the substrate scope from simple aryl boronic acids to
complex natural products\textsuperscript{20} and peptides.\textsuperscript{21} While the coupling of arylboronic acids with other aryl or alkenyl halides has been thoroughly explored, the related alkylboronic acid SMCC has received less attention.

### 3.1.4 SMCC of Alkyl\textsubscript{C-B}–Aryl\textsubscript{C-X} coupling partners

The first example of an alkyl boronic ester in the SMCC reaction was reported by Suzuki and co-workers (Scheme 3.2).\textsuperscript{22} The reaction of alkyl-boronic esters was found to only proceed with either Tl\textsubscript{2}CO\textsubscript{3} or TlOH in the presence of catalytic PdCl\textsubscript{2}(dppf). The thallium salts were used as a transmetallation promoter and were crucial as their absence resulted in no conversion. While effective, the toxic nature of thallium limited the wide-spread application of this method.

\begin{equation*}
\begin{array}{c}
\text{R} \text{B(O)} \text{O}_3 \\
\text{R} = \text{alkyl or aryl} \\
\end{array} + \begin{array}{c}
\text{X} \text{R'} \\
\text{X} = \text{Br, I} \\
\end{array}
\xrightarrow{3 \text{ mol} \% \text{PdCl}_2(\text{dppf})} \begin{array}{c}
\text{R} \text{C} \text{R'} \\
\text{R} = \text{alkyl or aryl} \\
\end{array} \\
\text{1.5 equiv Tl}_2\text{CO}_3 \\
\text{41 - 93\% yield}
\end{equation*}

**Scheme 3.2.** Seminal report of the SMCC of alkyl boronic esters and aryl halides

To address the limitations of the initial report by Suzuki and co-workers, the Falck group sought out alternative bases.\textsuperscript{23} It was found that by substituting K\textsubscript{2}CO\textsubscript{3} for Tl\textsubscript{2}CO\textsubscript{3} and the addition of superstoichiometric Ag\textsubscript{2}O as the transmetallation promoter resulted in high yields for the SMCC reaction (Scheme 3.3).\textsuperscript{24} While effective for the alkylation of aryl-halides, this method is limited by the expensive Ag\textsuperscript{1}-salts.

\begin{equation*}
\begin{array}{c}
\text{R} \text{B(OH)}_2 \text{OH} \\
\text{R} = \text{alkyl or aryl} \\
\end{array} + \begin{array}{c}
\text{X} \text{R'} \\
\text{X} = \text{Br, I} \\
\text{R'} = \text{EDG/EWG} \\
\end{array}
\xrightarrow{10 \text{ mol}\% \text{PdCl}_2(\text{dppf})} \begin{array}{c}
\text{R} \text{C} \text{R'} \\
\text{R} = \text{alkyl or aryl} \\
\end{array} \\
\text{3.0 equiv K}_2\text{CO}_3 \\
\text{THF, 80°C} \\
\text{2.5 equiv Ag}_2\text{O} \\
\text{38 - 92\% yield}
\end{equation*}

**Scheme 3.3.** Ag\textsubscript{2}O promoted SMCC of alkyl boronic acids

In 2002, Molander and co-workers developed conditions for the SMCC of alkyl boronic acids without the need of a silver additive (Scheme 3.4).\textsuperscript{25} The addition of water was found to be beneficial to the formation of the alkyl arenes. Chloro-nitropyridines were also found to be viable substrates, and moderate yields (52-53% yield) were obtained for the cross-coupled
products. In more demanding circumstances, such as with sterically hindered coupling partners, decomposition of the boronic acid was observed.

\[
\text{R}^\text{'}\text{B(OR)} + X \xrightarrow{10 \text{ mol}\% \text{PdCl}_2(\text{dppe})} \xrightarrow{3.0 \text{ equiv K}_2\text{CO}_3} \text{R}^\text{'}\text{B} = \text{alkyl or aryl} \quad \text{X} = \text{Br, I, OTf} \quad \text{R}' = \text{EDG/EWG} \quad \text{THF:H}_2\text{O (10:1), 80 °C} \quad \text{42 - 87 % yield}
\]

**Scheme 3.4.** SMCC of alkyl boronic acids in THF:H₂O mixture

### 3.1.5 Organoboronate SMCC

Facile decomposition pathways and side product formation of alkyl boronic acids necessitate their use in superstoichiometric loadings to efficiently participate in the SMCC reaction.³ Degradation of alkyl boronic acids is attributed to complexation of external reagents with the vacant p-orbital of the organoboronic acid.²⁶ This interaction, whilst enabling for the effective transmetallation, must be mitigated under ambient conditions to avoid side reactions. Occupation of the empty p-orbital by a stabilizing ligand inhibits decomposition pathways and thereby promotes cross-coupling. Potassium trifluoroborates (RBF₃K) and MIDA-boronates (R-BMIDA) are among the most successful solutions to address the challenges pertaining to the SMCC of alkyl boronic acids (Figure 3.3).

\[
\text{R}_3\text{BF₃M} \quad \text{MeN} \quad \text{R}_3\text{BF₃M} \quad \text{N-methyliminodiacetylboronates} \quad \text{R-BMIDA}
\]

**Figure 3.3.** General structure of potassium trifluoroborates and N-methyliminodiacetylboronates

### 3.1.6 Potassium Organotrifluoroborates

Originally introduced by Vedejs and co-workers, potassium organotrifluoroborates (RBF₃K) are stable tetracoordinate boron species (Scheme 3.5. **3.1.08**).²⁷ The tetrahedral geometry is enforced
by the formation of the strong boron-fluorine bond. Substitution of the fluorine ligand by external Lewis base is disfavoured due to the strength of the B-F bond, rendering the potassium trifluoroborate moiety amenable to common synthetic transformations. The inherent stability of these reagents allows for the production of functionalized boron-containing small molecules that can be used in a subsequent SMCC reaction.

![Scheme 3.5. Formation of potassium phenyltrifluoroborate 3.1.08](image)

**3.1.7 SMCC of Primary Potassium Alkyltrifluoroborates**

The stability of RBF₃K reagents has enabled the development of an alkyl SMCC reaction that does not require superstoichiometric loading of an organometallic coupling partner. Molander and co-workers reported the first example of an alkyl-BF₃K SMCC reaction with aryl halide and aryl-triflates (Scheme 3.6). The alkyl-BF₃K SMCC reaction affords the alkylated arenes in moderate to excellent yields (50-96% yield) over 18 hours. One prominent feature of this method is that the organoboron coupling partner is used as the limiting reagent.

![Scheme 3.6. First report of alkyl-BF₃K SMCC](image)

Following the seminal report by Molander and Ito, further development of the SMCC reaction with functionalized substrates was initiated. In this area, the introduction of an alkoxymethyl-BF₃K moiety via SMCC is an important advance (Scheme 3.7). Other functionalized BF₃K reagents can be accessed from the S_{N}2-displacement reaction of potassium bromomethyltrifluoroborate and nucleophilic components (e.g. amines, imides, heteroaryl).
Scheme 3.7. SMCC of potassium alkoxyethyltrifluoroborates and aryl chlorides

The chemoselectivity and stability of trifluoroborates in the SMCC reaction demonstrates a viable method for the introduction of functional groups to aryl compounds. This has allowed for late stage employment of the SMCC in a number of total syntheses. A lack of compatibility with standard purification methods limits the utility of RBF₃K in a multi-step synthetic sequence.

3.1.8  \(N\)-Methyliminodiacetylorganoboronates (R-B[MIDA])

The formation of neutral \(sp^2\)-hybridized boron compounds that are stable to common organic reagents would permit the early introduction of the C-B functionality and late-stage engagement. First described in 1986 by Mancilla and Contreras, the condensation of \(N\)-methyliminodiacetic acid (Figure 3.4, 3.1.09, MIDA) and boronic acids yields the corresponding rigid bicyclic MIDA boronates. It was not until 20 years later that Burke and co-workers investigated MIDA boronates as cross-coupling partners in the SMCC reaction. As a result, the application of the MIDA boronate has been demonstrated in a number of methodologies and total syntheses of \(sp^2\)-rich natural products.

![Figure 3.4. Structure of \(N\)-methyliminodiacetic acid (MIDA)](image)

3.1.9  SMCC of MIDA Boronates

In contrast to trivalent boronic acids/esters, the tetravalent MIDA boronates are stable to a number of common reagents and anhydrous SMCC reactions. In addition, MIDA boronates
are amenable to column chromatography and long term storage.\textsuperscript{41} Due to these enabling features, MIDA boronates can be introduced early in a multi-step synthetic sequence for late-stage functionalization (Figure 3.5).

![Figure 3.5. Natural products synthesized from MIDA-cross-coupling](image)

In 2007, the iterative SMCC reaction of MIDA boronates was described.\textsuperscript{40} This method utilized haloboronic acid (3.1.12) as a bifunctional building block for a divergent SMCC reaction (Figure 3.6). The first step is a chemoselective functionalization of the C-X bond in the presence of the C-B bond. The resulting aryl boronic acid (3.1.13) is then subjected to a second C-B coupling after NaOH cleavage of the MIDA ligand resulting in the biaryl system (3.1.14). The chemoselective and iterative SMCC enables the synthesis of differently substituted aryl systems, which are found in oligoarene polymers and natural products.\textsuperscript{42}

![Figure 3.6. Iterative SMCC of halo-MIDA boronates](image)
3.2 Primary Alkyl MIDA boronate SMCC development

3.2.1 Proposal

The application of the SMCC reaction with MIDA boronates has currently been limited to aryl and vinyl partners. To date, there have been no examples of unactivated primary alkyl MIDA boronate SMCC reactions. Successful development of this methodology would enable the introduction of \( sp^2 \)-hybridized functional groups to complex systems at a late stage.

\[ \text{Previous alkylBF}_2\text{K SMCC} \]

\[ \text{Proposed} \]

3.2.2 Reaction Condition Optimization

At the outset of this investigation, \( B \)-benzyl MIDA boronate (3.201) and bromobenzene served as prototypical coupling partners. A variety of palladium catalysts and ligands were screened and their cross-coupling performance was measured via internally calibrated gas-chromatography (Table 3.1). Moderate to excellent conversion ratios were observed in every example, however selectivity of the reaction varied. The dialkyl-biaryl phosphine ligand S-Phos, in combination with \( \text{Pd(OAc)}_2 \), performed poorly providing only 24% yield and 36% selectivity (entry 2).\(^{43} \) \( \text{Pd(PPh}_3\text{)}_4 \) afforded high conversion, but afforded only 50% selectivity for diphenylmethane 3.2.03 (entry 3). The facile oxidative addition of \( \text{Pd(OAc)}_2/\text{S-Phos} \) and \( \text{Pd(PPh}_3\text{)}_4 \) to the C-Br bond of bromobenzene resulted in more deleterious side reactions and lower selectivity.\(^{44} \) Commercially available \( \text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2 \) (entry 8, 3.2.02) proved to be the optimal catalyst, delivering excellent conversion and yield over 21 hours (entry 8). High selectivity for the desired product is presumed to be due to the slower rate of oxidative addition as compared to \( \text{Pd(PPh}_3\text{)}_4 \) and \( \text{Pd(OAc)}_2/\text{S-Phos} \).\(^{45} \) The efficiency of 3.2.02 in the presence of other bases was also tested to uncover the optimal set of reaction conditions. A screen of inorganic bases confirmed \( \text{K}_2\text{CO}_3 \) to be optimal for this methodology (Table 3.2).\(^{46} \)
With the optimized reaction conditions in hand, we sought to expand the scope of aryl halide partners. As illustrated in Table 3.3, the cross-coupling of 3.2.01 with a number of aryl bromides resulted in the desired benzylated arenes in good yields. The electronic nature of the aryl bromides had an impact on the overall behaviour of the cross-coupling reaction. Electron-poor aryl bromides afforded higher yields over 24 hours, whereas electron-rich bromides required 48 hours to proceed to completion (entries 6 and 7). In addition, bromopyridines (entries 10-12) also required extended reaction times and increased loading of 3.2.01. The requirement for the higher loading of 3.2.01 can be attributed to the coordination of the Lewis basic pyridine to the [Pd]-centre, which inhibits the progression of the reaction.\textsuperscript{43c}
Table 3.2. Optimization of inorganic bases

<table>
<thead>
<tr>
<th>entry</th>
<th>base</th>
<th>conversion %&lt;sup&gt;a&lt;/sup&gt;</th>
<th>yield of 3.2.03 %&lt;sup&gt;b&lt;/sup&gt;</th>
<th>selectivity&lt;sup&gt;c&lt;/sup&gt;</th>
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<tr>
<td>8</td>
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</tbody>
</table>

Reaction Conditions: 1.1 equiv 3.2.01, 1.0 equiv. bromobenzene. Reactions stopped at 21 h for comparative purposes.<sup>a,b</sup> Determined by calibrated GC analysis against internal standard (naphthalene).<sup>c</sup> Selectivity = % yield/ % conversion

The nature of the halide also proved to be crucial to the outcome of the coupling reaction. Aryl chlorides were unreactive under our reaction conditions, resulting in the recovery of starting material. This observation is corroborated by the finding that bromo-2-chlorobenzene undergoes cross-coupling selectively at the bromide position in high yield (Table 3.3, entry 3).<sup>47</sup> Aryl iodides proved to be extremely reactive, resulting in the undesired homocoupled product in 41% yield (entry 9). As such, the reactivity trend appears to be I>Br>>Cl, which is similar to that observed for potassium trifluoroborates.

Table 3.3. SMCC of benzyl MIDA boronate 3.2.01

<table>
<thead>
<tr>
<th>entry</th>
<th>arylBr</th>
<th>product</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.03</td>
<td>3.2.03</td>
<td>3.2.14</td>
<td></td>
</tr>
</tbody>
</table>
1. \( \text{Br} \)  
   \[ \text{3.2.03} \]

2. \( \text{Br} \) \( \text{OCH}_3 \)  
   \[ \text{3.2.04} \]

3. \( \text{Cl} \)  
   \[ \text{3.2.05} \]

4. \( \text{Br} \) \( \text{NO}_2 \)  
   \[ \text{3.2.06} \]

5. \( \text{Br} \) \( \text{H}_3\text{C} \)  
   \[ \text{3.2.07} \]

6. \( \text{Br} \) \( \text{NO}_2 \)  
   \[ \text{3.2.08} \]

7. \( \text{Br} \) \( \text{CH}_3\text{CO} \)  
   \[ \text{3.2.09} \]

8. \( \text{Br} \) \( \text{O} \)  
   \[ \text{3.2.10} \]

9. \( \text{I} \) \( \text{CH}_3\text{CO} \)  
   \[ \text{3.2.11} \]
Other non-activated alkyl MIDA boronates were tested with various coupling partners (Table 3.4). The cross-coupling reaction of unactivated primary alkyl MIDA boronates (3.2.15-3.2.17) with aryl bromides was found to require extended reaction times (48 hours). Even upon prolonged exposure, the desired alkylated products were obtained in good yields. The diminished reactivity of $B$-$n$-alkyl MIDA boronates (3.2.15-3.2.17) is consistent with their reduced transmetallation potential.\textsuperscript{48}

**Table 3.4. SMCC of unfunctionalized primary MIDA boronates\textsuperscript{a}**

<table>
<thead>
<tr>
<th>entry</th>
<th>MIDA boronate</th>
<th>aryl Br</th>
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<th>% yield</th>
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</table>
3.2.3  SMCC of Functionalized Alkyl MIDA Boronates

3.2.3.1 Synthesis of Functionalized Alkyl MIDA Boronates

The application of the alkyl MIDA boronate SMCC to commercially available unfunctionalized substrates was successful. To demonstrate the chemoselectivity of the SMCC of alkyl MIDA boronates we sought to screen functionalized substrates in the SMCC reaction. Therefore, we...
synthesized a number of alkyl MIDA boronates through a hydroboration/MIDA introduction sequence starting from terminal alkenes (Figure 3.7). The hydroboration/MIDA sequence is amenable to a number of different functional groups and can be extended to complex systems in the future.

![Chemical reaction](attachment:image.png)

**Figure 3.7.** Functionalized MIDA boronates via hydroboration/MIDA introduction sequence

### 3.2.4 SMCC of Functionalized Alkyl MIDA Boronates

The functionalized MIDA boronates (3.2.32 – 3.2.36) were then subjected to the optimized SMCC conditions. The cross-coupling of 3.2.32 – 3.2.36 with aryl bromides afforded the alkylated arenes in good yields (Table 3.5). It was observed that the Ar-Cl bond was not affected by the SMCC reaction conditions. This result was attributed to the decreased oxidative potential of 3.2.02 towards the C-Cl bond. The ester containing MIDA boronate (3.2.32) chemoselectively cross-coupled with bromobenzene without any hydrolyzed byproduct.
Table 3.5. SMCC of functionalized MIDA boronates

\[
\text{MeN} \quad \text{O} \quad \text{O} \quad \text{B}^+ \quad \text{Br} \quad \text{MeN} \quad \text{O} \quad \text{O} \quad \text{B}^+ \\
\text{R} \quad \text{O} \quad \text{O} \quad \text{Br} \quad \text{R}^1 \quad \text{R} \quad \text{O} \quad \text{O} \quad \text{Br} \quad \text{R}^1
\]

![Chemical Structures](image.png)

<table>
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<tr>
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<th>aryBr</th>
<th>product</th>
<th>% yield</th>
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</table>

3.2.5 Comparison to Pinacol Ester

Organoboronic esters, namely pinacol esters, are prone to side reactions (e.g. protodeborylation and β-hydride elimination) from the interaction of incoming nucleophiles with the vacant p-orbital under SMCC conditions. MIDA boronates, which are \( sp^3 \)-hybridized boron species, do not interact with external nucleophiles therefore, are not prone to these side reactions. We sought to quantify the cross-coupling efficiency of both \( B \)-benzyl MIDA boronate (3.2.01) and the \( B \)-benzyl pinacol boronic ester (3.2.42) with bromobenzene under the optimized reaction.
conditions. The cross-coupling of 3.2.42 and bromobenzene afforded 3.2.03 in a moderate 69% assay yield. In contrast, the corresponding 3.2.01 cross-couples with bromobenzene in 89% assay yield. The observed variation in assay yield alludes to a greater cross-coupling efficiency of MIDA boronates over pinacol boronic esters.\(^\text{50}\)

![Scheme 3.8. Comparison of cross-coupling efficiencies of 3.2.01 and 3.2.42](image)

3.2.5.1 Preliminary Alkyl MIDA Boronate – Aryl Chloride Cross – Coupling

The successful development of an alkyl MIDA boronate SMCC with aryl bromides led us to investigate the potential for the intermolecular SMCC with aryl chlorides. Aryl chlorides are readily available but are inherently less reactive, as compared to the corresponding bromide or iodides. This behaviour is exemplified in Table 3.3, entry 3. An increase in oxidative addition potential of the Pd\(^0\)-catalyst would promote reactivity with the C-Cl bond.
Figure 3.8 Select Buchwald ligands, including the 2nd generation RuPhos-Pd\textsuperscript{II} precatalyst 3.2.43

The electron rich and bulky nature of these ligands results in the preferential formation of a coordinatively unsaturated Pd\textsuperscript{0}-centre.\textsuperscript{51} As a result, the oxidative addition and transmetallation processes are more favourable.\textsuperscript{52} The introduction of the electron-rich dialkylbiaryl phosphine (Buchwald ligands)\textsuperscript{53} and P(tBu)\textsubscript{3}\textsuperscript{54} has transformed the field of SMCC (Figure 3.8).\textsuperscript{55}

In order to react with C-Cl bonds, a sterically demanding supporting ligand (e.g. RuPhos) is required. The large phosphine results in less steric shielding around the Pd\textsuperscript{0}-centre which facilitates the oxidative addition step. This requirement led us to utilize a Buchwald ligand, and more specifically a Ruphos-Pd\textsuperscript{II} -precatalyst (Figure 3.8, 3.2.42) to investigate the intermolecular SMCC of functionalized alkyl MIDA boronates and aryl chlorides.

Scheme 3.9. General scheme for the synthesis of methylene-substituted MIDA boronates

Methylene-linked alkyl MIDA boronates (3.2.45) have been developed by Dr. Shinya Adachi in the Yudin group.\textsuperscript{56} These functionalized boronates are derived from the Mitsunobu reaction of hydroxymethyl MIDA boronate (3.2.44) and soft nucleophiles. We chose to utilize these novel substrates as an investigational platform for the Ar-Cl SMCC (Scheme 3.9). In the limited number of examples, it was demonstrated that methylene-substituted alkyl MIDA boronates and 4-chlorobenzonitrile undergo efficient cross-coupling to provide the methylene-linked benzonitriles (Scheme 3.10, 3.2.46 – 3.2.48).
3.3.1 General Information

In summary, we have demonstrated the first use of primary $B$-alkyl-MIDA boronates in the intermolecular alkyl MIDA boronates SMCC reaction with aryl bromides. This development has allowed for the efficient synthesis of unsymmetrical methylene diaryls and alkylated arenes. In addition, we have demonstrated in a limited number of substrates that aryl chlorides and methylene substituted MIDA boronates also participate in the SMCC reaction mediated by Pd$^{II}$-Ruphos system. With these results, the alkyl MIDA boronate SMCC can be further applied to more complicated systems and the total synthesis of natural products.

3.3 Supporting Information

3.3.1 General Information

Tetrahydrofuran (THF) was purified by distillation from sodium/benzophenone ketyl radical under an atmosphere of nitrogen. Acetonitrile (MeCN) was purified by distillation from 3Å molecular sieves (3Å MS). Dichloromethane, methanol (MeOH) and triethylamine (Et$_3$N) were purified by distillation from CaH$_2$, respectively. Diethyl ether (Et$_2$O), toluene and dimethyl formamide (DMF), was purified through a solvent purification system. All other reagents were purchased from commercial sources and used as received.

Chromatography
Flash column chromatography was carried out using Silicycle 230-400 mesh silica gel. Thin-layer chromatography (TLC) was performed on Macherey Nagel pre-coated glass backed TLC plates (SIL G/UV254, 0.25 mm) and visualized using a UV lamp (254 nm), KMnO₄, ninhydrin, curcumin or I₂ stain in case of no UV activity.

**Nuclear Magnetic Resonance Spectroscopy**

Proton (¹H-NMR), carbon (¹³C-NMR) and 2D NMR experiments were performed on Bruker 400 MHz or Varian 300, 400, or 500 MHz spectrometers. NMR spectra chemical shifts (δ) are reported in parts per million (ppm) referenced to residual protonated solvent peak (CDCl₃, δ = 7.26, DMSO-d₆, δ = 2.49, acetone-d₆ δ = 2.05). Spectral data is reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, ddt = doublet of doublet of triplets, dtd= doublet of triplet of doublets, m = multiplet, br = broad), coupling constant (J) in Hertz (Hz), and integration. ¹³C NMR spectra chemical shifts (δ) are reported in parts per million (ppm) were referenced to carbon resonances in the NMR solvent (CDCl₃, δ = 77.0; DMSO-d₆, δ = 39.5, center line, acetone-d₆ = 206.2 centre line, 29.8). ¹¹B NMR was recorded using a Bruker Avance III 400 MHz spectrometer and referenced to an external standard of BF₃·OEt₂

**Infrared Spectroscopy**

IR spectra were recorded on a Perkin-Elmer 100 instrument equipped with a single-reflection diamond/ZnSe ATR accessory. Performed on an NaCl disc as a thin layer.

**Mass Spectrometry**

High-Resolution Mass Spectra were obtained at the University of Toronto mass spectrometry centre. High resolution mass spectra were obtained on a VG 70- 250S (double focusing) mass spectrometer at 70 eV or on an ABI/Sciex Qstar mass spectrometer with ESI source, MS/MS and accurate mass capabilities.

**Gas Chromatography**

Gas-phase chromatography (GC) was performed on a Hewlett Packard HP-6890 series instrument using a DB-35 column (crosslinked 35% phenyl methylsiloxane, 30 m x 0.32 mm x
0.25 μm film thickness). Oven was heated at 160 °C for 3 min followed by a temperature gradient of 60 °C/min to 240 °C followed by being held at 240 °C for 5 min. Inlet temperature and pressure were 250 °C and 4.88 psi respectively, with a split ratio of 50:1. Hydrogen was the carrier gas.

Internal standard was napthalene (T = 3.08 min).

**Commerically Available Primary Alkyl MIDA Boronates**

![Commerically Available Primary Alkyl MIDA Boronates](image)

**3.3.2 Synthesis of Primary Alkyl MIDA Boronates**

**Synthesis of Boronic Acid - Procedure A**

To an oven dried, stir bar equipped vial was added alkene followed by the dropwise addition of neat catechol borane. The reaction flask was then warmed to 65 °C for 24 hrs. Upon complete consumption of starting alkene the reaction was removed from the reaction block and allowed to cool to room temperature. Then distilled water (10 mL) was added to the reaction mixture and allowed to stir for 2-3 hrs at which time the solid precipitate was filtered to yield the crude boronic acid.

**Synthesis of Boronic Acid – Procedure B**

A reaction flask was equipped with a magnetic stir-bar and reflux condenser and to it was added terminal alkene (10 mmol, 1.0 equiv) and DCM (10 mL). HBBr$_2$·SMe$_2$ (20 mmol, 1.0 M in DCM, 2.0 equiv) was then added dropwise along the wall of the flask and upon complete addition the mixture was warmed to reflux for 24 hours. The reaction was then removed from heat and cooled to 0 °C in an ice-water bath. The cooled reaction mixture was then transferred to a pre-cooled 0 °C mixture of Et$_2$O (25 mL) and H$_2$O (5 mL). The resulting mixture was allowed to stir for 30 minutes and then the organic layer was separated. The aqueous layer was subsequently extracted with 5 x 25 mL of Et$_2$O. The combined organics were then washed with
H₂O (50 mL). The organics were then dried (MgSO₄), filtered and concentrated to yield crude boronic acid.⁵⁸

**Synthesis of alkyl MIDA boronate**

The crude boronic acid was then dissolved in DMF (0.3 M) and N-methyliminodiacetic acid (1.0 equiv) was added. The mixture was warmed to 80 °C for 24 hours. The reaction was then removed from heat and concentrated *in vacuo*. To the residue was added 50 mL H₂O, 50 mL sat. NaHCO₃ and 100 mL EtOAc at which time the organic was the separated. The aqueous layer was the extracted 5 x 75 mL EtOAc. The combined organics were washed with brine, dried over Na₂SO₄ and concentrated to yield crude MIDA boronate. The crude MIDA boronate was then purified via SiO₂ using hexanes:acetone to yield pure primary alkyl MIDA boronate as a white solid.

(4-(benzoyloxy)butyl)MIDA boronate (3.2.32)

26% over two steps, white solid

¹H NMR (400 MHz, Acetonitrile-ᵈ₃)

δ 8.14 – 7.99 (m, 2H), 7.71 – 7.62 (m, 1H), 7.59 – 7.47 (m, 2H), 4.35 (t, J = 6.6 Hz, 2H), 3.96 (d, J = 16.9 Hz, 2H), 3.80 (d, J = 16.9 Hz, 2H), 2.88 (s, 3H), 1.89 – 1.76 (m, 2H), 1.52 (m, 2H), 0.76 – 0.63 (m, 2H)

¹³C NMR (101 MHz, Acetonitrile-ᵈ₃)

δ 167.8, 165.9, 132.5, 130.3, 128.8, 128.2, 64.3, 61.4, 45.2, 31.0, 20.1

¹¹B NMR (128 MHz, Acetonitrile-ᵈ₃)

δ 13.1

HRMS [DART-MS] (M+H⁺)

m/z calculated for C₁₆H₂₁BNO₆ = 334.1461

m/z found = 334.1462

TLC (hexanes:acetone 1:1)

Rᵣ = 0.28
(3-(trimethylsilyl)propyl)MIDA boronate (3.2.33)
60% yield over two steps, white solid

$^1$H NMR (400 MHz, Acetonitrile-$d_3$)
$$\delta \, 3.93 \,(d, \, J = 16.9 \, Hz, \, 2H), \, 3.77 \,(d, \, J = 16.9 \, Hz, \, 2H), \, 2.85 \,(s, \, 3H), \, 1.51 - 1.28 \,(m, \, 2H),$$
$$0.72 - 0.51 \,(m, \, 4H), \, 0.00 \,(s, \, 9H)$$

$^{13}$C NMR (101 MHz, Acetonitrile-$d_3$)
$$\delta \, 168.1, \, 61.5, \, 45.4, \, 19.9, \, 18.4, \, -2.6$$

$^{11}$B NMR (128 MHz, Acetonitrile-$d_3$)
$$\delta \, 13.0$$

HRMS [DART-MS] (M+Na$^+$)
$$m/z \text{ calculated for } C_{11}H_{22}BNO_4NaSi = 294.103$$
$$m/z \text{ found } = 294.1309$$

TLC (hexanes:acetone 3:4)
$$R_f = 0.46$$

(4-chlorophenethyl)MIDA boronate (3.2.34)
66% yield over two steps, white solid

$^1$H NMR (400 MHz, Acetonitrile-$d_3$)
$$\delta \, 7.31 - 7.14 \,(m, \, 2H), \, 6.96 - 6.82 \,(m, \, 2H), \, 3.98 \,(d, \, J = 16.9 \, Hz, \, 2H), \, 3.82 \,(d, \, J = 16.9$$
$$Hz, \, 2H), \, 2.89 \,(s, \, 3H), \, 2.81 - 2.53 \,(m, \, 2H), \, 1.07 - 0.78 \,(m, \, 2H)$$

$^{13}$C NMR (101 MHz, Acetonitrile-$d_3$)
$$\delta \, 168.7, \, 158.2, \, 137.9, \, 129.3, \, 114.2, \, 62.3, \, 55.3, \, 46.2, \, 29.7$$

$^{11}$B NMR (128 MHz, Acetonitrile-$d_3$)
$$\delta \, 13.0$$

HRMS [DART-MS] (M+H$^+$)
$$m/z \text{ calculated for } C_{13}H_{16}BClNO_4 = 296.0892$$
$$m/z \text{ found } = 296.0893$$

TLC (hexanes:acetone 4:3)
$$R_f = 0.29$$
(4-methoxyphenethyl) MIDA boronate (3.2.35)

54% yield over two steps, white solid

$^1$H NMR (400 MHz, Acetonitrile-$d_3$)

$\delta$ 7.26 – 7.10 (m, 2H), 6.98 – 6.80 (m, 2H), 3.98 (d, $J = 16.9$ Hz, 2H), 3.82 (d, $J = 16.9$ Hz, 2H), 3.78 (s, 3H), 2.89 (s, 3H), 2.65 – 2.56 (m, 2H), 0.99 – 0.86 (m, 2H)

$^{13}$C NMR (101 MHz, Acetonitrile-$d_3$)

$\delta$ 169.1, 158.6, 138.3, 129.7, 114.6, 62.8, 55.8, 46.6, 30.2

$^{11}$B NMR (128 MHz, Acetonitrile-$d_3$)

$\delta$ 13.0

IR (thin film)

$\nu$ 2964, 2914, 2359, 2332, 1743, 1512, 1300, 1247, 1024

HRMS [DART-MS] (M+NH$_4^+$)

$m/z$ calculated for C$_{14}$H$_{22}$BN$_2$O$_5$ = 309.1621

$m/z$ found = 309.1627

TLC (hexanes:acetone 1:1)

$R_f$ = 0.54

(3-phenoxypropyl)MIDA boronate (3.2.36)

31% yield over two steps, white solid

$^1$H NMR (400 MHz, Acetonitrile-$d_3$)

$\delta$ 7.36 – 7.27 (m, 2H), 6.99 – 6.92 (m, 3H), 4.04 – 3.94 (m, 4H), 3.83 (d, $J = 17.0$ Hz, 2H), 2.91 (s, 3H), 1.86 – 1.76 (m, 3H), 0.86 – 0.67 (m, 2H)

$^{13}$C NMR (101 MHz, Acetone-$d_6$)

$\delta$ 168.76, 130.20, 121.0, 115.3, 70.7, 62.7, 46.3, 25.0

$^{11}$B NMR (128 MHz, Acetonitrile-$d_3$)

$\delta$ 12.9

HRMS [DART-MS] (M+H$^+$)
$m/z$ calculated for $C_{14}H_{19}BNO_5 = 292.1356$

$m/z$ found = 292.1357

TLC (hexanes:acetone 1:1)

$R_f = 0.62$

3.3.3 General Method for the Suzuki-Miyaura Cross-Coupling between $B$-alkyl-MIDA-boronates and Aryl Bromides

To a Teflon lined 2 dram screw-top vial equipped with a magnetic stir bar was added $B$-alkyl-MIDA-boronate (3.2.01, 4.5 mmol, 1.1 equiv.) and PdCl$_2$(dppf)·CH$_2$Cl$_2$ (3.2.02) (0.4 mmol, 10 mol%). The vial was evacuated under vacuum and a nitrogen atmosphere was introduced. Freshly distilled THF (4.0 mL, 0.1 M) was added followed by aryl bromide (4.0 mmol, 1.0 equiv.) and nitrogen (N$_2$)-sparged and distilled H$_2$O (0.8 mL). The reaction was stirred at room temperature for approximately 5 minutes followed by addition of K$_2$CO$_3$ (12.0 mmol, 6.0 equiv). The reaction was sealed with a screw-cap and placed in an 80 °C reaction block for the required time as judged by GC analysis (24-72 h). Upon starting material consumption the reaction vial was cooled to room temperature and 2 mL H$_2$O was added. The aqueous mixture was extracted 3x with Et$_2$O, dried over MgSO$_4$ and concentrated under reduced pressure. The coupled products were purified via silica gel chromatography using pentanes:Et$_2$O as eluent.

Diphenylmethane (3.2.03)

GC retention time bromobenzene: 2.08 min

77% yield, clear oil

Spectra matched literature reports

$^1$H NMR (399 MHz, Chloroform-$d$)

$\delta$ 7.35 – 7.29 (m, 4H), 7.27 – 7.20 (m, 6H), 4.02 (s, 2H)

$^{13}$C NMR (100 MHz, Chloroform-$d$)

$\delta$ 141.1, 128.9, 128.4, 126.0, 41.9
1-benzyl-4-methoxybenzene (3.2.04)

GC retention time of 4-bromoanisole: 3.07 min

Spectra matched literature reports:

74% yield (95% pure), clear oil

$^1$H NMR (399 MHz, Chloroform-$d$)

\[ \delta 7.31 - 7.24 \text{ (m, 3H)}, 7.22 - 7.15 \text{ (m, 3H)}, 7.13 - 7.08 \text{ (m, 2H)}, 6.92 - 6.75 \text{ (m, 2H)}, 3.93 \text{ (s, 2H)}, 3.78 \text{ (s, 3H)} \]

$^{13}$C NMR (75 MHz, Chloroform-$d$)

\[ \delta 133.2, 129.8, 128.9, 128.7, 128.4, 125.9, 113.8, 109.9, 55.2, 41.0 \]

TLC (hexanes:Et$_2$O 1:1)

$R_f = 0.51$

1-benzyl-2-chlorobenzene (3.2.05)

GC retention time of 2-chloro-bromobenzene: 2.75 min

85% yield, clear oil

$^1$H NMR (300 MHz, Chloroform-$d$)

\[ \delta 7.41 - 7.34 \text{ (m, 2H)}, 7.34 - 7.22 \text{ (m, 2H)}, 7.24 - 7.11 \text{ (m, 5H)}, 4.11 \text{ (s, 2H)} \]

$^{13}$C NMR (75 MHz, Chloroform-$d$)

\[ \delta 139.4, 138.6, 134.2, 130.9, 129.5, 128.9, 128.4, 127.6, 126.7, 126.2, 39.1 \]

HRMS [DART-MS] (M$^+$)

\[ m/z \text{ calculated for C}_{13}\text{H}_{11}\text{Cl} = 202.0549 \]

\[ m/z \text{ found} = 202.0549 \]

TLC (hexanes:Et$_2$O 1:1)

$R_f = 0.47$

4-benzyl-1-fluoro-2-nitrobenzene (3.2.06)

84%, yellow oil
GC retention time of 4-bromo-1-fluoro-2-nitrobenzene: 3.89 min

$^1$H NMR (500 MHz, Chloroform-$d$)

$\delta$ 7.87 (dd, $J = 7.1, 2.3$ Hz, 1H), 7.45 – 7.41 (m, 1H), 7.36 – 7.31 (m, 2H), 7.28 – 7.24 (m, 1H), 7.22 – 7.15 (m, 3H), 4.03 (m, 2H)

$^{13}$C NMR (126 MHz, Chloroform-$d$)

$\delta$ 157.0, 154.5 (d, $^{1}J_{CF} = 263.3$ Hz), 139.0, 138.2 (d, $^{1}J_{CF} = 4.3$ Hz), 135.7 (d, $^{1}J_{CF} = 8.3$ Hz), 128.8, 128.6, 126.8, 125.9, (d, $^{1}J_{CF} = 2.9$ Hz), 118.4 (d, $^{1}J_{CF} = 20.8$ Hz), 40.7

HRMS [TOF-MS] (M$^+$)

$m/z$ calculated for C$_{13}$H$_{10}$NO$_2$F = 231.0696

$m/z$ found = 231.0695

TLC (hexanes:Et$_2$O 1:1)

$R_f$ = 0.32

1-benzyl-2-methylbenzene (3.2.07)

GC retention time of 2-bromotoluene: 2.28 min

Spectra matched literature reports:


77% yield, clear oil

$^1$H NMR (500 MHz, Chloroform-$d$)

$\delta$ 7.31 – 7.26 (m, 2H), 7.22 – 7.17 (m, 3H), 7.16 – 7.09 (m, 4H), 4.00 (s, 2H), 2.26 (s, 3H)

$^{13}$C NMR (126 MHz, Chloroform-$d$)

$\delta$ 140.3, 138.9, 136.6, 130.2, 129.9, 128.7, 128.3, 126.4, 125.9, 125.8, 39.4, 19.6

1-benzyl-4-nitrobenzene (3.2.08)

GC retention time 4-nitrobromobenzene: 4.05 min

68 % yield, yellow oil

$^1$H NMR (500 MHz, Chloroform-$d$)
$\delta$ 8.21 – 8.05 (m, 2H), 7.37 – 7.29 (m, 4H), 7.28 – 7.23 (m, 1H), 7.20 – 7.15 (m, 2H), 4.08 (s, 2H)

$^{13}$C NMR (126 MHz, Chloroform-$d$)
$\delta$ 148.8, 146.5, 139.1, 129.6, 128.9, 128.8, 126.7, 123.7, 41.7

HRMS [DART-MS] (M$^+$)
$m/z$ calculated for C$_{13}$H$_{12}$NO$_2$ = 214.0868
$m/z$ found = 214.0865

TLC (hexanes:Et$_2$O 1:1)
$R_f$ = 0.5

1-(3-benzylphenyl)ethan-1-one (3.2.09)

GC retention time of 3-bromoacetophenone: 3.35 min

90% yield, clear oil

$^1$H NMR (500 MHz, Chloroform-$d$)
$\delta$ 7.84 – 7.79 (m, 2H), 7.42 – 7.38 (m, 2H), 7.34 – 7.29 (m, 2H), 7.25 – 7.22 (m, 1H), 7.22 – 7.17 (m, 2H), 4.06 (s, 2H), 2.59 (s, 3H)

$^{13}$C NMR (126 MHz, Chloroform-$d$)
$\delta$ 198.2, 141.6, 140.3, 137.3, 133.7, 128.8, 128.8, 128.7, 128.6, 128.6, 126.3, 41.7, 26.7

HRMS [DART-MS] (M+H$^+$)
$m/z$ calculated for C$_{15}$H$_{15}$O = 211.1122
$m/z$ found = 211.1125

TLC (hexanes:Et$_2$O 5:1)
$R_f$ = 0.21

5-benzylbenzo[d][1,3]dioxole (3.2.10)

GC retention time of 5-bromobenzo[d][1,3]dioxole: 3.71 min

72% yield, clear oil

$^1$H NMR (300 MHz, Chloroform-$d$)
\[ \delta 7.29 \text{ (m, 2H), } 7.24 - 7.15 \text{ (m, 3H), } 6.74 \text{ (m, 1H), } 6.67 \text{ (m, 2H), } 5.91 \text{ (m, 2H), } 3.90 \text{ (m, 2H)} \]

\[ ^{13}\text{C NMR (100 MHz, Chloroform-}d\text{)} \]
\[ \delta 147.6, 145.8, 141.2, 134.9, 128.7, 128.4, 126.0, 121.7, 109.4, 108.1, 100.8, 41.6 \]

\[ \text{HRMS [DART-MS] (M+H}^+\text{)} \]
\[ m/z \text{ calculated for C}_{14}\text{H}_{13}\text{O}_2 = 213.09155 \]
\[ m/z \text{ found} = 213.0909 \]

TLC (hexanes:Et\textsubscript{2}O 2:1)
\[ R_f = 0.29 \]

\[ 1,1'-([1,1'-biphenyl]-4,4'-diyl)bisis(ethan-1-one) (3.2.11) \]

GC retention time of \textbf{4-iodoacetophenone}: 4.78 min
41% yield, opaque residue

\[ ^1\text{H NMR (500 MHz, Chloroform-}d\text{)} \]
\[ \delta 8.15 - 7.96 \text{ (m, 4H), } 7.77 - 7.68 \text{ (m, 4H), } 2.65 \text{ (s, 6H)} \]

\[ ^{13}\text{C NMR (126 MHz, Chloroform-}d\text{)} \]
\[ \delta 197.5, 144.3, 136.5, 128.9, 127.4, 26.7 \]

\[ \text{HRMS [DART-MS] (M+H}^+\text{)} \]
\[ m/z \text{ calculated for C}_{16}\text{H}_{15}\text{O}_2 = 239.1072 \]
\[ m/z \text{ found} = 239.1067 \]

TLC (hexanes:Et\textsubscript{2}O 1:1)
\[ R_f = 0.19 \]

\[ 2\text{-benzyl-6-methoxypyridine (3.2.12)} \]

GC retention time of \textbf{2-bromo-6-methoxypyridine} = 2.82 min
52% yield, clear residue

\[ ^1\text{H NMR (300 MHz, Chloroform-}d\text{)} \]
δ 7.44 (m, 1H), 7.34 – 7.27 (m, 4H), 7.25 – 7.18 (m, 1H), 6.65 (d, J = 7.2 Hz, 1H), 6.54 (d, J = 8.1 Hz, 1H), 4.03 (s, 2H), 3.92 (s, 3H)

$^{13}$C NMR (101 MHz, Chloroform-$d$)

δ 163.6, 158.7, 139.7, 138.9, 129.2, 128.3, 126.2, 115.4, 107.7, 53.2, 44.3

HRMS [DART-MS] (M+H$^+$)

$m/z$ calculated for C_{13}H_{14}NO = 200.1062

$m/z$ found = 200.1065

TLC (hexanes:EtOAc 5:1)

$R_f$ = 0.23

3-benzylpyridine (3.2.13)

GC retention time 3-bromopyridine: 2.24 min

78% yield (approx. 85% pure), clear oil

Spectra matched literature reports

$^1$H NMR (500 MHz, Chloroform-$d$)

δ 8.54 – 8.48 (m, 1H), 8.46 (dd, J = 4.8, 1.6 Hz, 1H), 7.47 (m, 1H), 7.34 – 7.28 (m, 2H), 7.26 – 7.15 (m, 4H), 3.99 (s, 2H)

$^{13}$C NMR (126 MHz, Chloroform-$d$)

δ 150.0, 147.5, 139.7, 136.5, 136.3, 128.8, 128.6, 126.4, 123.4, 39.0

HRMS [DART-MS] (M+H$^+$)

$m/z$ calculated for C_{12}H_{12}N = 170.0967

$m/z$ found = 170.0966

TLC (hexanes:Et$_2$O 1:4)

$R_f$ = 0.28

5-benzyl-2-methoxypyridine (3.2.14)

GC retention time of 5-bromo-2-methoxypyridine: 2.64 min

52%, clear oil

$^1$H NMR (500 MHz, Chloroform-$d$)
δ 8.03 (m, 1H), 7.36 (m, 1H), 7.32 – 7.27 (m, 2H), 7.24 – 7.15 (m, 3H), 6.67 (m, 1H), 3.92 (s, 3H), 3.90 (s, 2H)

$^{13}$C NMR (126 MHz, Chloroform-$d$)
δ 162.8, 146.3, 140.5, 139.3, 129.1, 128.6, 128.5, 126.2, 110.7, 53.3, 38.1

HRMS [DART-MS] (M+H$^+$)

$m/z$ calculated for C$_{13}$H$_{14}$NO = 200.1062

$m/z$ found = 200.1065

TLC (hexanes:EtOAc 4:1)

$R_f$ = 0.44

1,2-diphenylethane (3.2.18)

GC retention time of bromobenzene: 2.08 min

77% yield, clear oil

Spectral data were identical to known structure in literature

$^1$H NMR (300 MHz, Chloroform-$d$)
δ 7.32 – 7.24 (m, 4H), 7.24 – 7.13 (m, 6H), 2.93 (s, 4H)

$^{13}$C NMR (75 MHz, Chloroform-$d$)
δ 141.7, 128.4, 128.3, 125.8, 37.9

1-(3-nitro-4-phenethylphenyl)ethanone (3.2.19)

GC retention time of 1-(4-bromo-3-nitrophenyl)ethan-1-one: 6.32 min

78% yield, white solid

$^1$H NMR (500 MHz, Chloroform-$d$)
δ 8.47 (m, 1H), 8.04 (m, 1H), 7.35 (m, 1H), 7.32 – 7.27 (m, 2H), 7.24 – 7.20 (m, 1H), 7.20 – 7.16 (m, 2H), 3.28 – 3.21 (m, 2H), 3.01 – 2.95 (m, 2H), 2.64 (m, 3H)

$^{13}$C NMR (126 MHz, Chloroform-$d$)
δ 195.4, 141.4, 140.2, 136.1, 132.7, 131.7, 128.5, 128.4, 126.4, 124.7, 36.6, 36.6, 35.4, 26.5
IR (thin film)

\[ \nu = 3021, 3001, 1687, 1616, 1529, 1492, 1456, 1406, 1352, 1247, 667 \]

HRMS [DART-MS] (M+NH\(_4^+\))

\[ m/z \text{ calculated for } C_{16}H_{19}N_2O_3 = 287.1357 \]
\[ m/z \text{ found } = 287.1394 \]

TLC (hexanes:Et\(_2\)O 1:1)

\[ R_f = 0.2 \]

1-methyl-2-phenethylbenzene (3.2.20)

GC retention time of 2-bromotoluene: 2.28 min

Spectra matched literature reports:


83% yield, clear oil

\(^1\)H NMR (500 MHz, Chloroform-\(d\))

\[ \delta = 7.33 - 7.28 \text{ (m, 2H), } 7.25 - 7.20 \text{ (m, 3H), } 7.18 - 7.11 \text{ (m, 4H), } 3.00 - 2.81 \text{ (m, 4H), } 2.32 \text{ (s, 3H)} \]

\(^{13}\)C NMR (126 MHz, Chloroform-\(d\))

\[ \delta = 141.9, 139.9, 135.9, 130.1, 128.7, 128.3, 128.3, 126.0, 125.9, 125.9, 36.7, 35.4, 19.2 \]

TLC (hexanes)

\[ R_f = 0.52 \]

1,3,5-trimethyl-2-phenethylbenzene (3.2.21)

GC retention time of 2-bromomesitylene: 3.28 min

Spectra matched literature reports:


73%, clear residue

\(^1\)H NMR (300 MHz, Chloroform-\(d\))
δ 7.37 – 7.27 (m, 2H), 7.27 – 7.16 (m, 3H), 6.86 (s, 2H), 2.94 – 2.83 (m, 2H), 2.78 – 2.68 (m, 2H), 2.32 (s, 6H), 2.26 (s, 3H)

13C NMR (100 MHz, Chloroform-d)
δ 142.3, 135.9, 135.4, 135.1, 128.9, 128.4, 128.2, 125.9, 35.5, 31.7, 20.8, 19.6

5-phenethylbenzo[d][1,3]dioxole (3.2.22)

GC retention time of 5-bromobenzo[d][1,3]dioxole: 3.71 min
81% yield, opaque residue

1H NMR (500 MHz, Chloroform-d)
δ 7.31 – 7.25 (m, 4H), 7.22 – 7.15 (m, 3H), 6.74 – 6.59 (m, 1H), 5.92 (s, 2H), 2.92 – 2.81 (m, 4H)

13C NMR (126 MHz, Chloroform-d)
δ 147.4, 145.6, 141.5, 135.6, 128.4, 128.3, 125.9, 121.1, 108.9, 108.0, 100.7, 38.1, 37.6

HRMS [DART-MS] (M+H+)

m/z calculated for C15H15O2 = 227.1072
m/z found = 227.1064

TLC (hexanes:Et2O 4:1)
Rf = 0.61

1-(3-benzylphenyl)ethan-1-one (3.2.23)

GC retention time of 4-bromoacetophenone: 3.93 min
92% yield, clear oil

1H NMR (500 MHz, Chloroform-d)
δ 7.81 – 7.77 (m, 1H), 7.75 (m, 1H), 7.39 – 7.34 (m, 2H), 7.28 (m, 2H), 7.23 – 7.18 (m, 1H), 7.18 – 7.15 (m, 2H), 3.02 – 2.96 (m, 2H), 2.96 – 2.92 (m, 2H), 2.57 (s, 3H)

13C NMR (126 MHz, Chloroform-d)
δ 198.3, 142.1, 141.1, 137.1, 133.3, 128.5, 128.4, 128.3, 128.2, 126.1, 126.0, 37.7, 26.6

HRMS [DART-MS] (M+)
\[ m/z \text{ calculated for } C_{16}H_{17}O = 225.1279 \]
\[ m/z \text{ found } = 225.1271 \]

TLC (hexanes:Et\textsubscript{2}O 6:1)
\[ R_f = 0.23 \]

![1-methoxy-4-phenethylbenzene](image)

1-methoxy-4-phenethylbenzene (3.2.24) (95% pure)

GC retention time of 4-bromoanisole: 3.07 min

54% yield, white residue

\(^{1}\)H NMR (500 MHz, Chloroform-\textit{d})
\[ \delta 7.30 - 7.26 (m, 3H), 7.22 - 7.16 (m, 2H), 7.12 - 7.08 (m, 2H), 6.85 - 6.81 (m, 2H), 3.79 (s, 3H), 2.91 - 2.86 (m, 4H) \]

\(^{13}\)C NMR (126 MHz, Chloroform-\textit{d})
\[ \delta 157.80, 141.8, 133.8, 129.3, 128.4, 128.2, 125.8, 125.8, 113.7, 113.6, 55.2, 38.1, 37.0 \]

HRMS [DART-MS] (M+\textsubscript{NH}_4\textsuperscript{+})
\[ m/z \text{ calculated for } C_{15}H_{20}NO = 230.1544 \]
\[ m/z \text{ found } = 230.1543 \]

TLC (hexanes:Et\textsubscript{2}O 9:1)
\[ R_f = 0.38 \]

![4-phenethylbenzonitrile](image)

4-phenethylbenzonitrile (3.2.25)

GC retention time of 4-bromobenzonitrile: 3.49 min

78% yield, clear oil

\(^{1}\)H NMR (500 MHz, Chloroform-\textit{d})
\[ \delta 7.57 - 7.53 (m, 1H), 7.50 (m, 1H), 7.32 - 7.27 (m, 2H), 7.25 - 7.19 (m, 3H), 7.14 - 7.10 (m, 1H), 7.04 - 6.97 (m, 1H), 2.99 (m, 2H), 2.96 - 2.90 (m, 2H) \]

\(^{13}\)C NMR (126 MHz, Chloroform-\textit{d})
\[ \delta 147.1, 140.5, 132.1, 129.3, 128.4, 128.3, 126.2, 119.0, 109.8, 37.9, 37.2 \]

HRMS [DART-MS] (M+H\textsuperscript{+})
$m/z$ calculated for C$_{15}$H$_{14}$N = 208.1126

$m/z$ found = 208.1120

TLC (hexanes:EtOAc 9:1)

$R_f$ = 0.32

2-methoxy-5-phenethylpyridine (3.2.26)

GC retention time of 5-bromo-2-methoxypyridine: 2.64 min

54% yield, clear oil

$^1$H NMR (500 MHz, Chloroform-$d$)

$\delta$ 7.93 (d, $J = 2.5$ Hz, 1H), 7.33 (m, 1H), 7.28 (m, 2H), 7.22 – 7.17 (m, 1H), 7.16 – 7.12 (m, 2H), 6.65 (d, $J = 8.4$ Hz, 1H), 3.91 (s, 3H), 2.92 – 2.80 (m, 4H)

$^{13}$C NMR (126 MHz, Chloroform-$d$)

$\delta$ 146.0, 141.0, 138.9, 129.4, 128.4, 128.3, 127.4, 126.0, 110.3, 53.2, 37.7, 33.9

HRMS [DART-MS] (M+H$^+$)

$m/z$ calculated for C$_{14}$H$_{16}$NO = 214.1231

$m/z$ found = 214.1227

TLC (hexanes:EtOAc 9:1)

$R_f$ = 0.34

1-(4-butylphenyl)ethan-1-one (3.2.27)

GC retention time of 4-bromoacetophenone: 3.93 min

61% yield, clear oil

$^1$H NMR (500 MHz, Chloroform-$d$)

$\delta$ 7.96 – 7.80 (m, 2H), 7.33 – 7.19 (m, 2H), 2.74 – 2.62 (m, 2H), 2.58 (s, 3H), 1.66 – 1.57 (m, 2H), 1.40 – 1.31 (m, 2H), 0.93 (t, $J = 7.4$ Hz, 3H)

$^{13}$C NMR (126 MHz, Chloroform-$d$)

$\delta$ 197.8, 148.8, 134.8, 128.5, 128.4, 128.3, 35.6, 33.2, 26.5, 22.3, 13.8

HRMS [DART-MS] (M+H$^+$)
\[m/z \text{ calculated for } C_{12}H_{17}O = 177.1279\]

\[m/z \text{ found } = 177.1279\]

TLC (hexanes:EtOAc 9:1)

\[R_f = 0.38\]

1-(4-butyl-3-nitrophenyl)ethan-1-one (3.2.28)

GC retention time of 1-(4-bromo-3-nitrophenyl)ethan-1-one: 6.32 min

91% yield, clear residue

\(^1\)H NMR (500 MHz, Chloroform-\(d\))

\[\delta 8.41 (d, J = 1.8, 1H), \ 8.07 (m, 1H), \ 7.46 (m, 1H), \ 2.96 - 2.90 (m, 2H), \ 2.63 (s, 3H), \ 1.69 - 1.59 (m, 2H), \ 1.46 - 1.35 (m, 2H), \ 0.95 (t, J = 7.4 \text{ Hz}, 3H)\]

\(^{13}\)C NMR (126 MHz, Chloroform-\(d\))

\[\delta 195.5, \ 142.6, \ 135.8, \ 132.3, \ 131.6 (2\text{C}), \ 124.5, \ 32.7, \ 32.6, \ 26.5, \ 22.6, \ 13.7\]

HRMS [DART-MS] (M+H\(^+\))

\[m/z \text{ calculated for } C_{12}H_{16}NO_3 = 222.1130\]

\[m/z \text{ found } = 222.1139\]

TLC (hexanes:Et\(_2\)O 1:2)

\[R_f = 0.44\]

4-butylnitrosobenzene (3.2.29)

GC retention time of 4-bromobutylnitrosobenzene: 3.49 min

67% yield (90% conversion), slightly yellow oil

\(^1\)H NMR (500 MHz, Chloroform-\(d\))

\[\delta 7.64 - 7.49 (m, 2H), \ 7.30 - 7.24 (m, 2H), \ 2.72 - 2.59 (m, 2H), \ 1.67 - 1.55 (m, 2H), \ 1.41 - 1.30 (m, 2H), \ 0.93 (t, J = 7.3 \text{ Hz}, 3H)\]

\(^{13}\)C NMR (126 MHz, Chloroform-\(d\))

\[\delta 148.5, \ 132.0, \ 129.1, \ 119.1, \ 109.4, \ 35.7, \ 33.0, \ 22.2, \ 13.8\]

HRMS [DART-MS] (M+NH\(_4\)^+)
\[ m/z \text{ calculated for } C_{11}H_{17}N_2 = 177.1391 \]
\[ m/z \text{ found } = 177.1404 \]

TLC (hexanes:Et₂O 1:1)
\[ R_f = 0.41 \]

p-tolylbenzaldehyde (3.2.30)
79% yield, clear oil
Spectra matched literature reports:
GC retention time of 4-bromobenzaldehyde: 3.35 min
\(^1\)H NMR (300 MHz, Chloroform-\(d\))
\[ \delta 9.96 (s, 1H), 7.93 - 7.63 (m, 2H), 7.45 - 7.19 (m, 2H), 2.44 (s, 3H) \]
\(^13\)C NMR (75 MHz, Chloroform-\(d\))
\[ \delta 192.0, 145.5, 134.1, 129.8, 129.7, 21.8 \]

3-methylacetophenone (3.2.31)
82% yield, clear oil
Spectra matched literature reports:
GC retention time of 3-bromoacetophenone: 3.94 min
\(^1\)H NMR (300 MHz, Chloroform-\(d\))
\[ \delta 7.86 - 7.63 (m, 2H), 7.49 - 7.30 (m, 2H), 2.59 (s, 3H), 2.41 (s, 3H) \]
\(^13\)C NMR (75 MHz, Chloroform-\(d\))
\[ \delta 198.3, 138.3, 137.1, 133.8, 128.7, 128.4, 125.5, 26.6, 21.3 \]

4-phenylbutyl benzoate (3.2.37)
58% yield, clear oil

GC retention time **bromobenzene**: 2.08 min

Spectra matched literature reports:


$^1$H NMR (500 MHz, Chloroform-$d$)

$\delta$ 8.07 – 7.99 (m, 2H), 7.58 – 7.48 (m, 1H), 7.47 – 7.38 (m, 2H), 7.32 – 7.27 (m, 2H), 7.22 – 7.16 (m, 3H), 4.41 – 4.29 (m, 2H), 2.73 – 2.66 (m, 2H), 1.86 – 1.77 (m, 4H)

$^{13}$C NMR (126 MHz, Chloroform-$d$)

$\delta$ 166.3, 142.0, 132.8, 130.4, 129.5, 128.3, 128.3, 128.3, 125.8, 64.8, 35.4, 28.3, 27.8

TLC (hexanes:Et$_2$O 4:1)

$R_f = 0.58$

1-(3-(2-(trimethylsilyl)ethyl)phenyl)ethan-1-one (**3.2.38**)  

72% yield, clear oil

GC retention time of **3-bromoacetophenone**: 3.94 min

2-conformations observed, major peaks reported

$^1$H NMR (500 MHz, Chloroform-$d$)

$\delta$ 7.82 – 7.68 (m, 2H), 7.42 – 7.31 (m, 2H), 2.70 – 2.66 (m, 3H), 2.60 (s, 3H), 1.67 – 1.58 (m, 2H), 0.58 – 0.50 (m, 2H), -0.02 (s, 9H)

$^{13}$C NMR (126 MHz, Chloroform-$d$)

$\delta$ 198.4, 143.2, 137.1, 133.3, 128.4, 128.1, 125.9, 39.7, 26.7, 26.0, 16.5, -1.7

HRMS [DART-MS] (M+H$^+$)

$m/z$ calculated for C$_{14}$H$_{23}$OSi = 235.1582  

$m/z$ found = 235.1522

TLC (hexanes:Et$_2$O 5:1)

$R_f = 0.48$

1-(3-(4-chlorophenethyl)phenyl)ethan-1-one (**3.2.39**)
76% yield, clear oil

GC retention time of **3-bromoacetophenone**: 3.94 min

$^1$H NMR (500 MHz, Chloroform-$d$)

$\delta$ 7.82 – 7.72 (m, 2H), 7.39 – 7.29 (m, 2H), 7.25 – 7.21 (m, 2H), 7.10 – 7.04 (m, 2H), 2.99 – 2.93 (m, 2H), 2.91 (m, 2H), 2.58 (s, 3H)

$^{13}$C NMR (126 MHz, Chloroform-$d$)

$\delta$ 198.2, 141.7, 139.5, 137.2, 133.3, 131.8, 129.8, 128.5, 128.4, 128.1, 126.2, 37.5, 37.02, 26.6

HRMS [DART-MS] (M+H$^+$)

$m/z$ calculated for C$_{16}$H$_{16}$ClO = 259.0889

$m/z$ found = 259.0877

TLC (hexanes:Et$_2$O 3:1)

$R_f$ = 0.24

3-(4-methoxyphenethyl)benzonitrile (**3.2.40**)

52% yield, clear oil

GC retention time of **3-bromobenzonitrile**: 3.36 min

$^1$H NMR (500 MHz, Chloroform-$d$)

$\delta$ 7.50 – 7.46 (m, 1H), 7.42 (m, 1H), 7.37 – 7.33 (m, 2H), 7.06 – 6.99 (m, 2H), 6.84 – 6.79 (m, 2H), 3.79 (s, 3H), 2.95 – 2.88 (m, 2H), 2.89 – 2.83 (m, 2H)

$^{13}$C NMR (126 MHz, Chloroform-$d$)

$\delta$ 158.0, 143.0, 133.1, 132.6, 132.0, 129.7, 129.3, 129.0, 119.0, 113.8, 112.2, 55.2, 37.6, 36.4

HRMS [ESI-MS] (M+H$^+$)

$m/z$ calculated for C$_{16}$H$_{16}$NO = 238.1226

$m/z$ found = 238.1227

TLC (hexanes:Et$_2$O 4:1)

$R_f$ = 0.36
1-(3-(3-phenoxypropyl)phenyl)ethan-1-one (3.2.41)
67% yield (84% brsm), clear oil

$^1$H NMR (399 MHz, Chloroform-$d$)
\[ \delta 7.83 - 7.75 \text{ (m, 2H)}, 7.45 - 7.36 \text{ (m, 2H)}, 7.31 - 7.26 \text{ (m, 1H)}, 6.94 - 6.87 \text{ (m, 3H)}, 3.97 \text{ (t, } J = 6.2 \text{ Hz, 2H)}, 2.89 \text{ (m, 2H)}, 2.57 \text{ (s, 3H)}, 2.19 - 2.07 \text{ (m, 2H)} \]

$^{13}$C NMR (100 MHz, Chloroform-$d$)
\[ \delta 198.2, 158.8, 142.0, 137.3, 133.3, 129.4, 128.6, 128.2, 126.1, 120.6, 114.4, 66.5, 32.0, 30.7, 26.6 \]

HRMS [DART-MS] (M+H$^+$)
\[ m/z \text{ calculated for } C_{17}H_{19}O_2 = 255.1385 \]
\[ m/z \text{ found } = 255.1381 \]

TLC (hexanes:Et$_2$O 3:1)
\[ R_f = 0.29 \]

3.3.4 SMCC of Alkoxymethyl MIDA boronates and Aryl Chlorides

To a Teflon lined 2-dram vial equipped with a stir bar was added phenol methylene MIDA boronate (0.11 g, 0.42 mmol, 1.1 equiv), 2nd generation RuPhos-Pd$^{2+}$pre-catalyst 3.2.43 (0.015 g, 0.019 mmol, 5 mol %) and 4-chlorobenzonitrile (0.0523 g, 0.38 mmol, 1.0 equiv.). The vial was fitted with a rubber septa and the atmosphere was flushed 3 times with N$_2$. Degassed toluene (2.0 mL) and degassed water (0.4 mL) were added sequentially and the reaction was allowed to stir for 5 minutes at which time Cs$_2$CO$_3$ (0.742 g, 2.28 mmol, 6.0 equiv.) was added. The addition of base was accompanied with immediate colour change indicating the formation of the mono-ligated [Pd$^0$] species. The rubber septum was exchanged for a screw-cap and the reaction mixture was brought to 100 °C and stirred for 24 hours. The reaction was then allowed to cool to room temperature and extracted with Et$_2$O (3 x 3 mL). The combined Et$_2$O was dried with anhydrous MgSO$_4$, filtered and removed in vacuo. The resulting residue was purified by SiO$_2$ chromatography to yield the coupled product as a clear residue.

\[ 4-((benzyloxy)methyl)benzonitrile (3.2.45) \]
81 % yield, clear oil
$^1$H NMR (500 MHz, Chloroform-$d$)
\[ \delta 7.67 – 7.62 \text{ (m, 2H)}, 7.49 – 7.46 \text{ (m, 2H)}, 7.40 – 7.29 \text{ (m, 5H)} \]

$^{13}$C NMR (126 MHz, Chloroform-$d$)
\[ \delta 143.8, 137.5, 132.2, 128.5, 127.9, 127.7, 118.8, 111.3, 72.7, 71.0 \]

HRMS [DART-MS] (M+NH$_4^+$)
\[ m/z \text{ calculated for C}_{15}H_{17}N_2O = 241.1340 \]
\[ m/z \text{ found } = 241.1332 \]

TLC (hexanes:EtOAc 1:9)
\[ R_f = 0.3 \]

9-(4-methylene-4-benzonitrile)-6-(diterbutoxyamino)purine (3.2.46)
54% yield, clear oil

$^1$H NMR (500 MHz, Chloroform-$d$)
\[ \delta 8.88 \text{ (s, 1H)}, 8.07 \text{ (s, 1H)}, 7.68 – 7.63 \text{ (m, 2H)}, 7.41 – 7.36 \text{ (m, 2H)}, 5.51 \text{ (s, 2H)}, 1.47 \text{ (s, 18H)} \]

$^{13}$C NMR (126 MHz, Chloroform-$d$)
\[ \delta 153.2, 152.5, 150.6, 150.5, 144.0, 140.0, 132.9, 128.7, 128.2, 127.6, 118.0, 112.7, 83.9, 46.9, 27.8 \]

HRMS [DART-MS] (M+H$^+$)
\[ m/z \text{ calculated for C}_{23}H_{27}N_6O_4 = 451.2093 \]
\[ m/z \text{ found } = 451.2102 \]

TLC (hexanes:EtOAc 1:1)
\[ R_f = 0.18 \]

4-(phenoxy)methyl)benzonitrile (3.2.48)
71% yield, clear oil

$^1$H NMR (500 MHz, Chloroform-$d$)
δ 7.76 – 7.63 (m, 2H), 7.63 – 7.46 (m, 2H), 7.41 – 7.19 (m, 2H), 7.07 – 6.85 (m, 3H), 5.13 (s, 2H)

13C NMR (126 MHz, Chloroform-d)

δ 158.1, 142.5, 132.3, 129.6, 127.5, 121.4, 118.6, 114.7, 111.6, 68.8

HRMS [DART] (M+NH4+)

m/z calculated for C_{14}H_{15}N_{2}O = 227.1184

m/z found = 227.1179

TLC (hexanes:EtOAc 2:1)

R_f = 0.16
3.4 References


14 See references 2, 3, 6 and 9


24 Ag₂O has also been used for secondary boronic ester couplings: Imao, D.; Glasspoole, B. W.; Laberge, V. S.; Crudden, C. M. *J. Am. Chem. Soc.* **2009**, *131*, 5024–5025.


44 Protodehalogenation was observed as a side reaction.


Steric effects also played a role in this reaction. 2-Bromotoluene and 2-mesitylene led to increased reaction times.


Assay yield determined via internally calibrated GC analysis using naphthalene as standard.


Copyright Acknowledgements

Title: Development of the Direct Suzuki–Miyaura Cross-Coupling of Primary B-Alkyl MIDA-boronates and Aryl Bromides

Author: Jeffrey D. St. Denis, Conor C. G. Scully, C. Frank Lee, and Andrei K. Yudin

Publication: Organic Letters
Publisher: American Chemical Society
Date: Mar 1, 2014
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Chapter Four

Rhodium-Catalyzed C-H Amination of Alkyl Boronates
4 Rhodium-Catalyzed C-H Amination of Alkyl Boronates

4.1 Introduction

Chemoselective C-H bond functionalization of complex organic molecules has emerged as an important transformation for the introduction of polar functional groups.\(^1\) The enabling feature of C-H bond functionalization, as opposed to the standard bond disconnections, is that reaction partners do not require pre-functionalization. This is in stark contrast to common Pd\(^0\)-catalyzed cross-couplings that requires organometallic and (pseudo)halide starting materials.\(^2\) Site-selective C-H bond functionalization is still an ongoing challenge. However, methodologies that introduce C-C,\(^3\) C-O,\(^4\) and C-N\(^5\) bonds in a chemoselective fashion have been reported.\(^6\)

![Figure 4.1](image)

**Figure 4.1.** Natural products synthesized by oxidative Rh\(^{II}\)-catalyzed C-H amination

The formation of the C-N bond constitutes an integral transformation in organic synthesis given the ubiquitous nature of the amine functionality in natural products, bioactive molecules and materials.\(^7\) Since the report by Du Bois in 2003, the transition metal-catalyzed C-H amination of unfunctionalized substrates has been developed as a convenient method for the synthesis of complex substrates (Figure 4.1).\(^8\) The chemoselective nature of the C-H amination reaction has been utilized in a number of total syntheses, including the densely functionalized (-)-tetrodotoxin (4.1.01)\(^9\) and (+)-saxitoxin (4.1.02) natural products.\(^10,11\)

4.1.1 Transition Metal Catalyzed C-H Amination

In a number of nitrogen-atom transfer reactions, the formation of an intermediate nitrene moiety is observed. Nitrenes are reactive functional groups and are only formed *in situ*. There are two common methods to access the nitrene intermediate: thermolysis (photolysis) of azides (4.1.03)
which generate N₂ gas or isocyanate decomposition (4.1.04) to yield carbon monoxide (Figure 4.2).¹² The potential of uncontrolled gas evolution and chemoselectivity issues associated with the formation of a discrete nitrene intermediate limits both methodologies. A mild method to yield the nitrene-intermediate is the α-elimination of a leaving group (4.1.05). This avoids gas evolution albeit with a decrease in atom-economy.

![Diagram](Image)

**Figure 4.2.** Nitrene generation via decomposition of the azide and isocyanates

Transition metal-mediated azide decomposition is an effective method to prevent uncontrolled reactivity and promote chemoselective transformations.¹³ The first example of transition metal mediated azide decomposition was pioneered almost 50 years ago (Figure 4.3).¹⁴ In this example, copper metal was effective at promoting sulfonyl azide decomposition and nitrogen transfer to cyclohexene via metal-bound nitrene intermediate (nitrenoid). Intermolecular transfer of the sulfonyl nitrene resulted in a mixture of products including aziridine, enesulfonamides and allyl sulfonamides. While a number of products were obtained, this method successfully demonstrated the utility of transition metals for nitrogen-atom transfer reactions. This report led to the development of other transition metal catalysts (e.g. [Cu], [Mn], [Fe], [Ru]) for mediating the C-H amination and other nitrogen transfer reactions.¹⁵ In the interest of brevity, only methods pertaining to the generation and synthetic application of nitrenoids formed via rhodium catalysis shall be discussed.
4.1.2 Rhodium Nitrenes

Breslow and Gellman performed some of the pioneering work into transition metal-catalyzed C-H amination reactions.\(^\text{16}\) Screening a number of transition metals/ligands with the metallonitrene precursor iminoiodinane (\textit{4.1.06}) found that the rhodium catalyst, Rh\(_2\)(OAc)\(_4\), was most effective in the formation of the cyclic product \textit{4.1.07}, whereas other transition metals were less effective (Scheme 4.1). The highly regioselective amination was attributed to the proximity of the C-H bond and metallo-nitrene shown in intermediate \textit{4.1.08}. This report represents one of the first chemoselective and regioselective \(sp^3\)-C-H amination reactions.

\textbf{Scheme 4.1.} Identification of the Rh\(_2\)(OAc)\(_4\) catalyzed intramolecular C-H amination\(^\text{16}\)

Following Breslow’s report, Müller and co-workers started a research program in order to engage the Rh\(_2\)(OAc)\(_4\) catalyst and iminoiodinanes for the \textit{intermolecular} C-H amination of alkanes.\(^\text{17}\) To investigate the regioselectivity of the intermolecular C-H amination reaction, indane (Scheme 4.2, \textit{4.1.09}) was used as the probe. The results of this study found that the C-H amination reaction exclusively affords the benzyllic product (\textit{4.1.11}) as opposed to the
homobenzylic sulfonamide. While effective for benzylic C-H amination, this methodology suffers from two important limitations: the alkane substrate must be used in large excess due to competing side-product formation, and challenges associated with isolation of the sulfonyliminoiodinane (4.1.10) as a pure compound.\textsuperscript{18}

\[
\begin{array}{c}
\text{Scheme 4.2. Müller’s investigations into the intermolecular C-H amination with sulfonyliminoiodinanes}
\end{array}
\]

Despite the in-depth studies on the intermolecular amination reaction, further development of the C-H amination reaction was stymied by challenges surrounding the isolation of the iminoiodinane reagents (Scheme 4.3, 4.1.10).\textsuperscript{18} In 2001, Du Bois and Espino found that primary carbamates (4.1.12) undergo a one-pot \textit{intramolecular} C-H amination to afford the five-membered oxazolidinone (4.1.14) without isolation of the nitrene precursor (4.1.13). The main advantage of the one-pot process is that it avoids isolation of the iminoiodinane.\textsuperscript{19} This method also demonstrated that the C-H amination reaction was not limited to sulfonamide substrates as metallo-nitrene precursors.

\[
\begin{array}{c}
\text{Scheme 4.3. Oxazolidinone formation via C-H amination}
\end{array}
\]

The exclusive formation of the oxazolidinone was attributed to the tethered carbamate.\textsuperscript{20} Access to the six-membered ring would require the use of a different functional group as the nitrene precursor; thus, the sulfamate moiety (4.1.15) was identified as an appropriate functional group (Scheme 4.4).\textsuperscript{21,22} The resulting oxathiazinanes (4.1.16) were obtained as single regioisomers in favour of the six-membered ring products.
Bias for six-membered ring formation can be rationalized from the bond angles of the sulfamate ester (Scheme 4.4B). For the six-membered oxathiazinane (4.1.18), the \( \angle N-S-O \) angle has been determined to be 104°. This geometry is consistent with the terminal sulfamate ester (4.1.17, 103°). The related five-membered ring (4.1.19) has an \( \angle N-S-O \) bond angle of 95°. As such, bias for six-membered ring formation can be rationalized by comparison of starting sulfamate and product \( \angle N-S-O \) angles.

**Scheme 4.4.** A) C-H amination of sulfamate esters. B) Bond angles for sulfamate starting materials and comparison to cyclized products

In addition to the geometric concerns of the intramolecular C-H amination, the electronic nature of the available C-H bond also influences the regioselectivity of the reaction (Figure 4.4). Comprehensive studies by the Du Bois group uncovered a trend in reactivity with \( \text{Rh}_2(\text{OAc})_4 \): 3° > \( \alpha \)-ethereal, \( \alpha \)-aminal, benzylic > 2° >> 1°. Generally, the C-H amination reaction favours the most stable carbocation although regioselectivity can be influenced by the choice of supporting carboxylate ligand.

**Figure 4.4.** Regioselectivity of the C-H amination reaction influenced by the catalyst choice

Rhodium catalysts have proven effective for promoting C-N bond formation. However, \( \text{Rh}_2(\text{OAc})_4 \) and related tetracarboxylates undergo significant structural modifications within five
Carboxylate ligand exchange is the most prevalent process. Rapid ligand exchange results leads to degradation/inactivation, therefore relatively high loadings of catalyst are required.

![Figure 4.5. The ‘strapped’ Rh$_2$(esp)$_2$ (4.1.21) catalyst](image)

A comprehensive study on the catalyst degradation products and mechanism led to the design of ‘strapped’ rhodium catalysts (Figure 4.5). While a number of tetradeutate carboxylate ligands were screened, it was found that the esp-ligand (3,3’-(1,4-phenylene)bis(2,2-dimethylpropanoic acid, 4.1.20) was most effective at inhibiting ligand exchange and led to the development of the Rh$_2$(esp)$_2$ catalyst (4.1.21). The lack of ligand exchange confers outstanding stability and reactivity to the rhodium centre, which permits low catalyst loadings of 4.1.21 (Scheme 4.5). Commercialization, high reactivity and low catalyst loadings has made 4.1.21 the catalyst of choice for the C-H amination reaction.

![Scheme 4.5. Differential performance of Rh$_2$(O$_2$CrBu)$_4$ and 4.1.21](image)

### 4.1.3 Amino Boronates

The *gem*-amino boronic acid motif (B-C-N), until recently, garnered little interest from the academic and pharmaceutical communities. Over the recent years, a number of studies have demonstrated the utility of amino-boronic acid containing small molecules in biological systems where high levels of affinity for proteases were observed. Protease specificity results from the reversible covalent interactions between the boronic acid moiety and nucleophilic amino acid
side chains, most notably serine and threonine.\textsuperscript{30} These studies culminated in the success of bortezomib (4.1.22, Velcade\textsuperscript{®}) as a treatment for multiple myeloma and Val-boroPro (4.1.23, Talabostat\textsuperscript{®}) an orally bio-available treatment of colorectal cancer currently in phase II trials (Figure 4.6).\textsuperscript{31} This has resulted in a renewed and growing interest in \textit{gem}-amino boronic acid containing small molecules.\textsuperscript{32}

![Figure 4.6](image-url)  
**Figure 4.6.** Bortezomib (4.1.22, Velcade\textsuperscript{®}), an FDA-approved treatment of multiple myeloma and Val-boroPro (4.1.23, Talabostat\textsuperscript{®}) a biologically active dipeptide for the treatment of colorectal cancer.

While interest in the biological activity of \textit{gem}-amino boron containing small molecules is gaining traction, there is a notable deficiency in mild synthetic methods available that generate this important motif.\textsuperscript{33} The most common approach involves the S\textsubscript{N}2-displacement of \(\alpha\)-halo alkyl boronates (4.1.24) by nitrogen nucleophiles (4.1.25).\textsuperscript{34} Additionally, the use of a chiral auxiliary can routinely achieve >100:1 diastereomeric ratio of \(\alpha\)-amino boronic acid ester products. This methodology, also known as the Matteson protocol, is used in the synthesis of 4.1.22 to access the amino boronic acid motif (Scheme 4.6).\textsuperscript{35}

![Scheme 4.6](image-url)  
**Scheme 4.6.** Matteson synthesis of amino boronic acid component of 4.1.22

The transition metal catalyzed addition of bis(pinacolato)diboron (B\textsubscript{2}Pin\textsubscript{2}) to electrophiles, notably chiral sulfinyl imines, also provides access to the amino boronic acid motif (Scheme 4.7).\textsuperscript{36,37} As demonstrated by Ellman and co-workers, in the presence of a copper catalyst B\textsubscript{2}Pin\textsubscript{2}...
adds to *N*-tert-butylsulfinyl imines in a highly diastereoselective manner (4.1.26). The amino boronic acid can be used in a Rh\(^{1}\)-catalyzed 1,2-addition to ketones thereby demonstrating the utility of the C-B bond (4.1.27).\(^{38}\)

![Scheme 4.7. Diastereoselective addition of B\(_2\)Pin\(_2\) to Ellman sulfinyl imines](image)

Lastly, the Tsuji-Trost amination is an effective method for the introduction of amines to boron containing electrophilic π-allyl systems (Scheme 4.8).\(^{39}\) Carreaux and co-workers found that the Ir\(^{1}\)-catalyzed Tsuji-Trost amination of potassium trifluoroboryl carbonates (4.1.28) with amines afforded the α-amino boronate (4.1.29) as a single branched product (Figure 14).\(^{40}\) The highly regioselective transformation is attributed to the polarization of the allyl species caused by the electron-rich trifluoroborate substituent.

![Scheme 4.8. Ir\(^{1}\)-catalyzed allylic amination](image)

### 4.2 Rhodium-Catalyzed C-H Amination of Alkyl Boronates

#### 4.2.1 Proposal

Small molecules containing the α-amino-boron motif are valuable for biological and materials studies. Our lab has reported two different methods, both derived from the Curtius rearrangement of boryl acyl azides, pertaining to the synthesis of α-amino boronic acid containing small molecules and peptides (Figure 4.7).\(^{41}\) Both of these methods constitute a significant advance for
the synthesis of amino boronates; however, these methods only afford linear products. Access to cyclic derivatives would increase the stability of these compounds in living systems, and but the synthesis of cyclic-amino boron-containing small molecules has not been realized to date. In an effort to gain access to these valuable scaffolds we sought to employ oxidative Rh\II-catalysis in the chemoselective $\alpha$C-H amination of alkyl MIDA boronates.

**Figure 4.7.** Previous work from the Yudin group for the synthesis of $\alpha$-amino boronates and the proposal which constitutes the basis of this chapter

### 4.2.2 Substrate Design

The Rh\II-catalyzed C-H amination has been thoroughly studied with sulfamate esters due to the ease of introduction and high reactivity as a nitrene precursor. In addition, the sulfamate moiety favours the six-membered ring, which may allow access not only to the $\alpha$-aminoboronate but also the $\beta$-regioisomer. Thus, we sought to investigate the potential for the intramolecular C-H amination of alkyl boronates with the corresponding boryl-sulfamates (Figure 4.7). As described in the introduction of this thesis, $\alpha$-MIDA boryl aldehydes are amenable to a number of common reagents and long multi-step sequences. These inherent attributes led us to utilize these boron-containing small molecules for the synthesis of the boryl-sulfamate ester via the boryl alcohol.
Scheme 4.9. Reduction of α-MIDA boryl aldehydes to the corresponding 1,2-boryl alcohols (4.2.01 - 4.2.09)

In an effort to evaluate the amination process, we sought to utilize the alkyl MIDA boryl sulfamate ester as the investigational substrate. At the outset, the reduction of aldehyde with NaBH(OAc)$_3$ afforded the corresponding desired 1,2-MIDA boryl alcohol as a white solid (Figure 4.8). Notably, the Peterson-type elimination of boric acid was not observed. The lack of elimination products is attributed to the conformationally rigid trivalent MIDA ligand that prevents complexation by the adjacent alcohol (Scheme 4.10).$^{45}$
With the 1,2-boryl alcohols in hand, sulfamate ester formation was attempted with a mixture of ClSO₂NCO/formic acid. Initially, the formation of the sulfamate was accompanied by the production of the corresponding formate ester (Figure 4.9). We found that the formation of the formate ester could be suppressed by quenching the reaction with water prior to removal of the solvent. As a result of the modified workup, the desired boryl-sulfamate esters were obtained in good yields (Scheme 4.11).
**Scheme 4.11. α-Boryl sulfamate ester formation**

### 4.2.3 Rh\textsuperscript{II}-Catalyzed C-H Amination of Aryl Boryl Sulphamates

Oxidative Rh\textsuperscript{II}-catalyzed C-H amination is an effective method for the introduction of the C-N bond. In the case of the boryl sulfamates, the rhodium catalyst can also induce transmetallation with the organometallic C-B bond (Figure 4.10).\textsuperscript{47} The transmetallation of the C-B bond would be detrimental to the formation of the α-amino boron moiety resulting in decomposition of the starting boryl-sulfamate. We postulated that the tetrahedral nature of the MIDA boronate would inhibit interaction with the Rh-catalyst and favour αC-H amination.\textsuperscript{48}
The potential for dual activation of the boryl sulfamate led us to screen conditions that would favour the α-C-H amination pathway. Using the sulfamate ester 5.1.16 as the substrate we found that 5 mol % Rh$_2$(OAc)$_4$ and PhI(OAc)$_2$ as the terminal oxidant afforded the α-C-H aminated product (4.2.19) in 56% conversion, as determined by $^1$H NMR. The reduced conversion was presumed to be due to the decomposition of the catalyst. Exchanging Rh$_2$(OAc)$_4$ for 2.5 mol % Rh$_2$(esp)$_2$ (4.1.21) afforded 4.2.19 in 82% isolated yield (Table 4.1, entry 4). Notably, there were no cyclization products observed from C-B functionalization (4.2.20) which suggests that the MIDA ligand is inhibiting transmetallation of the C-B bond.

Table 4.1. Optimization of reaction conditions

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>oxidant</th>
<th>solvent</th>
<th>time (h)</th>
<th>% conversion (CH:CB)</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rh$_2$(OAc)$_4$</td>
<td>PhI(OAc)$_2$</td>
<td>PrOAc</td>
<td>18</td>
<td>56 (&gt;95:5)</td>
<td>ND</td>
</tr>
<tr>
<td>2</td>
<td>Rh$_2$(esp)$_2$ (4.1.21)</td>
<td>PhI(OAc)$_2$</td>
<td>DCM</td>
<td>6</td>
<td>38 (&gt;95:5)</td>
<td>ND</td>
</tr>
<tr>
<td>3</td>
<td>4.1.21</td>
<td>PhI(OAc)$_2$</td>
<td>PrOAc</td>
<td>6</td>
<td>83 (&gt;95:5)</td>
<td>ND</td>
</tr>
<tr>
<td>4$^c$</td>
<td>4.1.21</td>
<td>PhI(O$_2$Bu)$_2$</td>
<td>PrOAc</td>
<td>18</td>
<td>100 (&gt;95:5)</td>
<td>78</td>
</tr>
<tr>
<td>5$^d$</td>
<td>4.1.21</td>
<td>PhI(O$_2$Bu)$_2$</td>
<td>PrOAc:MeCN</td>
<td>10</td>
<td>85 (&gt;95:5)</td>
<td>40</td>
</tr>
<tr>
<td>6</td>
<td>none</td>
<td>PhI(O$_2$Bu)$_2$</td>
<td>PrOAc</td>
<td>10</td>
<td>0 (N/A)</td>
<td>ND</td>
</tr>
</tbody>
</table>

$^a$Reaction Conditions: 1.25 equiv oxidant, 2.5 equiv MgO, in N$_2$-sparged anhydrous solvent $^b$Measured by comparison of corresponding NCH$_2$ of SM/Product by crude $^1$H NMR, $^c$2.5 mol % Rh$_2$(esp)$_2$ $^d$4:1 $^f$PrOAc:MeCN

With the optimized reaction conditions in hand, we extended this methodology to other aryl substrates (Scheme 4.12). The intramolecular C-H amination of aryl boryl sulfamates (4.2.10 - 4.2.18) resulted in the formation of the corresponding oxathiazolidines (five-membered), which
were obtained in good yield as a single regioisomer. Exclusive formation of the oxathiazolidine product is due to the sole, reactive C-H bond. This details the first example of an effective synthesis of cyclic amino-boronates.

\[
\text{MeN} - \text{B} - \text{OSO}_2\text{NH}_2 \quad \overset{2.5 \text{ mol} \% \text{Rh(II)} \text{ catalyst}}{\xrightarrow{2.5 \text{ equiv } \text{Ph}(\text{O})_2\text{Bu}, 1.25 \text{ equiv } \text{MgO}, \text{PrOAc, } 45\, ^\circ\text{C}}} \quad \text{MeN} - \text{B} - \text{HN} - \text{SO}_2\text{NH}_2
\]

Scheme 4.12. αC-H amination of aryl α-boryl sulfamates

4.2.4 Rh\textsuperscript{II}-Catalyzed C-H Amination of Alkyl α-Boryl Sulfamates

The inherent structural characteristics of aryl boryl sulfamate esters affords the five-membered amino boronate as a single regioisomer (Scheme 4.12). The increased electron-density at the α-carbon is also proposed to stabilize the nascent α-carbocation. In contrast, alkyl-substituted boryl sulfamates (4.2.15 - 4.2.18) possess multiple \(sp^3\)-centres; therefore regioisomeric amino boronates could result. Comparison of the regioselectivity of C-N bond formation would provide information regarding any influence of the MIDA substituent on the insertion process.
Initially, we exposed the benzyl boryl sulfamate (4.2.27) to the optimized reaction conditions and resulted in the formation of the β-amination product, which was confirmed by single crystal X-ray analysis. In addition to the known stability of benzyl cations, it is conceivable that the electron-rich $sp^3$-boron can stabilize partial positive charges.\(^{49}\) This process is suggested to be the driver for the [1,2]-boryl migration in the rearrangement reaction of epoxy-MIDA boronates. In addition, the proposed β-stabilization is similar to the well-known β-silicon effect (Figure 4.11).\(^{50}\) We attribute the exclusive formation of the β-amino boronate to both of these factors.
The six-membered oxathiazine was characterized by 2D NMR experiments and single crystal X-ray analysis. Information gathered by X-ray analysis was informative to the geometry of the \textbf{4.2.27} (Figure 4.12). The bond angles ($\angle$N-S-O) of the six-membered ring are consistent with literature reports ($103.81^\circ$ vs. $104^\circ$). Thus, it can be concluded that benzylic C-H insertion is favoured by maintaining sulfamate bond angles and the stabilization of the $\beta$-carbocation intermediate.

We attempted to calculate the A-value of the MIDA substituent in the form of the cyclohexyl MIDA boronate. Through analysis over a wide range of temperature we could not observe any cyclohexane ring inversion. This suggests that the barrier to inversion is cannot be less than 5.0 kcal/mol.

\textbf{Figure 4.11.} Proposed stabilization of $\alpha$- and $\beta$-carbocations by $sp^3$-boronates

In the absence of benzyl substitution, a diastereo- and regioisomeric mixture of $\alpha$- and $\beta$-amination was obtained.\textsuperscript{51} Further investigation into the effect of $sp^3$-boronates on the regioselectivity of the amination reaction is required.

\textbf{Figure 4.12.} X-ray structure of \textbf{4.2.27}
4.2.5 Mechanistic Studies

Mechanistic investigations by the groups of Du Bois and Bach have reported discrepancies with [Rh]-catalyzed C-H amination processes, noting that heterolytic C-H activation/nitrene insertion may not always be the operating mechanism. Evidence to support a radical mechanism includes: racemization of stereocentres in intermolecular C-H amination reactions as well as dinuclear [Rh]-catalysts with differing oxidation states. Additionally, alkyl MIDA boronates have been shown to undergo α-radical formation (4.2.28) via Barton decarboxylation (Figure 4.13).

![Figure 4.13. Formation of α-MIDA boryl radical (4.2.28) via Barton decarboxylation](image)

In order to determine whether the αC-H activation reaction proceeds through a heterolytic mechanism, we exposed the cyclopropyl boryl sulfamate ester (4.2.17) to the optimized reaction conditions (Scheme 4.14). The reaction resulted in the formation of the cyclopropyl oxathiazolidine (4.2.23) in 59% yield. Analysis of the crude reaction mixture by 1H NMR found no discernible cyclopropane fragmentation products corresponding to the formation of a radical intermediate. This result suggests that the intramolecular C-H amination of boryl sulfamates proceeds through a heterolytic mechanism.

![Scheme 4.14. Exclusive formation of the cyclopropyl oxathiazolidine 4.2.23](image)
4.2.6 Summary

The intramolecular C-H amination of alkyl boronates has been accomplished without engagement of the valuable C-B bond. Aryl substrates undergo exclusive five-membered ring formation, while alkyl boryl sulfamates afford a mixture of regioisomers. A mechanistic study suggests that the C-H amination proceeds through an insertion pathway and not a radical intermediate. Further studies are required to completely elucidate the impact of the MIDA boronate on the C-H amination reaction and other nitrene (carbene) reactions.

4.3 Supporting Information

4.3.1 General Information

Tetrahydrofuran (THF) was purified by distillation from sodium/benzophenone ketyl radical under an atmosphere of nitrogen. Acetonitrile (MeCN) was purified by distillation from 3Å molecular sieves (3Å MS). Dichloromethane, methanol (MeOH) and triethylamine (Et₃N) were purified by distillation from CaH₂ respectively. Diethyl ether (Et₂O), toluene, dimethyl formamide (DMF), was purified through a solvent purification system. All other reagents were purchased from commercial sources used as received.

Chromatography

Flash column chromatography was carried out using Silicycle 230-400 mesh silica gel. Thin-layer chromatography (TLC) was performed on Macherey Nagel pre-coated glass backed TLC plates (SIL G/UV254, 0.25 mm) and visualized using a UV lamp (254 nm) KMnO₄, ninhydrin, or I₂ stain in case of no UV activity.

Nuclear Magnetic Resonance Spectroscopy

Proton (¹H-NMR), carbon (¹³C-NMR) and 2D NMR experiments were performed on Bruker 400 MHz or Varian 300, 400, or 500 MHz spectrometers. NMR spectra chemical shifts (δ) are reported in parts per million (ppm) referenced to residual protonated solvent peak (CDCl₃, δ = 7.26, DMSO-d₆, δ = 2.49, acetone-d₆ δ = 2.05, acetonitrile-d₃ δ = 1.94). Spectral data is reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd =
doublet of doublets, dt = doublet of triplets, ddt = doublet of doublet of triplets, dtd= doublet of triplet of doublets, m = multiplet, br = broad), coupling constant \( (J) \) in Hertz (Hz), and integration. \(^{13}\)C NMR spectra chemical shifts (\( \delta \)) are reported in parts per million (ppm) were referenced to carbon resonances in the NMR solvent (CDCl\(_3\), \( \delta = 77.0 \); DMSO-\(d_6\), \( \delta = 39.5 \), center line, acetone-\(d_6\), \( \delta = 206.2, 29.8 \) (centre line), acetonitrile-\(d_3\), \( \delta = 118.2, 1.3 \) (centre line)).

High-Resolution Mass Spectra was obtained at the University of Toronto mass spectrometry centre.

**Infrared Spectroscopy**

IR spectra were recorded on a Perkin-Elmer 100 instrument equipped with a single-reflection diamond/ZnSe ATR accessory. Performed on an NaCl disc as a thin layer.

**Mass Spectrometry**

High resolution mass spectra were obtained on a VG 70-250S (double focusing) mass spectrometer at 70 eV or on an ABI/Sciex Qstar mass spectrometer with ESI source, MS/MS and accurate mass capabilities.

4.3.2 Synthesis of Cyclopropyl-\(\alpha\)-MIDA Boryl Aldehyde

To an oven dried, stir bar quipped vial was added alkene (10 mmol) followed by the dropwise addition of neat catechol borane (22 mmol). The reaction flask was then warmed to 65 °C for 24 hrs. Upon complete consumption of starting alkene the reaction was removed from the reaction block and allowed to cool to room temperature. Then distilled water (10 mL) was added to the reaction mixture and allowed to stir for 2-3 hrs at which time the solid precipitate was filtered to yield the crude boronic acid.

The crude boronic acid was then dissolved in DMF (0.3 M) and \(N\)-methyliminodiacetic acid (1.1 equiv) was added. The mixture was warmed to 80 °C for 24 hours. The reaction was then removed from heat and concentrated in vacuo. To the residue was added 50 mL H\(_2\)O, 50 mL sat. NaHCO\(_3\) and 100 mL EtOAc and the organic was then separated. The aqueous layer was the extracted 5 x 75 mL EtOAc. The combined organics were washed with brine, dried over NaSO\(_4\)
and concentrated to yield crude MIDA boronate. The crude MIDA boronate was then purified via SiO₂ using hexanes:acetone to yield pure primary alkyl MIDA boronate as a white solid.⁵⁹

(E)-(2-cyclopropylvinyl)MIDA boronate
82%, white solid

¹H NMR (399 MHz, Acetonitrile-d₃)
δ 5.58 (dd, J = 17.6, 8.4 Hz, 1H), 5.47 (d, J = 17.6 Hz, 1H), 3.93 (d, J = 16.9 Hz, 2H), 3.77 (d, J = 16.9 Hz, 2H), 2.78 (s, 3H), 1.50 (m, 1H), 0.82 – 0.70 (m, 2H), 0.52 – 0.38 (m, 2H)

¹³C NMR (101 MHz, Acetonitrile-d₃)
δ 168.0, 149.3, 60.9, 46.2, 15.7, 6.2

¹¹B NMR (128 MHz, Acetonitrile-d₃)
δ 10.6

HRMS [DART-MS] (M+H⁺)

m/z calculated for C₁₀H₁₅BNO₄ = 224.1094
m/z found = 224.1097

TLC (hexanes:acetone 1:1)

Rf = 0.38

4.3.2.1 Epoxidation/Rearrangement

To an oven dried round bottom flask equipped with a magnetic stir was charged cyclopropyl vinyl MIDA boronate followed by a 0.06 M solution of dimethyldioxirane in acetone (2.5 equiv). The mixture was allowed to stir for overnight at room temperature, at which time ¹H NMR analysis showed complete consumption of starting alkene. The reaction was then concentrated in vacuo to yield a white solid. The solid was then dissolved in a mixture of toluene and MeCN (approx. 1:1) and evaporated under reduced pressure (five times) to azeotrope the residual water. The solid was then evacuated under high-vacuum for at least 1 hour.
The solid was then suspended in DCM (0.05 M) and cooled to -40 °C with a MeCN-dry ice bath. Next, BF$_3$·OEt$_2$ (1.25 equiv) was added dropwise over the course of five minutes. Upon complete addition of the BF$_3$·OEt$_2$ the flask was transferred to an ice-water bath and allowed to stir for another 45 minutes. The reaction was then quenched with the addition of sat. NaHCO$_3$, transferred to a separatory funnel and extracted with EtOAc (5x). The combined organics were then dried over anhydrous Na$_2$SO$_4$, filtered and concentrated to yield a white residue. The crude material was then purified via SiO$_2$ purification to yield the cyclopropyl aldehyde as a white solid.

α-MIDA-cyclopropyl boryl aldehyde
71% yield, white solid

$^1$H NMR (500 MHz, Acetone-$d_6$)

δ 9.80 (d, J = 3.0 Hz, 1H), 4.30 (d, J = 17.1 Hz, 1H), 4.25 (d, J = 16.8 Hz, 1H), 4.09 (d, J = 17.1 Hz, 1H), 4.04 (d, J = 16.8 Hz, 1H), 3.18 (s, 3H), 1.61 – 1.54 (m, 1H), 1.04 (m, 1H), 0.66 – 0.55 (m, 2H), 0.32 – 0.26 (m, 1H), 0.13 – 0.06 (m, 1H)

$^{13}$C NMR (126 MHz, Acetone-$d_6$)

δ 206.2, 167.6, 167.3, 62.5, 62.2, 46.0, 7.0, 4.8, 4.2

$^{11}$B NMR (128 MHz, Acetone-$d_6$)

δ 11.4

HRMS [DART-MS] (M+H$^+$)

$m/z$ calculated for C$_{10}$H$_{13}$BNO$_5$ = 240.1043

$m/z$ found = 240.1042

TLC (hexanes:acetone 1:2)

$R_f$ = 0.4

4.3.3 General Procedure for the Synthesis of Boryl Alcohols

To a 3-neck oven dried round bottom equipped with a magnetic stir-bar was added boryl aldehyde. The flask was then immersed in an ice water bath and subsequently charged with 1,2-
dichloroethane (4 vol.) and stirred for 5 minutes. AcOH (1 vol.) was slowly added to the reaction flask and stirred for another 10 minutes to yield a homogenous solution. The resulting molarity in boryl aldehyde was 0.1 M. NaBH(OAc)$_3$ (1.25 equivalents) was added to the stirring solution and allowed to stir for one hour at 0°C. A total of 5.0 equivalents of NaBH(OAc)$_3$ was added to the reaction flask at 1.25 equiv/hour over 4 hours with addition every hour. Upon complete addition of NaBH(OAc)$_3$ the reaction flask was removed from the ice-water bath and allowed to warm to room temperature. Upon starting material consumption, as determined by TLC the solvent is removed in vacuo to yield an oily residue. The reaction flask was placed back into an ice-water bath and EtOAc (2 vol.) was added to the residue with stirring. To the cooled EtOAc solution was slowly added pH 7 phosphate buffer and stirred for 10 minutes to destroy remaining hydride source. The mixture was then transferred to separatory funnel and extracted with EtOAc (5 x 2 vol.), dried and concentrated to yield a white solid. The solid was then purified by SiO$_2$ to yield the desired alcohol.

![MIDA boronate](image)

(2-hydroxy-1-phenylethyl)MIDA boronate (4.2.01)

56% yield, white solid

$^1$H NMR (400 MHz, Acetonitrile-$d_3$)

$\delta$ 7.29 – 7.22 (m, 3H), 7.28 – 7.12 (m, 2H), 4.03 (d, $J = 16.5$ Hz, 1H), 3.91 (m, 3H), 3.77 (m, 1H), 3.51 (d, $J = 17.0$ Hz, 1H), 2.99 (s, 3H), 2.82 (m, 1H), 2.52 (t, $J = 7.9$ Hz, 1H)

$^{13}$C NMR (126 MHz, Acetonitrile-$d_3$)

$\delta$ 169.2, 169.1, 143.8, 130.0, 129.1, 126.3, 65.8, 63.7, 63.1, 47.0

$^{11}$B NMR (128 MHz, Acetonitrile-$d_3$)

$\delta$ 12.5

HRMS [DART] (M+NH$_4^+$)

$m/z$ calculated for C$_{13}$H$_{20}$BN$_2$O$_5$ = 295.1465

$m/z$ found = 295.1474

TLC (hexanes:acetone 1:2)

$R_f = 0.31$
(2-hydroxy-1-(p-tolyl)ethyl)MIDA boronate (4.2.02)

53% yield, white solid

$^1$H NMR (500 MHz, Acetonitrile-$d_3$)

$\delta$ 7.15 – 7.13 (m, 2H), 7.12 – 7.09 (m, 2H), 4.00 (d, $J$ = 16.6 Hz, 1H), 3.92 – 3.87 (m, 2H), 3.84 (dd, $J$ = 10.0, 8.1 Hz, 1H), 3.73 (dd, $J$ = 10.0, 7.8 Hz, 1H), 3.47 (d, $J$ = 17.0 Hz, 1H), 2.97 (s, 3H), 2.46 (t, $J$ = 7.9 Hz, 1H), 2.31 (s, 3H)

$^{13}$C NMR (126 MHz, Acetonitrile-$d_3$)

$\delta$ 168.3, 168.3, 139.5, 134.7, 128.9, 128.8, 64.9, 62.7, 62.1, 45.9, 20.0

$^{11}$B NMR (128 MHz, Acetonitrile-$d_3$)

$\delta$ 12.4

HRMS [DART-MS] (M+NH$_4^+$)

$m/z$ calculated for C$_{14}$H$_{22}$BN$_2$O$_5$ = 309.1621

$m/z$ found = 309.1628

TLC (hexanes:acetone 1:2)

$R_f$ = 0.32

(1-(4-fluorophenyl)-2-hydroxyethyl)MIDA boronate (4.2.03)

X-ray quality crystals of 4.2.03 were grown from a solution of hexanes:acetone via slow evaporation

94% yield, white solid
$^1$H NMR (500 MHz, Acetone-$d_6$)
\[ \delta 7.31 - 7.25 \text{ (m, 2H)}, 7.01 - 6.95 \text{ (m, 2H)}, 4.22 - 4.10 \text{ (m, 3H)}, 3.91 \text{ (dd, } J = 9.8, 8.3 \text{ Hz, 1H)}, 3.80 - 3.72 \text{ (m, 2H)}, 3.16 \text{ (s, 3H)}, 2.62 - 2.56 \text{ (m, 1H)} \]

$^{13}$C NMR (126 MHz, Acetone-$d_6$)
\[ \delta 168.1, 167.92, 160.87 \text{ (d, } J = 240.7 \text{ Hz)}, 139.13 \text{ (d, } J = 3.2 \text{ Hz)}, 130.58 \text{ (d, } J = 7.6 \text{ Hz)}, 114.47 \text{ (d, } J = 20.9 \text{ Hz)} 65.1, 62.8, 62.1, 45.8 \]

$^{11}$B NMR (128 MHz, Acetone-$d_6$)
\[ \delta 12.4 \]

$^{19}$F NMR (282 MHz, Acetone-$d_6$)
\[ \delta -120.39 \]

HRMS [DART-MS] (M+NH$_4^+$)
\[ m/z \text{ calculated for } C_{13}H_{19}BFN_2O_5 = 313.1370 \]
\[ m/z \text{ found = 313.1370} \]

TLC (hexanes:acetone 1:2)
\[ R_f = 0.34 \]

(1-cyclopropyl-2-hydroxyethyl)MIDA boronate (4.2.04)
57 % yield, white solid

$^1$H NMR (400 MHz, Acetonitrile-$d_3$)
\[ \delta 4.01 - 3.74 \text{ (m, 4H)}, 3.63 \text{ (dd, } J = 9.7, 5.3 \text{ Hz, 1H)}, 3.48 \text{ (t, } J = 9.2 \text{ Hz, 1H)}, 2.93 \text{ (s, 3H)}, 2.76 \text{ (br s, 1H)}, 0.54 \text{ (m, 1H)}, 0.48 - 0.39 \text{ (m, 1H)}, 0.37 - 0.23 \text{ (m, 2H)}, 0.13 \text{ (m, 1H)}, -0.01 \text{ (m, 1H).} \]

$^{13}$C NMR (101 MHz, Acetonitrile-$d_3$)
\[ \delta 168.5, 168.1, 63.5, 62.2, 61.8, 45.6, 29.5, 9.9, 4.5, 3.5 \]

$^{11}$B NMR (128 MHz, Acetonitrile-$d_3$)
\[ \delta 13.2 \]

HRMS [DART-MS] (M+NH$_4^+$)
\[ m/z \text{ calculated for } C_{10}H_{20}BN_2O_5 = 259.1465 \]
\[ m/z \text{ found = 259.1461} \]
TLC (hexanes:acetone 1:2)

\[ R_f = 0.41 \]

(1-((1'-biphenyl)-4-yl)-2-hydroxyethyl)MIDA boronate (4.2.05)

64% yield, white solid

\[^1\text{H} \text{NMR} \ (400 \text{ MHz}, \text{Acetone}-d_6)\]

\[ \delta 7.69 – 7.64 \ (m, 2H), \ 7.59 – 7.53 \ (m, 2H), \ 7.46 \ (dd, J = 8.4, 7.0 \text{ Hz}, 2H), \ 7.42 – 7.38 \ (m, 2H), \ 7.37 – 7.31 \ (m, 1H), \ 4.32 – 4.10 \ (m, 3H), \ 4.01 \ (m, 1H), \ 3.87 \ (m, 1H), \ 3.76 \ (d, J = 17.0 \text{ Hz}, 1H), \ 3.22 \ (s, 3H), \ 2.69 – 2.61 \ (m, 1H) \]

\[^{13}\text{C} \text{NMR} \ (101 \text{ MHz}, \text{Acetone}-d_6)\]

\[ \delta 169.0, \ 168.8, \ 143.4, \ 141.9, \ 138.6, \ 130.5, \ 129.6, \ 127.7, \ 127.4, \ 127.3, \ 66.0, \ 63.7, \ 63.0, \ 46.8 \]

\[^{11}\text{B} \text{NMR} \ (128 \text{ MHz}, \text{Acetone}-d_6)\]

\[ \delta 12.5 \]

HRMS [DART-MS] (M+NH\(_4^+\))

\[ m/z \text{ calculated for } C_{19}H_{24}BN_2O_5 = 371.1772 \]

\[ m/z \text{ found } = 371.1770 \]

TLC (hexanes:acetone 3:4)

\[ R_f = 0.28 \]

(1-hydroxy-5-methylhexan-2-yl)MIDA boronate (4.2.06)

82% yield, white solid

\[^1\text{H} \text{NMR} \ (400 \text{ MHz}, \text{Acetonitrile}-d_3)\]

\[ \delta 4.04 \ (d, J = 16.4 \text{ Hz}, 1H), \ 3.95 \ (d, J = 17.2 \text{ Hz}, 1H), \ 3.88 \ (d, J = 8.1 \text{ Hz}, 1H), \ 3.84 \ (d, J = 7.3 \text{ Hz}, 1H), \ 3.64 \ (dd, J = 9.7, 5.3 \text{ Hz}, 1H), \ 3.47 \ (t, J = 9.3 \text{ Hz}, 1H), \ 3.01 \ (s, 3H), \ 1.58 – 1.42 \ (m, 2H), \ 1.36 – 1.17 \ (m, 3H), \ 1.13 – 1.02 \ (m, 1H), \ 0.91 \ (dd, J = 6.6, 3.4 \text{ Hz}, 6H) \]
13C NMR (101 MHz, Acetonitrile-d$_3$)
\[ \delta 169.7, 169.3, 63.8, 63.5, 62.9, 46.7, 38.8, 29.1, 26.3, 22.9, 22.5 \]

11B NMR (128 MHz, Acetonitrile-d$_3$)
\[ \delta 13.2 \]

HRMS [DART-MS] (M+NH$_4^+$)
\[ m/z \text{ calculated for } C_{12}H_{26}BN_2O_5 = 289.1934 \]
\[ m/z \text{ found } = 289.1942 \]

TLC (hexanes:acetone 1:1)
\[ R_f = 0.25 \]

(1-hydroxy-3-phenylpropan-2-yl)MIDA boronate (4.2.07)
81% yield, white solid

1H NMR (500 MHz, Acetone-d$_6$)
\[ \delta 7.33 – 7.17 (m, 4H), 7.18 – 7.10 (m, 1H), 4.22 (m, 2H), 4.11 – 4.02 (m, 2H), 3.91 – 3.83 (m, 1H), 3.49 (m, 1H), 3.42 (m, 1H), 3.26 (s, 3H), 3.00 (dd, \( J = 14.0, 3.4 \text{ Hz}, 1H)), 2.40 (dd, \( J = 14.0, 11.6 \text{ Hz}, 1H)), 1.52 (m, 1H) \]

13C NMR (126 MHz, Acetone-d$_6$)
\[ \delta 168.3, 168.1, 143.1, 128.6, 128.0, 125.3, 62.9, 62.4, 62.1, 45.7, 33.8 \]

11B NMR (128 MHz, Acetone-d$_6$)
\[ \delta 13.4 \]

IR (thin film)
\[ \nu 3207, 3024, 2359, 2341, 2332, 1747, 1624, 1452, 1342, 1300, 1251, 1193, 1159, 1105, 1070, 1026, 962, 893, 734, 700 \]

HRMS [DART-MS] (M+NH$_4^+$)
\[ m/z \text{ calculated for } C_{14}H_{22}BN_2O_5 = 309.1621 \]
\[ m/z \text{ found } = 309.1628 \]

TLC (hexanes:acetone 1:1)
\[ R_f = 0.28 \]
(1-hydroxyhexan-2-yl)MIDA boronate (4.2.08)

75% yield, white solid

$^1$H NMR (400 MHz, Acetone-$d_6$)

$\delta$ 4.21 (d, $J = 7.7$ Hz, 1H), 4.16 (d, $J = 8.7$ Hz, 1H), 4.05 (d, $J = 6.2$ Hz, 1H), 4.01 (d, $J = 5.2$ Hz, 1H), 3.72 (dd, $J = 9.4$, 5.0 Hz, 1H), 3.54 (t, $J = 9.4$ Hz, 1H), 3.22 (s, 3H), 1.55 (m, 1H), 1.43 (m, 1H), 1.38 – 1.23 (m, 4H), 1.23 – 1.09 (m, 1H), 0.91 (t, $J = 6.9$ Hz, 3H)

$^{13}$C NMR (101 MHz, Acetone-$d_6$)

$\delta$ 169.5, 169.0, 64.1, 63.7, 63.0, 46.6, 32.1, 28.6, 23.9, 14.4

$^{11}$B NMR (128 MHz, Acetone-$d_6$)

$\delta$ 13.3

HRMS [ESI-MS] (M+Na$^+$)

$m/z$ calculated for C$_{11}$H$_{20}$BNO$_2$Na = 280.1326

$m/z$ found = 280.1317

TLC (hexanes:acetone 1:1)

$R_f = 0.27$

(1-hydroxy-4-phenylbutan-2-yl)MIDA boronate (4.2.09)

67% yield, white solid

$^1$H NMR (399 MHz, Acetonitrile-$d_3$ + D$_2$O)

$\delta$ 7.33 – 7.26 (m, 2H), 7.26 – 7.22 (m, 2H), 7.21 – 7.16 (m, 1H), 4.01 (d, $J = 16.4$ Hz, 1H), 3.94 (d, $J = 17.1$ Hz, 1H), 3.87 (d, $J = 7.9$ Hz, 1H), 3.83 (d, $J = 7.3$ Hz, 1H), 3.70 (m, 1H), 3.55 (td, $J = 9.3$, 3.7 Hz, 1H), 2.97 (s, 3H), 2.86 (t, $J = 3.8$ Hz, 1H), 2.74 (m, 1H), 2.60 (m, 1H), 1.82 – 1.70 (m, 1H), 1.57 (m, 1H), 1.16 (m, 1H)

$^{13}$C NMR (126 MHz, Acetonitrile-$d_3$+ D$_2$O)

$\delta$ 168.7, 168.4, 143.3, 128.3, 128.2, 125.5, 62.8, 62.7, 62.2, 45.9, 34.6, 29.9

HRMS [DART-MS] (M+NH$_4^+$)
**m/z** calculated for C\textsubscript{15}H\textsubscript{24}BN\textsubscript{2}O\textsubscript{5} = 323.1778

**m/z** found = 323.1776

TLC (hexanes:acetone 1:2)

R\textsubscript{f} = 0.25

### 4.3.4 General Procedure for the Synthesis of α-Boryl Sulfamate Esters

To an oven dried three-neck round bottom flask equipped with a magnetic stir bar was added CISO\textsubscript{2}NCO (1.5 equiv.) The reaction flask was then immersed in an ice-water bath and stirred for 10 minutes at which time 99% formic acid (1.5 equiv.) was added to the mixture dropwise over 5 minutes. The solution solidified within that time. The flask was allowed to age for 5 minutes then MeCN (4 mL) was added along the wall and allowed to stir overnight (12 hours) slowly warming to room temperature. The flask was then cooled back to 0 °C and a solution of boryl alcohol (1.0 equiv) pyridine (1.5 equiv.) and MeCN (4 mL) was added via syringe pump over the course of 30 minutes. The syringe pump was removed following the addition and the reaction mixture was removed from the ice bath and allowed to warm to room temperature. Upon complete consumption of alcohol (2-5 hours) EtOAc and H\textsubscript{2}O were added to the reaction flask and subsequently transferred to a separatory funnel. The aqueous layer was extracted 5x and then the combined organics were dried with Na\textsubscript{2}SO\textsubscript{4}, filtered and concentrated to yield a clear oily residue which was purified via SiO\textsubscript{2} to provide the desired sulfamate esters as white solids.

![MIDA boronate](image)

(1-phenyl-2-(sulfamoyloxy)ethyl)MIDA boronate (**4.2.10**)

71% yield, white solid

\(^1\text{H}\) NMR (400 MHz, Acetonitrile-\textit{d}_3)

\[ \delta 7.39 \text{ – } 7.30 \text{ (m, 4H), 7.26 \text{ (m, 1H), 5.60 \text{ (s, 2H), 4.56 \text{ (dd, J = 9.8, 5.1 Hz, 1H), 4.46 \text{ (dd, J = 10.7, 9.8 Hz, 1H), 4.00 \text{ (d, J = 17.1 Hz, 1H), 3.95 \text{ – } 3.83 \text{ (m, 2H), 3.23 \text{ (d, J = 16.9 Hz, 1H), 2.90 \text{ (s, 3H), 2.85 \text{ – } 2.76 \text{ (m, 1H)}})\text{]}\]}

\(^{13}\text{C}\) NMR (101 MHz, Acetonitrile-\textit{d}_3)
1^1^B NMR (128 MHz, Acetonitrile-\textit{d}_3)
\[ \delta 11.5 \]

HRMS [DART-MS] (M+H^+)
\[ m/z \text{ calculated for C}_{13}H_{18}BN_2O_7S = 357.0927 \]
\[ m/z \text{ found} = 357.0925 \]

TLC (hexanes:acetone 1:2)
\[ R_f = 0.39 \]

(2-(sulfamoyloxy)-1-(p-tolyl)ethyl)MIDA boronate (4.2.11)
53% yield, hygroscopic white solid

\(^1^H\) NMR (400 MHz, Acetonitrile-\textit{d}_3)
\[ \delta 7.23 – 7.16 (m, 4H), 5.56 (br s, 2H), 4.50 (dd, J = 9.8, 5.0 Hz, 1H), 4.39 (dd, J = 10.8, 9.8 Hz, 1H), 3.95 (d, J = 17.2 Hz, 1H), 3.91 – 3.78 (m, 2H), 3.16 (d, J = 16.9 Hz, 1H), 2.86 (s, 3H), 2.71 (dd, J = 10.7, 5.0 Hz, 1H), 2.30 (s, 3H) \]

\(^1^3^C\) NMR (101 MHz, Acetonitrile-\textit{d}_3)
\[ \delta 167.8, 167.3, 136.9, 135.6, 129.1, 128.7, 73.2, 62.3, 62.2, 45.8, 29.7, 19.9 \]

11^B NMR (128 MHz, Acetonitrile-\textit{d}_3)
\[ \delta 11.5 \]

HRMS [DART-MS] (M+H^+)
\[ m/z \text{ calculated for C}_{14}H_{20}BN_2O_7S = 371.1084 \]
\[ m/z \text{ found} = 371.1087 \]

TLC (EtOAc:MeCN 9:1)
\[ R_f = 0.25 \]
(1-(4-fluorophenyl)-2-(sulfamoyloxy)ethyl)MIDA boronate (4.2.12)

43% yield, white solid

$^1$H NMR (500 MHz, Acetone-$d_6$)

$\delta$ 7.40 – 7.24 (m, 2H), 7.04 – 7.00 (m, 2H), 4.54 (dd, $J = 9.9$, 5.0 Hz, 1H), 4.39 (dd, $J = 10.7$, 9.8 Hz, 1H), 4.27 (d, $J = 17.1$ Hz, 1H), 4.18 (d, $J = 17.0$ Hz, 1H), 4.11 (d, $J = 17.1$ Hz, 1H), 3.51 (d, $J = 17.0$ Hz, 1H), 3.08 (s, 3H), 2.84 (dd, $J = 10.7$, 5.0 Hz, 1H)

$^{13}$C NMR (101 MHz, Acetone-$d_6$)

$\delta$ 167.3, 167.0, 161.0 (d, $J = 242.0$ Hz), 136.5 (d, $J = 3.3$ Hz), 130.4 (d, $J = 7.8$ Hz), 114.7 (d, $J = 21.0$ Hz), 72.6, 62.3, 62.2, 45.7

$^{11}$B NMR (128 MHz, Acetone-$d_6$)

$\delta$ 11.5

$^{19}$F NMR (282 MHz, Acetone-$d_6$)

$\delta$ -119.1

IR (thin film)

$\nu$ 2956, 2922, 2854, 2343, 2324, 1766, 1747, 1508, 1363, 1340, 1301, 1178, 1028

HRMS [DART-MS] (M+Na$^+$)

$m/z$ calculated for C$_{13}$H$_{16}$BN$_2$O$_7$FNaS = 397.0658

$m/z$ found = 397.0648

TLC (hexanes:acetone 3:4)

$R_f$ = 0.23

(1-cyclopropyl-2-(sulfamoyloxy)ethyl)MIDA boronate (4.2.13)

56% yield, white solid

$^1$H NMR (500 MHz, Acetonitrile-$d_3$)

$\delta$ 5.67 (s, 2H), 4.24 – 4.18 (m, 2H), 4.00 (dd, $J = 17.0$, 9.3 Hz, 2H), 3.86 (dd, $J = 17.0$, 5.0 Hz, 2H), 2.96 (s, 3H), 0.73 – 0.60 (m, 2H), 0.57 – 0.44 (m, 2H), 0.22 - 0.19 (m, 2H)

$^{13}$C NMR (101 MHz, Acetonitrile-$d_3$)

$\delta$ 168.0, 168.0, 73.0, 62.4, 62.3, 46.1, 9.8, 4.8, 3.8

$^{11}$B NMR (128 MHz, Acetonitrile-$d_3$)
$\delta$ 12.4

HRMS [DART-MS] (M+H$^+$)

$m/z$ calculated for C$_{10}$H$_{18}$BN$_2$O$_7$S = 321.0927

$m/z$ found = 321.0940

TLC (hexanes:acetone 1:2)

$R_f = 0.31$

(1-([1,1'-biphenyl]-4-yl)-2-(sulfamoyloxy)ethyl)MIDA boronate (4.2.14)

40% yield, white solid

$^1$H NMR (500 MHz, Acetonitrile-$d_3$)

$\delta$ 7.70 – 7.66 (m, 2H), 7.65 – 7.61 (m, 2H), 7.51 – 7.44 (m, 2H), 7.43 – 7.34 (m, 3H), 5.63 (s, 2H), 4.57 (dd, $J = 9.9, 5.1$ Hz, 1H), 4.48 (dd, $J = 10.8, 9.9$ Hz, 1H), 4.01 (d, $J = 17.1$ Hz, 1H), 3.96 – 3.86 (m, 2H), 3.33 (d, $J = 16.9$ Hz, 1H), 2.93 (s, 3H), 2.85 (dd, $J = 10.7, 5.1$ Hz, 1H)

$^{13}$C NMR (126 MHz, Acetonitrile-$d_3$)

$\delta$ 167.9, 167.4, 140.5, 139.7, 138.6, 129.5, 128.8, 128.8, 127.2, 127.0, 126.7, 126.6, 73.1, 62.5, 62.4, 46.0

$^{11}$B NMR (128 MHz, Acetonitrile-$d_3$)

$\delta$ 11.6

HRMS [DART-MS] (M+H$^+$)

$m/z$ calculated for C$_{19}$H$_{22}$BN$_2$O$_7$S = 433.1240

$m/z$ found = 433.1249

TLC (hexanes:acetone 1:2)

$R_f = 0.46$
(5-methyl-1-(sulfamoyloxy)hexan-2-yl)MIDA boronate

37% yield, white solid

$^1$H NMR (400 MHz, Acetonitrile-$d_3$)

$\delta$ 5.66 (br s, 2H), 4.16 – 4.12 (m, 2H), 3.99 (d, $J = 9.0$ Hz, 1H), 3.95 (d, $J = 9.0$ Hz, 1H), 3.86 (d, $J = 6.5$ Hz, 1H), 3.82 (d, $J = 6.5$ Hz, 1H), 2.95 (s, 3H), 1.60 – 1.44 (m, 2H), 1.44 – 1.19 (m, 4H), 0.89 (dd, $J = 6.6$, 3.3 Hz, 6H)

$^{13}$C NMR (100 MHz, Acetonitrile-$d_3$)

$\delta$ 168.1, 72.1, 62.7, 62.4, 46.1, 37.3, 28.2, 25.0, 22.1, 21.7

$^{11}$B NMR (96 MHz, Acetonitrile-$d_3$)

$\delta$ 12.6

HRMS [DART-MS] (M+Na$^+$)

$m/z$ calculated for C$_{12}$H$_{23}$BN$_2$O$_7$SNa = 372.1248

$m/z$ found = 372.1249

TLC (EtOAc:MeCN 9:1)

$R_f = 0.54$

(1-phenyl-3-(sulfamoyloxy)propan-2-yl)MIDA boronate (4.2.16)

60% yield, white solid

$^1$H NMR (500 MHz, Acetone-$d_6$)

$\delta$ 7.33 – 7.24 (m, 4H), 7.24 – 7.14 (m, 1H), 4.29 (d, $J = 17.2$ Hz, 1H), 4.23 (d, $J = 16.9$ Hz, 1H), 4.09 – 3.99 (m, 4H), 3.21 (s, 3H), 3.02 – 2.97 (m, 1H), 2.67 – 2.58 (m, 1H), 1.90 – 1.69 (m, 1H)

$^{13}$C NMR (126 MHz, Acetone-$d_6$)

$\delta$ 167.8, 167.8, 141.7, 128.8, 128.2, 125.8, 70.9, 62.9, 62.5, 46.1, 33.4

$^{11}$B NMR (128 MHz, Acetone-$d_6$)

$\delta$ 12.6

HRMS [DART-MS] (M+NH$_4^+$)
m/z calculated for C$_{14}$H$_{23}$BN$_3$O$_7$S = 388.1344
m/z found = 388.1330

TLC (DCM:acetone 3:1)
$R_f = 0.52$

(1-(sulfamoyloxy)hexan-2-yl)MIDA boronate (∗4.2.17∗)
41% yield, white solid

$^1$H NMR (400 MHz, Acetone-$d_6$)
$\delta$ 6.64 (s, 2H), 4.32 – 4.20 (m, 4H), 4.09 (m, 2H), 3.23 (s, 3H), 1.69 – 1.57 (m, 1H), 1.55 – 1.39 (m, 3H), 1.39 – 1.25 (m, 3H), 0.92 (t, $J = 7.2$ Hz, 3H)

$^{13}$C NMR (101 MHz, Acetone-$d_6$)
$\delta$ 168.7, 168.7, 72.7, 63.7, 63.3, 46.8, 31.4, 28.4, 23.8, 14.3

$^{11}$B NMR (128 MHz, Acetone-$d_6$)
$\delta$ 12.5

HRMS [ESI-MS] (M+Na$^+$)
m/z calculated for C$_{11}$H$_{21}$BN$_2$NaO$_7$S = 359.1089
m/z found = 359.1089

TLC (hexanes:acetone 3:4)
$R_f = 0.37$

(4-phenyl-1-(sulfamoyloxy)butan-2-yl)MIDA boronate (∗4.2.18∗)
55% yield, white solid

$^1$H NMR (500 MHz, Acetonitrile-$d_3$)
$\delta$ 7.33 – 7.18 (m, 5H), 5.68 (s, 2H), 4.31 – 4.22 (m, 2H), 3.98 (m, 2H), 3.89 – 3.81 (m, 2H), 2.89 (s, 3H), 2.84 – 2.78 (m, 1H), 2.68 – 2.60 (m, 1H), 1.86 – 1.65 (m, 2H), 1.44 – 1.39 (m, 1H)

$^{13}$C NMR (126 MHz, Acetonitrile-$d_3$)
\[ \delta 167.9 \text{ (2C)}, 142.7, 128.4, 128.3, 125.7, 71.9, 62.6, 62.4, 46.0, 34.0, 29.5 \]

\[ ^{11} \text{B NMR (128 MHz, Acetonitrile-} \text{d}_3) \]
\[ \delta 12.3 \]

\[ \text{HRMS [DART-MS] (M+H^+) } \]
\[ m/z \text{ calculated for C}_{15}\text{H}_{22}\text{BN}_2\text{O}_7\text{S} = 385.1240 \]
\[ m/z \text{ found } = 385.1250 \]

\[ \text{TLC (hexanes:acetone 1:2) } \]
\[ R_f = 0.59 \]

### 4.3.5 Characterization Data for α-Boryl Formate Esters

(2-(formyloxy)-1-phenylethyl)MIDA boronate (4.2.10a)

27% yield, white solid

\[ ^1 \text{H NMR (400 MHz, Acetonitrile-} \text{d}_3) \]
\[ \delta 7.96 \text{ (s, 1H)}, 7.42 – 7.31 \text{ (m, 4H)}, 7.31 \text{ (s, 1H)}, 4.66 \text{ (dd, } J = 11.2, 4.6 \text{ Hz, 1H}), 4.45 \text{ (d, } J = 11.1 \text{ Hz, 1H)}, 3.99 \text{ (d, } J = 17.2 \text{ Hz, 1H)}, 3.90 \text{ (d, } J = 5.1 \text{ Hz, 1H)}, 3.86 \text{ (d, } J = 5.4 \text{ Hz, 1H)}, 3.24 \text{ (d, } J = 16.8 \text{ Hz, 1H)}, 2.90 \text{ (s, 3H)}, 2.71 \text{ (dd, } J = 11.1, 4.6 \text{ Hz, 1H}) \]

\[ ^{13} \text{C NMR (126 MHz, Acetonitrile-} \text{d}_3) \]
\[ \delta 167.8, 167.4, 161.3, 141.0, 129.0, 128.5, 125.9, 66.7, 62.3, 62.3, 45.9, 29.8 \]

\[ ^{11} \text{B NMR (128 MHz, Acetonitrile-} \text{d}_3) \]
\[ \delta 11.5 \]

\[ \text{HRMS [DART-MS] (M+NH}_4^+\text{) } \]
\[ m/z \text{ calculated for C}_{14}\text{H}_{20}\text{BN}_2\text{O}_6 = 323.1414 \]
\[ m/z \text{ found } = 323.1421 \]

\[ \text{TLC (hexanes:acetone 1:2) } \]
\[ R_f = 0.44 \]
(2-(formyloxy)-1-(p-tolyl)ethyl)MIDA boronate (4.2.11a)

$^1$H NMR (500 MHz, Acetonitrile-$d_3$)

$\delta$ 7.94 (s, 1H), 7.20 – 7.16 (m, 2H), 7.16 – 7.11 (m, 2H), 4.62 (dd, $J = 11.1, 4.6$ Hz, 1H), 4.40 (t, $J = 11.1$ Hz, 1H), 3.97 (d, $J = 17.2$ Hz, 1H), 3.88 (d, $J = 6.7$ Hz, 1H), 3.84 (d, $J = 7.0$ Hz, 1H), 3.20 (d, $J = 16.8$ Hz, 1H), 2.88 (s, 3H), 2.65 (dd, $J = 11.0, 4.5$ Hz, 1H), 2.31 (s, 3H)

$^{13}$C NMR (126 MHz, Acetonitrile-$d_3$)

$\delta$ 168.0, 167.5, 161.4, 137.7, 135.5, 129.1, 128.9, 66.8, 62.3, 62.2, 45.8, 20.0

$^{11}$B NMR (128 MHz, Acetonitrile-$d_3$)

$\delta$ 11.5

HRMS [DART-MS] (M+NH$_4^+$)

$m/z$ calculated for C$_{15}$H$_{22}$BNO$_6$ = 337.1570

$m/z$ found = 337.1579

TLC (hexanes:acetone 3:4)

$R_f = 0.38$

(1-(4-fluorophenyl)-2-(formyloxy)ethyl)MIDA boronate (4.2.12a)

17% yield, white solid

$^1$H NMR (400 MHz, Acetone-$d_6$)

$\delta$ 8.00 (s, 1H), 7.41 – 7.33 (m, 2H), 7.10 – 7.02 (m, 2H), 4.64 (dd, $J = 11.2, 4.5$ Hz, 1H), 4.51 – 4.41 (m, 1H), 4.29 (d, $J = 17.1$ Hz, 1H), 4.22 – 4.10 (m, 2H), 3.52 (d, $J = 16.8$ Hz, 1H), 3.12 (s, 3H), 2.84 – 2.80 (m, 1H)

$^{13}$C NMR (101 MHz, Acetone-$d_6$)

$\delta$ 168.4, 168.1, 162.1 (d, $J = 482$ Hz), 160.9, 138.2 (d, $J = 3.2$ Hz), 131.6 (d, $J = 7.7$ Hz), 115.8 (d, $J = 20.9$ Hz), 67.6, 63.3, 63.3, 46.8
11B NMR (128 MHz, Acetone-d6)
\[ \delta \ 11.5 \]

19F NMR (282 MHz, Acetone-d6)
\[ \delta \ -119.2 \]

HRMS [DART-MS] (M+NH₄⁺)
\[
m/z \text{ calculated for } C_{14}H_{19}BFN_2O_6 = 341.1320
\]
\[
m/z \text{ found } = 341.1324
\]

TLC (hexanes:acetone 1:2)
\[ R_f = 0.54 \]

4.3.6 General Procedure for the Rh-Catalyzed C-H-Amination of α-Boryl Sulfonamides

To a flame dried flask equipped with a reflux condenser was added boryl sulphonamide (1.0 mmol), MgO (25 equiv), and Rh₂(esp)₂ (2.5 % mol). The flask was evacuated and refilled with N₂ then was added nitrogen sparged iPrOAc (0.1 M). Upon addition of iPrOAc the solution acquires a green colour that may or may not persist throughout the reaction. A solution of PhI(O₂tBu)₂ in iPrOAc (0.1M, 1.25 equiv) was added to the reaction via syringe pump over 1 hour. The syringe was then removed and the flask was warmed to 45 °C for 12-24 hours. Upon complete consumption of starting sulfamate ester, as determined by TLC analysis, the reaction was removed from the heat source and allowed to cool to room temperature. The solvent was then removed in vacuo and subsequently purified via SiO₂ chromatography resulting in a white solid.

(2,2-dioxido-4-phenyl-1,2,3-oxathiazolidin-4-yl)MIDA boronate (4.2.19)

78% yield, white solid

1H NMR (500 MHz, Acetonitrile-d₃)
δ 7.65 – 7.57 (m, 2H), 7.46 – 7.38 (m, 2H), 7.38 – 7.32 (m, 1H), 5.78 (s, 1H), 4.93 – 4.78 (m, 2H), 4.05 – 3.95 (m, 1H), 3.87 (d, J = 17.5 Hz, 1H), 3.78 (d, J = 16.7 Hz, 1H), 2.86 – 2.73 (m, 3H), 2.48 (d, J = 16.7 Hz, 1H)

$^{13}$C NMR (126 MHz, Acetonitrile-$d_3$)
δ 167.5, 166.4, 138.9, 128.6, 127.6, 126.7, 81.5, 63.4, 62.4, 45.5, 29.8

$^{11}$B NMR (128 MHz, Acetonitrile-$d_3$)
δ 9.9

HRMS [DART-MS] (M+NH$_4^+$)
$m/z$ calculated for C$_{13}$H$_{19}$BN$_3$O$_7$S = 372.1036
$m/z$ found = 372.1031

TLC (hexanes:acetone 1:1)
$R_f$ = 0.27

(2,2-dioxido-4-(p-tolyl)-1,2,3-oxathiazolidin-4-yl) MIDA boronate (4.2.21)
73% yield, white solid

$^1$H NMR (500 MHz, Acetonitrile-$d_3$)
δ 7.59 – 7.40 (m, 2H), 7.25 – 7.23 (m, 2H), 5.77 (s, 1H), 4.89 – 4.83 (m, 2H), 4.02 (d, J = 17.6 Hz, 1H), 3.88 (d, J = 17.5 Hz, 1H), 3.80 (d, J = 16.6 Hz, 1H), 2.83(s, 3H), 2.51 (d, J = 16.7 Hz, 1H), 2.36 (s, 3H)

$^{13}$C NMR (126 MHz, Acetonitrile-$d_3$)
δ 167.5, 166.5, 137.6, 135.6, 129.2, 126.6, 81.5, 63.3, 62.4, 45.4, 29.9, 19.9

$^{11}$B NMR (128 MHz, Acetonitrile-$d_3$)
δ 9.9

HRMS [DART-MS] (M+NH$_4^+$)
$m/z$ calculated for C$_{14}$H$_{21}$BN$_3$O$_7$S = 386.1193
$m/z$ found = 386.1206

TLC (hexanes:acetone 1:2)
$R_f$ = 0.67
(4-(4-fluorophenyl)-2,2-dioxido-1,2,3-oxathiazolidin-4-yl)MIDA boronate (4.2.22)

81 %, white solid

$^1$H NMR (500 MHz, Acetone-$d_6$)

$\delta$ 7.80 – 7.61 (m, 2H), 7.31 – 7.07 (m, 2H), 4.98 – 4.79 (m, 2H), 4.42 (d, $J$ = 17.6 Hz, 1H), 4.16 – 4.08 (m, 2H), 3.17 (s, 3H), 2.88 (d, $J$ = 16.8 Hz, 1H)

$^{13}$C NMR (126 MHz, Acetone-$d_6$)

$\delta$ 172.7, 171.4, 167.1 (d, $J$ = 244.7 Hz), 140.8 (d, $J$ = 3.1 Hz), 134.1 (d, $J$ = 8.2 Hz), 120.3 (d, $J$ = 21.5 Hz), 86.4, 68.9, 68.0, 50.8

$^{11}$B NMR (128 MHz, Acetone-$d_6$)

$\delta$ 10.1

$^{19}$F NMR (377 MHz, Acetone-$d_6$)

$\delta$ -117.13

HRMS [DART-MS] (M+NH$_4^+$)

$m/z$ calculated for C$_{13}$H$_{18}$BFN$_3$O$_7$S = 390.0942

$m/z$ found = 390.0943

TLC (hexanes:acetone 1:1)

$R_f$ = 0.37

(4-cyclopropyl-2,2-dioxido-1,2,3-oxathiazolidin-4-yl)MIDA boronate (4.2.23)

59% yield, white solid

$^1$H NMR (500 MHz, Acetonitrile-$d_3$)

$\delta$ 5.33 (s, 1H), 4.54 (d, $J$ = 9.2 Hz, 1H), 4.24 (d, $J$ = 9.2 Hz, 1H), 4.15 – 4.11 (m, 1H), 4.11 – 4.06 (m, 1H), 4.02 – 3.94 (m, 2H), 3.15 – 3.10 (m, 3H), 0.8 – 0.74 (m, 1H), 0.65 – 0.47 (m, 4H)

$^{13}$C NMR (126 MHz, Acetonitrile-$d_3$)
δ 167.5, 166.9, 75.2, 63.3, 62.7, 46.0, 14.0, 1.8

$^{11}$B NMR (128 MHz, Acetonitrile-$d_3$)

δ 10.4

HRMS [ESI-MS] (M+H$^+$)

$m/z$ calculated for C$_{10}$H$_{16}$BN$_2$O$_7$S = 319.0771

$m/z$ found = 319.0766

TLC (hexanes:acetone 1:2)

$R_f$ = 0.35

(4-([1,1'-biphenyl]-4-yl)-2,2-dioxido-1,2,3-oxathiazolidin-4-yl)MIDA boronate (4.2.24)

71% yield, white solid

$^1$H NMR (400 MHz, Acetonitrile-$d_3$)

δ 7.80 – 7.64 (m, 6H), 7.57 – 7.46 (m, 2H), 7.46 – 7.36 (m, 1H), 5.87 (s, 1H), 5.01 – 4.84 (m, 2H), 4.06 (d, $J$ = 17.6 Hz, 1H), 3.93 (d, $J$ = 17.6 Hz, 1H), 3.84 (d, $J$ = 16.7 Hz, 1H), 2.87 (s, 3H), 2.69 (d, $J$ = 16.7 Hz, 1H)

$^{13}$C NMR (126 MHz, Acetonitrile-$d_3$)

δ 167.5, 166.5, 140.1, 139.8, 138.0, 128.9, 127.6, 127.3, 127.0, 126.8, 104.9, 81.4, 63.5, 62.5, 45.6

$^{11}$B NMR (128 MHz, Acetonitrile-$d_3$)

δ 10.0

HRMS [ESI-MS] (M$^+$)

$m/z$ calculated for C$_{19}$H$_{19}$BN$_2$O$_7$S = 430.1116

$m/z$ found = 430.1115

TLC (hexanes:acetone 1:2)

$R_f$ = 0.51
(2-oxo-4-phenyloxazolidin-4-yl)MIDA boronate (4.2.25)
78% yield, white solid

$^1$H NMR (399 MHz, Acetonitrile-$d_3$)

$\delta$ 7.33 – 7.28 (m, 4H), 7.25 – 7.20 (m, 1H), 4.84 (dd, $J = 11.0, 4.3$ Hz, 1H), 4.72 (t, $J =$ 11.1 Hz, 1H), 3.97 (d, $J =$ 17.2 Hz, 1H), 3.90 – 3.80 (m, 2H), 3.17 (d, $J =$ 16.8 Hz, 1H), 2.83 (s, 3H)

$^{11}$B NMR (128 MHz, Acetonitrile-$d_3$)

$\delta$ 11.3

HRMS [ESI-MS] (M+H$^+$)

$m/z$ calculated for C$_{10}$H$_{16}$BN$_2$O$_7$S = 319.0771

$m/z$ found = 319.0766

TLC (hexanes:acetone 1:2)

$R_f$ = 0.28

$anti$-((4S,5R)-2,2-dioxido-4-phenyl-1,2,3-oxathiazinan-5-yl)MIDA boronate (4.2.27)

X-ray quality crystals were grown by slow evaporation from a solution of 4.2.27 in hexanes:acetone

58% yield, white solid
d.r.$\geq$ 20:1 ($anti$:syn)

$^1$H NMR (399 MHz, Acetone-$d_6$)

$\delta$ 7.64 – 7.52 (m, 2H), 7.47 – 7.32 (m, 3H), 6.01 (d, $J =$ 8.7 Hz, 1H), 4.81 – 4.64 (m, 3H), 4.11 (d, $J =$ 17.3 Hz, 1H), 3.98 (d, $J =$ 17.3 Hz, 1H), 3.82 (d, $J =$ 16.5 Hz, 1H), 2.84 (s, 3H), 2.30 (td, $J =$ 11.8, 5.7 Hz, 1H), 2.22 (d, $J =$ 16.5 Hz, 1H)
$^{13}$C NMR (100 MHz, Acetone-$d_6$)
$\delta$ 167.3, 166.5, 139.7, 129.0, 128.7, 128.7, 75.4, 63.0, 62.6, 61.7, 46.1

$^{11}$B NMR (128 MHz, Acetone-$d_6$)
$\delta$ 11.2

IR (thin film)
$\nu$ 3265, 2956, 1766, 1456, 1431, 1367, 1342, 1300, 1247, 1186, 1105, 1058, 1024, 1003, 704

HRMS [DART-MS] (M+NH$_4^+$)
$m/z$ calculated for C$_{14}$H$_{21}$BN$_3$O$_7$S = 386.1193
$m/z$ found = 386.1192

TLC (hexanes:acetone 1:2)
$R_f$ = 0.29

$^1$H NMR (500 MHz, Acetonitrile-$d_3$) + minor contamination with other diastereomer
$\delta$ 7.42 – 7.33 (m, 2H), 7.31 – 7.24 (m, 3H), 5.14 (d, $J$ = 9.2 Hz, 1H), 4.73 – 4.65 (m, 1H), 4.62 – 4.57 (m, 1H), 4.05 (dd, $J$ = 17.3, 1.5 Hz, 2H), 3.98 – 3.90 (m, 1H), 3.87 (dd, $J$ = 17.1, 0.4 Hz, 1H), 3.16 (dd, $J$ = 13.9, 3.9 Hz, 1H), 2.95 (s, 3H), 2.78 (dd, $J$ = 13.9, 10.5 Hz, 1H), 1.57 (ddd, $J$ = 10.5, 8.8, 4.5 Hz, 1H)

$^{13}$C NMR (126 MHz, Acetonitrile-$d_3$)
$\delta$ 167.9, 167.0, 138.5, 129.3, 128.3, 126.4, 74.1, 62.4, 60.0, 46.4, 40.1

$^{11}$B NMR (128 MHz, Acetonitrile-$d_3$)
$\delta$ 11.1

HRMS [DART-MS] (M+NH$_4^+$)
$m/z$ calculated for C$_{14}$H$_{21}$BN$_3$O$_7$S = 386.1193
$m/z$ found = 386.1192

(4S,5S)-4-benzyl-2,2-dioxido-1,2,3-oxathiazinan-5-yl)MIDA boronate (4.2.28b)

38% yield, white solid
d.r. = 4:1 (anti:syn)
TLC (hexanes:acetone 1:3)

R_t = 0.44

\[
\begin{align*}
((4R,5S)-4-benzyl-2,2-dioxido-1,2,3-oxathiazinan-5-yl)\text{MIDA boronate (}4.2.28b\text{)}
\end{align*}
\]

8% yield, white solid

\(^1\)H NMR (500 MHz, Acetonitrile-\(d_3\)) + minor contamination with other diastereomer

\[
\delta 7.34 – 7.30 (m, 3H), 7.27 – 7.17 (m, 2H), 5.23 (d, J = 6.1 \text{ Hz}, 1H), 4.91 – 4.80 (m, 1H), 4.62 – 4.54 (m, 1H), 4.09 – 4.02 (m, 2H), 3.92 (d, J = 17.0 \text{ Hz}, 1H), 3.86 (d, J = 17.3 \text{ Hz}, 1H), 3.79 – 3.71 (m, 1H), 3.52 – 3.47 (m, 1H), 3.03 (s, 3H), 2.87 – 2.81 (m, 1H), 1.93 – 1.89 (m, 1H)
\]

\(^{13}\)C NMR (126 MHz, Acetonitrile-\(d_3\))

\[
\delta 167.6, 167.3, 139.9, 129.4, 128.1, 126.1, 72.5, 62.0, 61.7, 60.2, 45.9, 34.3
\]

\(^{11}\)B NMR (128 MHz, Acetonitrile-\(d_3\))

\[
\delta 11.0
\]

HRMS [ESI-MS] (M+NH\(_4^+\))

\[
m/z \text{ calculated for } C_{15}H_{23}BN_3O_7S = 400.1381
\]

\[
m/z \text{ found } = 400.1379
\]

TLC (hexanes:acetone 1:3)

R_t = 0.41

\[
\begin{align*}
((2,2-dioxido-4-phenethyl-1,2,3-oxathiazolidin-4-yl)\text{MIDA boronate (}4.2.28a\text{)}
\end{align*}
\]

38% yield, white solid

\(^1\)H NMR (500 MHz, Acetonitrile-\(d_3\))

\[
\delta 7.35 – 7.26 (m, 4H), 7.25 – 7.15 (m, 1H), 5.68 (s, 1H), 4.73 – 4.62 (m, 2H), 4.09 – 4.02 (m, 2H), 3.98 (d, J = 10.1 \text{ Hz}, 1H), 3.95 (d, J = 9.9 \text{ Hz}, 1H), 3.17 (s, 3H), 2.86 – 2.71 (m, 2H), 2.08 – 1.98 (m, 2H)
\[ {^{13}\text{C}} \text{NMR} (126 \text{ MHz}, \text{Acetonitrile-}d_3) \]
\[ \delta 167.5, 167.1, 141.8, 128.4, 128.3, 125.9, 73.8, 63.1, 62.6, 45.7, 38.2, 29.5 \]

\[ {^{11}\text{B}} \text{NMR} (128 \text{ MHz}, \text{Acetonitrile-}d_3) \]
\[ \delta 9.9 \]

HRMS [DART-MS] (M+NH\textsubscript{4}\textsuperscript{+})
\[ m/z \text{ calculated for C}_{15}\text{H}_{23}\text{BN}_3\text{O}_7\text{S} = 400.1375 \]
\[ m/z \text{ found} = 400.1375 \]

TLC (hexanes:acetone 1:3)
\[ R_f = 0.63 \]

(4-isopentyl-2,2-dioxido-1,2,3-oxathiazolidin-4-yl)MIDA boronate (4.2.29a)

20% yield, white solid

Product ratio 1.75:1 6 vs 5

\[ {^1\text{H}} \text{NMR} (400 \text{ MHz}, \text{Acetonitrile-}d_3) \]
\[ \delta 4.58 (d, J = 9.5 \text{ Hz}, 1\text{H}), 4.47 (d, J = 9.6 \text{ Hz}, 1\text{H}), 4.03 (d, J = 5.8 \text{ Hz}, 1\text{H}), 3.99 (d, J = 6.0 \text{ Hz}, 1\text{H}), 3.94 (d, J = 2.3 \text{ Hz}, 2\text{H}), 3.90 (d, J = 2.7 \text{ Hz}, 1\text{H}), 3.13 (s, 3\text{H}), 1.83 – 1.64 (m, 2\text{H}), 1.56 – 1.47 (m, 1\text{H}), 1.40 – 1.22 (m, 2\text{H}), 0.92 (d, J = 2.8 \text{ Hz}, 3\text{H}), 0.91 (d, J = 2.8 \text{ Hz}, 3\text{H}) \]

\[ {^{13}\text{C}} \text{NMR} (101 \text{ MHz}, \text{Acetonitrile-}d_3) \]
\[ \delta 167.0, 166.5, 73.3, 62.5, 62.1, 45.1, 33.4, 31.5, 27.8, 21.4, 21.1 \]

\[ {^{11}\text{B}} \text{NMR} (128 \text{ MHz}, \text{Acetonitrile-}d_3) \]
\[ \delta 9.9 \]

HRMS [DART-MS] (M+NH\textsubscript{4}\textsuperscript{+})
\[ m/z \text{ calculated for C}_{12}\text{H}_{25}\text{BN}_3\text{O}_7\text{S} = 366.1506 \]
\[ m/z \text{ found} = 366.1506 \]

TLC (hexanes:acetone 1:2)
\[ R_f = 0.39 \]
anti-4-isobutyl-2,2-dioxido-1,2,3-oxathiazinan-5-yl) MIDA boronate (4.2.29b)

32% combined yield, white solid
d.r. = 2:1 (anti: syn)

anti-diastereomer

$^1$H NMR (500 MHz, Acetonitrile-$d_3$)

δ 5.33 (d, J = 6.2 Hz, 1H), 4.81 – 4.70 (m, 1H), 4.51 (dd, J = 12.3, 3.6 Hz, 1H), 4.02 (d, J = 16.0 Hz, 1H), 3.98 (d, J = 16.0 Hz, 1H), 3.90 (d, J = 17.0 Hz, 1H), 3.83 (d, J = 17.0 Hz, 1H), 3.69 – 3.59 (m, 1H), 2.99 (s, 3H), 1.91 – 1.78 (m, 2H), 1.20 – 1.11 (m, 1H), 0.95 (d, J = 6.8 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H)

$^{13}$C NMR (101 MHz, Acetonitrile-$d_3$)

δ 168.4, 168.3, 73.5, 62.9, 62.5, 56.8, 46.8, 38.0, 25.3, 24.0

$^{11}$B NMR (128 MHz, Acetonitrile-$d_3$)

δ 11.0

HRMS [DART-MS] (M+NH$_4^+$)

$m/z$ calculated for C$_{12}$H$_{21}$BN$_2$O$_7$S = 366.1506
$m/z$ found = 366.1523

TLC (hexanes:acetone 1:2)

$R_f = 0.26$

syn-4-isobutyl-2,2-dioxido-1,2,3-oxathiazinan-5-yl) MIDA boronate (4.2.29b)

syn-diastereomer

$^1$H NMR (500 MHz, Acetonitrile-$d_3$) – 2 conformations, major peaks reported

δ 5.03 – 4.95 (m, 1H), 4.61 – 4.51 (m, 2H), 4.07 – 3.95 (m, 2H), 3.95 – 3.82 (m, 2H), 3.71 – 3.65 (m, 1H), 3.00 (s, 3H), 1.92 – 1.92 (m, 1H), 1.62 – 1.50 (m, 1H), 1.42 – 1.34 (m, 1H), 0.99 – 0.94 (m, 1H), 0.94 – 0.87 (m, 6H)
$^{13}$C NMR (126 MHz, Acetonitrile-$d_3$) – 2 conformations

$\delta$ 167.9, 167.7, 167.6, 167.1, 74.9, 74.5, 62.5, 62.5, 65.6, 55.8, 46.6, 45.8, 43.1 (2C), 28.4, 27.7, 23.7, 22.9, 22.6, 19.9

$^{11}$B NMR (128 MHz, Acetonitrile-$d_3$

$\delta$ 11.2

HRMS [DART-MS] (M+NH$_4^+$)

$m/z$ calculated for C$_{12}$H$_{25}$BN$_3$O$_7$S = 366.1506

$m/z$ found = 366.1523

TLC (hexanes:acetone 1:2)

$R_f$ = 0.18

(4-butyl-2,2-dioxido-1,2,3-oxathiazolidin-4-yl)MIDA boronate (4.2.30a)

17% yield, white solid

$^1$H NMR (400 MHz, Acetonitrile-$d_3$)

$\delta$ 5.42 (s, 1H), 4.62 (d, $J = 9.5$ Hz, 1H), 4.52 (d, $J = 9.5$ Hz, 1H), 4.08 – 4.01 (m, 2H), 3.98 – 3.93 (m, 2H), 3.16 (s, 3H), 1.84 – 1.66 (m, 2H), 1.53 – 1.26 (m, 4H), 0.97 (t, $J = 7.1$ Hz, 3H)

$^{13}$C NMR (101 MHz, Acetonitrile-$d_3$)

$\delta$ 167.0, 166.5, 73.4, 62.5, 62.0, 45.1, 35.2, 24.91, 22.3, 12.7

$^{11}$B NMR (128 MHz, Acetonitrile-$d_3$

$\delta$ 10.0

IR (thin film)

$\nu$ 3277, 3265, 2958, 2874, 1760, 1751, 1627, 1460, 1340, 1296, 1249, 1182, 1151, 1097, 1037, 995, 960, 895, 873

HRMS [DART-MS] (M+H$^+$)

$m/z$ calculated for C$_{11}$H$_{20}$BN$_2$O$_7$S = 335.1078

$m/z$ found = 335.1075

TLC (EtOAc:MeCN 9:1)

$R_f$ = 0.7
(2,2-dioxido-4-propyl-1,2,3-oxathiazinan-5-yl)MIDA boronate (4.2.30b)

29% combined yield, white solid
d.r. = 1:1

Diastereomer A:

$^1$H NMR (400 MHz, Acetonitrile-d$_3$)

$\delta$ 5.35 – 5.28 (m, 1H), 4.80 (dd, $J = 12.2, 11.2$ Hz, 1H), 4.63 – 4.50 (m, 1H), 4.08 – 3.79 (m, 4H) 3.66 – 3.54 (m, 1H), 3.03 (s, 3H), 2.30 – 2.15 (m, 2H), 1.87 – 1.82 (m, 1H), 1.75 – 1.58 (m, 1H), 1.53 – 1.31 (m, 1H), 0.97 (t, $J = 7.3$ Hz, 3H)

$^{13}$C NMR (101 MHz, Acetonitrile-d$_3$)

$\delta$ 167.4, 167.3, 72.4, 61.8, 61.5, 57.7, 45.7, 30.5, 28.6, 19.4, 12.8

$^{11}$B NMR (128 MHz, Acetonitrile-d$_3$)

$\delta$ 11.0

HRMS [ESI-MS] (M+H$^+$)

$m/z$ calculated for C$_{11}$H$_{20}$BN$_2$O$_7$S = 335.1078

$m/z$ found = 335.1075

TLC (EtOAc:MeCN 9:1)

$R_f$ = 0.61

Diastereoisomer B

$^1$H NMR (400 MHz, Acetonitrile-d$_3$)

$\delta$ 4.92 (d, $J = 9.4$ Hz, 1H), 4.62 – 4.46 (m, 2H), 4.04 – 3.91 (m, 2H), 3.93 – 3.77 (m, 2H), 3.60 (qd, $J = 9.6, 3.6$ Hz, 1H), 2.97 (s, 3H), 2.18 (s, 2H), 1.70 – 1.47 (m, 2H), 1.50 – 1.28 (m, 1H), 0.89 (t, $J = 7.3$ Hz, 3H)

$^{13}$C NMR (101 MHz, Acetonitrile-d$_3$)

$\delta$ 167.4, 166.8, 74.0, 62.1, 62.1, 57.7, 46.1, 35.7, 28.4, 18.0, 12.4

$^{11}$B NMR (128 MHz, Acetonitrile-d$_3$)

$\delta$ 11.2

HRMS [ESI-MS] (M+H$^+$)
$m/z$ calculated for $\text{C}_{11}\text{H}_{20}\text{BN}_{2}\text{O}_{7}\text{S} = 335.1078$

$m/z$ found = 335.1075

TLC (EtOAc:MeCN 9:1)

$R_f = 0.54$
4.4 References


The cyclopropyl sulfamate, with an estimated rate constant of $8.8 \times 10^7 \text{M} \cdot \text{s}^{-1}$, was subjected to the boroalkyl C-H amination conditions.


Chapter Five

*Tsuji–Trost Allylic Alkylation of α-Boryl Aldehydes*
5  Tsuji-Trost Allylic Alkylation of α-Boryl Aldehydes

5.1  Introduction

5.1.1  Tsuji–Trost Allylic Alkylation

The development of mild and chemoselective transition-metal catalyzed reactions has played a pivotal role in the synthesis of small molecules and natural products. A myriad of transition metal-catalyzed reactions, such as the Suzuki-Miyaura, Stille, Negishi, and Sonogashira couplings as well as hydrogenations and epoxidations, involve bond formation at \( sp \)- or \( sp^2 \)-centres. In stark contrast, the palladium-catalyzed allylic alkylation reaction ([Pd]-AAA or Tsuji–Trost reaction) involves bond formation at \( sp^3 \)-centres between an electrophilic carbon and a variety of carbon and heteroatom based nucleophiles (Scheme 5.1).

\[
\begin{align*}
R & \quad X \quad + \quad \text{Nu}^- \\
\text{[Pd]} & \rightarrow \\
R & \quad \text{Nu} \quad + \quad X^-
\end{align*}
\]

\textbf{Scheme 5.1.} General [Pd]-catalyzed Tsuji–Trost allylic alkylation reaction

5.1.2  Catalytic Cycle

The mechanism of the Tsuji–Trost allylic alkylation reaction has been thoroughly studied and involves several elementary steps (Figure 5.1):

\textbf{Pd}^0 \rightarrow \textbf{5.1.01}: Starting from the Pd\(^0\)-catalyst complexation to the \( \pi \)-system affords the \( (\eta^2\text{-allyl})\text{palladium}^0 \)-species (\textbf{5.1.01}).

\textbf{5.1.01} \rightarrow \textbf{5.1.02}: Oxidative addition of the Pd\(^0\) to the allyl electrophile generates a neutral \( (\eta^3\text{-allyl})\text{palladium(II)} \)-complex (\textbf{5.1.02}) and then undergoes allyl-isomerization to the most stable W-form.

\textbf{5.1.02} \rightarrow \textbf{5.1.03}: Deligation of the phosphine ligand results in the formation of a cationic species. The cationic-(allyl)palladium(II)-species is more electrophilic and undergoes substitution by nucleophiles. Upon substitution, the [Pd\(^0\)]-catalyst is regenerated.
5.1.03→Pd⁰: Decomplexation of the π-palladium⁰-species (5.1.03) results in the regeneration of the active catalyst and formation of the alkylation product.

![Diagram of the general mechanism of the Tsuji–Trost allylic alkylation reaction]

**Figure 5.1.** General mechanism of the Tsuji–Trost allylic alkylation reaction

### 5.1.3 Development of the [Pd]-Allylic Alkylation Reaction

Based upon the initial report by Trost and coworkers in 1973, the addition of a phosphine-ligand to the catalytic cycle increased the scope of this transformation.⁷ This subsequently led to the development of asymmetric variants, known as the [Pd]-asymmetric allylic alkylation ([Pd]-AAA).⁸,⁹ The design of a [Pd]-AAA reaction benefits from the $sp^3$-bond forming event, which is unique to this class of transition metal catalyzed reactions (*vide supra*). The [Pd]-AAA reaction is able to transform achiral, prochiral or chiral racemic mixtures of starting materials into enantio-enriched products (Scheme 5.2). Additionally, this inherent property of the [Pd]-AAA enables the production of a single enantiomer *via* dynamic kinetic resolution (DKR).¹⁰ This is illustrated in the dynamic kinetic resolution of allyl acetate 5.1.04 with malonate nucleophiles in the presence of the chiral Trost ligand 5.1.06.
**Scheme 5.2.** Desymmetrization of *rac*-allyl-acetate (5.1.04) via Tsuji–Trost asymmetric allylic alkylation with the phenyl-Trost ligand 5.1.06

Besides malonates, other stabilized carbon nucleophiles have been utilized in the preparation of enantioenriched materials via the [Pd]-AAA reaction. The DKR of *meso*-dibenzoate (5.1.07) with the stabilized nitro-sulfone (5.1.08) afforded the intermediate allyl benzoate 5.1.09. The addition product 5.1.09 then participates in a second, intramolecular [Pd]-AAA (Scheme 5.3). The resultant bicyclic-structure 5.1.10 was obtained in greater than 87% yield and 99% ee. Enantiopure 5.1.10 was used to complete the total synthesis of (+)-valeinamine (5.1.11).

**Scheme 5.3.** Desymmetrization of *meso*-dibenzoate 5.1.07 with nitro-sulfone 5.1.08 towards the synthesis of 5.1.11

Unstabilized enolates have a distinctly anionic character and interact with the palladium-ligand complex. The complexation of the enolate to the [Pd]-catalyst results in a reductive elimination (net retention) versus the S_N2-type displacement observed with soft-nucleophiles. Illustrated in Scheme 5.4, the intermolecular [Pd]-AAA of tetralone 5.1.12 results in the formation of the quaternary stereocentre product 5.1.13 in approximately 85% ee. The generation of quaternary...
stereocentres further the synthetic potential of the [Pd]-AAA reaction for asymmetric C-C bond formation.

Scheme 5.4. [Pd]-AAA of unstabilized tetralone enolate to form an all-carbon quaternary α-
stereocentre

Chiral amines are a ubiquitous moiety in natural products and bioactive small molecules, and the
stereoselective carbon-nitrogen bond formation remains an important challenge in synthetic
chemistry.\textsuperscript{14} This has prompted a significant interest in the development of the [Pd]-AAA
reaction with amines.\textsuperscript{15} However, there are numerous challenges including: poly-alkylation,
regioselectivity, and rate of addition vs \(\eta^3-\eta^1-\eta^3\)-isomerization of the Pd\(^\text{II}\)-allyl complex.\textsuperscript{1}
Prediction of the regiochemical outcome of complex allylic substrates is difficult due to
isomerization of the kinetic product to the thermodynamic product.\textsuperscript{16} This challenging
isomerization, which is acid mediated, has limited the application of allyl amines in the [Pd]-AAA reaction.

Scheme 5.5. Kinetic (5.1.14) vs. thermodynamic (5.1.15) product distribution controlled by
added base

Inhibition of the acid-mediated isomerization process of allylic amines is required to access the
kinetic amine product.\textsuperscript{16} The Yudin group has developed a research program to understand and
address the challenges of allylic amine isomerization in the [Pd]-AAA reaction.\textsuperscript{17} A number of
bases were screened in an effort to mitigate the proton-mediated isomerization. DBU was
identified as the optimal base in which to shut down the isomerization and resulted in the highest
levels of the tetrahydroisoquinoline branched product 5.1.14. In contrast, the linear product was favoured with the weaker pyridine base (Scheme 5.5, 5.1.15). Moreover, the solvent and ligand played a key role in this process, where THF and P(OEt)₃ were found to be optimal. This methodology has also been applied to allylation of NH-aziridines (5.1.16) and the ring contraction of cyclic-allyl amines (Scheme 5.6). Mechanistic understanding of the catalytic cycle of the [Pd]-allylic alkylation reaction has provided the necessary insight to rationalize regioselective transformations, such as those presented in this chapter.

Scheme 5.6. A) [Pd]-AAA of aziridines afford the branched product (5.1.16). B) [Pd]-catalyzed ring contraction of cyclic-allylamine to afford the pendant alkene 5.1.17

5.1.4 Regiochemical Considerations of the [Pd]-AAA

Successful application of the [Pd]-AAA with amines is dependent on inhibiting the isomerization of the kinetic-branched amine to the thermodynamic linear allyl amine (Scheme 5.5). The isomerization process relies on the ambivalent characteristics of amines as both nucleophile and leaving group in the same transformation. Interestingly, this duality is not observed in other systems, such as the addition of malonates to the electrophilic [(π-allyl)Pd]⁺-complex.
**Figure 5.2.** A) Symmetrical allylic substrate (5.1.18b) results in a single product (5.1.19). B) Unsymmetrical allylic substrates (5.1.20d) have two different electrophilic sites and can give rise to regioisomers (5.1.21a and 5.1.21b).

The rapid equilibration of the electrophilic PdII-complex and the irreversible C-C bond formation are important factors to consider in a regioselective [Pd]-AAA transformation. Both factors favour an attack at the more sterically accessible carbon, which affords the kinetic product (Figure 5.2).\(^2\) In simple systems, oxidative addition of [Pd⁰] to the allylic substrate results in the symmetrical [(π-allyl)-Pd⁴]-complex (Figure 5.2A, 5.1.18b). The symmetry of the complex (5.1.18b) affords a completely regioselective allylic alkylation reaction (5.1.19). Unsymmetrical allylic substrates, such as 5.1.20a, allow for potential discrimination between the two electrophilic sites, C₁ and C₃ (Figure 5.2B). The formation of the linear product is steric in nature, where R is larger than R'.\(^1\) Exploiting the different steric demands of the π-allyl system is demonstrated in the [Pd]-AAA of cyclohexane 5.1.22 with a variety of nucleophiles to yield a single regioisomer 5.1.23 (Scheme 5.7).\(^3\)

**Scheme 5.7.** Regioselective nucleophile addition to an unsymmetrical alkene
5.1.5 Enolate Chemistry

The development of simple and efficient strategies for the production of complex molecules underpins organic synthesis. One of the most powerful strategies for the introduction of functional groups is the α-substitution of carbonyl compounds. The most common types of functionalization reactions are: aldol, Mannich, Michael, oxidation, and halogenation (Figure 5.3). Recently, the α-functionalization of carbonyl compounds has been accomplished via organocatalysis, photoredox catalysis and Lewis acid catalysis. The discussion within this section will be limited to the generation of discrete enolate chemistry, available methods for the introduction of stereochemistry, and application to [Pd]-AAA.

![Figure 5.3. Selected enolate functionalization reactions](image)

Enolate chemistry remains one of the most versatile and reliable transformations in organic synthesis for the formation of C-X (C-C, C-O, C-N, C-F, C-Cl, C-Br, C-I) bonds. Not only are enolates primed for α-functionalization, but stereochemistry can also be introduced. In order to effectively promote an asymmetric transformation at the α-position, two factors must be controlled: enolate geometry, and re- or si- facial attack. These concepts and the methods to control them are discussed in the following sections.
5.1.6 Enantioselective Enolate Reactions

Enolization of a carbonyl results in the formation of a planar \( \pi \)-system.\(^{28}\) The reactivity of achiral enolates does not favour the approach of the electrophile to either face of the enolate.\(^{30}\) Approach of the electrophile to either face of the \( \pi \)-system is commonly addressed by the use of chiral auxiliaries or chiral ligands (Figure 5.4).\(^{31}\)

![Figure 5.4](image)

**Figure 5.4.** Diastereoselective enolate reactivity by steric blocking

5.1.7 Catalytic Enolate Alkylation

The catalytic reactivity of enolates has received a sustained interest from the chemical community, partially to address the limitations surrounding auxiliary technology.\(^{32}\) This has led to the development of Lewis acid and transition metal complexes to promote the reactivity of carbonyl functionalities.\(^{33}\) Transition metal catalyzed reactions of enolates are known for the synthesis of simple branched products. However, formation of quaternary stereocenters still remains a main challenge.\(^{34}\) Catalytic enolate alkylation via [Pd]-AAA is one method to access the quaternary products.

![Figure 5.5](image)

**Figure 5.5.** [Pd]-AAA approaches to quaternary allylated products 5.1.27
The synthesis of quaternary stereocentres from [Pd\(^0\)]-catalyzed decomposition of alloc esters was independently developed by the groups of Stoltz\(^35\) and Trost.\(^36\) The general mechanism for the [Pd]-AAA of alloc esters \textbf{5.1.24}, is described in Figure 5.5. First, oxidative addition of the [Pd\(^0\)]-catalyst to \textbf{5.1.24} results in the formation of the ketone enolate (\textbf{5.1.25}), electrophilic allyl complex (\textbf{5.1.26}), and one equivalent of CO\(_2\). Alkylation of \textbf{5.1.25} results in quaternary \(\alpha\)-stereocentre formation in high yields and high enantioselectivities (\textbf{5.1.27}). While effective, all substrates must be independently synthesized, which limits the methodology.

![Scheme 5.8. [Pd]-AAA of aldehydes by Tamaru and co-workers\(^37\)](image)

To address the limitations of the alloc-decomposition method put forth by Stoltz\(^35\) and Trost\(^36\), Tamaru found that aldehydes undergo the [Pd]-AA reaction to form quaternary \(\alpha\)-stereocentres (Scheme 5.8).\(^37\) Lewis acid activation was found to promote enolization of the aldehyde substrate, as well as activating the allylic alcohol towards oxidative addition (Scheme 5.8).\(^38\) The \(\alpha\)-allylation reaction of simple aldehydes was found to be generally useful. However, the accessibility of the electrophilic aldehyde resulted in the formation of a number of side products, including the homoallylic alcohol (\textbf{5.1.29}). No example of an enantioselective transformation or downstream application of the quaternary aldehyde products was reported.

![Scheme 5.9. Combination of transition metal, Bronsted acid and organocatalysis for the enantioselective \(\alpha\)-alkylation of aldehydes](image)

Further development in the area of enantioselective aldehyde alkylation with allyl alcohols was reported by List and Jiang.\(^39\) By combining transition metal (Pd(PPh\(_3\))\(_4\)), Brønsted acid (\textbf{5.1.30}),
and enamine catalysis (Ph₂CH₂NH₂) the authors were able to effectively alkylate racemic aldehydes to form all carbon quaternary centres, in up to 94% ee (Scheme 5.9). High enantioselectivities are attributed to the predominant formation of the E-enamine, derived from the condensation of diphenethyl amine and aldehyde. Facial approach is controlled by the large phosphoric acid catalyst. This constitutes an interesting example of multiple catalytic concepts for the α-alkylation of aldehydes.

5.2 Tsuji–Trost Allylic Alkylation of α-Boryl Aldehydes

5.2.1 Proposal

Transformations of α-boryl aldehydes are typically performed at the aldehyde moiety due to the lack of competing reactive sites.⁴⁰ The direct enolization of the aldehyde moiety with strongly basic reagents, such as LDA, is a challenging proposition due to a high number of carbonyl-moieties present within the molecule and unproductive aldehyde addition (Figure 5.6). Given the synthetic potential of α-boryl aldehydes for downstream transformations, we sought to explore the potential for chemoselective enolization of the aldehyde moiety while preserving the valuable C-B bond.

![Figure 5.6. Chemoselectivity issues of α-boryl aldehydes](image)

5.2.2 α-Boryl Aldehyde Enolization

α-MIDA boryl aldehydes, given the multiple sites of reactivity, require mild conditions that will enable preferential aldehyde enolization. A number of Lewis acids in combination with weak amine bases have been shown to promote chemoselective aldehyde enolization. These include strongly Lewis acidic magnesium salts, dialkylboryl halides andtrialkylsilyl (pseudo)halides
with Et₃N or iPr₂NEt.⁴¹ The chemoselective enolization of boryl aldehydes would not only illustrate the ability to engage the one carbonyl moiety, but also the formation of a bis-enolate (Figure 5.7, 5.2.01).

![Figure 5.7. C,O-bis-enolate 5.2.01](image)

To gauge the chemoselective nature of the enolization process of α-boryl aldehydes, we exposed the boryl aldehyde 5.2.02 to triisopropylsilyl triflate (TIPSOTf) and DBU in THF (Scheme 5.10). Upon complete consumption of the aldehyde starting material, the ¹H NMR analysis of the crude reaction mixture resulted in the exclusive formation of the aldehyde silyl enol ether 5.2.03. No products from the enolization of the MIDA ligand were observed. This result provides evidence for the chemoselective αC-H enolization of MIDA boryl aldehydes.

![Scheme 5.10. Formation of Z-silylenol ether 5.2.03](image)

The exclusive formation of the α-MIDA boryl silyl-enol ether (5.2.03) illustrates the enolization potential of boryl aldehydes. The bis-enolate 5.2.01 is proposed to have an increased electron density at the α-position due to the electron rich nature of the sp³-hybridized MIDA boronate. To harness the increased nucleophilicity, we sought to engage the bis-enolate towards the [Pd]-AAA reaction.
5.2.3 Optimization of Reaction Conditions

The allylation of unstabilized enolates can be accomplished with the [Pd]-AAA reaction. As discussed previously, Tamaru and co-workers successfully employed the [Pd]-AAA reaction for the generation of symmetrical quaternary aldehyde products (Scheme 5.8). Taking inspiration from the Tamaru report, the [Pd]-AAA reaction of α-boryl aldehydes was first attempted with the reported literature procedure. Butyl boryl aldehyde (5.2.04) was screened under the reaction conditions and resulted in the recovery of starting material (Table 5.1, entry 1). Subsequent attempts resulted in no reaction. Modification of the reaction conditions found that 5 mol % Pd(PPh₃)₄ in combination with 4Å MS afforded the quaternary allyl boryl aldehyde 5.2.09 in 57% yield as a white solid (entry 5).
Table 5.1. Optimization of Tsuji–Trost Allylation Reaction Conditions

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst (mol %)</th>
<th>allyl alcohol (eq)</th>
<th>Lewis Acid (eq)</th>
<th>additive (eq)</th>
<th>temperature (°C)</th>
<th>time (h)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)$_2$ (10)</td>
<td>allyl alcohol (1.5)</td>
<td>Et$_3$B (2.4)</td>
<td>LiCl (1.0)</td>
<td>50</td>
<td>24</td>
<td>trace</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)$_2$ (10)</td>
<td>allyl alcohol (1.5)</td>
<td>Et$_3$B (3.0)</td>
<td>LiCl (1.0)</td>
<td>50</td>
<td>48</td>
<td>trace</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)$_2$ (10)</td>
<td>allyl alcohol (1.5)</td>
<td>Et$_3$B (2.4)</td>
<td>LiCl (1.0)</td>
<td>50</td>
<td>72</td>
<td>trace</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)$_2$ (10)</td>
<td>allyl alcohol (1.5)</td>
<td>Et$_3$B (2.4)</td>
<td>LiCl (1.0)</td>
<td>reflux</td>
<td>72</td>
<td>trace</td>
</tr>
<tr>
<td>5</td>
<td>Pd(PPh$_3$)$_4$ (5)</td>
<td>allyl alcohol (1.5)</td>
<td>Et$_3$B (3.0)</td>
<td>4Å MS (2.0)</td>
<td>50</td>
<td>48</td>
<td>57</td>
</tr>
</tbody>
</table>

5.2.4 α-Boryl Aldehyde Substrate Scope

Upon optimization of the reaction conditions, a systematic scope of boryl aldehydes was performed in the presence of symmetrical allylic alcohols. Allylation of 5.2.04 was further attempted with 1,3-pentadien-3-ol and 2-methallyl alcohol, both of which provided the linear products 5.2.18 and 5.2.19 respectively (Scheme 5.11). Extension to other boryl aldehydes was met with similar results, with 5.2.05 and 5.2.08 affording slightly higher yields of the allylated products. The difference in reaction performance of aryl vs alkyl boryl aldehydes is attributed to the increased acidity of the αC-H bond due to the electron-withdrawing properties of the aryl ring.

Substitution on the allylic alcohol was also generally tolerated. However cyclohexen-2-ol proved to be ineffective (5.2.13 and 5.2.14). The lack of cyclohexene incorporation is attributed to the increased steric demand of adjacent quaternary and tertiary carbon centres. This behaviour was also observed with cyclohexyl boryl aldehyde 5.2.20.
Next, an investigation into the regioselectivity of the [Pd]-AAA reaction with α-boryl aldehydes was performed (Scheme 5.12). Unsymmetrical allylic alcohols, which possess two distinct reactive sites, were also screened with a small number of boryl aldehydes for the formation of linear or branched products. Upon workup, $^1$H NMR analysis found exclusive formation of the linear regioisomer which is in agreement with literature reports.$^1$
5.2.5 Preliminary Results Concerning the Enantioselective [Pd]-AAA of α-Boryl Aldehydes

In an effort to confirm the ($\pi$-allylPd$^{II}$)-isomerization, cis-pentenol was subjected to allylation conditions with 5.2.05. The crude $^1$H NMR of the allylation reaction showed exclusive formation of the linear trans-product (Scheme 5.12, 5.2.25). These results confirm the ($\pi$-allylPd$^{II}$)-formation and isomerization mechanism is operational for the allylation of α-boryl aldehydes and occurs prior to C-C bond formation. The exclusive formation of the linear product and lack of reactivity with cyclohexyl substrates provides evidence for the C-C bond forming event being under kinetic control.\(^1\)

5.2.5 Preliminary Results Concerning the Enantioselective [Pd]-AAA of α-Boryl Aldehydes

The [Pd]-AAA reaction of carbonyl compounds is a well-known transformation that proceeds in the presence of a number of chiral ligands.\(^1\) To date the most efficient formation of chiral-organoboronic acids or boronates relies on the use of chiral auxiliaries\(^{43}\) or harsh reaction
conditions that are not amenable to highly-functionalized starting materials.\textsuperscript{44} While having successfully demonstrated the racemic [Pd]-AAA reaction with α-boryl aldehydes we have not investigated the asymmetric variant (Figure 5.9). Therefore, we sought to investigate the asymmetric allylation of boryl-aldehydes as an effective entry into the synthesis of enantioenriched quaternary alkyl boryl aldehydes.

![Diagram](image_url)

**Figure 5.9.** Enantioselective Tsuji–Trost allylation of α-boryl aldehydes

At the outset we employed \textbf{5.2.05} as the generic boryl aldehyde for the investigation into the enantioselective [Pd]-AAA. The racemic reaction utilized Pd(PPh\textsubscript{3})\textsubscript{4}, which would result in a substantial background rate and therefore would be detrimental to the formation of enantioenriched products. Therefore, the allylation reaction was screened in the presence several chiral ligands (Figure 5.10) and phosphine-free palladium sources. The initial screening attempt used Pd(OAc)\textsubscript{2} as the palladium source and (S)-BINAP ligand in an effort to induce asymmetric allylation (Table 5.2). This resulted in 100% conversion of starting material over the course of 48 hours and a low enantioinduction of 20% ee. Changing the palladium source to Pd\textsubscript{2}(dba)\textsubscript{3} afforded similar enantio-induction (21% ee). At room temperature, the same reaction afforded reduced induction, presumably due to the higher temperatures required for (S)-BINAP \textbf{(5.2.28)} to displace the dba ligand from the Pd\textsuperscript{II}-centre.\textsuperscript{45}

![Diagram](image_url)

**Figure 5.10.** Chiral phosphine ligands screened in the enantioselective [Pd]-AAA reaction of allyl alcohol with \textbf{5.2.05}
It was presumed that ligand 5.2.28 could not induce high levels of enantioselectivity in the allylation reaction due to the modest steric bulk provided by the substituents on the phosphorous atom and the wide-bite angle.\textsuperscript{46} Turning to the \( \text{Pd}_2(\text{dba})_3/5.1.06 \) metal-ligand combination resulted in a moderate enantio-induction of 44\% ee and a reduced conversion (71\%). These results were comparable to those obtained the larger 5.2.30 ligand. Turning back to \( \text{Pd(OAc)}_2 \) as the palladium source in combination with 5.2.30 afforded the highest level of enantioinduction, albeit a modest 64\% ee over the course of 72 hours. The moderate enantioselectivity obtained in this study led us to forgo further investigations.

**Table 5.2.** Screen of \( \text{Pd}^{II} \)/ligand combinations for the allylation of 5.2.05

<table>
<thead>
<tr>
<th>entry</th>
<th>[Pd]-catalyst</th>
<th>ligand</th>
<th>temperature ((^\circ)C)</th>
<th>conversion (%)\textsuperscript{a}</th>
<th>e.e. (%)\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \text{Pd(OAc)}_2 )</td>
<td>(S)-BINAP (5.2.28)</td>
<td>50</td>
<td>100</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>(MeCN)(_2)\text{PdCl}_2</td>
<td>5.2.28</td>
<td>50</td>
<td>100</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>( \text{Pd}_2\text{dba}_3 )</td>
<td>5.2.28</td>
<td>50</td>
<td>100</td>
<td>21</td>
</tr>
<tr>
<td>4</td>
<td>( \text{Pd}_2\text{dba}_3 )</td>
<td>5.2.28</td>
<td>RT</td>
<td>100</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>( \text{Pd}_2\text{dba}_3 )</td>
<td>5.2.29</td>
<td>RT</td>
<td>100</td>
<td>17</td>
</tr>
<tr>
<td>6</td>
<td>( \text{Pd(PPh}_3)_4 )</td>
<td>none</td>
<td>RT</td>
<td>100</td>
<td>ND</td>
</tr>
<tr>
<td>7</td>
<td>( \text{Pd}_2\text{dba}_3 )</td>
<td>5.1.06</td>
<td>RT</td>
<td>71</td>
<td>44</td>
</tr>
<tr>
<td>8\textsuperscript{c}</td>
<td>( \text{Pd}_2\text{dba}_3 )</td>
<td>5.2.30</td>
<td>RT</td>
<td>64</td>
<td>40</td>
</tr>
<tr>
<td>9\textsuperscript{c}</td>
<td>( \text{Pd(OAc)}_2 )</td>
<td>5.2.30</td>
<td>RT</td>
<td>100</td>
<td>64</td>
</tr>
</tbody>
</table>

\( ^{\text{a}} \) Conversion determined by \(^1\text{H} \) NMR analysis of crude reaction mixture \( ^{\text{b}} \) Enantioselectivity was determined by HPLC-analysis of the crude reaction mixture. \( ^{\text{c}} \) 72 hours HPLC-conditions: Chiralcel OD-H: hexanes/iPrOH (50:50), flow rate = 0.8 ml/min, UV = 220 nm, \( R_T = 21.3 \) min, \( R_T = 23.1 \) min. ND = Not Determined
5.2.6 Transformations of α- Allyl α-Boryl Aldehydes

The products of the Tsuji–Trost allylation reaction are highly functionalized, unsymmetrically substituted aldehydes. The alkyl-boronate functional group provides a handle for the chemoselective introduction of a number of polar moieties. As such, the quaternary α-boryl aldehydes offer the potential for α-hydroxy-aldehyde synthesis via alkyl boronate oxidation with alkaline H₂O₂ (Scheme 5.13).

![Scheme 5.13. Synthesis of α-hydroxy-α-allyl-aldehydes via oxidation of alkyl-boronate](image)

The initial attempts at direct oxidation of the α-boryl aldehyde (5.2.16) with alkaline H₂O₂ failed to produce the desired α-hydroxy aldehyde. The sole product of the reaction was found to be the α-allyl phenyl acetaldehyde (5.2.31). Further attempts at direct oxidation with other oxidants (e.g. Oxone or NaBO₃) only resulted in the formation of 5.2.31 or complete decomposition of the starting material (Scheme 5.14).

![Scheme 5.14. Attempted direct oxidation of α-boryl aldehyde (5.2.16) afford protodeborylated product exclusively (5.2.31)](image)

The formation of 5.2.31 as the sole product can be related to the stabilization of the C-bound boryl enolate afforded by the MIDA ligand (Scheme 5.14).⁴⁷ Hydrolysis of the MIDA-ligand from the boron atom of α-boryl aldehydes removes the stabilizing tridentate complexation (5.2.32) and a rapid C-O-migration affords the O-boron enolate (5.2.33). The O-enolate hydrolyzes to deliver the protodeborylated aldehyde (5.2.31). This process is extremely rapid and therefore no oxidation products are observed (Scheme 5.15).
Scheme 5.15. Proposed mechanism for the formation of protodeborylated aldehydes

Direct oxidation of α-boryl aldehydes to the corresponding α-hydroxy aldehyde cannot be accomplished due to rapid enolization; therefore, it was necessary to protect the aldehyde prior to C-B bond functionalization. Introduction of the 1,3-propanediol protecting group via acid catalysis afforded the α-boryl acetal (5.2.34) in 76% yield. Exposure of 5.2.34 to alkaline oxidation conditions resulted in the acetal protected α-hydroxyaldehyde as a clear oil in 92% yield (Scheme 5.16, 5.2.35).

Scheme 5.16. Protection/oxidation sequence for acetal protected α-hydroxy aldehyde (5.2.35)

In addition to the functionalization of the C-B bond, the aldehyde moiety can undergo chemoselective oxidation (Scheme 19). Exposure of the aldehyde (5.2.16) to Pinnick oxidation conditions produced the corresponding boryl-carboxylic acid (5.2.36) in 82% yield without any observed C-B oxidation products. The carboxylic acid can be further functionalized with TMSCHN₂ in DCM/MeOH to produce the boryl methyl ester (Scheme 5.17, 5.2.37).

Scheme 5.17. Pinnick oxidation of 5.2.16 to afford the carboxylic acid (5.2.36) which is then methylated to afford the methylester (5.2.37)
The utility of the boryl-carboxylic acid (5.2.36) towards coupling reactions, and more notably activation with electrophiles, can create unique intermediates for further transformations (Scheme 5.18). In the presence of DPPA, the carboxylic acid undergoes a Curtius rearrangement to afford the stable quaternary boryl-isocyanate (5.2.38) in good yield. The highly electrophilic carbon centre permits the introduction of amines for the production of quaternary ureas (5.2.40) or acid hydrolysis to afford the boryl-ammonium salt (5.2.39). Both transformations produce highly functionalized boryl-amine motifs from the starting quaternary α-allyl boryl aldehyde.

**Scheme 5.18.** Synthesis of the boryl isocyanate (5.2.38) and subsequent functionalization to boryl ammonium salts (5.2.39) and boryl ureas (5.2.40)

5.2.7 Summary

The chemoselective enolization of boryl aldehydes affords the C,O-bis-enolate intermediate. The bis-enolate was then subjected to the [Pd]-AAA reaction resulting in the formation of quaternary α-allyl alkyl boronates. The [Pd]-AAA reaction of boryl aldehydes results in the formation of quaternary α-allylated products in good yield and as single regioisomers. In a brief asymmetric investigation, the highest enantioselectivity obtained was 64% with the large naphthyl Trost ligand (5.2.30). The quaternary alylated boryl aldehydes can be further elaborated to carboxylic acid, ester and the highly prized boryl amine motif.
5.3 Experimental Details

5.3.1 General Information

Methylene chloride (DCM/CH$_2$Cl$_2$), methanol (MeOH) and triethylamine (Et$_3$N) were distilled from CaH$_2$ under nitrogen. Acetonitrile (MeCN) was distilled from activated 3Å MS under nitrogen. Toluene was purified via solvent purification system. Tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketyl. All other solvents were of reagent grade quality and dried over 4Å MS prior to use and if stated solvents were sparged with a rapid flow of dry N$_2$(g) for at least 30 minutes prior to use. All reagents were purchased from commercial sources and used as received. α-MIDA boryl aldehydes were synthesized according to literature procedures.\textsuperscript{40} Supporting information for compounds 5.2.38 - 5.2.40 is found in He, Z.; Zajdlik, A.; St Denis, J. D.; Assem, N.; Yudin, A. K. \textit{J. Am. Chem. Soc.} \textbf{2012}, \textit{134}, 9926–9929.

**Chromatography:** Flash column chromatography was carried out using Silicycle 230-400 mesh silica gel, or ISCO Teledyne Combiflash R$_f$ 200 Flash system. Thin-layer chromatography (TLC) was performed on Macherey Nagel pre-coated glass backed TLC plates (SIL G/UV254, 0.25 mm) and visualized using a UV lamp (254 nm), KMnO$_4$, I$_2$, or curcumin stain.

**High-Performance Liquid Chromatography:** Enantiomeric excess (ee’s) were determined on an analytical Diacel Chiralcel OJ-H column monitoring at 210 nm and 254 nm. Mobile phase was consisted of HPLC grade methyl tert-butyl ether (MTBE) and acetonitrile (MeCN).

**Nuclear Magnetic Resonance Spectroscopy:** $^1$H, $^{13}$C, and 2D NMR spectra were recorded on Varian Mercury 300 MHz, 400 MHz, 500 MHz, 600 MHz or 700 MHz spectrometers. $^{11}$B NMR were recorded using Bruker 400 MHz spectrometer at 125 MHz and referenced to an external standard of BF$_3$·Et$_2$O ($\delta = 0$ ppm). $^1$H NMR spectra chemical shifts (δ) are reported in parts per million (ppm) referenced to residual protonated solvent peak (CDCl$_3$, δ = 7.26, DMSO-$d_6$, δ = 2.49, acetone-$d_6$ δ = 2.05). Spectral data is reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doubles, dt = doublet of triplets, ddt = doublet of doublet of triplets, dtd = doublet of triplet of doublets, m = multiplet, br = broad), coupling constant (J) in Hertz (Hz), and integration. $^{13}$C NMR spectra chemical shifts (δ) are reported in parts per million (ppm) were referenced to carbon resonances in the NMR solvent (CDCl$_3$, δ = 77.0; DMSO-$d_6$, δ = 39.5, center line, acetone-$d_6$= 206.2 centre line, 29.8). Carbons
exhibiting significant line broadening brought about by boron substituents were not reported (quadrupolar relaxation).

**Infrared Spectroscopy**

IR spectra were recorded on a Perkin-Elmer 100 instrument equipped with a single-reflection diamond/ZnSe ATR accessory. Performed on an NaCl disc as a thin layer.

**Mass Spectroscopy**: High resolution mass spectra were obtained on a VG 70-250S (double focusing) mass spectrometer at 70 eV or on an ABI/Sciex Qstar mass spectrometer with ESI source, MS/MS and accurate mass capabilities.

5.3.2 Synthesis of (Z)-(1-bromo-2-((triisopropylsilyl)oxy)vinyl)MIDA Boronate

To a flame dried round bottom flask equipped with a magnetic stir bar was added bromo aldehyde (10 mmol) followed by THF (10 mL) and subsequently cooled to 0 °C with a water-ice bath. The reaction mixture was stirred for 5 minutes at this temperature and then DBU (3.0 equiv) was added along the wall with precipitate formation upon complete addition. TIPS-OTf (1.25 equiv) was then added dropwise along the wall. The precipitate dissolved upon complete addition of TIPS-OTf. The mixture was stirred at 0 °C for approx. 10 minutes and then removed from ice-water bath and allowed to warm to room temperature for 4 hours at which time TLC analysis showed consumption of starting material. The reaction was then diluted with EtOAc (1 vol) and quenched with sat. NH₄Cl and allowed to stir for 5 minutes. The mixture was transferred to a separatory funnel and the organic layer was removed. The aqueous was extracted 4 x EtOAc. The combined organics were dried with Na₂SO₄ and concentrated in *vacuo*. The yellow residue was then purified via SiO₂ to yield the Z-alkene as a white solid.

![Z-(1-bromo-2-((triisopropylsilyl)oxy)vinyl)MIDA boronate (5.2.03)](image)

(Z)-(1-bromo-2-((triisopropylsilyl)oxy)vinyl)MIDA boronate **5.2.03**

Z:E > 20:1
77% yield, white solid

$^1$H NMR (400 MHz, Acetonitrile-$d_3$)

$\delta$ 7.13 (s, 1H), 4.05 (d, $J = 17.1$ Hz, 2H), 3.91 (d, $J = 17.1$ Hz, 2H), 2.91 (s, 3H), 1.35 – 1.20 (m, 3H), 1.14 (s, 18H)

$^{13}$C NMR (126 MHz, Acetonitrile-$d_3$)

$\delta$ 173.1, 151.8, 67.5, 66.4, 51.7, 22.2, 17.0

$^{11}$B NMR (128 MHz, Acetonitrile-$d_3$)

$\delta$ 9.8

IR (thin film)

$\nu$ 2945, 2893, 2868, 1770, 1627, 1461, 1320, 1288, 1155, 1130, 1033, 822

HRMS [DART-MS] [M+H$^+$]

$m/z$ calculated for C$_{16}$H$_{30}$BBrNO$_5$Si = 434.1196

$m/z$ found = 434.1196

TLC (hexanes:acetone 1:1)

$R_f = 0.52$

5.3.3 General Procedure for the Synthesis of Allylated $\alpha$-MIDA Boryl Aldehydes

To an oven dried Teflon lined vial was added activated powdered 4Å molecular sieves (2 equiv. based on the mass of the boryl aldehyde). The reaction vessel was allowed to cool to room temperature under vacuum. $\alpha$-Boryl aldehyde (1.0 equiv.) and Pd(PPh$_3$)$_4$ (5 mol%) were added sequentially. The mixture was then evacuated for approximately 5 minutes and then back filled with nitrogen. THF (0.2 M) was added, followed by allyl alcohol (2.0 equiv.), Et$_3$N (1.5 equiv.), and Et$_3$B (1.0 M in THF, 3.0 equiv.). The vial was then sealed and then transferred to a preheated 50 °C oil bath (or reaction block). The reaction was stirred for 48 hours at which time the mixture was cooled to room temperature and unreacted Et$_3$B was destroyed with the addition of saturated NaHCO$_3$ solution. The mixture was extracted with EtOAc (3 x), the combined organic layers were washed with brine, dried over anhydrous Na$_2$SO$_4$, and concentrated in vacuo. The resultant residue was purified via silica gel chromatography using hexanes:EtOAc, or hexanes:acetone as eluent. All compounds were isolated as white solids.
2-allyl-2-MIDA boryl hexanaldehyde (5.2.09)

57% yield, white solid

$^1$H NMR (300 MHz, Chloroform-$d$)

$\delta$ 9.75 (s, 1H), 5.96 – 5.82 (m, 1H), 5.14 – 5.05 (m, 2H), 3.81 – 3.68 (m, 4H), 2.97 (s, 3H), 2.65 – 2.45 (m, 2H), 1.97 – 1.79 (m, 2H), 1.44 – 1.15 (m, 4H), 0.88 (t, $J = 6.6, 7.2$Hz, 3H)

$^{13}$C NMR (75 MHz, Chloroform-$d$)

$\delta$ 211.3, 166.4, 166.2, 134.6, 117.6, 76.8, 63.5, 46.5, 33.8, 30.3, 26.7, 23.7, 14.1

$^{11}$B NMR (125 MHz, Chloroform-$d$)

$\delta$ 11.7

HRMS [DART-MS] [M+H$^+$]

$m/z$ calculated for C$_{14}$H$_{23}$BNO$_5$ = 296.1669

found = 296.1676

TLC (hexanes:EtOAc 1:4)

$R_f = 0.27$

(E)-4-phenyl-2-dienyl-2-MIDA boryl aldehyde (5.2.10)

61% yield, white solid

$^1$H NMR (400 MHz, Chloroform-$d$)

$\delta$ 9.82 (s, 1H), 7.37 – 7.26 (m, 3H), 7.26 – 7.14 (m, 2H), 6.39 – 6.29 (m, 1H), 6.23 – 6.17 (m, 1H), 5.84 (dt, $J = 14.9, 7.4$ Hz, 1H), 5.19 (d, $J = 16.8$ Hz, 1H), 5.08 (dd, $J = 10.0$ Hz, 1H), 3.85 – 3.65 (m, 4H), 2.96 (s, 3H), 2.90 – 2.47 (m, 4H), 2.27 – 1.98 (m, 2H)

$^{13}$C NMR (75 MHz, Chloroform-$d$)

$\delta$ 141.4, 128.7, 128.1, 127.4, 65.0, 61.0, 50.3, 32.0, 31.9, 23.7

$^{11}$B NMR (125 MHz, Chloroform-$d$)

$\delta$ 11.5

HRMS [DART-MS] [M+H$^+$]

$m/z$ calculated for C$_{20}$H$_{25}$BNO$_5$ = 370.1825
found = 370.1839

TLC (hexanes:acetone 1:2)

\( R_f = 0.56 \)

4-phenyl-2-methallyl-2-MIDA boryl aldehyde (5.2.11)

65% yield, white solid

\(^1\)H NMR (300 MHz, Chloroform-\(d\))

\[ \delta 9.91 \text{ (s, 1H)}, 7.34 - 7.04 \text{ (m, 5H)}, 4.90 \text{ (m, 2H)}, 3.80 - 3.66 \text{ (m, 4H)}, 3.07 \text{ (s, 3H)}, 2.97 - 2.54 \text{ (m, 3H)}, 2.19 - 2.09 \text{ (m, 1H)}, 2.04 - 1.81 \text{ (m, 1H)}, 1.68 \text{ (s, 3H)} \]

\(^{13}\)C NMR (100 MHz, Chloroform-\(d\))

\[ \delta 212.2, 166.7, 166.5, 142.8, 142.4, 128.6, 128.5, 126.1, 115.7, 63.5, 63.2, 46.6, 38.7, 33.3, 31.5, 24.3 \]

\(^{11}\)B NMR (125 MHz, Chloroform-\(d\))

\[ \delta 11.6 \]

HRMS [ESI-MS] [M+H\(^+\)]

\[ m/z \text{ calculated for C}_{19}\text{H}_{25}\text{BNO}_{5} = 358.1814 \]

\[ \text{found} = 358.1820 \]

TLC (hexanes:EtOAc 1:6)

\( R_f = 0.26 \)

4-phenyl-2-allyl-2-MIDA boryl aldehyde (5.2.12)

60% yield, white solid

\(^1\)H NMR (300 MHz, Chloroform-\(d\))

\[ \delta 9.81 \text{ (s, 1H)}, 7.28 \text{ (m, 2H)}, 7.20 \text{ (m, 3H)}, 5.98 \text{ (m, 1H)}, 5.24 - 5.15 \text{ (m, 2H)}, 3.73 \text{ (m, 4H)}, 3.00 \text{ (s, 3H)}, 2.80 - 2.51 \text{ (m, 4H)}, 2.25 - 2.06 \text{ (m, 2H)} \]

\(^{13}\)C NMR (75 MHz, Chloroform-\(d\))

\[ \delta 210.5, 165.9, 165.8, 142.1, 134.1, 128.4, 128.3, 126.0, 117.9, 63.5, 46.3, 33.8, 32.7, 30.7, 22.2, 14.3 \]

\(^{11}\)B NMR (125 MHz, Chloroform-\(d\))
δ 10.9
IR (thin film)
ν 3026, 3007, 2956, 2926, 1768, 1701, 1637, 1338, 1292, 1051, 1028, 993
TLC (hexanes:acetone 1:2)
Rf = 0.56

2-methallyl-2-MIDA boryl phenyl acetaldehyde (5.2.15)
70% yield, white solid

1H NMR (300 MHz, Chloroform-d)
δ 10.05 (s, 1H), 7.59 (m, 2H), 7.30 (m, 2H), 7.20 (t, J = 7.2Hz, 1H), 4.72 (s, 1H), 4.54 (s, 1H), 3.71 (m, 3H), 3.16 (m, 3H), 2.62 (s, 3H), 1.45 (s, 3H)

13C NMR (75 MHz, Chloroform-d)
δ 211.3, 166.5, 166.4, 142.1, 139.3, 128.9, 127.8, 126.7, 114.7, 64.1, 64.0, 47.4, 42.0, 24.3

B NMR (125 MHz, Chloroform-d)
δ 11.0

HRMS [DART-MS] [M+NH4]+
m/z calculated for C17H24BN2O5 = 347.1778
found = 347.1786

TLC (EtOAc)
Rf = 0.48

2-allyl-2-phenyl-2-MIDA boryl aldehyde (5.2.16)
78% yield, white solid

1H NMR (300 MHz, Chloroform-d)
δ 9.92 (s, 1H), 7.34 (m, 4H), 7.21 (1H), 5.63 (m, 1H), 5.15 (d, J = 15.6Hz, 1H), 5.02 (d, J = 9.3Hz, 1H), 4.04 (d, J = 15.9Hz, 1H), 3.75 (m, 2H), 3.39 (d, J = 16.8Hz, 1H), 3.12 (m, 2H), 2.56 (s, 3H)

13C NMR (75 MHz, Chloroform-d)
\( \delta 211.3, 166.9, 166.8, 139.2, 133.8, 129.2, 127.6, 126.8, 118.7, 64.2, 64.1, 47.9, 39.4 \)

\(^{11}\)B NMR (125 MHz, Chloroform-\(d\))

\( \delta 11.2 \)

HRMS [ESI-MS] [M+H\(^+\)]

\( m/z \) calculated for \( C_{16}H_{19}BNO_5 \) = 316.1350

found = 316.1346

TLC (hexanes:EtOAc 1:6)

\( R_f = 0.33 \)

HPLC (Chiralcel OD-H, hexanes:iPrOH)

Gradient = isocratic 50:50 Flow rate = 0.8 mL/min UV-monitor = 220 nm

\( R_{T1} = 21.3 \) min

\( R_{T2} = 23.1 \) min

2-(\( E \))-diaryl-2-phenyl-2-MIDA boryl aldehyde (5.2.17)

70% yield, white solid

\(^1\)H NMR (300 MHz, Chloroform-\(d\))
$\delta$ 9.81 (s, 1H), 7.37 – 7.29 (m, 4H), 7.26 – 7.21 (m, 1H), 6.18 – 6.06 (m, 2H), 5.48 – 5.38 (m, 1H), 5.02 - 4.97 (m, 1H), 4.88 – 4.85 (m, 1H), 3.94 (d, $J = 15.4$ Hz, 1H), 3.82 – 3.70 (m, 2H), 3.32 (d, $J = 16.5$ Hz, 1H), 3.14 – 2.97 (m, 2H), 2.48 (s, 3H)

$^{13}$C NMR (100 MHz, Chloroform-$d$)

$\delta$ 211.2, 167.1, 166.9, 139.1, 136.7, 134.7, 129.6, 129.2, 127.6, 126.9, 116.5, 64.2, 64.1, 47.9, 38.2

$^{11}$B NMR (125 MHz, Chloroform-$d$)

$\delta$ 11.4

IR (thin film)

$\nu$ 3088, 3057, 3010, 2958, 1768, 1705, 1643, 1627, 1448, 1340, 1290, 1039, 993

HRMS [DART-MS] [M+H$^+$]

$m/z$ calculated for C$_{18}$H$_{21}$BNO$_5$ = 342.1526
found = 342.1520

TLC (hexanes:EtOAc 1:3)

$R_f$ = 0.40

(E)-2-dienyl-2-MIDA boryl hexanaldehyde (5.2.18)

57% yield, white solid

$^1$H NMR (300 MHz, Chloroform-$d$)

$\delta$ 9.76 (s, 1H), 6.28 – 6.19 (m, 1H), 6.08 – 6.01 (m, 1H), 5.72 – 5.64 (m, 1H), 5.07 – 4.93 (m, 2H), 3.88-3.48 (m, 4H), 2.98 (s, 3H), 2.65-2.24 (m, 2H), 1.88 – 1.72 (m, 2H), 1.33 – 1.11 (m, 4H), 0.89 (t, $J = 6.9$ Hz, 3H)

$^{13}$C NMR (100 MHz, Chloroform-$d$)

$\delta$ 210.9, 166.4, 166.2, 136.5, 133.5, 130.2, 116.2, 63.3, 46.3, 32.3, 30.2, 29.7, 26.5, 23.5, 13.9

$^{11}$B NMR (125 MHz, Chloroform-$d$)

$\delta$ 11.7

HRMS [DART-MS] [M+H$^+$]

$m/z$ calculated for C$_{16}$H$_{25}$BNO$_5$ = 322.1825
found = 322.1825

TLC (hexanes:EtOAc 1:7)

$R_f$ = 0.22
2-methallyl-2-MIDA boryl hexanaldehyde (5.2.19)

48% yield, white solid

$^1$H NMR (400 MHz, Chloroform-$d$)

$\delta$ 9.88 (s, 1H), 4.85 (s, 1H), 4.77 (s, 1H), 3.78 (m, 4H), 3.08 (s, 3H), 2.81 (d, $J = 14.4$ Hz, 1H), 2.58 (d, $J = 14.4$ Hz, 1H), 1.90 – 1.82 (m, 1H), 1.69 (m, 1H), 1.67 (s, 3H), 1.44 (m, 4H), 0.90 (t, $J = 7.2$ Hz, 3H)

$^{13}$C NMR (100 MHz, Chloroform-$d$)

$\delta$ 212.9, 166.4, 166.2, 142.5, 115.4, 63.6, 63.4, 46.6, 38.7, 30.7, 27.2, 24.3, 24.0, 14.1

$^{11}$B NMR (125 MHz, Chloroform-$d$)

$\delta$ 11.3

HRMS [DART-MS] [M+H$^+$]

$m/z$ calculated for C$_{15}$H$_{25}$BNO$_5$ = 310.1825

found = 310.1823

TLC (hexanes:acetone 1:2)

$R_f$ = 0.56

2-methallyl-2-tolyl-2-MIDA boryl aldehyde (5.2.21)

86% yield, white solid

$^1$H NMR (400 MHz, Chloroform-$d$)

$\delta$ 10.02 (s, 1H), 7.46 (d, $J = 8.0$ Hz, 2H), 7.10 – 7.08 (m, 2H), 4.71 (s, 1H), 4.53 (s, 1H), 3.76 – 3.70 (m, 3H), 3.19 – 3.07 (m, 3H), 2.63 (s, 3H), 2.28 (s, 3H), 1.45 (s, 3H)

$^{13}$C NMR (100 MHz, Chloroform-$d$)

$\delta$ 211.1, 166.9, 166.8, 144.2, 136.3, 135.9, 129.6, 114.5, 64.0, 63.9, 47.2, 41.8, 24.4, 21.1

HRMS [DART-MS] [M+H$^+$]

$m/z$ calculated for C$_{18}$H$_{23}$BNO$_5$ = 344.1669

found = 344.1677

TLC (EtOAc)
R_f = 0.45

2-allyl-2-tolyl-2-MIDA boryl aldehyde (5.2.22)
72% yield, white solid

^1^H NMR (300 MHz, Chloroform-^d^)
δ 9.94 (s, 1H), 7.28 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 7.8 Hz, 2H), 5.63 (m, 1H), 5.64 – 5.54 (m, 1H), 5.05 (d, J = 9.3 Hz, 1H), 4.05 (d, J = 16.2 Hz, 1H), 3.74 – 3.70 (m, 2H), 3.41 (d, J = 16.8 Hz, 1H), 5.63 – 5.54 (m, 1H), 5.05 (d, J = 9.3 Hz, 1H), 4.05 (d, J = 16.2 Hz, 1H), 3.74 – 3.70 (m, 2H), 3.41 (d, J = 16.8 Hz, 1H), 3.12 (m, 2H), 2.62 (s, 3H), 2.34 (s, 3H)

^13^C NMR (100 MHz, Chloroform-^d^)
δ 211.1, 166.7, 166.5, 136.2, 135.6, 133.9, 133.8, 129.6, 127.3, 118.4, 64.0, 63.9, 47.7, 39.1, 20.8

^11^B NMR (125 MHz, Chloroform-^d^)
δ 11.1

HRMS [ESI-MS] [M+H^+] 
m/z calculated for C_{17}H_{21}BNO_5 = 330.1512
found = 330.1505

TLC (hexanes:EtOAc 1:4)
R_f = 0.37

(E)-2-cinnamyl-2-phenyl 2-MIDA boryl aldehyde (5.2.23)
78% yield, white solid

^1^H NMR (300 MHz, Chloroform-^d^)
δ 9.92 (s, 1H), 7.50-7.22 (m, 5H), 7.21-7.05 (m, 5H), 6.42 (d, J = 15.7 Hz, 1H), 5.89 (m, 1H), 3.96 (d, J = 15.7 Hz, 1H), 3.70 – 3.64 (m, 2H), 3.31 (d, J = 16.5 Hz, 1H), 3.22 – 3.19 (m, 2H), 2.49 (s, 3H)

^13^C NMR (100 MHz, Chloroform-^d^)
δ 211.2, 166.7, 166.4, 139.0, 137.0, 133.4, 132.1, 129.1, 128.5, 128.4, 127.4, 126.7, 126.1, 125.4, 64.0, 38.6, 29.3

^11^B NMR (125 MHz, Chloroform-^d^)
\[ \delta 11.7 \]

HRMS [DART-MS] [M+H\(^+\)]

\[ m/z \text{ calculated for } C_{22}H_{23}BNO_5 = 392.1669 \]

found = 392.1659

TLC (hexanes:acetone 1:1)

\[ R_f = 0.47 \]

\((E)-2\text{-butenyl-2-MIDA phenyl acetaldehyde (5.2.24)}\)

77% yield, white solid

\(^1\)H NMR (300 MHz, Chloroform-\(d\))

\[ \delta 9.84 \text{ (s, 1H), 7.33-7.10 \text{ (m, 5H), 5.61-5.49 \text{ (m, 1H), 5.2-5.12 \text{ (m, 1H), 3.94 \text{ (d, J = 16.0 Hz, 1H), 3.70-3.60 \text{ (m, 2H), 3.29 \text{ (d, J = 16.7 Hz, 1H), 3.03-2.94 \text{ (m, 2H), 2.50 \text{ (s, 3H), 1.55 – 1.53 \text{ (m, 3H)}}}}}}\]

\(^13\)C NMR (75 MHz, Chloroform-\(d\))

\[ \delta 211.8, 166.9, 166.6, 139.4, 129.4, 129.1, 127.7, 126.7, 126.0, 64.2, 64.1, 47.8, 38.2, 18.1 \]

\(^11\)B NMR (125 MHz, Chloroform-\(d\))

\[ \delta 11.4 \]

HRMS [ESI-MS] [M+H\(^+\)]

\[ m/z \text{ calculated for } C_{17}H_{21}BNO_5 = 330.1507 \]

found = 330.1520

TLC (hexanes:acetone 1:2)

\[ R_f = 0.56 \]

\((E)-2\text{-pentenyl-2-MIDA phenyl acetaldehyde (5.2.25)}\)

79% yield, white solid

\(^1\)H NMR (400 MHz, Acetone-\(d_6\)) + 5% impurity

\[ \delta 10.01 \text{ (s, 1H), 7.59-7.43 \text{ (m, 2H), 7.43-7.32 \text{ (m, 2H), 7.32-7.23 \text{ (m, 1H), 5.52 – 5.44 \text{ (m, 1H), 5.34-5.16 \text{ (m, 1H), 4.15 \text{ (d, J = 17.2 Hz, 1H), 4.09 \text{ (d, J = 16.7 Hz, 1H), 3.78 \text{ (d, J =}}}}}}\]
16.7 Hz, 1H), 3.61 (d, J = 17.2 Hz, 1H), 3.15-2.97 (m, 2H), 2.82 (s, 3H), 1.95-1.81 (m, 2H), 0.86 (t, J = 7.5 Hz, 3H)

$^{13}$C NMR (100 MHz, Acetone-$d_6$)

$\delta$ 209.2, 168.3, 167.9, 140.5, 136.1, 129.2, 129.0, 126.8, 125.6, 64.2, 47.8, 37.7, 27.4, 24.3, 14.2

$^{11}$B NMR (125 MHz, Acetone-$d_6$)

$\delta$ 11.0

HRMS [ESI-MS] [M+Na$^+$]

$m/z$ calculated for C$_{18}$H$_{22}$BNO$_5$Na = 366.1483

found = 366.1491

TLC (hexanes:acetone 1:1)

$R_f$ = 0.46

(E)-2-cinnamyl-2-MIDA boryl hexanaldehyde (5.2.26)

76% yield, white solid

$^{1}$H NMR (400 MHz, Acetone-$d_6$)

$\delta$ 9.84 (s, 1H), 7.39 – 7.35 (m, 2H), 7.29 (m, 2H), 7.24 – 7.13 (m, 1H), 6.53 (d, J = 15.8, 1H), 6.39 – 6.31 (m, 1H), 4.28 (d, J = 8.0 Hz, 1H), 4.24 (d, J = 7.8 Hz, 1H), 4.06 (d, J = 9.2 Hz, 1H), 4.01 (d, J = 9.4 Hz, 1H), 3.15 (s, 3H), 2.81 – 2.74 (m, 1H), 2.7 – 2.64 (m, 1H), 2.00 – 1.82 (m, 2H), 1.53 – 1.40 (m, 1H), 1.35 – 1.24 (m, 3H), 0.88 (t, J = 7.1 Hz, 3H)

$^{13}$C NMR (100 MHz, Acetone-$d_6$)

$\delta$ 209.5, 168.1, 167.9, 138.7, 132.6, 129.3, 128.2, 127.7, 126.9, 64.0, 63.8, 47.0, 33.2, 27.4, 24.3, 14.2

$^{11}$B NMR (125 MHz, Acetone-$d_6$)

$\delta$ 11.0

HRMS [DART-MS] [M+H$^+$]

$m/z$ calculated for C$_{20}$H$_{27}$BNO$_5$ = 372.1982

found = 372.1976

TLC (hexanes:acetone 1:1)

$R_f$ = 0.44
(E)-4-phenyl-2-cinnamyl-2-MIDA boryl aldehyde (5.2.27)

72% yield, white solid

$^1$H NMR (400 MHz, Acetone-$d_6$)

$\delta$ 9.92 (s, 1H), 7.45 – 7.39 (m, 2H), 7.31 (m, 2H), 7.25 – 7.17 (m, 5H), 7.15 – 7.09 (m, 1H), 6.70 – 6.61 (m, 1H), 6.48 – 6.40 (m, 1H), 4.29 (m, 2H), 4.09 (d, $J = 10.1$ Hz, 1H), 4.05 (d, $J = 10.1$ Hz, 1H), 3.19 (s, 3H), 2.95 (m, 1H), 2.85 – 2.76 (m, 2H), 2.65 – 2.57 (m, 1H), 2.23 – 2.09 (m, 2H)

$^{13}$C NMR (75 MHz, Chloroform-$d$)

$\delta$ 209.2, 168.1, 167.9, 143.8, 138.6, 133.1, 132.7, 129.2, 129.1 128.0, 126.9, 126.5, 64.0, 63.8, 47.1, 33.6, 33.3, 31.6, 29.7

$^{11}$B NMR (125 MHz, Chloroform-$d$)

$\delta$ 10.9

HRMS [DART-MS] [M+H$^+$]

$m/z$ calculated for C$_{24}$H$_{27}$BNO$_5$ = 420.1982

found = 420.1987

TLC (hexanes:acetone 1:2)

$R_f = 0.42$

5.3.4 Synthesis of 1,3-Propyl $\alpha$-Allyl-$\alpha$-MIDA Boryl Phenyl Acetal (5.2.34)

To a stirring flask containing $\alpha$-allyl-$\alpha$-MIDA-$\alpha$-phenyl boryl aldehyde (0.150 g, 0.41 mmol, 1.0 equiv) and THF (12 ml), was added MgSO$_4$ (5.0 g, 41.6 mmol, 100 equiv), TsOH·H$_2$O (0.021 g, 0.1 mmol, 0.25 equiv.) and anhydrous 1,3 propanediol (0.312 g, 0.3 ml, 4.1 mmol, 10 equiv). The mixture was stirred for 72 hours at room temperature at which time the solvent was removed under reduced pressure. The residue was treated with standard workup procedures and purified via column chromatography to yield 5.2.34 as a white solid.
1,3-propyl α-allyl-α-MIDA boryl phenyl acetal (5.2.34)

76% yield + 10% impurity white solid

$^1$H NMR (300 MHz, Acetonitrile-$d_3$) + 10 % impurity

$\delta$ 7.69 – 7.62 (m, 2H), 7.30 – 7.22 (m, 2H), 7.17 – 7.10 (m, 1H), 5.77 – 5.63 (m, 1H), 5.00 – 4.85 (m, 2H), 4.85 (s, 1H), 4.22 – 4.08 (m, 2H), 3.96 – 3.64 (m, 4H), 3.59 (d, $J = 17.4$ Hz, 1H), 2.91 – 2.82 (m, 1H), 2.72 – 2.64 (m, 1H), 2.24 (s, 3H), 2.16 – 1.99 (m, 1H), 1.46 – 1.39 (m, 1H)

$^{13}$C NMR (101 MHz, Acetonitrile-$d_3$)

$\delta$ 169.4, 168.5, 143.9, 136.9, 129.6, 128.2, 125.7, 116.6, 106.8, 67.8, 67.3, 64.7, 64.4, 47.9, 26.2

$^{11}$B NMR (128 MHz, Acetonitrile-$d_3$)

$\delta$ 12.0

HRMS [DART-MS] [M+H$^+$]

$m/z$ calculated for C$_{19}$H$_{25}$BNO$_6$ = 374.1774

found = 374.1776

TLC (hexanes:EtOAc 1:4)

$R_f$ = 0.24

5.3.5 Synthesis of 1,3-Propyl-α-Hydroxy-α-Allyl-α-Phenyl Acetal (5.2.35)

A flask containing 1,3-propyl α-allyl-α-MIDA boryl phenyl acetal (0.124 g, 0.33 mmol, 1.0 equiv.) and THF (5 mL) was cooled to 0 °C in an ice bath. To the stirring mixture was added dropwise 1.0 M NaOH (0.165 ml, 1.65 mmol, 5 equiv.) followed by the dropwise addition of 30% H$_2$O$_2$ (0.96 mL, 3.3 mmol, 10 equiv.) the mixture was stirred overnight warming to room temperature at which point TLC examination of the reaction showed consumption of the starting material. The reaction mixture was diluted with 5 mL H$_2$O, extracted with EtOAc (3 x 10 mL), dried with anhydrous Na$_2$SO$_4$ and concentrated in vacuo. The residue was purified via silica gel chromatography to yield the benzylic alcohol as a clear oil.
α-allyl-β-1,3-dioxanyl-benzyl alcohol (5.2.35)

92% yield, clear oil

$^1$H NMR (300 MHz, Chloroform-$d$)

$\delta$ 7.46 – 7.40 (m, 1H), 7.30 – 7.23 (m, 1H), 7.21 – 7.15 (m, 3H), 5.67 – 5.53 (m, 1H), 5.04 – 4.89 (m, 2H), 4.56 (s, 1H), 4.20 – 4.11 (m, 2H), 3.81 – 3.70 (m, 2H), 2.76 (s, 1H), 2.72 (t, $J = 1.3$ Hz, 1H), 2.70 (t, $J = 1.3$ Hz, 1H), 2.12 – 1.93 (m, 1H), 1.36 – 1.30 (m 1H)

$^{13}$C NMR (100 MHz, Chloroform-$d$)

$\delta$ 151.1, 133.2, 127.7, 126.8, 126.1, 118.3, 104.4, 67.1, 67.1, 41.5, 25.6

HRMS [DART-MS] (M+Na$^+$)

$m/z$ calculated for C$_{14}$H$_{18}$O$_3$Na = 257.1599

found = 257.1598

TLC (hexanes:EtOAc 1:1)

$R_f$ = 0.65

5.3.6 Synthesis of α-Allyl-α-MIDA Boryl Phenyl Acetic Acid (5.2.36)

To a mixture of $t$-BuOH (5mL) and cyclohexene (0.431 ml, 4.2 mmol, 12 equiv), was added α-allyl-α-MIDA boryl phenyl acetaldehyde (0.100 g, 0.36 mmol), NaH$_2$PO$_4$ (0.120 g, 0.87 mmol, 2.4 equiv) and NaClO$_2$ (0.099 g, 0.87 mmol 2.4 equiv.) dissolved in H$_2$O (5 ml). This mixture was warmed to 40 °C overnight and subsequently allowed to cool to room temperature. Brine was then added followed by extraction with EtOAc (3 x 15mL). The combined organic extracts were concentrated in vacuo. To the resulting residue was added benzene (5 x 15 mL) and $t$BuOH were azeotrope off. The crude residue was sufficiently pure for subsequent transformations, but the purity could be further increased by silica gel column chromatography using (EtOAc:MeOH:DCM:AcOH: 45:45:10:0.1) as eluent.
α-allyl-α-MIDA boryl phenyl acetic acid (5.2.36)
82% yield + 5% impurity, white solid

$^1$H NMR (399 MHz, Chloroform-$d$) + 5% impurity

$\delta$ 7.43 – 7.33 (m, 2H), 7.33 – 7.23 (m, 2H), 7.22 – 7.11 (m, 1H), 5.81 – 5.71 (m, 1H),
4.94 (d, $J = 17.1$, 1H), 4.87 – 4.85 (m, 1H), 4.16 – 3.82 (m, 3H), 3.61 – 3.59 (m, 1H), 3.02 –
2.97 (m, 1H), 2.87 – 2.82 (m, 1H), 2.62 (s, 3H)

$^{13}$C NMR (100 MHz, Chloroform-$d$)

$\delta$ 180.6, 168.8, 168.2, 140.4, 135.7, 129.0, 127.6, 126.6, 117.7, 76.9, 65.0, 64.4, 48.6, 41.2

$^{11}$B NMR (125 MHz, Chloroform-$d$)

$\delta$ 11.5

HRMS [ESI-MS] [M+H$^+$]

$m/z$ calculated for C$_{16}$H$_{19}$BNO$_6$ = 332.1299

found = 332.1304

TLC (DCM:EtOAc:MeOH:AcOH 45:45:10:0.1)

$R_f$ = 0.45

5.3.7 Synthesis of Methyl α-Allyl-α-MIDA Boryl Phenyl Acetate

To a flask containing α-allyl-α-MIDA boryl phenyl acetic acid (0.082 g, 0.24 mmol) dissolved
in a 1:1 mixture of MeOH:DCM (2 ml) was added TMSCHN$_2$ (0.056 g, 0.48 mmol). This mixture
was allowed to stir at room temperature for 2 hours at which point TLC examination confirmed
that the reaction was complete. The solvent was removed in vacuo and residue purified via silica
gel chromatography to yield a white solid.

Methyl 2-allyl-2-MIDA boryl phenyl acetate (5.2.37)

76% yield, white solid

$^1$H NMR (400 MHz, Acetone-$d_6$)

$\delta$ 7.32 – 7.24 (m, 4H), 7.19 – 7.15 (m, 1H), 5.84 – 5.74 (m, 1H), 4.90 – 4.84 (m, 1H),
4.79 – 4.75 (m, 1H), 4.33 (d, $J = 17.5$ Hz, 1H), 4.21 – 4.03 (m, 2H), 3.92 (d, $J = 17.5$ Hz,
1H), 3.79 (s, 3H), 2.99 (m, 1H), 2.85 – 2.71 (m, 1H), 2.62 (s, 3H)

$^{13}$C NMR (100 MHz, Acetone-$d_6$)
\[ \delta 177.7, 168.7, 168.0, 142.9, 137.3, 129.1, 128.4, 126.6, 116.5, 65.2, 64.8, 51.9, 48.7 \]

\[ ^{11} \text{B} \text{ NMR (125 MHz, Chloroform-} d \text{)} \]
\[ \delta 11.5 \]

HRMS [ESI-MS] [M\(^+\)]
\[ m/\text{z calculated for C}_{17}\text{H}_{20}\text{BNO}_6 = 345.1498 \]
\[ \text{found} = 345.1494 \]

TLC (hexanes:EtOAc 1:2)
\[ R_f = 0.56 \]
5.4 References


The bicyclic MIDA boronate moiety also places substantial steric demand on the α-position


Copyright Acknowledgements

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Chapter Six

α-Boryl Enamines and Enamides and their Applications towards Heterocycle Synthesis
6 α-Boryl Enamines and Enamides

6.1 Introduction

Pioneered by Stork in the 1950’s, enamines have proven to be useful reagents and/or intermediates for organic transformations (Scheme 6.1).\(^1\) As described in the introduction of this thesis, enamines are derived from the condensation of amines and carbonyl moieties. Enamines have been used as enolate equivalents for a number of years and participate in a number of transformations including: Michael, alkylation, aldol and Mannich reactions.\(^2\)

\[
\begin{align*}
\text{Scheme 6.1. Classical stoichiometric enamine reactivity}
\end{align*}
\]

The α-substitution of carbonyl compounds by a catalytic quantity of primary or secondary amine via an enamine intermediate constitutes enamine catalysis. This process is thought of as the catalytic version of the chemistry pioneered and developed by Gilbert Stork.\(^3\) The first step of enamine catalysis involves the condensation of substoichiometric amine component and carbonyl compound (6.1.01) forming the iminium cation with concomitant expulsion of H₂O (Figure 6.1, 6.1.02). The LUMO-lowering effect of the iminium cation increases the acidity of the αC-H bond. This electronic effect is crucial for enamine formation resulting in 6.1.03, which can undergo either α-substitution or α-addition reactivity, yielding the α-functionalized iminium cation (6.1.04). Finally, hydrolysis of 6.1.04 reforms the amine catalyst and releases the carbonyl product (Figure 6.1).
Figure 6.1. Enamine catalysis

The Hajos-Parrish-Eder-Sauer-Wiechert reaction of tricarbonyl 6.1.05 is arguably the first report of enamine catalysis (Scheme 6.2). Discovered in the 1970’s, its development languished in organic circles due to the perceived misconceptions of mechanism. In the early 21st century, List and co-workers reinitiated the field with the discovery of the proline-catalyzed direct asymmetric intermolecular aldol reaction. Since the initial example, there has been a flood of reports pertaining to the development of new methodologies, design of catalysts, utility in total syntheses and mechanistic studies. In this thesis, only select examples of α-chlorination and α-bromination of enamines will be discussed.

Scheme 6.2. Hajos-Parrish-Eder-Sauer-Wiechert Reaction

6.1.1 Catalytic Asymmetric α-Chlorination of Enamines

Enantioenriched α-chloro aldehydes are important synthetic intermediates for downstream transformations. These reagents are useful for the synthesis of chiral epoxides, aziridines, amino alcohols and heterocyclic structures. Access to these important substrates via mild and economical method is an important undertaking.
Scheme 6.3. First examples of a catalytic asymmetric chlorination of enamines

In 2004, simultaneous reports from the groups of MacMillan and Jørgensen conveyed the catalytic asymmetric chlorination of enamines (Scheme 6.3). In both examples, a variety of mono-substituted aldehydes were subjected to electrophilic chlorination, and the corresponding chloro-species were obtained in high yields with excellent enantioselectivity. Further development of this process has included organo-SOMO chlorination and a per-fluoro variant of the imidazolindinone catalyst (6.1.06) for easier recovery.

6.1.2 Catalytic Asymmetric α-Bromination of Enamines

The first catalytic, asymmetric bromination of aldehydes and ketones was reported by Jørgensen and coworkers in 2005 (Scheme 6.4). Through substantial screening of reagents, the authors turned to the air-stable compound 6.1.08 as the optimal source of electrophilic bromine. In combination with the diphenylpyrrolidine catalyst 6.1.07, the same catalyst used for the α-chlorination of aldehydes, high levels of enantioselectivity were obtained. Ketones were also suitable substrates affording only mono-brominated carbonyls.

Scheme 6.4. Catalytic asymmetric bromination of aldehydes with the pyrrolidine catalyst 6.1.07
6.1.3 Enamides

Over the recent years, the interest in enamides as a useful functional group for downstream transformations has increased. Enamides are stable enamine surrogates and have been used as key intermediates for heterocycles, chiral amides, and a number of total syntheses. The enamine-like character affords a polarized alkene. The polarization within the alkene can be modified with the substituent on the nitrogen, such as carbamate and sulfonyl groups (Figure 6.2). Using consistent nomenclature as described in this thesis, the $\alpha$-carbon is nucleophilic whereas the $\beta$-carbon is electrophilic in nature.

![Figure 6.2. Classes of enamides](image)

Enamides present a platform for the development of new methodology based upon the regioselective engagement of the alkene moiety. The direct metal-catalyzed functionalization of enamides has been at the forefront of this endeavor with exciting results. Select examples in this area will be discussed.

![Figure 6.3. Intramolecular cyclization of enamide 6.1.09](image)

The intramolecular Heck reaction has enabled the synthesis of nitrogen heterocycles from enamides. The cyclization of enamide 6.1.09 resulted in the 5-exo-trig cyclization onto the $\beta$-carbon of the enamide moiety (Figure 6.3, 6.1.09a). The reduced product (6.1.09b) was also isolated from the reaction mixture which is the result of protonation of the [Pd]-enolate.
Scheme 6.5. Regioisomer formation via intramolecular Heck cyclization

Employment of the Heck reaction does not always afford the exo-trig product. Rigby and coworkers sought to form the quaternary stereocentre via 6-exo-trig cyclization (Scheme 6.5, 6.1.10b). However, the unexpected 7-endo-trig product was isolated as the major product (6.1.10a).\textsuperscript{18} The addition of bulky phosphine ligands, such as P(o-tolyl)\textsubscript{3}, resulted in the 6-exo-trig product 6.1.10b, albeit in low yield. This approach was subsequently utilized by the group of Tozer for the synthesis of conformationally constrained phenylalanine analogues.\textsuperscript{19}

Scheme 6.6. Intramolecular cyclization of sulfonamides

Enesulfonamides are also effective substrates for the synthesis of heterocycles (Scheme 6.6).\textsuperscript{20} In this example the pendant aryl bromide was efficiently cyclized onto the endocyclic alkene moiety. While only three examples were reported, this is a valuable entry to cyclic sulfonamides (6.1.11). The authors did note there was alkene isomerization of the product.
6.2 Boron-Containing Enamine and Enamide Linchpins in the Synthesis of Nitrogen Heterocycles

6.2.1 Proposal

Innovative approaches to new synthetic transformations are likely to emerge by thorough consideration of underutilized combinations of functional groups in reaction substrates. In this regard, advances in catalysis directed towards chemical synthesis would benefit from the rational deployment of novel metal- and metalloid-containing intermediates. Our recent explorations in the area of kinetically amphoteric molecules have led to α-boryl aldehydes, which have in turn opened doors to several other amphoteric species. As part of this investigation, we reported the first example of C-B fragment migration driven by a Curtius rearrangement. Since then, we have pursued the application of densely functionalized boron-containing building blocks with the goal of exploiting uncommon intermediates towards the synthesis of nitrogen-containing heterocycles. A particularly intriguing possibility has been to explore the synthesis and application of boryl enamines and enamides as synthetic linchpins (Figure 6.4).

![Proposed utility of the B-C-C-N intermediate](image)

**Figure 6.4.** Proposed utility of the B-C-C-N intermediate

We now demonstrate that parent α-boryl enamines and enamides are useful in the synthesis of α-halogenated boryl aldehydes. These halogenated products are in turn amenable to annulation to form previously underexplored borylated heterocycles. Moreover, we show that α-boryl enamines and enamides act as linchpin reagents in several transformations including intramolecular Suzuki–Miyaura cross-coupling (SMCC) and Heck coupling at the βC–H bond.
6.2.2 Identification of α-Boryl Enamine

As part of our effort in exploiting the chemistry of boryl enamines and enamides, we have pursued the parent (unsubstituted) α-MIDA boryl aldehyde 6.2.01. Ozonolysis of allyl MIDA boronate on multigram scale provided an efficient means for preparation of the parent α-boryl aldehyde 6.2.01, which was isolated as a white solid (Scheme 6.7) 25 With the aldehyde in hand, we subsequently sought to investigate the formation of α-boryl enamine 6.2.02 via condensation of α-boryl aldehyde 6.2.01 with pyrrolidine. Pyrrolidine was chosen as the preferred secondary amine due to its increased nucleophilicity and reduced steric hindrance relative to other aliphatic amines.26 The condensation of equimolar amounts of 6.2.01 and pyrrolidine in acetonitrile-$d_3$ was monitored by $^1$H NMR. Complete consumption of the aldehyde 6.2.01 was accompanied by quantitative formation of enamine 6.2.02 ($\geq 20:1$ \textit{E}:\textit{Z}) within 5 minutes of mixing.27

![Scheme 6.7. Synthesis of parent boryl aldehyde 6.2.01 and formation of enamine 6.2.02](image)

Examination of enamine formation with increasing pyrrolidine concentration was performed to gauge the potential for catalytic turnover.28 Through $^1$HNMR analysis, we dissolved phenyl boryl aldehyde (Figure 6.6, 6.2.03) in MeCN-$d_3$ and was used as our baseline spectra. In separate 5mm
NMR tubes we introduced a solution of 6.2.03 in MeCN-d₃. We added between 10 – 100 mol % pyrrolidine in 10 mol % increments, agitated the solution and then submitted the sample for analysis. It was found that 10 mol % pyrrolidine cleanly delivers a 9:1 aldehyde:enamine (6.2.04) ratio in solution. This was consistent with every pyrrolidine concentration examined. The results correspond to a linear relationship between the enamine formation and the concentration of pyrrolidine. This data, in conjunction with data from the formation of 6.2.02 led us to evaluate the reactivity of boryl enamines as nucleophilic intermediates in α-substitution chemistry, particularly in α-halogenation. ²⁹

![Chemical Structures](image)

**Figure 6.6.** Increasing α-boryl enamine 6.2.04 formation relative to pyrrolidine concentration

### 6.2.3 Halogenation of Boryl Enamines

At the outset, we subjected the parent α-boryl aldehyde 6.2.01 to electrophilic bromination conditions using N-bromosuccinimide (NBS) at room temperature in the presence of 10 mol %
pyrrolidine.\textsuperscript{30} This resulted in a full consumption of the starting aldehyde in 4 hours; however, a mixture of mono- and di-brominated species was obtained. Cooling the reaction to 0 °C and adding NBS as a solution over one hour afforded the mono-brominated boryl aldehyde in 67% yield as the exclusive product (Scheme 6.8, \textbf{6.2.05a}) as a stable white solid. The use of acetic acid and water was found to be optimal for pyrrolidine turnover and reduced reaction times.

\begin{equation}
\begin{align*}
\text{MeN} & \begin{array}{c}
\text{O} \\
\text{O} \\
\end{array} \\
\text{B} & \begin{array}{c}
\text{O} \\
\text{O} \\
\end{array} \\
\text{MeN} & \begin{array}{c}
\text{O} \\
\text{O} \\
\end{array} \\
\text{B} & \begin{array}{c}
\text{O} \\
\text{O} \\
\end{array} \\
\text{MeN} & \begin{array}{c}
\text{O} \\
\text{O} \\
\end{array} \\
\text{B} & \begin{array}{c}
\text{O} \\
\text{O} \\
\end{array} \\
\text{MeN} & \begin{array}{c}
\text{O} \\
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\end{array} \\
\text{B} & \begin{array}{c}
\text{O} \\
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\text{MeN} & \begin{array}{c}
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\text{MeN} & \begin{array}{c}
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\text{O} \\
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\text{MeN} & \begin{array}{c}
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\text{B} & \begin{array}{c}
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\text{O} \\
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\text{MeN} & \begin{array}{c}
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\text{B} & \begin{array}{c}
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\text{MeN} & \begin{array}{c}
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\text{MeN} & \begin{array}{c}
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\text{MeN} & \begin{array}{c}
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\text{B} & \begin{array}{c}
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\text{MeN} & \begin{array}{c}
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\text{B} & \begin{array}{c}
\text{O} \\
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\text{MeN} & \begin{array}{c}
\text{O} \\
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\text{B} & \begin{array}{c}
\text{O} \\
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\text{MeN} & \begin{array}{c}
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\text{MeN} & \begin{array}{c}
\text{O} \\
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\text{MeN} & \begin{array}{c}
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\text{B} & \begin{array}{c}
\text{O} \\
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\end{array} \\
\text{MeN} & \begin{array}{c}
\text{O} \\
\text{O} \\
\end{array}
\end{align*}
\end{equation}

\textbf{Scheme 6.8. Substrate scope of the }\alpha\text{-halogenation reaction}

Application of the bromination protocol to a variety of substituted }\alpha\text{-boryl aldehydes was successful (Scheme 6.8). Both electron-rich and electron-poor aryl substrates as well as alkyl variants were smoothly converted to the }\alpha\text{-brominated products in good yields. The corresponding chlorinated compounds were readily obtained by substituting NCS for NBS and increasing the reaction temperature to 45 °C.\textsuperscript{31}
6.2.4 Enantioselective Halogenation of Substituted Boryl Aldehydes

The asymmetric variant of the Matteson protocol is a common method for the synthesis of α-halogenated alkyl boronates in excellent diastereoselectivity. The high levels of d.r. is obtained by the chiral diol complexed to the boron centre (Scheme 6.9). This process is limited by the use of harshly basic reagents and low atom-economy. In contrast, the process described in the previous subsection is not only mild but also catalytic in nature. As such, we sought to investigate the potential for the catalytic, asymmetric halogenation of boryl enamines to provide a route to enantioenriched α-halo alkyl boronates.

Scheme 6.9. Examples of diastereoselective Matteson homologation

At the outset, we chose to investigate the asymmetric chlorination of boryl enamines with L-proline, as it is most similar to pyrrolidine. Under the optimized reaction conditions we found complete consumption of 6.2.03 by $^1$H NMR analysis. Analysis of the crude reaction mixture by chiral, stationary phase HPLC found an enantioinduction of 48% (Table 6.1, entry 1). Increasing the catalyst loading to 100 mol % afforded only a modest increase in enantioinduction to 57% (entry 5). This represents the first example of a catalytic asymmetric process for enantioenriched α-halo alkyl boronates.
Table 6.1. Screen of chiral secondary amines for enantioinduction

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>% conversion a</th>
<th>% ee b</th>
<th>entry</th>
<th>catalyst</th>
<th>% conversion a</th>
<th>% ee b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>100</td>
<td>48</td>
<td>5</td>
<td></td>
<td>100</td>
<td>57</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>100</td>
<td>43</td>
<td>6</td>
<td></td>
<td>100</td>
<td>7</td>
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<tr>
<td>3</td>
<td></td>
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<td>0</td>
<td>7</td>
<td></td>
<td>61</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>100</td>
<td>46</td>
<td>8</td>
<td></td>
<td>0</td>
<td>ND</td>
</tr>
</tbody>
</table>

All results the average of at least two iterations. a conversion determined by crude $^1$H NMR, b determined by HPLC analysis, Chiralcel OJ-H (1.0 mL/min 95:5 MTBE:MeCN, @ 210 nm) c 100 mol % L-proline, d bromination results.

$\alpha$-Methyl L-proline is commonly used in circumstances where L-proline fails to promote a highly enantioselective transformation.\(^{34}\) Surprisingly, we found that a 50 mol % loading of $\alpha$-methyl L-proline afforded the chlorination product in 7 % ee (Table 6.1, entry 6). Screening of other chiral secondary amines resulted in modest enantioinduction. Modification of acid, halogenation source and additives had a detrimental effect on ee and conversion.
Scheme 6.10. Enantioenriched α-halogenated boryl aldehydes

It was postulated that the limitation of the asymmetric transformation was a function of the boryl aldehyde, therefore, we screened the optimized halogenation conditions with other boryl aldehydes (Scheme 6.10). In general, aryl boryl aldehydes resulted in similar levels of enantioinduction as that obtained for 6.2.10b. Alkyl substituted boryl aldehydes were also subjected to the asymmetric chlorination reaction which resulted in low levels of enantioinduction. Extension to the bromination reaction resulted in a decrease in enantioselectivity.

The disappointing enantioinduction results led us to forgo further investigations; however several key observations were made during the course of this study. The asymmetric chlorination reaction, albeit with modest enantioinduction, confirms the boryl enamine intermediate. This process also affords a novel route for the production enantioenriched α-halogenated alkyl boronates.
6.2.5 Condensation/Cyclization Sequence of α-Halogenated Boryl Aldehydes

The synthesis of boryl heterocycles commonly accomplished with organometallic reagents under cryogenic conditions and is effective for simple and/or highly-biased heteroaromatic substrates. Extension of this chemistry to functionally richer molecules has been problematic due to functional group tolerance and chemoselectivity. To demonstrate the utility of α-halogenated boryl aldehydes in the preparation of borylated heterocycles, we set out to investigate the feasibility of a one-pot aldehyde condensation/bromide displacement.

Scheme 6.11. Condensation/bromide displacement with thioamides and thioureas

Thioamides are known to undergo annulation with α-halogenated aldehydes. α-Bromoboryl aldehyde was subjected to cyclization conditions with a variety of primary thioamides which resulted in the formation of the corresponding 2,5-borylated thiazoles as single regioisomers (Scheme 6.11, 6.2.15a-c). In addition, thioureas also participated in the condensation reaction with 6.2.05a to produce a variety of 2-amino-5-borylthiazoles in good yields (Scheme 6.11, 6.2.15 d-g).
**Figure 6.7.** Condensation/halide displacement affords ready access to both boryl-thiazole regioisomers

While 2,4-regioisomers can be accessed from our previously reported α-brominated acyl boronates, the regioisomeric 2,5-series of borylated heterocycles can now be accessed by the “bromoboryl” building block 6.2.05a with “swapped” oxidation states at the adjacent carbons (Figure 6.7). As a testament to the rarity of the 2,5-disubstituted thiazole, examination of the PDB database found only 7 biologically relevant structures that incorporated this heterocycle motif. Access to the 2,5-disubstituted boryl thiazole extends the suite of building blocks for use in both medicinal chemistry and materials science.

### 6.2.6 α-Boryl Enamides

The condensative synthesis of borylated thiazoles proceeds through an equilibrating N-acyl imine/enamide intermediate. Identification of the enamide component encouraged us to investigate boron’s influence on the enamide functionality, in particular its attenuation of nitrogen’s nucleophilicity. This led us to pursue the preparation of α-boryl enamide scaffolds for downstream applications towards nitrogen-containing heterocycles.
Initially, we subjected the aldehyde 6.2.01 to a variety of primary amines which resulted in a mixture of α-boryl imine and α-boryl enamine products as indicated by $^1$H NMR. Fortunately, we were able to trap these intermediates with acyl chlorides, which led to the formation of α-boryl enamides as white solids after purification (Scheme 6.12). In addition, the boryl imine intermediate can also be trapped by sulfonyl chlorides to yield the corresponding sulfonyl...
enamide 6.2.16g. Of particular note, we did not observe any products from the \( C\rightarrow N \) migration of the boryl substituent, which is contrast to a previous report from the Yudin lab.

![Comparison of proton chemical shifts of 6.2.16g and 6.2.17](image)

**Figure 6.8.** Comparison of proton chemical shifts of 6.2.16g and 6.2.17

The boryl enamide 6.2.16g, in comparison to \( N \)-benzyl-\( N \)-propenyl benzamide (6.2.17), possesses a relatively electron-rich \( \alpha \)-carbon (Figure 6.9). In addition, boron substitution results in enhanced electrophilicity of the \( \beta \)-carbon as indicated by a downfield shift of the \( H_b \) (\(^1\)H NMR) signal by 0.4 ppm relative to its alkyl counterpart. We attribute this polarity to the presence of the sp\(^3\)-MIDA boronate and resonance structure of the enamide functional group.

![X-ray structure of 6.2.16i](image)

**Figure 6.9.** X-ray structure of 6.2.16i. Hydrogen atoms are omitted for clarity *Inset: zoom-in of enamide geometry*

Another important insight into the electronic nature of boryl enamides was obtained through single crystal X-ray analysis of 6.2.16i (Figure 6.9). Specifically, the enamide functionality features an abcd torsion angle of 127.7\(^\circ\), which stands in contrast to the value of 180\(^\circ\) typically seen in other crystal structures of enamides. The atypical torsion angle recorded for 6.2.16i results in the electronic isolation of both amide and alkene functional groups. We became
interested in exploring the polarized electronic character of α-boryl enamides in intramolecular transformations with the goal of gaining access to a range of nitrogen-containing heterocycles.

![Chemical structure](image)

Scheme 6.13. Borylated methylene-isoindolones 6.2.18a-f via 5-exo-trig cyclization of α-boryl enamides 6.2.16a-f

To probe the possibility of α-boryl enamide cyclization, we turned to the Heck reaction as electron-rich alkene substrates are known to facilitate the migratory insertion process. When 6.2.16b was subjected to Heck reaction conditions with Pd(PPh₃)₄, exclusive formation of the methylene-isoindolone derived from a 5-exo-trig cyclization was observed. The product was formed as a mixture of E/Z alkene isomers (Scheme 6.13, 6.2.18b). A number of other boryl enamides were next subjected to cyclization conditions, delivering similar results. The benzyl bromide 6.2.16g, enesulfonamide 6.2.16h, and the trisubstituted enamide 6.2.16i did not afford the corresponding cyclized products. Subsequent hydrogenation of the methyleneisoindolones
was performed without further purification to afford the reduced organoboron-containing isoindolones (Scheme 6.13).  

![Image](image1)

**Figure 6.10.** B-C-Pd intermediate 6.2.19 of the Heck cyclization

In addition to the steric effects, the 5-exo-trig cyclization is kinetically favoured. As a result of the regioselective migratory insertion, the Pd$^{II}$-species migrates to the α-carbon forming the gem-bis-metallo B-C-Pd intermediate 6.2.19. The electron-rich $sp^3$-MIDA boronate is proposed to destabilize 6.2.19 due to the lack of empty p-orbital-anion interaction. This destabilization is proposed to result in a rapid β-hydride elimination.

![Image](image2)

**Scheme 6.14.** Intramolecular Suzuki-Miyaura cross-coupling of borylated isoindolones
In addition to Heck-cyclization of the enamide, we were also interested in engaging the $sp^3$ C–B bond through Suzuki–Miyaura cross-coupling (SMCC).\textsuperscript{51,52} A comprehensive literature search revealed only two-reports of small-ring synthesis via SMCC reaction\textsuperscript{53} and a single example of 7-membered ring syntheses.\textsuperscript{54} This lack of precedent is attributed to the challenges associated with transmetalation to form the medium ring palladacycle. Indeed, these difficulties were confirmed with the isolation of the boronic acid \textbf{6.2.20e}. Oxidative addition had occurred, however, ring closing failed to take place affording the protodehalogenated product. This process likely reflects the fine balance between relative rates and a possible amide/Pd interaction. Fortunately, the less electron-rich alkyl MIDA boronates \textbf{6.2.18c–d} were readily converted to the corresponding tetracyclic-lactams \textbf{6.2.20c–d} in good yields (Scheme 6.14). The intramolecular SMCC reaction enables access to this biologically relevant class of polycyclic scaffolds.\textsuperscript{55}

\textbf{6.2.7 Summary}

In summary, we have demonstrated the synthetic utility of boryl enamines and enamides as linchpin reagents for the synthesis of nitrogen-containing heterocycles. Mild $\alpha$-halogenation is enabled by employment of boryl enamines as transient intermediates. The halogenated products can be used in the regioselective synthesis of 2,5-disubstituted boryl thiazoles. Boryl aldehydes also undergo quantitative condensation with primary amines and subsequent acylation results in stable $\alpha$-boryl enamides. Heck cyclization of the enamides affords the privileged isoindolone scaffold. The application of the Heck products through SMCC engagement of the C–B bond enables convenient access to biologically useful tetracyclic scaffolds. This realizes the synthetic potential of $\alpha$-boryl enamine and $\alpha$-boryl enamide as linchpins for production of nitrogen heterocycles.

\textbf{6.3 Supporting Information}

\textbf{6.3.1 General Information}

Methylene chloride (DCM/CH$_2$Cl$_2$), methanol (MeOH) and triethylamine (Et$_3$N) were distilled from CaH$_2$ under nitrogen. Acetonitrile (MeCN) was distilled from activated 3Å MS under nitrogen. Toluene was purified via solvent purification system. Tetrahydrofuran (THF) was
freshly distilled from sodium benzophenone ketyl. All other solvents were of reagent grade quality and dried over 4Å MS prior to use and if stated solvents were sparged with a rapid flow of dry N₂(g) for at least 30 minutes prior to use. All reagents were purchased from commercial sources and used as received.

**Chromatography**: Flash column chromatography was carried out using Silicycle 230-400 mesh silica gel, or ISCO Teledyne Combiflash Rf 200 Flash system. Thin-layer chromatography (TLC) was performed on Macherey Nagel pre-coated glass backed TLC plates (SIL G/UV254, 0.25 mm) and visualized using a UV lamp (254 nm), KMnO₄, I₂, or curcumin stain.

**High-Performance Liquid Chromatography**: Enantiomeric excess (ee’s) were determined on an analytical Diacel Chiralcel OJ-H column monitoring at 210 nm and 254 nm. Mobile phase was consisted of HPLC grade methyl tert-butyl ether (MTBE) and acetonitrile (MeCN).

**Nuclear Magnetic Resonance Spectroscopy**: ¹H, ¹³C, and 2D NMR spectra were recorded on Varian Mercury 300 MHz, 400 MHz, 500 MHz, 600 MHz or 700 MHz spectrometers. ¹¹B NMR were recorded using Bruker 400 MHz spectrometer at 125 MHz and referenced to an external standard of BF₃·Et₂O (δ = 0 ppm). ¹H NMR spectra chemical shifts (δ) are reported in parts per million (ppm) referenced to residual protonated solvent peak (CDCl₃, δ = 7.26, DMSO-d₆, δ = 2.49, acetone-d₆ δ = 2.05). Spectral data is reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, ddt = doublet of doublet of triplets, dtd = doublet of triplet of doublets, m = multiplet, br = broad), coupling constant (J) in Hertz (Hz), and integration. ¹³C NMR spectra chemical shifts (δ) are reported in parts per million (ppm) were referenced to carbon resonances in the NMR solvent (CDCl₃, δ = 77.0; DMSO-d₆, δ = 39.5, center line, acetone-d₆ = 206.2 centre line, 29.8). Carbons exhibiting significant line broadening brought about by boron substituents were not reported (quadrupolar relaxation). Some 2-MIDA boryl thiazoles did not exhibit the expected ¹³C spectrum; however their ¹H, ¹¹B, HRMS were all consistent with the expected product.

**Infrared Spectroscopy**

IR spectra were recorded on a Perkin-Elmer 100 instrument equipped with a single-reflection diamond/ZnSe ATR accessory. Performed on an NaCl disc as a thin layer.
**Mass Spectroscopy:** High resolution mass spectra were obtained on a VG 70- 250S (double focusing) mass spectrometer at 70 eV or on an ABI/Sciex Qstar mass spectrometer with ESI source, MS/MS and accurate mass capabilities.

### 6.3.2 Synthesis of Parent Boryl Aldehyde (6.2.01)

![Chemical Structure](image)

**Step1: allyl-MIDA boronate**

To an oven-dried 5 L three-neck flask was equipped with a magnetic stir-bar, 500 mL pressure equalizing addition funnel, and two-rubber septa was added THF (500 mL) and B(OMe)₃ (39.65 mL, 36.95 g, 385 mmol, 1.1 equiv). The flask was then cooled to -78 °C and the addition funnel was charged with allyl-MgBr (1.0 M in Et₂O, 350 mL, 350 mmol, 1.0 equiv). The Grignard reagent was added dropwise over the course of 2 hours at -78 °C at which time the flask was removed from the -78 °C bath and allowed to warm to room temperature for 4 hours resulting in a dense white suspension.

At the same time as the addition of the Grignard, in a separate 3 L three neck flask equipped with a thermometer in the central neck, simple distillation apparatus and 500 mL addition funnel was added N-methyliminodiacetic acid (124 g, 2.2 equiv) and DMSO (500 mL). The DMSO solution was warmed to an internal temperature of 130-150 °C at which time the addition funnel was charged with reagent grade hexanes (500 mL) and added dropwise over the course of 2 hours. Upon complete addition of the hexanes the addition funnel was replaced with a rubber septum and sealed.

The prepared boronate suspension was then added via cannula under a positive pressure of N₂(g) to the dried MIDA/DMSO solution over the course of 2 hours, while maintaining the internal temperature between 130-150 °C. Upon complete addition of the boronate suspension the reaction vessel was washed with THF (2 x 50 mL) and added to the MIDA/DMSO flask by cannula. After complete transfer of the boronate wash the cannula was detached and the flask...
was allowed to continue to distill for another 30 minutes at 130-150 °C. Once no distillate is produced the reaction was removed from the heat source and allowed to cool to room temperature for 1 hour. The reaction mixture was then transferred to a 4 L separatory funnel and added water (1 L), brine (1 L), EtOAc (1.5 L) and acetone (1 L). The organic layer was then removed and the aqueous layer was extracted twice with EtOAc:acetone (1.5 L, 3:2) and a final extraction with EtOAc (500 ml). The combined organics were washed with brine (500 mL) and dried with anhydrous MgSO$_4$. The dried organics were filtered and concentrated under reduced pressure. The resulting brown solid was then dissolved in a minimal amount of acetone (approx 200 mL), transferred to a 4 L beaker and precipitated with diethyl ether (3 L). The precipitate was then filtered to yield a tan-brown solid. The solid was then dissolved in acetone (800 mL) and added activated charcoal. The acetone solution was then stirred for 30 minutes and then filtered through Celite. The Celite plug was washed with acetone (2 x 100 mL) and then resulting acetone solution was concentrated in vacuo to afford the allyl MIDA boronate (38 g, 188 mmol) as a white solid and used in the next step without further purification.

**Step 2: Ozonolysis**

In a 3-L round-bottom flask equipped with a magnetic stir bar was added allyl-MIDA boronate (37 g, 188 mmol) followed by reagent grade DCM (1.4 L) and MeOH (450 mL). The mixture was stirred for 10 minutes and resulted in a clear solution. The gas diffuser was placed into the solution and attached to an ozone generator. The generator was then set to 0.55 g/min and allowed to stir at -78 °C for 3.5 hours at which time the reaction mixture started to turn blue. The ozone was then stopped and N$_2$(g) was bubbled through the solution until colourless. A sample was then analyzed by $^1$H NMR and showed complete consumption of starting material. The flask was then charged with Me$_2$S (58.34 g, 69 mL, 939 mmol, 5.0 equiv) and stirred at -78 °C for one hour then warmed to room temperature overnight. After stirring overnight a white suspension had formed. The solvent was then removed in vacuo to yield a white solid. DCM (150 mL) was introduced and the suspension was filtered to yield the product plus a minor impurity.
α-MIDA boryl acetaldehyde (6.2.01)
62% yield, white solid

$^1$H NMR (399 MHz, DMSO-$d_6$)
$\delta$ 9.64 (t, $J = 3.8$ Hz, 1H), 4.25 (d, $J = 17.0$ Hz, 2H), 4.01 (d, $J = 17.0$ Hz, 2H), 2.88 (s, 3H), 2.15 (d, $J = 3.9$ Hz, 2H)

$^{13}$C NMR (100 MHz, DMSO-$d_6$)
$\delta$ 203.8, 168.9, 62.1, 46.6

$^{11}$B NMR (128 MHz, Acetone-$d_6$)
$\delta$ 11.3

HRMS [DART-MS] (M+NH$_4^+$)
$m/z$ calculated for C$_7$H$_{14}$BN$_2$O$_5$ = 217.0995
$m/z$ found = 217.0989

TLC (hexanes:acetone 1:2)
$R_f$ = 0.29

6.3.3 Determination of Enamine Geometry 6.2.02 by $^1$H NMR

(E)-(2-(pyrrolidin-1-yl)vinyl)MIDA boronate (6.2.02)

$E:Z$ >20:1

$^1$H NMR (400 MHz, Acetonitrile-$d_3$)
$\delta$ 6.52 (d, $J = 15.4$ Hz, 1H), 3.84 (d, $J = 16.8$ Hz, 2H), 3.70 (d, $J = 16.8$ Hz, 2H), 3.44 (d, $J = 15.4$ Hz, 1H), 3.14 – 3.08 (m, 4H), 2.74 (s, 3H), 1.87 – 1.80 (m, 4H)

$^{13}$C NMR (101 MHz, Acetonitrile-$d_3$)
$\delta$ 168.2, 144.7, 60.2, 47.6, 45.8, 24.3

$^{11}$B NMR (128 MHz, Acetonitrile-$d_3$)
$\delta$ 12.6
6.3.4 \(^1\)H NMR Study of Boryl Enamine Formation via Pyrrolidine Titration

![Diagram](image)

To a 2-dram vial was added phenyl \(\alpha\)-MIDA boryl aldehyde (0.027 g, 0.1 mmol, 1.0 equiv) and MeCN-\(d_3\) (1.0 mL). The solid was dissolved via agitation and then pyrrolidine (0.8 \(\mu\)L, 10 mol \%) was then added via calibrated pipette. The volume was then transferred to a 5 mm NMR tube and submitted for analysis. The same procedure was used for subsequent concentrations of pyrrolidine.

(Z)-(1-phenyl-2-(pyrrolidin-1-yl)vinyl)MIDA boronate (6.2.04)

\(^1\)H NMR (400 MHz, Acetonitrile-\(d_3\))

\(\delta\) 7.30 – 7.16 (m, 4H), 7.14 – 7.05 (m, 1H), 6.57 (s, 1H), 3.81 (d, \(J = 16.9\) Hz, 2H), 3.43 (d, \(J = 16.8\) Hz, 2H), 2.94 – 2.88 (m, 4H), 2.74 (s, 3H), 1.71 – 1.63 (m, 4H)

\(^13\)C NMR (101 MHz, Acetonitrile-\(d_3\))

\(\delta\) 169.4, 143.6, 143.4, 132.1, 128.0, 125.2, 62.7, 52.3, 47.2, 26.0

\(^11\)B NMR (128 MHz, Acetonitrile-\(d_3\))

\(\delta\) 12.4

6.3.5 General Procedure for Organocatalyzed Bromination

To flamed dried screw top vial was added MeCN (2 mL), \(\alpha\)-MIDA boryl aldehyde (0.1 mmol, 1.0 equiv), pyrrolidine (0.01 mmol, 10 mol \%) water (0.5 mmol, 5.0 equiv) and AcOH (0.1 mmol, 1.0 equiv). The mixture was subsequently cooled to 0 °C then \(N\)-bromosuccinimide (0.15
mmol, 1.5 equiv) was added via syringe pump over 1 hour. The reaction was allowed to warm to room temperature and stirred until complete by TLC. At which point the solvent was removed and the residue was purified via column chromatography to yield pure product.

(1-bromo-2-oxoethyl)MIDA boronate (6.2.05a)
89% yield, white solid

$^1$H NMR (500 MHz, Acetonitrile-$d_3$)

$\delta$ 9.54 (d, $J = 2.0$ Hz, 1H), 4.25 (s, 1H), 4.14 – 4.11 (m, 1H), 4.10 – 4.07 (m, 1H), 4.04 – 4.01 (m, 1H), 4.00 – 3.97 (m, 1H), 3.09 (s, 3H)

$^{13}$C NMR (126 MHz, Acetonitrile-$d_3$)

$\delta$ 195.1, 167.2, 167.0, 63.0, 62.8, 46.2

$^{11}$B NMR (128 MHz, Acetonitrile-$d_3$)

$\delta$ 9.6

HRMS [DART-MS] [M+NH$_4^+$]

$m/z$ calculated for C$_7$H$_{13}$BBrN$_2$O$_5$ = 295.0100

$m/z$ found = 295.0095

TLC (hexanes:acetone 3:4)

$R_f$ = 0.47

(2-bromo-1-oxo-3-phenylpropan-2-yl)MIDA boronate (6.2.06a)

84% yield, white solid

$^1$H NMR (399 MHz, Acetonitrile-$d_3$)

$\delta$ 9.64 (s, 1H), 7.34 – 7.25 (m, 3H), 7.25 – 7.19 (m, 2H), 4.18 – 4.10 (m, 3H), 4.04 – 3.95 (m, 2H), 3.30 (d, $J = 14.9$ Hz, 1H), 2.99 (s, 3H)

$^{13}$C NMR (100 MHz, Acetonitrile-$d_3$)

$\delta$ 199.1, 168.0, 167.9, 137.1, 131.6, 128.8, 127.9, 64.5, 64.2, 47.3, 41.0, 30.8.

$^{11}$B NMR (128 MHz, Acetonitrile-$d_3$)

$\delta$ 9.8

HRMS [DART-MS] [M+NH$_4^+$]
m/z calculated for C_{14}H_{19}BBrN_{2}O_{5} = 385.0570

m/z found = 385.0576

TLC (hexanes:acetone 1:1)
R_{f} = 0.27

(1-bromo-1-cyclohexyl-2-oxoethyl)MIDA boronate (6.2.07a)
70% yield, hygroscopic white solid

$^1$H NMR (500 MHz, Acetone-$d_6$) - hygroscopic
δ 9.69 (s, 1H), 4.39 – 4.31 (m, 1H), 4.27 (d, J = 16.9 Hz, 1H), 4.19 (d, J = 16.9 Hz, 1H), 4.05 (d, J = 17.2 Hz, 1H), 3.10 (s, 3H), 2.28 – 2.23 (m, 1H), 2.13 – 2.06 (m, 1H), 1.83 – 1.73 (m, 2H), 1.71 – 1.59 (m, 2H), 1.50 – 1.40 (m, 1H), 1.37 – 1.24 (m, 3H), 1.22 – 1.09 (m, 1H)

$^{13}$C NMR (101 MHz, Acetonitrile-$d_3$)
δ 199.0, 166.7, 166.6, 63.2, 63.0, 46.2, 42.5, 26.2, 22.9, 21.8

$^{11}$B NMR (128 MHz, Chloroform-$d$)
δ 10.0

HRMS [DART-MS] [M+NH$_4^+$]

m/z calculated for C_{13}H_{22}BBrN_{2}O_{5} = 377.0883

m/z found = 377.0888

TLC (hexanes:acetone 1:1)
R_{f} = 0.38

(2-bromo-1-oxohexan-2-yl)MIDA boronate (6.2.08a)
72% yield, white solid (90% pure)

$^1$H NMR (500 MHz, Acetone-$d_6$)
δ 9.51 (s, 1H), 4.42 (d, J = 17.3 Hz, 1H), 4.34 (d, J = 16.9 Hz, 1H), 4.26 (d, J = 16.9 Hz, 1H), 4.18 (d, J = 17.3 Hz, 1H), 3.21 (s, 3H), 2.45 (m, 1H), 1.57 – 1.43 (m, 1H), 1.42 – 1.27 (m, 3H), 1.25 – 1.12 (m, 1H), 0.91 (t, J = 7.3 Hz, 3H)

$^{13}$C NMR (126 MHz, Acetone-$d_6$)
δ 197.8, 166.8, 166.8, 63.5, 63.3, 46.2, 34.3, 27.8, 22.4, 13.2
$^{11}$B NMR (128 MHz, Acetonitrile-$d_3$)  
$\delta$ 9.7

HRMS [ESI-MS] [M+Na$^+$]  
$m/z$ calculated for C$_{11}$H$_{17}$BNO$_5$NaBr = 356.0275  
$m/z$ found = 356.0263

TLC (hexanes:acetone 1:1)  
$R_f = 0.34$

(2-bromo-4-methyl-1-oxopentan-2-yl)MIDA boronate (6.2.09a)  
70% yield, white solid

$^1$H NMR (400 MHz, Acetonitrile-$d_3$)  
$\delta$ 9.62 (s, 1H), 4.13 – 4.01 (m, 3H), 3.95 (d, $J = 17.3$ Hz, 1H), 2.99 (s, 3H), 2.35 (dd, $J = 15.1, 8.3$ Hz, 1H), 2.13 (dd, $J = 15.1, 4.3$ Hz, 1H), 1.96 – 1.87 (m, 1H), 1.01 (d, $J = 6.8$ Hz, 3H), 0.83 (d, $J = 6.7$ Hz, 3H)

$^{13}$C NMR (101 MHz, Acetonitrile-$d_3$)  
$\delta$ 199.0, 166.7, 166.6, 63.2, 63.0, 46.2, 42.5, 26.1, 22.9, 21.8

$^{11}$B NMR (128 MHz, Acetonitrile-$d_3$)  
$\delta$ 9.7

HRMS [DART-MS] [M+NH$_4^+$]  
$m/z$ calculated for C$_{11}$H$_{21}$BBrN$_2$O$_5$ = 351.0726  
$m/z$ found = 351.0783

TLC (hexanes:acetone 1:2)  
$R_f = 0.58$

(1-bromo-2-oxo-1-phenylethyl)MIDA boronate (6.2.10a)  
72%, white solid

$^1$H NMR (500 MHz, Acetonitrile-$d_3$)  
$\delta$ 9.62 (s, 1H), 7.57 – 7.51 (m, 2H), 7.41 (t, $J = 7.4, 6.1$ Hz, 2H), 7.39 – 7.32 (m, 1H), 4.06 (dd, $J = 17.1$ Hz, 2H), 3.97 (d, $J = 17.1$ Hz, 2H), 2.84 (s, 3H)
\(^{13}\)C NMR (126 MHz, Acetonitrile-\(d_3\))
\[ \delta 194.4, 167.2, 167.0, 135.3, 128.9, 128.6, 128.2, 63.9, 63.9, 63.7, 47.7 \]

\(^{11}\)B NMR (128 MHz, Acetone-\(d_6\))
\[ \delta 9.97 \]

IR (thin film)
\[ \nu 3032, 2982, 1768, 1705, 1643, 1492, 1446, 1417, 1402, 1338, 1276, 1193, 1161, 1145, 1049, 1016, 999, 960, 887, 734, 700 \]

HRMS [DART-MS] [M+H\(^+\)]
\[ m/z \text{ calculated for } C_{13}H_{14}BBrNO_5 = 354.0148 \]
\[ m/z \text{ found} = 354.0155 \]

TLC (hexanes:acetone 1:2)
\[ R_f = 0.58 \]

HPLC (DIACEL OJ-H, MTBE:MeCN: 95:5, flow rate: 1.5 mL/min, UV = 254 nm)
\[ R_t = 20.24 \text{ min} \]
\[ R_t = 25.85 \text{ min} \]
\[ \text{ee %} = 40 \% \]

Racemic

Enantioenriched
(1-bromo-1-(4-fluorophenyl)-2-oxoethyl)MIDA boronate (6.2.11a)

81% yield, white solid

$^1$H NMR (500 MHz, Acetonitrile-$d_3$)

$\delta$ 9.61 (s, 1H), 7.66 – 7.36 (m, 2H), 7.19 – 7.11 (m, 2H), 4.08 (dd, $J = 17.1, 9.1$ Hz, 2H), 4.03 – 3.97 (m, 2H), 2.85 (s, 3H)

$^{13}$C NMR (126 MHz, Acetonitrile-$d_3$)

$\delta$ 194.3, 167.1, 167.0, 162.3 (d, $J = 246.8$ Hz), 131.4 (d, $J = 3.3$ Hz), 131.1 (d, $J = 8.4$ Hz), 115.3 (d, $J = 21.9$ Hz), 63.9, 63.7, 47.6

$^{11}$B NMR (128 MHz, Acetonitrile-$d_3$)

$\delta$ 9.8

$^{19}$F NMR (377 MHz, Acetonitrile-$d_3$)
\( \delta -115.4 \)

HRMS [DART-MS] \([\text{M}+\text{NH}_4^+]\)

\[ m/z \text{ calculated for } C_{13}H_{16}BBF_2O_5 = 389.0319 \]
\[ m/z \text{ found } = 389.0323 \]

TLC (hexanes:acetone 1:1)

\[ R_f = 0.3 \]

(1-bromo-2-oxo-1-(p-tolyl)ethyl)MIDA boronate \((6.2.12a)\)

78\% yield, white solid

\(^1\)H NMR (400 MHz, Acetonitrile-\(d_3\))

\[ \delta \ 9.64 \ (s, 1H), 7.50 – 7.37 \ (m, 2H), 7.26 \ (d, J = 8.1 \text{ Hz}, 2H), 4.15 – 3.89 \ (m, 4H), 2.87 \ (s, 3H) \]

\(^{13}\)C NMR (126 MHz, Acetonitrile-\(d_3\))

\[ \delta \ 194.5, 167.2, 167.0, 138.4, 132.2, 129.2, 128.8, 63.8, 63.7, 47.7, 20.0 \]

\(^{11}\)B NMR (128 MHz, Acetonitrile-\(d_3\))

\[ \delta \ 9.9 \]

HRMS [ESI-MS] \([\text{M}+\text{Na}^+]\)

\[ m/z \text{ calculated for } C_{14}H_{15}BNO_5NaBr = 390.0122 \]
\[ m/z \text{ found } = 390.0118 \]

TLC (hexanes:acetone 1:1)

\[ R_f = 0.43 \]

6.3.6 Pyrrolidine-Catalyzed Chlorination

6.3.7 Modified Procedure for the Synthesis of \(\alpha\)-Chloro-Boryl Aldehyde \((6.2.05b)\)

To a solution of the parent boryl aldehyde \((6.2.01)\) (1.5 mmol, 1.0 equiv) in CH\(_3\)CN (15 ml) was added pyrrolidine (3.0 mmol, 2.0 equiv), AcOH (1.5 mmol, 1.0 equiv) and H\(_2\)O (7.5 mmol, 5.0 equiv). The mixture was stirred for 5 minutes. \(N\)-chlorosuccinimide (1.5 mmol, 1 equiv) was added in one portion and the reaction mixture stirred at room temperature for 5 hours.
Afterwards the solvent was removed in vacuo to afford the crude chlorinated enamine. The crude residue was passed through a silica gel column (hexanes/EtOAc 8:2 → EtOAc) to afford the \( \alpha \)-chloroaldehyde.

\[
\text{(1-chloro-2-oxoethyl)MIDA boronate (6.2.05b)}
\]

81\% yield, white solid

\( ^1 \text{H NMR (400 MHz, Acetonitrile-} d_3 \text{)} \)

\[ \delta \ 9.64 \ (d, J = 1.0 \text{ Hz}, 1\text{H}), \ 4.38 \ (\text{br s}, 1\text{H}), \ 4.09 \ (d, J = 17.1 \text{ Hz}, 1\text{H}), \ 4.08 \ (d, J = 17.2 \text{ Hz}, 1\text{H}), \ 3.96 \ (d, J = 17.2 \text{ Hz}, 1\text{H}), \ 3.95 \ (d, J = 17.1 \text{ Hz}, 1\text{H}), \ 3.08 \ (s, 3\text{H}) \]

\( ^{13} \text{C NMR (125 MHz, Acetonitrile-} d_3 \text{)} \)

\[ \delta \ 196.8, \ 168.4, \ 168.1, \ 63.8, \ 63.7, \ 47.1 \]

\( ^{11} \text{B NMR (192 MHz, Acetonitrile-} d_3 \text{)} \)

\[ \delta \ 9.5 \]

HRMS [DART-MS] [M+NH\(_4^+\)]

\[ m/z \text{ calculated for C}_{7}H_{13}BClN_{2}O_{5} = 251.0606 \]

\[ m/z \text{ found} = 251.0606 \]

TLC (EtOAc)

\[ R_f = 0.60 \]

6.3.8 General Procedure for Pyrrolidine-Catalyzed Chlorination

To flame-dried screw top vial was added MeCN, boryl aldehyde (1.0 equiv) and L-proline (0.5 equiv) water (5.0 equiv) and AcOH (1.0 equiv). The mixture was stirred for 5 minutes and then was added \( N \)-chlorosuccinimide (2.0 equiv). The mixture was heated to 45-50 °C for 4-5 hours. At which point the vial was allowed to cool and the solvent was removed in vacuo. To the residue was worked up using standard procedures. The residue was purified via column chromatography to yield pure product.
(2-chloro-1-oxo-3-phenylpropan-2-yl)MIDA boronate (6.2.06b)

84% yield, white solid

$^1$H NMR (400 MHz, Acetonitrile-$d_3$)

$\delta$ 9.80 (s, 1H), 7.36 – 7.27 (m, 3H), 7.27 – 7.17 (m, 2H), 4.22 – 4.04 (m, 3H), 4.02 – 3.85 (m, 2H), 3.26 (d, $J = 14.7$ Hz, 1H), 2.97 (s, 3H)

$^{13}$C NMR (101 MHz, Acetonitrile-$d_3$)

$\delta$ 199.8, 168.1, 168.0, 136.4, 131.6, 128.9, 127.9, 64.3, 64.0, 47.2, 40.7

$^{11}$B NMR (128 MHz, Acetonitrile-$d_3$)

$\delta$ 9.6

HRMS [DART-MS] [M+NH$_4^+$]

$m/z$ calculated for C$_{14}$H$_{19}$BClN$_2$O$_5$= 341.1075

$m/z$ found= 341.1082

TLC (hexanes:acetone 3:4)

$R_f = 0.38$

HPLC (DIACEL OJ-H, MTBE:MeCN: 95:5, flow rate: 1.5 mL/min, UV = 210 nm)

$R_t = 16.69$ min

$R_t = 27.47$ min

ee % = 4 %

Racemic

Enantioenriched
(1-chloro-1-cyclohexyl-2-oxoethyl)MIDA boronate (6.2.07b)

83% yield, white solid

$^1$H NMR (400 MHz, Acetone- $d_6$)

$\delta$ 9.79 (s, 1H), 4.34 (d, $J = 17.2$ Hz, 1H), 4.27 (d, $J = 16.8$ Hz, 1H), 4.16 (d, $J = 16.8$ Hz, 1H), 4.02 (d, $J = 17.2$ Hz, 1H), 3.07 (s, 3H), 2.32 – 2.24 (m, 1H), 2.15 – 2.07 (m, 1H), 1.83 – 1.69 (m, 3H), 1.66 – 1.61 (m, 1H), 1.49 – 1.37 (m, 1H), 1.34.- 1.11 (m, 4H)

$^{13}$C NMR (101 MHz, Acetone-$d_6$)

$\delta$ 202.1, 168.0, 167.8, 64.0, 63.7, 47.3, 45.6, 29.4, 29.0, 27.2, 27.2, 26.7

$^{11}$B NMR (128 MHz, Acetone-$d_6$)

$\delta$ 9.8

HRMS [DART-MS] (M+NH$_4^+$)

$m/z$ calculated for C$_{13}$H$_{23}$BClN$_2$O$_5$ = 333.1388

$m/z$ found= 333.1394

TLC (hexanes:acetone 1:1)

$R_f$ = 0.42
(2-chloro-1-oxohexan-2-yl)MIDA boronate (6.2.08b)

81% yield, white solid

$^1$H NMR (400 MHz, Acetonitrile-$d_3$)

$\delta$ 9.61 (s, 1H), 4.12 – 3.96 (m, 3H), 3.89 (d, $J = 17.3$ Hz, 1H), 2.93 (s, 3H), 2.40 (ddd, $J = 14.7$, 11.6, 4.7 Hz, 1H), 2.03 – 1.95 (m, 1H), 1.55 – 1.42 (m, 1H), 1.36 – 1.27 (m, 2H), 1.17 – 1.00 (m, 1H), 0.89 (t, $J = 7.3$ Hz, 3H)

$^{13}$C NMR (101 MHz, Acetonitrile-$d_3$)

$\delta$ 200.3, 168.1, 168.0, 64.3, 63.9, 47.2, 34.8, 27.0, 23.3, 14.0

$^{11}$B NMR (128 MHz, Acetonitrile-$d_3$)

$\delta$ 9.6

HRMS [DART-MS] [M+NH$_4^+$]

$m/z$ calculated for C$_{11}$H$_{21}$BClN$_2$O$_5$ = 307.1236

$m/z$ found = 307.1232

TLC (hexanes:acetone 1:1)

$R_f$ = 0.48

(2-chloro-4-methyl-1-oxopentan-2-yl)MIDA boronate (6.2.09b)

86% yield, white solid

$^1$H NMR (400 MHz, Acetonitrile-$d_3$)

$\delta$ 9.65 (s, 1H), 4.00 – 3.88 (m, 3H), 3.80 (d, $J = 17.3$ Hz, 1H), 2.84 (s, 3H), 2.21 (dd, $J = 15.0$, 8.3 Hz, 1H), 1.96 (dd, $J = 15.0$, 4.6 Hz, 1H), 1.84 – 1.72 (m, 1H), 0.88 (d, $J = 6.7$ Hz, 3H), 0.71 (d, $J = 6.6$ Hz, 3H)

$^{13}$C NMR (101 MHz, Acetonitrile-$d_3$)

$\delta$ 201.1, 168.1, 168.0, 64.3, 64.1, 47.3, 43.3, 30.3, 25.6, 24.2, 24.2, 23.3

$^{11}$B NMR (128 MHz, Acetonitrile-$d_3$)

$\delta$ 9.4

IR (thin film)

$\nu$ 2956, 2929, 2874, 2858, 1724, 1693, 1446, 1384, 1263, 1193, 1120, 1070, 1039, 993

HRMS [ESI-MS] [M+H$^+$]

$m/z$ calculated for C$_{11}$H$_{18}$BClNO$_5$ = 290.0961

$m/z$ found = 290.0914

TLC (hexanes:acetone 1:1)
\[ R_f = 0.56 \]

\[ \text{\( \alpha \)-chloro \( \alpha \)-MIDA boryl phenyl acetaldehyde (6.2.10b)} \]

95% yield, white solid

\[ ^1H \text{ NMR (400 MHz, Acetonitrile-d}_3 \]

\[ \delta 9.69 (d, J = 1.0 \text{ Hz, 1H}), 7.77 – 7.56 (m, 2H), 7.52 – 7.45 (m, 2H), 7.44 – 7.37 (m, 1H), 4.14 – 4.01 (m, 3H), 3.94 (d, J = 17.1 \text{ Hz, 1H}), 2.89 (s, 3H) \]

\[ ^13C \text{ NMR (126 MHz, Acetonitrile-d}_3 \]

\[ \delta 195.1, 167.2, 167.0, 134.6, 128.6, 128.0, 127.6, 63.6, 63.3, 47.1, 29.9 \]

\[ ^{11}B \text{ NMR (128 MHz, Acetonitrile-d}_3 \]

\[ \delta 9.5 \]

HRMS [ESI-MS] (M+NH\textsubscript{4}\textsuperscript{+})

\[ m/z \text{ calculated for } \text{C}_{13}\text{H}_{17}\text{BClN}_{2}\text{O}_5 = 327.0955 \]

\[ m/z \text{ found} = 327.0948 \]

TLC (hexanes:acetone 1:1)

\[ R_f = 0.38 \]

HPLC (DIACEL OJ-H, MTBE:MeCN: 95:5, flow rate: 1.0 mL/min, UV = 210 nm)

\[ R_t = 15.98 \text{ min} \]

\[ R_t = 20.41 \text{ min} \]

\[ \text{ee } \% = 48 \% \]

Racemic

Enantioenriched
(1-chloro-1-(4-fluorophenyl)-2-oxoethyl)MIDA borona te (6.2.11b)

94% yield, white solid

$^1$H NMR (400 MHz, Acetone-$d_6$)

$\delta$ 9.72 (s, 1H), 7.82 – 7.61 (m, 2H), 7.40 – 7.12 (m, 2H), 4.46 (d, $J = 8.9$ Hz, 1H), 4.42 (d, $J = 8.9$ Hz, 1H), 4.26 (d, $J = 17.0$ Hz, 1H), 4.19 (d, $J = 17.0$ Hz, 1H), 3.11 (s, 3H)

$^{13}$C NMR (101 MHz, Acetone-$d_6$)

$\delta$ 195.5, 167.9, 167.8, 163.1 (d, $J = 245.8$ Hz), 132.0 (d, $J = 3.2$ Hz), 130.9 (d, $J = 8.3$ Hz), 116.0 (d, $J = 21.8$ Hz), 64.6, 64.3, 47.8

$^{11}$B NMR (128 MHz, Acetone-$d_6$)

$\delta$ 9.61
$^{19}$F NMR (377 MHz, Acetone-$d_6$)
\[ \delta = -116.29 \]

HRMS [DART-MS] (M+NH$_4^+$)
\[ m/z \text{ calculated for C}_{13}\text{H}_{16}\text{BCIFN}_2\text{O}_5 = 345.0861 \]
\[ m/z \text{ found } = 345.0860 \]

TLC (hexanes:acetone 1:1)
\[ R_f = 0.45 \]

HPLC (DIACEL OJ-H, MTBE:MeCN: 95:5, flow rate: 1.0 mL/min, UV = 210 nm)
\[ R_t = 10.45 \text{ min} \]
\[ R_t = 13.36 \text{ min} \]
\[ \text{ee } \% = 49 \% \]

Racemic

![Racemic](image)

Enantioenriched

![Enantioenriched](image)
α-chloro α-MIDA boryl p-tolyl acetaldehyde (6.2.12b)

89% yield, white solid

$^1$H NMR (400 MHz, Chloroform- $d$)

$\delta$ 9.44 (s, 1H), 7.45 – 7.31 (m, 2H), 7.14 (d, $J = 8.1$ Hz, 2H), 3.97 – 3.77 (m, 3H), 3.72 (d, $J = 16.6$ Hz, 1H), 2.81 (s, 3H), 2.27 (s, 3H)

$^{13}$C NMR (101 MHz, Chloroform- $d$)

$\delta$ 194.53, 166.49, 166.38, 138.27, 130.68, 129.58, 127.56, 63.95, 63.74, 47.46, 20.96.

$^{11}$B NMR (128 MHz, Chloroform- $d$)

$\delta$ 9.9

HRMS [ESI-MS] [M+Na$^+$]

$m/z$ calculated for C$_{14}$H$_{13}$BNO$_5$ClNa = 346.0624

$m/z$ found= 346.0624

TLC (hexanes:acetone 1:2)

$R_f = 0.29$

(2-chloro-1-oxo-4-phenylbutan-2-yl)MIDA boronate (6.2.13b)

89% yield, white solid
$^1$H NMR (400 MHz, Acetonitrile-$d_3$)

$\delta$ 9.65 (s, 1H), 7.33 – 7.26 (m, 2H), 7.25 – 7.18 (m, 3H), 4.08 – 3.96 (m, 3H), 3.91 (d, $J$ = 17.2 Hz, 1H), 2.96 (s, 3H), 2.82 (ddd, $J$ = 12.5, 11.6, 4.2 Hz, 1H), 2.69 (ddd, $J$ = 14.2, 11.4, 5.0 Hz, 1H), 2.46 (td, $J$ = 12.5, 5.0 Hz, 1H), 2.25 (ddd, $J$ = 14.2, 11.6, 4.2 Hz, 1H)

$^{13}$C NMR (101 MHz, Acetonitrile-$d_3$)

$\delta$ 199.9, 168.0, 167.9, 142.1, 129.4, 129.4, 127.0, 64.3, 64.0, 47.2, 37.1, 31.0

$^{11}$B NMR (128 MHz, Acetonitrile-$d_3$)

$\delta$ 9.68

HRMS [ESI-MS] (M+NH$_4^+$)

$m/z$ calculated for C$_{15}$H$_{21}$BClN$_2$O$_5$ = 355.1232

$m/z$ found = 355.1228

TLC (hexanes:acetone 3:4)

$R_f$ = 0.44

HPLC (DIACEL OJ-H, MTBE:MeCN: 95:5, flow rate: 1.5 mL/min, UV = 210 nm)

$R_t$ = 7.18 min

$R_t$ = 14.23 min

ee % = 2%

Racemic

Enantioenriched
(1-[(1,1'-biphenyl)-4-yl]-1-chloro-2-oxoethyl)MIDA boronate (6.2.14b)

89% yield, white solid

$^1$H NMR (399 MHz, Acetonitrile-$d_3$)

$\delta$ 9.70 (d, $J = 1.2$ Hz, 1H), 7.75 – 7.60 (m, 6H), 7.50 – 7.45 (m, 2H), 7.42 – 7.35 (m, 1H), 4.12 – 4.00 (m, 3H), 3.94 (d, $J = 17.1$ Hz, 1H), 2.89 (d, $J = 1.4$ Hz, 3H)

$^{13}$C NMR (126 MHz, Acetone-$d_6$)

$\delta$ 194.5, 167.0, 166.9, 140.3, 139.9, 134.1, 128.8, 128.4, 127.5, 126.8, 126.8, 63.6, 63.4, 47.0

$^{11}$B NMR (128 MHz, Acetonitrile-$d_3$)

$\delta$ 9.6

HRMS [DART-MS] [M+NH$_4^+$]

$m/z$ calculated for C$_{19}$H$_{21}$BClN$_2$O$_5$ = 403.1232

$m/z$ found 40+ = 403.1232

TLC (hexanes:acetone 2:1)

$R_f$ = 0.21

HPLC (DIACEL OJ-H, MTBE:MeCN: 95:5, flow rate: 1.5 mL/min, UV = 210 nm)

$R_t$ = 9.41 min

$R_t$ = 14.45 min

ee % = 49 %

Racemic
Enantioenriched

6.3.9 Preparation of 2,5-disubstituted MIDA Boryl Thiazoles and 2-amino-5-MIDA Boryl Thiazoles

To a flame dried flask was added bromo boryl aldehyde, thioamide (1.5 equiv) and MeCN. The reaction mixture was warmed to 85 °C for 48 hours (or until complete by TLC analysis). The reaction was allowed to cool to room temperature and Amberlite IRA-67 (0.5 g) was added to
the mixture and agitated for approx. 30 min. The suspension was then filtered, washed with MeCN and then concentrated in vacuo. The residue was directly purified via SiO$_2$ chromatography to afford the borylated heterocycle.

(2-(2-ethylpyridin-4-yl)thiazol-5-yl)MIDA boronate (6.2.15a)

64% yield, slightly yellow residue

$^1$H NMR (600 MHz, Acetonitrile-$d_3$)

$\delta$ 8.58 (d, $J = 5.2$ Hz, 1H), 8.02 (s, 1H), 7.79 (br s, 1H), 7.70 (d, $J = 5.1$ Hz, 1H), 4.14 (d, $J = 17.1$ Hz, 2H), 3.98 (d, $J = 17.1$ Hz, 2H), 2.86 (q, $J = 7.6$ Hz, 2H), 2.72 (s, 3H), 1.30 (t, $J = 7.6$ Hz, 3H)

$^{13}$C NMR (126 MHz, Acetone-$d_6$)

$\delta$ 167.5, 164.5, 150.1, 149.7, 140.5, 118.2, 117.5, 104.9, 61.7, 47.5, 30.9, 13.1

$^{11}$B NMR (128 MHz, Acetonitrile-$d_3$)

$\delta$ 10.3

HRMS [DART-MS] [M+H$^+$]

$m/z$ calculated for C$_{15}$H$_{17}$BN$_3$O$_4$S = 346.1032

$m/z$ found = 346.1021

TLC (hexanes:acetone 3:4)

$R_f$ = 0.16

(2-phenylthiazol-5-yl)MIDA boronate (6.2.15b)

60% yield, white solid

$^1$H NMR (500 MHz, Acetonitrile-$d_3$)

$\delta$ 8.06 – 8.00 (m, 2H), 7.95 (s, 1H), 7.54 – 7.47 (m, 3H), 4.15 (d, $J = 17.1$ Hz, 2H), 4.02 – 3.95 (m, 2H), 2.74 (s, 3H)

$^{13}$C NMR (126 MHz, Acetonitrile-$d_3$)

$\delta$ 171.6, 167.7, 149.3, 133.6, 130.1, 129.1, 126.4, 61.6, 47.6

$^{11}$B NMR (128 MHz, Acetonitrile-$d_3$)
\[ \delta 10.3 \]

**HRMS [DART-MS] [M+H\(^{+}\)]**

- \( m/z \) calculated for \( C_{14}H_{14}BN_{2}O_{4}S = 317.0767 \)
- \( m/z \) found = 317.0758

**TLC (hexanes:acetone 3:4)**

\[ R_f = 0.31 \]

(2-methylthiazol-5-yl)MIDA boronate \( (6.2.15c) \)

54% yield, clear residue

**\(^1\)H NMR (500 MHz, Acetonitrile-\( d_3 \))**

- \( \delta 7.70 \) (s, 1H), 4.11 (d, \( J = 17.1 \) Hz, 2H), 3.94 (d, \( J = 17.0 \) Hz, 2H), 2.71 (s, 3H), 2.68 (s, 3H)

**\(^{13}\)C NMR (126 MHz, Acetonitrile-\( d_3 \))**

- \( \delta 167.8, 148.0, 61.5, 47.4, 18.0 \)

**\(^{11}\)B NMR (128 MHz, Acetonitrile-\( d_3 \))**

- \( \delta 10.4 \)

**IR (thin film)**

- \( \nu 3381, 2956, 2926, 1763, 1627, 1452, 1338, 1278, 1172, 1039, 985, 833 \)

**HRMS [DART-MS] [M+H\(^{+}\)]**

- \( m/z \) calculated for \( C_9H_9BN_2O_4S = 255.0610 \)
- \( m/z \) found = 255.0610

**TLC (hexanes:acetone 3:4)**

\[ R_f = 0.19 \]

(2-(phenylamino)thiazol-5-yl)MIDA boronate \( (6.2.15d) \)

78% yield, slightly yellow residue

**\(^1\)H NMR (500 MHz, Acetone-\( d_6 \))**

- \( \delta 7.73 – 7.67 \) (m, 2H), 7.34 – 7.29 (m, 3H), 7.00 – 6.94 (m, 1H), 4.36 (d, \( J = 17.0 \) Hz, 2H), 4.17 (d, \( J = 16.9 \) Hz, 2H), 2.97 (s, 3H)


\[ \text{C NMR (126 MHz, Acetone-}d_6) \]
\[ \delta 167.7, 145.0, 141.4, 128.8 (2C), 121.4, 117.1, 61.4, 47.2 \]

\[ \text{B NMR (128 MHz, Acetonitrile-}d_3) \]
\[ \delta 10.5 \]

HRMS [DART-MS] [M+H\(^+\)]
\[ m/z \text{ calculated for C}_{14}H_{15}BN_3O_4S = 332.0876 \]
\[ m/z \text{ found } = 332.0876 \]

TLC (hexanes:acetone 1:1)
\[ R_f = 0.15 \]

(2-((2,4,6-trichlorophenyl)amino)thiazol-5-yl)MIDA boronate (6.2.15e)
77% yield, white residue

\[ \text{H NMR (500 MHz, Acetone-}d_6) \]
\[ \delta 7.76 \text{ (s, 2H), 7.61 – 7.57 (m, 1H), 4.46 (d, } J = 17.1 \text{ Hz, 2H), 4.30 (d, } J = 17.1 \text{ Hz, 2H), 3.16 (s, 3H) \]

\[ \text{C NMR (126 MHz, Acetone-}d_6) \]
\[ \delta 167.3, 134.9, 134.5, 133.5, 132.5, 130.5, 129.4, 62.0, 47.7 \]

\[ \text{B NMR (128 MHz, Acetonitrile-}d_3) \]
\[ \delta 9.4 \]

HRMS [DART-MS] [M+H\(^+\)]
\[ m/z \text{ calculated for C}_{14}H_{12}BCl_3N_3O_4S = 433.9707 \]
\[ m/z \text{ found } = 433.9713 \]

TLC (hexanes:acetone 1:2)
\[ R_f = 0.37 \]

(2-(pyridin-2-ylamino)thiazol-5-yl)MIDA boronate (6.2.15f)

\[ \text{H NMR (500 MHz, DMSO-}d_6) \]
δ 11.22 (s, 1H), 8.28 (d, J = 5.1 Hz, 1H), 7.68 – 7.65 (m, 1H), 7.34 (s, 1H), 7.05 (d, J = 8.4 Hz, 1H), 6.89 (dd, J = 7.2, 5.1 Hz, 1H), 4.32 (d, J = 17.2 Hz, 2H), 4.11 (d, J = 17.2 Hz, 2H), 2.66 (s, 3H)

13C NMR (126 MHz, DMSO- d6)
δ 169.3, 163.5, 152.2, 147.0, 143.6, 138.2, 116.3, 111.2, 61.8, 47.9

11B NMR (128 MHz, Acetonitrile- d3)
δ 10.6

IR (thin film)
ν 3362, 3269, 2955, 2926, 1764, 1753, 1612, 1548, 14 79, 1440, 1411, 1334, 1278, 1159, 1035

HRMS [DART-MS] [M+H+]
m/z calculated for C13H14BN4O4S = 333.0828
m/z found = 333.0845

TLC (hexanes:acetone 1:3)
Rf = 0.29

(2-((4-(trifluoromethyl)phenyl)amino)thiazol-5-yl)MIDA boronate (6.2.15g)
78% yield, slightly yellow residue

1H NMR (500 MHz, Acetone- d6)
δ 7.95 – 7.91 (m, 2H), 7.67 – 7.62 (m, 2H), 7.41 (s, 1H), 4.38 (d, J = 17.0 Hz, 2H), 4.19 (d, J = 17.0 Hz, 2H), 2.99 (s, 3H)

13C NMR (126 MHz, Acetone- d6)
δ 167.7, 145.0, 126.1, 126.1, 116.6, 61.4, 47.2

11B NMR (128 MHz, Acetone- d6)
δ 10.5

19F NMR (377 MHz, Acetone- d6)
δ -62.0

HRMS [DART-MS] [M+H+]
m/z calculated for C15H14BF3N3O4S = 400.0750
m/z found = 400.0752

TLC (hexanes:acetone 1:2)
6.3.10 Synthesis of (E)-Boryl Enamides

The boryl aldehyde (0.400 g, 2 mmol, 1.0 equiv) was suspended in MeCN (20 mL) at room temperature and 2-chlorobenzyl amine (0.96 mL, 8 mmol, 4.0 equiv) was slowly added along the wall. After 5 minutes of stirring at room temperature the suspension has dissolved to yield a clear solution. Stirring was continued at room temperature for a total of two hours at which time it was cooled to 0 °C in an ice-water bath. Triethylamine (2.8 mL, 10 mmol, 10.0 equiv) and DMAP (0.012 g, 0.1 mmol, 5 mol %) were added to the solution then 2-iodobenzoyl chloride (4.25 g, 16 mmol, 8 equiv) was added. The reaction is stirred at 0 °C for 10 minutes. At which time the ice-water bath is removed and the reaction is stirred at room temperature for 5 hours. The resulting reaction mixture is filtered over a bed of Celite and subsequently concentrated onto Celite. The absorbed residue was then transferred onto a plug of SiO$_2$. The residue was washed with hexanes (250 mL), diethyl ether (250 mL), 2% MeOH in diethyl ether. The organic wash was discarded. The plug was washed with MeCN (250 mL) and concentrated in vacuo. The resulting enamide determined to be >90 % pure and used without further purification. In some instances, the enamide exhibits conformational flux and therefore only major peaks are reported.

Note: if product is not obtained >90% pure, repeat the wash cycle.

\[ R_f = 0.46 \]

\( (E)-(2-(2-bromo-N-(4-methylbenzyl)benzamido)vinyl)MIDA \) boronate (6.2.16a)

79% yield, white solid

$^1$H NMR (400 MHz, Acetone-\( d_6 \))

\[ \delta 7.54 – 7.47 \text{ (m, 1H), } 7.40 – 7.30 \text{ (m, 1H), } 7.30 – 7.22 \text{ (m, 2H), } 7.20 – 7.14 \text{ (m, 2H), } 7.02 – 6.85 \text{ (m, 2H), } 6.44 \text{ (d, } J = 15.8 \text{ Hz, 1H), } 5.03 \text{ (d, } J = 15.5 \text{ Hz, 1H), } 4.87 \text{ (d, } J = 15.5 \text{ Hz, 1H), } 4.76 \text{ (d, } J = 15.8 \text{ Hz, 1H), } 3.93 \text{ (d, } J = 17.0 \text{ Hz, 2H), } 3.61 – 3.53 \text{ (m, 2H), } 2.48 \text{ (s, 3H), } 1.92 \text{ (s, 3H) } \]

$^{13}$C NMR (126 MHz, Acetone-\( d_6 \))
δ 168.3, 167.7, 137.7, 136.8, 136.8, 136.3, 134.0, 131.1, 129.0, 128.7, 128.1, 127.2, 118.8, 61.0, 46.2, 44.8, 20.2

$^{11}$B NMR (128 MHz, Acetone-$d_6$)

δ 11.2

HRMS [DART-MS] [M+H$^+$]

$m/z$ calculated for C$_{22}$H$_{23}$BBrN$_2$O$_5$ = 485.0883

$m/z$ found = 485.0890

TLC (hexanes:acetone 1:1)

$R_f$ = 0.31

\[(E)-(2-(2-bromo-N-isopropylbenzamido)vinyl)MIDA boronate (6.2.16b)\]

85% yield, tan solid

$^1$H NMR (400 MHz, Acetonitrile-$d_3$)

δ 7.71 (d, $J$ = 8.1 Hz, 1H), 7.49 – 7.45 (m, 1H), 7.37 – 7.33 (m, 2H), 6.41 (d, $J$ = 16.0 Hz, 1H), 5.12 (d, $J$ = 16.0 Hz, 1H), 4.83 (s, 1H), 3.92 – 3.87 (m, 2H), 3.69 – 3.64 (m, 2H), 2.68 (s, 3H), 1.54 (d, $J$ = 6.9 Hz, 6H)

$^{13}$C NMR (126 MHz, Acetonitrile-$d_3$)

δ 168.95, 139.92, 137.84, 133.65, 131.48, 129.33, 129.00, 119.47, 62.98, 62.06, 47.57, 47.47, 19.64.

$^{11}$B NMR (128 MHz, Acetonitrile-$d_3$)

δ 10.9

HRMS [DART-MS] [M+H$^+$]

$m/z$ calculated for C$_{17}$H$_{21}$BBrN$_2$O$_5$ = 423.0726

$m/z$ found = 423.0730

TLC (EtOAc:MeCN 9:1)

$R_f$ = 0.37
(E)-(2-(N-(2-chlorophenethyl)-2-iodobenzamido)vinyl)MIDA boronate (6.2.16c)

87% yield, white solid 3:1 E:Z mixture of inseparable enamides

$^1$H NMR (399 MHz, Acetone-$d_6$)

$\delta$ 7.90 (d, $J = 7.9$ Hz, 1H), 7.77 (d, $J = 16.8$ Hz, 0.3H), 7.53 – 7.10 (m, 9H), 6.87 (d, $J = 7.6$ Hz, 0.3H), 6.55 (d, $J = 16.0$ Hz, 0.3H), 5.28 (d, $J = 16.8$ Hz, 0.3H), 5.14 (d, $J = 16.0$ Hz, 1H), 4.32 – 4.21 (m, 1H), 4.20 – 4.07 (m, 6H), 3.93 (dd, $J = 17.0$, 9.0 Hz, 2H), 3.22 – 3.17 (m, 3H), 3.03 (s, 3H)

$^{13}$C NMR (126 MHz, Acetone-$d_6$)

$\delta$ 170.0, 169.6, 169.0, 168.9, 168.8, 168.4, 143.0, 142.7, 140.0, 139.8, 138.4, 138.1, 137.5, 136.7, 135.1, 134.6, 132.3, 132.2, 131.5, 131.2, 130.3, 130.2, 129.7, 129.4, 129.21, 129.0, 128.8, 128.6, 128.2, 126.1, 93.1, 92.9, 62.9, 62.5, 62.0, 47.8, 47.5, 47.0, 45.8, 42.2, 32.0, 31.1, 21.4

$^{11}$B NMR (128 MHz, Acetonitrile-$d_3$)

$\delta$ 11.3

HRMS [DART-MS] [M+H$^+$]

$m/z$ calculated for C$_{22}$H$_{22}$BClIN$_2$O$_5$ = 567.0355

$m/z$ found = 567.0357

TLC (hexanes:acetone 3:4)

$R_f$ = 0.38

(6.2.16d)

(E)-(2-(N-(2-chlorobenzyl)-2-iodobenzamido)vinyl)MIDA boronate (6.2.16d)

91% yield, white solid

$^1$H NMR (400 MHz, Acetone-$d_6$)

$\delta$ 7.96 (d, $J = 8.1$ Hz, 1H), 7.59 (t, $J = 7.5$ Hz, 1H), 7.55 – 7.43 (m, 3H), 7.43 – 25 (m, 3H), 6.74 (d, $J = 15.8$ Hz, 1H), 5.28 – 5.14 (m, 2H), 4.82 (t, $J = 15.8$ Hz, 1H), 4.13 (d, $J = 17.0$ Hz, 2H), 3.87 (d, $J = 17.0$ Hz, 2H), 2.82 (s, 3H)

$^{13}$C NMR (126 MHz, Acetone-$d_6$)

$\delta$ 169.7, 167.7, 167.6, 141.6, 139.3, 136.9, 133.7, 132.3, 130.9, 129.3, 128.6, 128.4, 128.2, 127.6, 127.1, 92.1, 61.5, 61.1, 46.4, 43.3

$^{11}$B NMR (128 MHz, Acetone-$d_6$)

$\delta$ 11.1

HRMS [DART-MS] [M+H$^+$]

$m/z$ calculated for C$_{21}$H$_{20}$BClIN$_2$O$_5$ = 553.0198
m/z found = 553.0205

TLC (hexanes:acetone 1:2)

R_f = 0.41

(E)-(2-(2-bromo-N-(2-chlorobenzyl)-4,5-dimethoxybenzamido)vinyl)MIDA boronate (6.2.16e)

82% yield, white solid (90% pure)

^1^H NMR (400 MHz, Acetone-^d_6)

δ 7.49 – 7.38 (m, 2H), 7.30 – 7.29 (m, 2H), 7.20 (s, 1H), 7.07 (s, 1H), 6.82 (d, J = 15.9 Hz, 1H), 5.22 (s, 1H), 5.10 (s, 1H), 4.73 (d, J = 15.9 Hz, 1H), 4.11 (d, J = 16.9 Hz, 2H), 3.86 (d, J = 16.9, 2H), 3.86 (s, 3H), 2.79 (s, 3H)

^1^3^C NMR (126 MHz, Acetone-^d_6)

δ 168.2, 167.8, 150.9, 149.3, 137.2, 133.8, 132.2, 129.2, 128.9, 128.4, 127.5, 127.1, 127.1, 115.6, 111.8, 109.4, 61.1, 55.7, 55.6, 46.3, 43.4

^1^1^B NMR (128 MHz, Acetone-^d_6)

δ 11.0

HRMS [ESI-MS] [M+H^+] 

m/z calculated for C_{23}H_{24}BBrClN_2O_7 = 565.0579

m/z found = 565.0568

TLC (hexanes:acetone 1:1)

R_f = 0.45

(E)-(2-(2-bromo-N-(2,3-dimethoxybenzyl)benzamido)vinyl)MIDA boronate (6.2.16f)

83% yield, white solid

^1^H NMR (500 MHz, Acetone-^d_6)

δ 7.70 (d, J = 8.1 Hz, 1H), 7.59 – 7.48 (m, 1H), 7.48 – 7.40 (m, 2H), 7.02 (dd, J = 8.2, 7.6 Hz, 1H), 6.96 – 6.90 (m, 2H), 6.63 (d, J = 15.8 Hz, 1H), 5.17 (d, J = 2.8 Hz, 2H), 4.83 (d, J = 15.8 Hz, 1H), 4.19 (d, J = 16.9 Hz, 1H), 4.14 – 4.03 (m, 3H), 3.90 (s, 3H), 3.86 (s, 3H), 2.72 (s, 3H)
\(^{13}\)C NMR (126 MHz, Acetone-\(\text{d}_6\))
\[\delta 168.2, 167.8, 167.6, 152.7, 146.7, 137.8, 136.9, 132.8, 131.0, 130.2, 128.7, 128.0, 123.8, 118.8, 118.7, 111.4, 61.4, 61.0, 59.7, 55.2, 46.2, 40.1\]

\(^{11}\)B NMR (128 MHz, Acetonitrile-\(\text{d}_3\))
\[\delta 11.2\]

HRMS [DART-MS] [M+H\(^+\)]
\[m/z\] calculated for C\(_{23}\)H\(_{25}\)BBrN\(_2\)O\(_7\) = 531.0938
\[m/z\] found = 531.0933

TLC (hexanes:acetone 3:4)
\[R_f = 0.39\]

\((E)-2-(N-(2-bromobenzyl)benzamido)vinyl\)MIDA boronate (6.2.16g)

\(^1\)H NMR (500 MHz, Acetone-\(\text{d}_6\))
\[\delta 7.67 - 7.62 (m, 3H), 7.56 - 7.47 (m, 4H), 7.43 - 7.35 (m, 1H), 7.32 - 7.27 (m, 1H), 7.22 (dd, \(J = 8.0, 7.2\) Hz, 1H), 5.08 (s, 2H), 4.69 (d, \(J = 16.0\) Hz, 1H), 4.11 (d, \(J = 16.9\) Hz, 2H), 3.90 (d, \(J = 16.9\) Hz, 2H), 2.79 (s, 3H)

\(^{13}\)C NMR (126 MHz, Acetone-\(\text{d}_6\))
\[\delta 170.2, 167.8, 135.6, 132.6, 130.5, 128.7, 128.4, 127.8, 127.3, 61.2, 46.3\]

\(^{11}\)B NMR (128 MHz, Acetone-\(\text{d}_6\))
\[\delta 11.2\]

IR (thin film)
\[\nu 3096, 3002, 2980, 1763, 1658, 1616, 1444, 1394, 1334, 1317, 1276, 1244, 1145, 1109, 1028, 987, 956, 862, 750, 732, 700\]

HRMS [DART-MS] [M+H\(^+\)]
\[m/z\] calculated for C\(_{21}\)H\(_{20}\)BBrN\(_2\)O\(_5\) = 471.0726
\[m/z\] found = 471.0725

TLC (hexanes:acetone 1:1)
\[R_f = 0.28\]
(E)-(2-((N-benzyl-2-bromophenyl)sulphonamido)vinyl)MIDA boronate (6.2.16h)

56% yield, white solid

$^1$H NMR (400 MHz, Acetone-$d_6$)

$\delta$ 8.16 (d, $J = 7.5$ Hz, 1H), 7.92 (d, $J = 7.5$ Hz, 1H), 7.69 – 7.58 (m, 2H), 7.41 (m, 2H), 7.34 (m, 2H), 7.25 (t, $J = 7.2$ Hz, 1H), 7.12 (d, $J = 16.1$ Hz, 1H), 4.90 (s, 2H), 4.61 (d, $J = 16.1$ Hz, 1H), 4.14 (d, $J = 16.9$ Hz, 2H), 3.87 (d, $J = 16.9$ Hz, 2H), 2.60 (s, 3H)

$^{13}$C NMR (126 MHz, Acetone-$d_6$)

$\delta$ 167.8 (2C), 138.7, 136.2, 135.9, 135.1, 134.5, 131.7, 128.3, 128.2, 127.0, 126.9, 119.5, 61.3, 61.2, 49.0, 46.2

$^{11}$B NMR (128 MHz, Acetone-$d_6$)

$\delta$ 11.2

IR (thin film)

$\nu$ 3100, 3081, 3001, 2987, 1753, 1620, 1448, 1421, 1336, 1282, 1168, 1126, 1055, 1028, 1006, 954, 927, 862, 825, 756, 736, 702

HRMS [DART-MS] [M+H$^+$]

$m/z$ calculated for C$_{20}$H$_{21}$BBN$_2$O$_6$S = 507.0397

$m/z$ found = 507.0407

TLC (hexanes:acetone 3:4)

$R_f$ = 0.4

(Z)-(2-(2-bromo-N-(2-chlorobenzyl)benzamido)-1-(p-tolyl)vinyl)MIDA boronate (6.2.16i)

46 % yield, white solid

$^1$H NMR (500 MHz, DMSO-$d_6$)

$\delta$ 7.77 – 7.71 (m, 1H), 7.54 – 7.49 (m, 2H), 7.38 – 7.23 (m, 5H), 7.09 – 7.03 (m, 2H), 6.91 (d, $J = 8.1$ Hz, 2H), 6.42 (s, 1H), 4.47 (s, 2H), 4.08 (d, $J = 17.2$ Hz, 2H), 3.38 (d, $J = 17.1$ Hz, 2H), 2.43 (s, 3H), 2.27 (s, 3H)
13C NMR (126 MHz, DMSO-d6)
\[ \delta \ 168.7, 168.2, 137.7, 135.9, 134.7, 133.6, 132.8, 132.7, 131.8, 131.3, 129.1, 129.1, 128.9, 128.8, 128.5, 128.4, 128.3, 128.1, 127.1, 118.3, 61.3, 46.5, 45.6, 20.8 \]

11B NMR (128 MHz, DMSO-d6)
\[ \delta \ 12.6 \]

HRMS [DART-MS] [M+H⁺]

\[ m/z \text{ calculated for } C_{28}H_{26}BBrClN_2O_5 = 595.0806 \]

\[ m/z \text{ observed} = 595.0805 \]

TLC (hexanes:acetone 4:3)
\[ R_f = 0.28 \]

6.3.11 Synthesis of Boryl Methylene Isoindolones

To a flame-dried microwave vial was charged with a magnetic stir bar, boryl enamide (1.0 equiv) and Pd(PPh₃)₄ (10 mol %). The flask was sealed with septum and evacuated under vacuum. The flask was then refilled with nitrogen. This process was repeated three times. Nitrogen-sparged DMF (2.5 mL) was then added to the flask followed by freshly-distilled Et₃N (5.0 equiv). The vial was then warmed to 110 °C for four hours. At which time TLC analysis showed complete consumption of starting material. The reaction was allowed to cool to room temperature and the reaction was diluted with EtOAc, followed by brine. The organic layer was separated and the aqueous layer was further extracted with EtOAc three times. The combined organics were dried with Na₂SO₄, filtered and concentrated in vacuo. The resulting residue was purified by SiO₂ to provide the desired boryl-isoindolone as a mixture of E:Z-isomers.

6.3.11.1 Hydrogenation of Methylene-Isoindolone MIDA Boronate

A flask charged with a magnetic stir-bar was added isoindoline (0.120g, 0.283 mmol, 1.0 equiv) and THF (10 mL) and subsequently sealed with a rubber septa. Pd/C (10 %, 0.1 g) was then added and the flask was evacuated under reduced pressure. A balloon of H₂ was then introduced to the evacuated flask and allowed to stir at room temperature for 18 hours at which time TLC analysis showed complete consumption of starting material. The reaction mixture was then filtered over Celite and concentrated under reduced pressure. The residue was purified via SiO₂ chromatography to yield the alkyl boronate product.
33% yield over two steps, white solid

$^{1}$H NMR (400 MHz, Acetone-$d_{6}$)

$\delta$ 7.77 (dd, $J = 19.3, 7.6$ Hz, 2H), 7.56 (t, $J = 7.5$ Hz, 1H), 7.47 (t, $J = 7.4$ Hz, 1H), 7.26 (d, $J = 8.0$ Hz, 2H), 7.13 (d, $J = 7.8$ Hz, 2H), 5.22 (d, $J = 15.0$ Hz, 1H), 4.55 (dd, $J = 9.2, 3.4$ Hz, 1H), 4.39 (d, $J = 15.0$ Hz, 1H), 4.30 (d, $J = 5.6$ Hz, 1H), 4.26 (d, $J = 5.8$ Hz, 1H), 4.11 (t, $J = 16.7$ Hz, 2H), 3.15 (s, 3H), 2.29 (s, 3H), 1.65 (dd, $J = 14.4, 3.4$ Hz, 1H), 0.98 (dd, $J = 14.4, 9.2$ Hz, 1H)

$^{13}$C NMR (126 MHz, Acetone-$d_{6}$)

$\delta$ 167.8, 167.3, 167.1, 148.1, 136.5, 135.3, 132.0, 130.9, 129.0, 128.1, 127.4, 123.8, 122.6, 61.5, 61.5, 56.5, 45.3, 42.4, 20.1

$^{11}$B NMR (128 MHz, Acetone-$d_{6}$)

$\delta$ 12.1

IR (thin layer)

$\nu$ 2974, 2953, 2872, 1755, 1666, 1558, 1516, 1471, 1410, 1338, 1296, 1170, 1153, 1031, 964, 950, 869, 842, 752

HRMS [DART-MS] [M+H$^+$]

$m/z$ calculated for C$_{22}$H$_{24}$BN$_2$O$_5$ = 407.1778

$m/z$ found = 407.1785

TLC (hexanes:acetone 1:2)

$R_f$ = 0.6

85 % yield, inseparable mixture of 1:1 ratio of E:Z alkene isomers

$^{1}$H NMR (400 MHz, Acetone-$d_{6}$)

$\delta$ 8.41 (d, $J = 7.9$ Hz, 1H), 7.89 (d, $J = 7.7$ Hz, 1H), 7.73 – 7.50 (m, 6H), 5.75 (s, 1H), 5.60 (s, 1H), 4.71 (m, 1H), 4.61 (m, 1H), 4.38 (dd, $J = 16.9, 8.6$ Hz, 4H), 4.24 (dd, $J = 16.8, 8.6$ Hz, 4H), 4.18 (dd, $J = 16.8, 8.6$ Hz, 4H), 2.29 (s, 3H), 1.65 (dd, $J = 14.4, 3.4$ Hz, 1H), 0.98 (dd, $J = 14.4, 9.2$ Hz, 1H)

((2-isopropyl-3-oxoisoindolin-1-ylidene)methyl)MIDA boronate (6.2.18b)
16.9, 8.0 Hz, 4H), 3.40 (s, 3H), 3.33 (s, 3H), 1.58 (d, J = 6.7 Hz, 6H), 1.53 (d, J = 6.9 Hz, 6H)

$^{13}$C NMR (126 MHz, Acetone-$d_6$)
\[ \delta \ 167.9, 167.8, 167.4, 166.1, 144.8, 144.1, 138.8, 136.2, 131.4, 130.9, 129.5, 128.9, 124.6, 121.7, 121.6, 119.9, 61.7, 61.6, 46.3, 46.2, 46.1, 43.2, 19.3, 19.2 \]

$^{11}$B NMR (128 MHz, Acetone-$d_6$)
\[ \delta \ 11.0, 10.3 \]

HRMS [DART-MS] [M+H$^+$]
\[ m/z \text{ calculated for } C_{17}H_{20}BN_2O_5 = 343.1465 \]
\[ m/z \text{ found } = 343.1461 \]

TLC (hexanes:acetone 3:4)
\[ R_f = 0.40 \]

\[ ((2-(2-chlorophenethyl)-3-oxoisxindolin-1-yl)methyl)MIDA boronate (6.2.18c) \]

60% yield, white solid

$^1$H NMR (400 MHz, Acetone-$d_6$) – two conformations observed
\[ \delta \ 7.86 – 7.77 (m, 1H), 7.69 (dd, J = 7.5, 1.1 Hz, 1H), 7.60 – 7.52 (m, 1H), 7.49 – 7.38 (m, 2H), 7.36 – 7.17 (m, 3H), 4.72 (dd, J = 9.2, 3.5 Hz, 1H), 4.35 – 4.27 (m, 2H), 4.23 – 4.08 (m, 3H), 3.59 (ddd, J = 14.1, 9.1, 5.5 Hz, 1H), 3.19 (s, 3H), 3.11 (ddd, J = 13.4, 9.0, 6.8 Hz, 1H), 2.80 (s, 1H), 1.53 (td, J = 15.8, 15.2, 3.6 Hz, 1H), 0.94 (ddd, J = 14.3, 9.2 Hz, 1H) \]

$^{13}$C NMR (126 MHz, Acetone-$d_6$) – two conformations observed
\[ \delta \ 167.7, 167.4, 166.9, 148.1, 137.0, 133.7, 132.1, 131.2, 130.8, 129.3, 128.0, 127.4, 127.1, 123.7, 122.3, 61.6, 61.6, 57.2, 45.4, 39.2, 31.9 \]

$^{11}$B NMR (128 MHz, Acetone-$d_6$)
\[ \delta \ 12.1 \]

HRMS [DART-MS] [M+H$^+$]
\[ m/z \text{ calculated for } C_{22}H_{23}BClN_2O_5 = 441.1388 \]
\[ m/z \text{ found } = 441.1378 \]

TLC (hexanes:acetone 1:2)
\[ R_f = 0.6 \]
(E)-((2-(2-chlorobenzyl)-3-oxoisoindolin-1-ylidene)methyl)MIDA boronate (E-6.2.18d)

X-ray quality crystals were grown from a saturated solution of (E-6.2.18d) in acetonitrile-d₃
55:45 ratio of separable alkene isomers
42% yield, white solid

¹H NMR (400 MHz, Acetone-d₆)
\[ \delta \text{ ppm} \]
8.50 (d, J = 7.9 Hz, 1H), 7.87 – 7.83 (m, 1H), 7.73 (t, J = 7.6 Hz, 1H), 7.63 (d, J = 7.4 Hz, 1H), 7.47 (d, J = 7.3 Hz, 1H), 7.34 – 7.24 (m, 2H), 7.05 (d, J = 6.2 Hz, 1H), 5.29 (s, 1H), 5.17 (s, 2H), 4.32 (d, J = 16.9 Hz, 2H), 4.08 (d, J = 16.9 Hz, 2H), 3.02 (s, 3H)

¹³C NMR (126 MHz, Acetonitrile-d₃)
\[ \delta \text{ ppm} \]
167.8, 166.5, 144.1, 136.0, 134.5, 132.3, 132.0, 130.3, 129.5, 129.4, 128.7, 127.7, 127.3, 124.5, 122.5, 61.6, 46.3, 40.0

¹¹B NMR (128 MHz, Acetone-d₆)
\[ \delta \text{ ppm} \]
10.6

HRMS [DART-MS] [M+H⁺]
\[ m/z \text{ calculated for C}_{21}H_{19}BClN_{2}O_{5} = 425.1077 \]
\[ m/z \text{ found } = 425.1067 \]

TLC (hexanes:acetone 1:2)
\[ R_f = 0.46 \]

(Z)-((2-(2-chlorobenzyl)-3-oxoisoindolin-1-ylidene)methyl)MIDA boronate (Z-6.2.18d)
42\% \text{ yield, white solid}

$^1$H NMR (500 MHz, Acetonitrile-$d_3$)

$\delta$ 8.01 (d, $J = 7.9$ Hz, 1H), 7.81 (d, $J = 7.5$ Hz, 1H), 7.74 (d, $J = 7.4$ Hz, 1H), 7.61 (t, $J = 7.5$ Hz, 1H), 7.45 – 7.41 (m, 1H), 7.25 – 7.21 (m, 1H), 7.16 (t, $J = 7.6$ Hz, 1H), 6.81 – 6.79 (m, 1H), 5.61 (s, 1H), 5.31 (s, 2H), 3.94 (d, $J = 16.9$ Hz, 2H), 3.80 (d, $J = 17.0$ Hz, 2H), 2.91 (s, 3H)

$^{13}$C NMR (126 MHz, Acetonitrile-$d_3$)

$\delta$ 168.1, 167.2, 144.1, 138.8, 135.7, 132.4, 132.0, 129.5, 129.2, 127.9, 127.9, 126.8, 126.0, 122.4, 120.2, 61.4, 46.4. 42.6

$^{11}$B NMR (128 MHz, Acetonitrile-$d_3$)

$\delta$ 10.0

HRMS [DART-MS] [M+H$^+$]

$m/z$ calculated for C$_{21}$H$_{19}$BClN$_2$O$_5$ = 425.1077

$m/z$ found = 425.1067

TLC (hexanes:acetone 1:2)

$R_f = 0.35$

(±)-(2-(2-chlorobenzyl)-3-oxoisooindolin-1-yl)methyl)MIDA boronate (6.2.18d)

94\% \text{ yield, white solid}

$^1$H NMR (600 MHz, Acetone-$d_6$)

$\delta$ 7.82 (d, $J = 7.7$ Hz, 1H), 7.74 (d, $J = 7.5$ Hz, 1H), 7.58 (t, $J = 7.5$ Hz, 1H), 7.48 (t, $J = 7.4$ Hz, 1H), 7.43 – 7.39 (m, 1H), 7.29 – 7.25 (m, 3H), 5.20 (d, $J = 16.1$ Hz, 1H), 4.68 (d, $J = 16.1$ Hz, 1H), 4.63 (dd, $J = 9.9$, 3.2 Hz, 1H), 4.23 (dd, $J = 16.9$, 2.1 Hz, 2H), 4.05 (d, $J = 16.9$ Hz, 2H), 3.12 (s, 3H), 1.69 (dd, $J = 14.4$, 3.2 Hz, 1H), 0.94 (dd, $J = 14.3$, 9.9 Hz, 1H)

$^{13}$C NMR (126 MHz, Acetone-$d_6$)

$\delta$ 167.7, 167.2, 167.1, 147.7, 135.4, 132.7, 131.7, 131.0, 129.5, 129.4, 128.7, 127.5, 127.2, 124.1, 122.6, 61.5, 61.5, 57.5, 45.3, 40.7

$^{11}$B NMR (192 MHz, Acetone-$d_6$)

$\delta$ 11.9

HRMS [DART-MS] [M+H$^+$]

$m/z$ calculated for C$_{21}$H$_{21}$BClN$_2$O$_5$ = 427.1232

$m/z$ found = 427.1237
TLC (hexanes:acetone 3:4)
\[ R_f = 0.26 \]

\[
\text{(2-(2-chlorobenzyl)-5,6-dimethoxy-3-oxoisoindolin-1-yl)methyl} \text{MIDA boronate (6.2.18e)}
\]
26% over two steps

\[ ^1\text{H NMR (500 MHz, Acetone-}d_6) \]
\[ \delta 7.50 \ (s, 1H), 7.42 - 7.39 \ (m, 1H), 7.29 - 7.24 \ (m, 3H), 7.20 \ (s, 1H), 5.15 \ (d, J = 16.1 \ Hz, 1H), 4.62 \ (d, J = 16.1 \ Hz, 1H), 4.51 \ (dd, J = 10.5, 2.8 \ Hz, 1H), 4.28 \ (d, J = 5.6 \ Hz, 1H), 4.24 \ (d, J = 5.6 \ Hz, 1H), 4.09 \ (d, J = 6.4 \ Hz, 1H), 4.06 \ (d, J = 6.4 \ Hz, 1H), 3.90 \ (s, 3H), 3.89 \ (s, 3H), 3.11 \ (s, 3H), 1.69 \ (dd, J = 14.1, 2.9 \ Hz, 1H), 0.81 \ (dd, J = 14.0, 10.5 \ Hz, 1H) \]

\[ ^{13}\text{C NMR (126 MHz, Acetone-}d_6) \]
\[ \delta 167.8, 167.5, 167.4, 152.5, 149.6, 141.3, 135.7, 132.6, 129.5, 129.3, 128.6, 127.2, 123.6, 107.3, 104.7, 61.6, 61.5, 57.2, 55.3, 55.3, 45.4, 40.7 \]

\[ ^{11}\text{B NMR (128 MHz, Acetone-}d_6) \]
\[ \delta 12.2 \]

HRMS [DART-MS] [M+H⁺]
\[ m/z \text{ calculated for C}_{23}\text{H}_{25}\text{BClN}_2\text{O}_7 = 487.1443 \]
\[ m/z \text{ found } = 487.1449 \]

TLC (hexanes:acetone 1:2)
\[ R_f = 0.6 \]

\[
\text{(2-(2,3-dimethoxybenzyl)-3-oxoisoindolin-1-yl)methyl} \text{MIDA boronate (6.2.18f)}
\]
29% over two steps, white solid

\[ ^1\text{H NMR (400 MHz, Acetone-}d_6) \]
\[ \delta 7.80 \ (d, J = 7.6Hz, 1H), 7.74 \ (d, J = 7.4 Hz, 1H), 7.56 \ (t, J = 7.5 Hz, 1H), 7.48 \ (t, J = 7.3 Hz, 1H), 7.04 - 6.92 \ (m, 2H), 6.81 \ (d, J = 7.4 Hz, 1H), 5.15 \ (d, J = 15.2 Hz, 1H), 4.60 \ (d, J = 15.2 Hz, 1H), 4.54 \ (dd, J = 10.3, 3.0 Hz, 1H), 4.25 \ (dd, J = 16.9, 3.8 Hz, 2H), \]
\[ \ldots \]
4.09 (d, $J = 9.5$ Hz, 1H), 4.05 (d, $J = 9.8$ Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.14 (s, 3H), 1.75 (dd, $J = 14.3$, 3.0 Hz, 1H), 0.83 (dd, $J = 14.3$, 10.3 Hz, 1H)

$^{13}$C NMR (126 MHz, Acetone-$d_6$)

$\delta$ 167.9, 167.1, 166.9, 152.8, 147.7, 147.0, 132.1, 131.4, 130.8, 127.4, 124.0, 123.9, 122.5, 121.0, 111.8, 61.4, 61.4, 60.1, 57.3, 55.1, 45.2, 37.3

$^{11}$B NMR (128 MHz, Acetone-$d_6$)

$\delta$ 12.2

HRMS [DART-MS] [M+H$^+$]

$m/z$ calculated for C$_{23}$H$_{26}$BN$_2$O$_7$ = 453.1833
$m/z$ found = 453.1836

TLC (hexanes:acetone 1:2)

$R_f$ = 0.29

### 6.3.12 Intramolecular Bsp$^3$-Csp$^2$ Suzuki-Miyaura Cross-Coupling

To a stir-bar equipped flamed-dried microwave vial sealed with a rubber septum was charged chloro(2-dicyclohexylphosphino-2’,6’-di-isopropoxy-1.1’-biphenyl)(2-amino-1,1'-bi-phenyl-2-yl)palladium(II) (2$^{nd}$ Generation RuPhos-Pd$^{2+}$precatalyst) (10 mol %) and Cs$_2$CO$_3$ (6.0 equiv). The atmosphere was then removed and nitrogen was introduced. This was repeated at least 3 times. Then a solution of alkyl boronate (0.071 g, 0.166 mmol, 1.0 equiv) in nitrogen-sparged 1,4-dioxane (5 mL) followed by the addition of nitrogen-sparged distilled H$_2$O (0.5 mL). The rubber septum was then removed and the vial was sealed with a microwave vial cap. The vial was then warmed to 100 °C in a reaction block and stirred at this temperature for 24 hours. After the specified time the vial was allowed to cool to room temperature and diluted with EtOAc (5mL). The organic layer was removed and the aqueous was further extracted with EtOAc (3 x 5 mL). The combined organics were then dried with NaSO$_4$, filtered and concentrated via rotary evaporator. The residue was then purified to afford the isoindoldone as a white solid.

![Isoindoldone structure](image)

7,8,13,13a-tetrahydro-5H-benzo[4,5]azepino[2,1-a]isoindol-5-one (6.2.20c)
84% yield, white solid

$^1$H NMR (400 MHz, Chloroform-$d$)
δ 7.82 (d, J = 7.5 Hz, 1H), 7.57 – 7.46 (m, 2H), 7.42 (t, J = 7.2 Hz, 1H), 7.24 (dt, J = 7.4, 3.6 Hz, 1H), 7.20 – 7.13 (m, 3H), 4.84 – 4.68 (m, 1H), 4.38 (d, J = 11.0 Hz, 1H), 3.23 (dd, J = 14.6, 1.8 Hz, 1H), 3.01 – 2.91 (m, 2H), 2.91 – 2.79 (m, 2H)

$^{13}$C NMR (126 MHz, Chloroform-d)

δ 167.0, 144.8, 141.3, 137.7, 131.9, 131.5, 129.8, 129.8, 128.4, 127.4, 127.0, 123.7, 122.0, 61.1, 42.5, 41.1, 36.2

IR (thin film)

ν 2910, 2858, 1678, 1616, 1467, 1448, 1419, 1280, 1263, 842, 756, 721, 690

HRMS [DART-MS] [M+H$^+$]

$m/z$ calculated for C$_{17}$H$_{16}$NO = 250.1231
$m/z$ found = 250.1225

TLC (hexanes:EtOAc 1:1)

$R_f$ = 0.44

11b,12-dihydroisoindolo[2,1-b]isoquinolin-7(5H)-one (6.2.20d)

82% yield, white solid

$^1$H NMR (500 MHz, Chloroform-d)

δ 7.92 (d, J = 7.6 Hz, 1H), 7.62 – 7.54 (m, 2H), 7.51 (t, J = 7.6 Hz, 1H), 7.31 – 7.19 (m, 4H), 5.51 – 5.25 (m, 1H), 4.63 (dd, J = 11.8, 4.3 Hz, 1H), 4.61 – 4.54 (m, 1H), 3.39 (dd, J = 15.4, 4.2 Hz, 1H), 2.64 (dd, J = 15.1, 11.8 Hz, 1H)

$^{13}$C NMR (126 MHz, Chloroform-d)

δ 167.2, 145.6, 132.5, 131.9, 131.7, 131.4, 129.1, 128.4, 127.1, 126.9, 126.8, 123.8, 122.0, 55.7, 42.0, 34.8

HRMS [DART-MS] [M+H$^+$]

$m/z$ calculated for C$_{16}$H$_{14}$NO = 236.1075
$m/z$ found = 236.1064

TLC (hexanes:EtOAc 2:1)

$R_f$ = 0.2

6.3.12.1 Isolation of boronic acid 6.2.20e
9,10-dimethoxy-11b,12-dihydroisoindolo[2,1-b]isoquinolin-7(5H)-one (6.2.20e)

X-ray quality crystals of 6.2.20e grown from a saturated solution of MeCN-\textit{d}_3 overnight

63\% yield, white solid

$^1$H NMR (500 MHz, Acetone-$\textit{d}_6$)

$\delta$ 7.31 (d, $J = 5.0$ Hz, 4H), 7.22 (d, $J = 11.7$ Hz, 3H)), 5.16 (d, $J = 15.4$ Hz, 1H), 4.53 (dd, $J = 9.7$, 4.7 Hz, 1H), 4.35 (d, $J = 15.4$ Hz, 1H), 3.89 (s, 3H), 3.83 (s, 3H), 1.60 (dd, $J = 15.2$, 4.7 Hz, 1H), 0.89 (dd, $J = 15.2$, 9.7 Hz, 1H)

$^{13}$C NMR (126 MHz, Acetone-$\textit{d}_6$)

$\delta$ 167.3, 152.7, 149.8, 141.8, 138.6, 128.4, 127.6, 126.9, 123.9, 105.6, 105.0, 56.5, 55.3, 55.2, 42.8

$^{11}$B NMR (128 MHz, Acetone-$\textit{d}_6$)

$\delta$ 31.0

HRMS [DART-MS] [$\text{M+H}^+$]

$m/z$ calculated for C$_{18}$H$_{21}$BNO$_5$ = 342.1544

$m/z$ found = 342.1525

TLC (hexanes:acetone 1:1)

$R_f$ = 0.40
6.4 References


25 Dr. Piera Trinchera (Yudin Lab) was first to synthesize **6.2.01** by this route


Recent review on the synthesis and utility of α-haloboronic esters: Matteson, D. S. J. Org. Chem. 2013, 78, 10009–10023. and the references therein


Appendix I – Chapter Two $^1$H, $^{13}$C NMR Spectra and X-Ray Data Tables
2.2.06

20140326_mercury_400_Hsl_1265-PC-PROTON_01

20140326_mercury_400_Hsl_1265-val_30-CARBON_01

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

n (ppm)

-11000 -10000 -9000 -8000 -7000 -6000 -5000 -4000 -3000 -2000 -1000 0
2.2.36
more polar

20130103_wmmr_500_3ud742-nil_17-PDTROR_01

20130105_wmmr_500_3ul742-nil_17-CARBON_01
2.2.36 less polar
Detailed X-Ray Crystallographic Information for rac-(R)-2-methyl-5-((R)-2-phenylaziridin-2-yl)-5-(pyrrolidin-1-yl)pent-3-yn-2-ol (2.2.29)

**Crystallization Conditions:** Slow diffusion of hexanes into ethyl acetate over 48 hours

![Crystal structure diagram](image)

**Table 1.** Crystal data and structure refinement for rac-(R)-2-methyl-5-((R)-2-phenylaziridin-2-yl)-5-(pyrrolidin-1-yl)pent-3-yn-2-ol (2.2.29)

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<td>97.4 %</td>
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<td>Absorption correction</td>
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Max. and min. transmission 1.146 and 0.653
Refinement method Full-matrix least-squares on F^2
Data / restraints / parameters 1589 / 1 / 198
Goodness-of-fit on F^2 1.116
Final R indices [I>2sigma(I)] R1 = 0.0539, wR2 = 0.1212
R indices (all data) R1 = 0.0636, wR2 = 0.1271
Largest diff. peak and hole 0.206 and -0.145 e.Å^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2x 10^3) for rac-(R)-2-methyl-5-((R)-2-phenylaziridin-2-yl)-5-(pyrrolidin-1-yl)pent-3-yn-2-ol (2.2.29). U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

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Table 3. Bond lengths [Å] and angles [°] for rac-(R)-2-methyl-5-((R)-2-phenylaziridin-2-yl)-5-(pyrrolidin-1-yl)pent-3-yn-2-ol (2.2.29)

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Symmetry transformations used to generate equivalent atoms:

**Table 4.** Anisotropic displacement parameters (Å² x 10³) for rac-(R)-2-methyl-5-((R)-2-phenylaziridin-2-yl)-5-(pyrrolidin-1-yl)pent-3-yn-2-ol (2.2.29).

The anisotropic displacement factor exponent takes the form: -2p²[ h² a*² U₁₁ + ... + 2 h k a* b* U₁₂ ]

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Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for *rac*-(*R*)-2-methyl-5-(*R*)-2-phenylaziridin-2-yl)-5-(pyrrolidin-1-yl)pent-3-yn-2-ol (2.2.29)

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Table 6. Hydrogen bonds for *rac*-(*R*)-2-methyl-5-(*R*)-2-phenylaziridin-2-yl)-5-(pyrrolidin-1-yl)pent-3-yn-2-ol (2.2.29) [Å and °].
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Symmetry transformations used to generate equivalent atoms:
#1 -x+1/2,y-1/2,-z
Appendix II – Chapter Three $^1$H and $^{13}$C NMR Spectra
3.2.33
Appendix III – Chapter Four $^1$H, $^{13}$C NMR Spectra and X-Ray Data Tables
4.2.06
4.2.12

[Chemical structure image]

20130905_wmsr_500_393_1020-product_DDO_B-PROTON_01

[Chemical structure image]

20130905_wmsr_500_393_1020-product_DDO_B-PROTON_01

[Chemical structure image]

20130905_wmsr_500_393_1020-product_DDO_B-PROTON_01

[Chemical structure image]
trans-4.2.29b
4.2.30b less polar

20131221-die-FLDMS-3-MeCN
chem_Proton_Day CD2CN 200pa data dce 15

20131221-die-FLDMS-3-MeCN
chem_Carbon_Neutral CD2CN 200pa data dce 15
Detailed X-Ray Crystallographic Information of (1-(4-fluorophenyl)-2-hydroxyethyl)MIDA boronate (4.2.01)

Crystallization Conditions: Slow evaporation of a solution of hexanes and acetone

Table 1. Crystal data and structure refinement for (1-(4-fluorophenyl)-2-hydroxyethyl) MIDA boronate (4.2.01)

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Absorption correction  
Semi-empirical from equivalents

Max. and min. transmission  
0.7456 and 0.6955

Refinement method  
Full-matrix least-squares on $F^2$

Data / restraints / parameters  
3123 / 1 / 211

Goodness-of-fit on $F^2$  
1.055

Final R indices [I>2sigma(I)]  
$R_1 = 0.0390$, $wR_2 = 0.1028$

R indices (all data)  
$R_1 = 0.0447$, $wR_2 = 0.1065$

Extinction coefficient  
n/a

Largest diff. peak and hole  
0.358 and -0.231 eÅ$^{-3}$

**Table 2.** Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\AA^2\times 10^3$) for (1-(4-fluorophenyl)-2-hydroxyethyl)MIDA boronate (4.2.01).

$U(\text{eq})$ is defined as one third of the trace of the orthogonalized $U_{ij}$ tensor.

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**Table 3.** Bond lengths [Å] and angles [°] for (1-(4-fluorophenyl)-2-hydroxyethyl)MIDA
boronate (4.2.01).

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Symmetry transformations used to generate equivalent atoms:

**Table 4.** Anisotropic displacement parameters (Å\(^2\) x 10\(^3\)) for (1-(4-fluorophenyl)-2-hydroxyethyl)MIDA boronate (4.2.01).

The anisotropic displacement factor exponent takes the form:  \(-2\pi^2 [h^2 a^*2U_{11} + ... + 2hk a^* b^* U_{12} ]\)
<table>
<thead>
<tr>
<th></th>
<th>U&lt;sup&gt;11&lt;/sup&gt;</th>
<th>U&lt;sup&gt;22&lt;/sup&gt;</th>
<th>U&lt;sup&gt;33&lt;/sup&gt;</th>
<th>U&lt;sup&gt;23&lt;/sup&gt;</th>
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Table 5. Hydrogen coordinates (x 10<sup>4</sup>) and isotropic displacement parameters (Å<sup>2</sup>x 10<sup>3</sup>) for (1-(4-fluorophenyl)-2-hydroxyethyl)MIDA boronate (4.2.01).
Table 6. Torsion angles [°] for (1-(4-fluorophenyl)-2-hydroxyethyl)MIDA boronate (4.2.01).

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C(2)-O(1)-B(1)-N(1) -19.02(12)
C(4)-O(3)-B(1)-O(1) 90.70(11)
C(4)-O(3)-B(1)-C(6) -141.38(10)
C(4)-O(3)-B(1)-N(1) -14.65(12)
C(8)-C(6)-B(1)-O(1) 88.22(16)
C(7)-C(6)-B(1)-O(1) -35.86(13)
C(8)-C(6)-B(1)-O(3) -37.36(17)
C(7)-C(6)-B(1)-O(3) -161.44(9)
C(8)-C(6)-B(1)-N(1) -154.65(15)
C(7)-C(6)-B(1)-N(1) 81.27(12)
C(5)-N(1)-B(1)-O(1) 147.36(10)
C(1)-N(1)-B(1)-O(1) 23.32(11)
C(3)-N(1)-B(1)-O(1) -92.87(10)
C(5)-N(1)-B(1)-O(3) -99.72(11)
C(1)-N(1)-B(1)-O(3) 136.24(9)
C(3)-N(1)-B(1)-O(3) 20.05(11)
C(5)-N(1)-B(1)-C(6) 22.92(14)
C(1)-N(1)-B(1)-C(6) -101.13(11)
C(3)-N(1)-B(1)-C(6) 142.69(10)

Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for (1-(4-fluorophenyl)-2-hydroxyethyl)MIDA boronate (4.2.01) [Å and °].

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<th>d(H...A)</th>
<th>d(D...A)</th>
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Symmetry transformations used to generate equivalent atoms:
#1 -x,y-1/2,-z+3/2
Detailed X-Ray Structure of rac-((4R,5S)-2,2-dioxido-4-phenyl-1,2,3-oxathiazinan-5-yl)MIDA boronate (4.2.27)

Crystallization Conditions: Slow precipitation from a concentrated solution of acetone

Table 1. Crystal data and structure refinement for rac-((4R,5S)-2,2-dioxido-4-phenyl-1,2,3-oxathiazinan-5-yl)MIDA boronate (4.2.27).

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Max. and min. transmission 0.7456 and 0.6917
Refinement method Full-matrix least-squares on $F^2$
Data / restraints / parameters 3974 / 1 / 269
Goodness-of-fit on $F^2$ 1.029
Final R indices [$I>2\sigma(I)$] $R1 = 0.0303$, $wR2 = 0.0819$
R indices (all data) $R1 = 0.0325$, $wR2 = 0.0837$
Extinction coefficient n/a
Largest diff. peak and hole 0.388 and -0.481 e.Å$^{-3}$

Table 2. Atomic coordinates (x $10^4$) and equivalent isotropic displacement parameters (Å$^2$x $10^3$) for rac-((4R,5S)-2,2-dioxido-4-phenyl-1,2,3-oxathiazinan-5-yl)MIDA boronate (4.2.27). U(eq) is defined as one third of the trace of the orthogonalized $U_{ij}$ tensor.

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Table 3. Bond lengths [Å] and angles [°] for rac-((4R,5S)-2,2-dioxido-4-phenyl-1,2,3-
oxathiazinan-5-yl)MIDA boronate (4.2.27).

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C(1)-N(1)-C(5)  112.48(9)  
C(1)-N(1)-C(3)  111.12(9)  
C(5)-N(1)-C(3)  109.90(8)  
C(1)-N(1)-B(1)  103.53(8)  
C(5)-N(1)-B(1)  117.61(8)  
C(3)-N(1)-B(1)  101.58(8)  
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O(2)-C(2)-C(1)  124.97(11)  
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N(1)-C(3)-H(3B)  110.7  
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O(4)-C(4)-C(3)  125.69(11)  
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H(5A)-C(5)-H(5C) 109.5
H(5B)-C(5)-H(5C) 109.5
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C(8)-C(6)-B(1) 111.61(8)
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C(8)-C(6)-H(6A) 108.8
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C(14)-C(9)-C(8) 121.01(10)
C(9)-C(10)-C(11) 120.59(11)
C(9)-C(10)-H(10A) 119.7
C(11)-C(10)-H(10A) 119.7
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O(1)-B(1)-N(1) 98.92(8)
C(6)-B(1)-N(1) 118.94(8)
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C(1S)-C(3S)-H(3SC)  109.5
H(3SA)-C(3S)-H(3SC)  109.5
C(1S)-C(3S)-H(3SC)  109.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (Å² x 10³) for rac-((4R,5S)-2,2-dioxido-4-phenyl-1,2,3-oxathiazinan-5-yl)MIDA boronate (4.2.27).

The anisotropic displacement factor exponent takes the form: 

\[ -2\sum_{ij} \mathbf{U}_{ij} a^i a^j \]

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**Table 5.** Hydrogen coordinates ($x \times 10^4$) and isotropic displacement parameters ($\AA^2 \times 10^3$) for rac-((4R,5S)-2,2-dioxido-4-phenyl-1,2,3-oxathiazinan-5-yl)MIDA boronate (4.2.27).

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**Table 6.** Torsion angles [°] for rac-((4R,5S)-2,2-dioxido-4-phenyl-1,2,3-oxathiazinan-5-yl)MIDA boronate (4.2.27).
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C(5)-N(1)-B(1)-C(6) -29.24(13)
C(3)-N(1)-B(1)-C(6) -149.19(9)

Symmetry transformations used to generate equivalent atoms:

**Table 7.** Hydrogen bonds for rac-((4R,5S)-2,2-dioxido-4-phenyl-1,2,3-oxathiazinan-5-yl)MIDA boronate (4.2.27) [Å and °].

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</table>

Symmetry transformations used to generate equivalent atoms:
#1 -x+1,y-1/2,-z+3/2
Appendix IV – Chapter Five $^1\text{H}$ and $^{13}\text{C}$ NMR Spectra
5.2.19
Appendix V – Chapter Six $^1$H, $^{13}$C NMR Spectra and X-Ray Data Tables
6.2.07b
6.2.08b
6.2.16e
5-6.2.18d

201409106_1124-01_C-01_30.18d
JSD 1124-01 30
chem_Proton_Day Acetone /app/data jeol 4

201409204_waters_500_1124-01فت_30-CARBON_01

201409204_waters_500_1124-01_30-CARBON_01
6.2.18d

[Image of NMR spectra with chemical structures and annotations]
Detailed X-Ray Crystallographic Information for (Z)-(2-(2-bromo-N-(2-chlorobenzyl)benzamido)-1-(p-tolyl)vinyl)MIDA boronate (6.2.16i)

Crystallization Conditions: X-ray quality crystals were grown from a saturated solution of MeCN-\(d_3\) over 3 hours.

Table 1. Crystal data and structure refinement for (Z)-(2-(2-bromo-N-(2-chlorobenzyl)benzamido)-1-(p-tolyl)vinyl) MIDA boronate (6.2.16i)

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<td></td>
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<td>Z</td>
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<tr>
<td>F(000)</td>
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Crystal size: 0.230 x 0.130 x 0.060 mm$^3$
Theta range for data collection: 1.522 to 27.655°.
Index ranges: -9 <= h <= 8, -21 <= k <= 17, -28 <= l <= 28
Reflections collected: 22195
Independent reflections: 6164 [R(int) = 0.0681]
Completeness to theta = 25.242°: 100.0%
Absorption correction: Semi-empirical from equivalents
Max. and min. transmission: 0.7456 and 0.6838
Refinement method: Full-matrix least-squares on F$^2$
Data / restraints / parameters: 6164 / 0 / 345
Goodness-of-fit on F$^2$: 1.008
Final R indices [I>2sigma(I)]: R1 = 0.0561, wR2 = 0.1185
R indices (all data): R1 = 0.1058, wR2 = 0.1364
Extinction coefficient: n/a
Largest diff. peak and hole: 1.123 and -1.159 e.Å$^{-3}$

**Table 2.** Atomic coordinates (x $10^4$) and equivalent isotropic displacement parameters (Å$^2$x $10^3$) for (Z)-(2-(2-bromo-N-(2-chlorobenzyl)benzamido)-1-(p-tolyl)vinyl)MIDA boronate (6.2.16i).

U(eq) is defined as one third of the trace of the orthogonalized U$_{ij}$ tensor.

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Table 3. Bond lengths [Å] and angles [°] for (Z)-(2-(2-bromo-N-(2-chlorobenzyl)benzamido)-1-(p-tolyl)vinyl)MIDA boronate (6.2.16i)
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O(1)-B(1)-N(1) 98.8(3)
C(6)-B(1)-N(1) 114.9(3)

Symmetry transformations used to generate equivalent atoms:

### Table 4. Anisotropic displacement parameters (Å² x 10³) for (Z)-(2-(2-bromo-N-(2-chlorobenzyl)benzamido)-1-(p-tolyl)vinyl)MIDA boronate (6.2.16i)

The anisotropic displacement factor exponent takes the form: \(-2\pi^2[ h^2 a^*U_{11} + ... + 2hka^*b^*U_{12} ]\)

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Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for (Z)-(2-(2-bromo-N-(2-chlorobenzyl)benzamido)-1-(p-tolyl)vinyl)MIDA boronate (6.2.16i)

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Table 6. Torsion angles [°] for (Z)-(2-(2-bromo-N-(2-chlorobenzyl)benzamido)-1-(p-tolyl)vinyl)MIDA boronate (6.2.16i)

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B(1)-O(1)-C(2)-O(2) 168.9(3)
B(1)-O(1)-C(2)-C(1) -10.1(4)
N(1)-C(1)-C(2)-O(2) 171.2(3)
N(1)-C(1)-C(2)-O(1) -9.8(4)
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B(1)-O(3)-C(4)-O(4) 178.4(3)
B(1)-O(3)-C(4)-C(3) -0.6(4)
N(1)-C(3)-C(4)-O(4) 163.9(3)
N(1)-C(3)-C(4)-O(3) -17.1(4)
C(22)-C(6)-C(7)-N(2) -5.7(5)
B(1)-C(6)-C(7)-N(2) 177.1(3)
C(8)-N(2)-C(7)-C(6) -55.0(4)
C(15)-N(2)-C(7)-C(6) 127.7(4)
C(15)-N(2)-C(8)-C(9) 122.3(3)
C(7)-N(2)-C(8)-C(9) -55.0(4)
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N(2)-C(8)-C(9)-C(14) -42.8(5)
C(14)-C(9)-C(10)-C(11) 3.0(5)
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C(8)-C(9)-C(10)-Cl(1) 2.1(5)
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Cl(1)-C(10)-C(11)-C(12) 176.3(3)
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C(11)-C(12)-C(13)-C(14) 1.8(7)
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C(7)-N(2)-C(15)-C(16) -4.7(4)
C(8)-N(2)-C(15)-C(16) 178.0(3)
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N(2)-C(15)-C(16)-C(17) 88.4(4)
O(5)-C(15)-C(16)-C(21) 82.7(4)
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C(15)-C(16)-C(17)-Br(1) -2.4(5)
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C(18)-C(19)-C(20)-C(21) -0.5(6)
C(19)-C(20)-C(21)-C(16) 0.8(6)
C(17)-C(16)-C(21)-C(20) -0.6(5)
C(15)-C(16)-C(21)-C(20) -177.5(3)
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C(6)-C(22)-C(23)-C(24) 178.4(3)
C(22)-C(23)-C(24)-C(25) 1.3(5)
C(23)-C(24)-C(25)-C(26) -0.5(5)
C(23)-C(24)-C(25)-C(28) 178.1(4)
C(24)-C(25)-C(26)-C(27) -0.6(5)
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C(4)-O(3)-B(1)-C(6) 140.7(3)
C(4)-O(3)-B(1)-N(1) 16.2(3)
C(2)-O(1)-B(1)-O(3) 129.9(3)
C(2)-O(1)-B(1)-C(6) -99.2(3)
C(2)-O(1)-B(1)-N(1) 23.0(3)
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C(22)-C(6)-B(1)-O(3) 171.4(3)
C(7)-C(6)-B(1)-O(1) -141.4(3)
C(22)-C(6)-B(1)-O(1) 41.3(4)
C(7)-C(6)-B(1)-N(1) 105.8(3)
C(22)-C(6)-B(1)-N(1) -71.5(4)
C(1)-N(1)-B(1)-O(3) -142.1(3)
C(2)-N(1)-B(1)-O(3) 94.3(3)
C(3)-N(1)-B(1)-O(3) -24.8(3)
C(1)-N(1)-B(1)-O(1) -27.1(3)
C(2)-N(1)-B(1)-O(1) -150.6(3)
C(3)-N(1)-B(1)-O(1) 90.2(3)
C(1)-N(1)-B(1)-C(6) 94.4(3)
C(5)-N(1)-B(1)-C(6) -29.3(4)
C(3)-N(1)-B(1)-C(6) -148.5(3)

Symmetry transformations used to generate equivalent atoms:

Detailed X-ray Crystallographic Information of (E)-2-((N-benzyl-2-bromophenyl)sulfonamido)vinyl)MIDA boronate (6.2.16h)
Crystallization Conditions: X-ray quality crystals were grown from the slow diffusion of hexanes into a saturated solution of sulphonamide in acetone over 24 hours.

Table 1. Crystal data and structure refinement for (E)-(2-((N-benzyl-2-bromophenyl)sulfonamido)vinyl)MIDA boronate (6.2.16h)

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Data / restraints / parameters 10244 / 0 / 589

Goodness-of-fit on $F^2$ 1.014

Final R indices [$I>2\sigma(I)$] $R1 = 0.0309$, $wR2 = 0.0658$

R indices (all data) $R1 = 0.0474$, $wR2 = 0.0708$

Extinction coefficient n/a

Largest diff. peak and hole 0.436 and -0.475 eÅ$^{-3}$

Table 2. Atomic coordinates (x 10$^4$) and equivalent isotropic displacement parameters (Å$^2$x 10$^3$) for (E)-(2-((N-benzyl-2-bromophenyl)sulfonamido)vinyl)MIDA boronate (6.2.16h).

U(eq) is defined as one third of the trace of the orthogonalized $U_{ij}$ tensor.

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Table 3. Bond lengths [Å] and angles [°] for (E)-(2-((N-benzyl-2-bromophenyl)sulfonamido)vinyl)MIDA boronate (6.2.16h)

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C(6B)-B(1B)-N(1B) 113.73(16)
C(2S)-C(1S)-H(1S1) 109.5
C(2S)-C(1S)-H(1S2) 109.5
H(1S1)-C(1S)-H(1S2) 109.5
C(2S)-C(1S)-H(1S3) 109.5
H(1S1)-C(1S)-H(1S3) 109.5
H(1S2)-C(1S)-H(1S3) 109.5
N(1S)-C(2S)-C(1S) 178.3(3)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($\AA^2 \times 10^3$) for (E)-(2-((N-benzyl-2-bromophenyl)sulfonamido)vinyl)MIDA boronate (6.2.16h).
The anisotropic displacement factor exponent takes the form: $-2\pi^2[ h^2 a^* U_{11} + ... + 2 h k a^* b^* U_{12} ]$

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**Table 5.** Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2x 10^3) for (E)-(2-((N-benzyl-2-bromophenyl)sulfonamido)vinyl)MIDA boronate (6.2.16h)
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**Table 6.** Torsion angles [°] for (E)-(2-((N-benzyl-2-bromophenyl)sulfamido)vinyl)MIDA boronate (6.2.16h)

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C(15A)-S(1A)-N(2A)-C(8A) -118.12(16)
C(3A)-N(1A)-C(1A)-C(2A) 81.14(19)
C(5A)-N(1A)-C(1A)-C(2A) -152.25(16)
B(1A)-N(1A)-C(1A)-C(2A) -27.88(19)
B(1A)-O(2A)-C(2A)-O(1A) -173.85(19)
B(1A)-O(2A)-C(2A)-C(1A) 3.8(2)
N(1A)-C(1A)-C(2A)-O(1A) -165.52(19)
N(1A)-C(1A)-C(2A)-O(2A) 16.8(2)
C(1A)-N(1A)-C(3A)-C(4A) -133.62(16)
C(5A)-N(1A)-C(3A)-C(4A) 98.39(18)
B(1A)-N(1A)-C(3A)-C(4A) -23.53(18)
B(1A)-O(3A)-C(4A)-O(4A) -172.6(2)
B(1A)-O(3A)-C(4A)-C(3A) 6.6(2)
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N(1A)-C(3A)-C(4A)-O(3A) 12.6(2)
B(1A)-C(6A)-C(7A)-N(2A) -171.58(18)
C(8A)-N(2A)-C(7A)-C(6A) 7.9(3)
S(1A)-N(2A)-C(7A)-C(6A) -179.57(16)
C(7A)-N(2A)-C(8A)-C(16A) -171.58(18)
C(7A)-N(2A)-C(8A)-C(17A) 2.0(3)
S(1A)-C(15A)-C(16A)-C(17A) -179.06(15)
C(15A)-C(16A)-C(17A)-C(18A) -0.5(3)
Br(1A)-C(16A)-C(17A)-C(18A) 179.34(16)
C(16A)-C(17A)-C(18A)-C(19A) -1.6(3)
C(17A)-C(18A)-C(19A)-C(20A) 2.0(3)
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Symmetry transformations used to generate equivalent atoms:

**Detailed X-ray Crystallographic Information of (E)-((2-(2-chlorobenzyl)-3-oxoisooindolin-1-ylidene)methyl)MIDA boronate (E-6.2.18d)**
Crystallography

**Crystallization Conditions:** X-ray quality crystals were grown from a saturated solution of isoindoline in MeCN over 24 hours.

**Table 1.** Crystal data and structure refinement for (E)-((2-(2-chlorobenzyl)-3-oxoisindolin-1-ylidene)methyl)MIDA boronate (E-6.2.18d)

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<tr>
<td></td>
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<tr>
<td></td>
<td>c = 11.273(3) Å, γ= 114.267(7)°.</td>
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<td>Absorption correction</td>
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Max. and min. transmission 0.7455 and 0.6895
Refinement method Full-matrix least-squares on F^2
Data / restraints / parameters 5067 / 0 / 300
Goodness-of-fit on F^2 1.034
Final R indices [I>2sigma(I)] R1 = 0.0335, wR2 = 0.0862
R indices (all data) R1 = 0.0366, wR2 = 0.0891
Extinction coefficient n/a
Largest diff. peak and hole 0.334 and -0.438 e.Å^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) (E)-(2-(2-chlorobenzyl)-3-oxoisoinolin-1-ylidene)methylMIDA boronate (E-6.2.18d). U(eq) is defined as one third of the trace of the orthogonalized U^ij tensor.

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Table 3. Bond lengths [Å] and angles [°] for (E)-((2-(2-chlorobenzyl)-3-oxoisooindolin-1-ylidene)methyl)MIDA boronate (E-6.2.18d)

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N(2)-C(7)-C(8)  104.58(9)
C(9)-C(8)-C(13)  119.53(10)
C(9)-C(8)-C(7)  132.16(10)
C(13)-C(8)-C(7)  108.31(9)
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C(11)-C(12)-H(12A)  121.2
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C(12)-C(13)-C(14)  128.81(10)
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O(5)-C(14)-C(13)  128.44(10)
N(2)-C(14)-C(13)  105.79(9)
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N(1S)-C(2S)-C(1S)  179.68(19)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (Å² x 10³) for (E)-(2-(2-chlorobenzyl)-3-oxoisindolin-1-ylidene)methyl)MIDA boronate (E-6.2.18d).
The anisotropic displacement factor exponent takes the form: -2π² [ h² a*²U₁₁ + ... + 2 h k a* b* U₁₂ ]

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Table 5. Hydrogen coordinates ($x \times 10^4$) and isotropic displacement parameters ($Å^2 \times 10^3$) for \((E)-(2-(2-chlorobenzyl)-3-oxoisoindolin-1-ylidene)methyl\)MIDA boronate (E-6.2.18d).

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Table 6. Torsion angles [°] for \((E)-(2-(2-chlorobenzyl)-3-oxoisoindolin-1-ylidene)methyl\)MIDA boronate (E-6.2.18d)

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N(1)-C(1)-C(2)-O(4)  8.66(12)
C(5)-N(1)-C(3)-C(4)  -145.33(9)
C(1)-N(1)-C(3)-C(4)  90.38(10)
B(1)-N(1)-C(3)-C(4)  -19.91(10)
B(1)-O(3)-C(4)-O(4)  -179.04(10)
B(1)-O(3)-C(4)-C(3)  -0.39(12)
N(1)-C(3)-C(4)-O(4)  -167.38(10)
N(1)-C(3)-C(4)-O(3)  13.99(11)
B(1)-C(6)-C(7)-N(2)  174.76(10)
B(1)-C(6)-C(7)-C(8)  -4.8(2)
C(14)-N(2)-C(7)-C(6)  179.73(10)
C(15)-N(2)-C(7)-C(6)  -4.79(16)
C(14)-N(2)-C(7)-C(8)  -0.64(11)
C(15)-N(2)-C(7)-C(8)  174.83(9)
C(6)-C(7)-C(8)-C(9)  0.5(2)
N(2)-C(7)-C(8)-C(9)  -179.08(11)
C(6)-C(7)-C(8)-C(13)  -179.44(12)
N(2)-C(7)-C(8)-C(13)  0.98(11)
C(13)-C(8)-C(9)-C(10)  -0.08(16)
C(7)-C(8)-C(9)-C(10)  179.99(11)
C(8)-C(9)-C(10)-C(11)  0.32(18)
C(9)-C(10)-C(11)-C(12)  -0.38(19)
C(10)-C(11)-C(12)-C(13)  0.19(17)
C(11)-C(12)-C(13)-C(8)  0.04(16)
C(11)-C(12)-C(13)-C(14)  -178.96(11)
C(9)-C(8)-C(13)-C(12)  -0.09(16)
C(7)-C(8)-C(13)-C(12)  179.85(10)
C(9)-C(8)-C(13)-C(14)  179.08(10)
C(7)-C(8)-C(13)-C(14)  -0.97(12)
C(7)-N(2)-C(14)-O(5)  -179.91(10)
C(15)-N(2)-C(14)-O(5)  4.59(17)
C(7)-N(2)-C(14)-C(13)  0.07(12)
C(15)-N(2)-C(14)-C(13)  -175.43(9)
C(12)-C(13)-C(14)-O(5)  -0.34(19)
C(8)-C(13)-C(14)-O(5)  -179.44(11)
C(12)-C(13)-C(14)-N(2)  179.68(11)
C(8)-C(13)-C(14)-N(2)  0.58(12)
C(14)-N(2)-C(15)-C(16)  107.99(11)
C(7)-N(2)-C(15)-C(16)  -67.02(13)
N(2)-C(15)-C(16)-C(21)  155.37(10)
N(2)-C(15)-C(16)-C(17)  -25.65(14)
C(21)-C(16)-C(17)-C(18)  0.72(17)
C(15)-C(16)-C(17)-C(18)  -178.30(10)
C(16)-C(17)-C(18)-C(19)  0.29(19)
C(17)-C(18)-C(19)-C(20)  -0.99(19)
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C(17)-C(16)-C(21)-C(20)  -1.05(17)
C(15)-C(16)-C(21)-C(20)  177.96(11)
C(17)-C(16)-C(21)-Cl(1)  179.14(8)
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C(19)-C(20)-C(21)-C(16)  0.38(19)
C(19)-C(20)-C(21)-Cl(1)  -179.81(10)
C(2)-O(1)-B(1)-O(3)  94.47(10)
C(2)-O(1)-B(1)-C(6)  -135.61(9)
C(2)-O(1)-B(1)-N(1)  -11.52(11)
C(4)-O(3)-B(1)-O(1)  -179.81(10)
C(4)-O(3)-B(1)-C(6)  113.48(10)
C(4)-O(3)-B(1)-N(1)  -11.79(11)
C(7)-C(6)-B(1)-O(1)  -71.58(14)
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C(7)-C(6)-B(1)-N(1)  171.99(10)
C(3)-N(1)-B(1)-O(1)  131.97(8)
C(5)-N(1)-B(1)-O(1)  -105.31(10)
C(1)-N(1)-B(1)-O(1)  15.55(10)
C(3)-N(1)-B(1)-O(3)  19.17(10)
C(5)-N(1)-B(1)-O(3)  141.89(9)
C(1)-N(1)-B(1)-O(3)  -97.25(9)
C(3)-N(1)-B(1)-C(6)  -106.57(10)
C(5)-N(1)-B(1)-C(6)  16.15(13)
C(1)-N(1)-B(1)-C(6)  137.01(9)

Symmetry transformations used to generate equivalent atoms:

**Detailed X-ray Crystallographic Information of** 
**((2-benzyl-5,6-dimethoxy-3-oxoisoxindolin-1-yl)methyl)boronic acid (6.2.20e)**

![Chemical Structure](image)

**Crystallization Conditions:** X-ray quality crystals were grown from a saturated solution of MeCN-\(d_3\) over 3 hours.
### Table 1. Crystal data and structure refinement for 6.2.20e

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<td>Independent reflections</td>
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<td>R indices (all data)</td>
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Table 2. Atomic coordinates \((x \times 10^4)\) and equivalent isotropic displacement parameters \((\text{Å}^2 \times 10^3)\) for 6.2.20e. \(U_{eq}\) is defined as one third of the trace of the orthogonalized \(U_{ij}\) tensor.

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Table 3. Bond lengths [Å] and angles [°] for 6.2.20e.

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C(12)-N(1)-C(8) 123.38(8)
O(1)-C(1)-N(1) 124.52(10)
O(1)-C(1)-C(2) 128.36(10)
N(1)-C(1)-C(2) 107.12(8)
C(7)-C(2)-C(3) 122.28(9)
C(7)-C(2)-C(1) 108.34(9)
C(3)-C(2)-C(1) 129.25(9)
C(4)-C(3)-C(2) 117.44(9)
C(4)-C(3)-H(3A) 121.3
C(2)-C(3)-H(3A) 121.3
O(4)-C(4)-C(3) 125.11(9)
O(4)-C(4)-C(5) 114.33(9)
C(3)-C(4)-C(5) 120.56(9)
O(5)-C(5)-C(6) 124.80(9)
O(5)-C(5)-C(4) 114.18(9)
C(6)-C(5)-C(4) 121.01(9)
C(5)-C(6)-C(7) 118.06(9)
C(5)-C(6)-H(6A) 121.0
C(7)-C(6)-H(6A) 121.0
C(2)-C(7)-C(6) 120.61(10)
C(2)-C(7)-C(8) 109.94(9)
C(6)-C(7)-C(8) 129.44(9)
N(1)-C(8)-C(7) 100.88(8)
N(1)-C(8)-C(9) 110.55(8)
C(7)-C(8)-C(9) 113.90(8)
N(1)-C(8)-H(8A) 110.4
C(7)-C(8)-H(8A) 110.4
C(9)-C(8)-H(8A) 110.4
C(8)-C(9)-B(1) 117.51(9)
C(8)-C(9)-H(9A) 107.9
B(1)-C(9)-H(9A) 107.9
C(8)-C(9)-H(9B) 107.9
B(1)-C(9)-H(9B) 107.9
H(9B)-C(9)-H(9B) 107.2
O(4)-C(10)-H(10A) 109.5
O(4)-C(10)-H(10B) 109.5
H(10A)-C(10)-H(10B) 109.5
O(4)-C(10)-H(10C) 109.5
H(10A)-C(10)-H(10C) 109.5
H(10B)-C(10)-H(10C) 109.5
O(5)-C(11)-H(11A) 109.5
O(5)-C(11)-H(11B) 109.5
H(11A)-C(11)-H(11B) 109.5
O(5)-C(11)-H(11C) 109.5
H(11B)-C(11)-H(11C) 109.5
N(1)-C(12)-C(13) 113.03(9)
Table 4. Anisotropic displacement parameters (Å² x 10³) for 6.2.20ee. The anisotropic displacement factor exponent takes the form: 

\[-2\pi^2\left( \sum h^2a^*aU_{11} + \ldots + 2hk a^*b^* U_{12} \right)\]

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Symmetry transformations used to generate equivalent atoms:

#1 -x,-y+1,-z+1

---

N(1)-C(12)-H(12A) 109.0
C(13)-C(12)-H(12A) 109.0
N(1)-C(12)-H(12B) 109.0
C(13)-C(12)-H(12B) 109.0
H(12A)-C(12)-H(12B) 107.8
C(18)-C(13)-C(14) 118.83(10)
C(18)-C(13)-C(12) 119.77(10)
C(14)-C(13)-C(12) 121.40(10)
C(15)-C(14)-C(13) 120.21(11)
C(15)-C(14)-H(14A) 119.9
C(13)-C(14)-H(14A) 119.9
C(16)-C(15)-C(14) 120.31(11)
C(16)-C(15)-H(15A) 119.8
C(14)-C(15)-H(15A) 119.8
C(17)-C(16)-C(15) 119.81(11)
C(17)-C(16)-H(16A) 120.1
C(15)-C(16)-H(16A) 120.1
C(16)-C(17)-C(18) 120.10(11)
C(16)-C(17)-H(17A) 120.0
C(18)-C(17)-H(17A) 120.0
C(17)-C(18)-C(13) 120.72(11)
C(17)-C(18)-H(18A) 119.6
C(13)-C(18)-H(18A) 119.6
O(3)-B(1)-O(2) 119.88(10)
O(3)-B(1)-C(9) 118.92(10)
O(2)-B(1)-C(9) 121.18(10)
C(3S)#1-C(1S)-C(2S) 119.94(15)
C(3S)#1-C(1S)-H(1S) 120.0
C(2S)-C(1S)-H(1S) 120.0
C(3S)-C(2S)-C(1S) 119.99(14)
C(3S)-C(2S)-H(2S) 120.0
C(1S)-C(2S)-H(2S) 120.0
C(2S)-C(3S)-C(1S)#1 120.07(14)
C(2S)-C(3S)-H(3S) 120.0
C(1S)#1-C(3S)-H(3S) 120.0
Table 5. Hydrogen coordinates ($x \times 10^4$) and isotropic displacement parameters ($\text{Å}^2 \times 10^{-3}$) for 6.2.20e

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<th>H(11C)</th>
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<td>z</td>
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**Table 6.** Torsion angles [°] for 6.2.20e
C(8)-N(1)-C(12)-C(13) 104.55(11)
N(1)-C(12)-C(13)-C(18) 106.46(11)
N(1)-C(12)-C(13)-C(14) -73.65(13)
C(18)-C(13)-C(14)-C(15) 1.46(17)
C(12)-C(13)-C(14)-C(15) -178.44(10)
C(13)-C(14)-C(15)-C(16) -0.87(18)
C(14)-C(15)-C(16)-C(17) -0.02(19)
C(15)-C(16)-C(17)-C(18) 0.30(18)
C(16)-C(17)-C(18)-C(13) 0.31(17)
C(14)-C(13)-C(18)-C(17) -1.18(16)
C(12)-C(13)-C(18)-C(17) 178.71(10)
C(8)-C(9)-B(1)-O(3) 10.98(15)
C(8)-C(9)-B(1)-O(2) -170.68(10)
C(3S)#1-C(1S)-C(2S)-C(3S) 0.3(2)
C(1S)-C(2S)-C(3S)-C(1S)#1 -0.3(2)

Symmetry transformations used to generate equivalent atoms:
#1 -x,-y+1,-z+1

Table 7. Hydrogen bonds for 6.2.20e [Å and °].

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Symmetry transformations used to generate equivalent atoms:
#1 -x,-y+1,-z+1  #2 -x+1,-y+1,-z+1  #3 x-1/2,-y+1/2,z-1/2