

# **Development of Transition Metal-Catalyzed Borylation Protocols using Symmetrical and Unsymmetrical Diboron Reagents**

Cheryl Lynne Peck

Dissertation submitted to the faculty of Virginia Polytechnic Institute and State  
University in partial fulfillment of the requirements for the degree of

**Doctor of Philosophy  
In  
Chemistry**

Webster L. Santos, Committee Chair  
David G. I. Kingston  
Richard D. Gandour  
Jatinder S. Josan

August 31, 2017  
Blacksburg, VA

Keywords: borylation, transition metal-catalyzed, conjugate addition, alkynes, diboron reagents

Copyright 2017 by Cheryl Peck

# Development of Transition Metal-Catalyzed Borylation Protocols using Symmetrical and Unsymmetrical Diboron Reagents

Cheryl Lynne Peck

## Abstract

The versatility of organoboron compounds has been demonstrated by their use as synthetic intermediates and more recently in therapeutic applications since the FDA approval of Velcade<sup>®</sup>. As a result, transition metal-catalyzed protocols to incorporate boron reagents into unsaturated compounds have been extensively researched. While an abundance of literature protocols have been reported, the majority utilize harsh reaction conditions in combination with expensive reagents. This dissertation discloses the author's contributions to the development of efficient, cost-effective, and operationally simple transition metal-catalyzed borylation protocols with alkynes and diboron reagents.

An open-to-air copper(II)-catalyzed aqueous borylation protocol of alkynoates and a symmetrical diboron reagent is reported. Conjugate addition of the boryl-copper species to the electrophilic  $\beta$ -carbon provided  $\beta$ -boryl- $\alpha,\beta$ -unsaturated esters in moderate to excellent yields. Exclusive (*Z*)-stereochemistry was confirmed by nOe experiments. The resulting vinyl boronate esters are useful cross-coupling partners.

The scope of the aqueous  $\beta$ -borylation protocol was extended to the unsymmetrical diboron reagent, pinB-Bdan. This alternative protecting group has emerged as an orthogonal protecting group and alters the reactivity of the boron moiety. Activation of the pinacol moiety

to form the Lewis acid-base adduct allowed for the chemoselective transfer of the 1,8-diaminonaphthalene moiety to the  $\beta$ -carbon.

An alternative novel synthesis of vinyl, allyl diboronate esters from propargylic alcohols has also been described. Formation of a leaving group *in-situ* with a palladium- and copper-catalyzed protocol can lead to several competing reaction pathways and the formation of multiple products. Fortunately, the resulting vinyl, allyl diboronate esters were stereoselectively synthesized in moderate GC yields despite significant decomposition during purification, as confirmed by stability studies. The terminal diboration of allenes was previously the only reported method for the synthesis of vinyl, allyl diboronate esters.

## General Audience Abstract

The unique properties of organoboron compounds allow them to be used as synthetic intermediates and as drugs targets. This dissertation discloses three environmentally friendly and simple methods to incorporate boron into alkynes using transition metal catalysts. In particular, alkynoates were successfully borylated under copper(II)-catalyzed aqueous conditions using symmetrical and unsymmetrical diboron reagents. Propargylic alcohols were also borylated using bimetallic conditions to afford vinyl, allyl diboronate esters, which were previously hard to obtain.



## Acknowledgements

First and foremost, I want express my sincerest gratitude to my advisor Dr. Webster Santos for his advice, guidance, and support throughout my time at Virginia Tech. He has been a remarkable mentor. He taught me to think independently and to never give up even when I would hit a road block in my research. Instead he encouraged me to research alternative routes and think critically about the fundamentals of chemistry. I will miss his cheerful attitude as he comes into lab to ask “how’s life?” and his age old question “where’s my compound?”. At the end of my first semester, I remember not knowing what group I would join even after all of the other first year students had been assigned their advisors. I am grateful that Dr. Santos allowed me to join his group. Without his guidance and leadership I am certain I would not have made it to this point.

I would also like to thank my advisory committee, Dr. David Kingston, Dr. Richard Gandour, Dr. Brian Hanson, and Dr. Jatinder Josan. I would particularly like to thank Dr. Josan for stepping in towards the end to replace Dr. Hanson after his retirement. Their constructive criticism has allowed me to improve my critical thinking, writing, and communication skills. I appreciate all of your efforts to ensure I have a strong foundation.

To all my friends and colleagues in the Santos group, Beth Childress, Russell Snead, Ashley Peralta, Ashley Gates, Jacob Murray, Chris Sibley, Hao Li, Yumin Dai, Jose Santiago-Rivera, Eric Medici, Russell Fritzeimer, and Laura Wonilowicz, thank you for all of your help and guidance. It has been a pleasure to work alongside each of you. The great atmosphere that has been established in our lab has made it more enjoyable to come to work and learn. I have gained a lot of unforgettable memories and will miss all of our group activities. I would also like

to acknowledge past group members, in particular, my mentor Joseph Calderone, for helping me adjust when I first joined the group and for your patience when teaching me techniques and concepts I was unfamiliar with. You have been a great role model and friend.

Finally, words cannot express how grateful I am to my family for all of their unconditional love and support. To my mother, Donna Peck, you have been there for me since the beginning and are constantly helping me achieve my goals, even when you didn't understand any of my work. I appreciate everything you have sacrificed for me so that I can get an education and further my career. To my grandparents, Mary and Edward Gray, thank you for always supporting me. To my boyfriend, Benjamin Babineau, I would have never made it this far without you. You have continuously pushed me to be better and encouraged me when things got difficult. Thank you to all of my friends outside of lab for helping me preserve my sanity throughout my time in graduate school.

## **Dedication**

To my family and grandparents.

You have been a wonderful influence in my life. I love you.

## Table of Contents

Abstract.....	iii
General Audience Abstract.....	iv
Acknowledgements.....	v
Dedication.....	vii
Chapter 1. Synthetic versatility of organoboron compounds.....	1
1.1 Structures, properties, and characteristics of boronic acids and boronic acid derivatives.....	1
1.2 Organoboron compounds as synthetic intermediates.....	5
1.3 Therapeutic applications of organoboron compounds.....	11
1.4 Dissertation overview.....	14
1.5 References for Chapter 1.....	15
Chapter 2. Copper(II)-catalyzed $\beta$ -borylation of acetylenic esters in water.....	32
2.1 Contributions.....	32
2.2 Abstract.....	33
2.3 Introduction.....	34
2.4 Optimizing the $\beta$ -borylation of alkynoates with $B_2pin_2$ .....	36
2.5 Preparation of alkynoates.....	37
2.6 Substrate scope for the copper(II)-catalyzed $\beta$ -borylation of alkynoates.....	39
2.7 Proposed mechanism.....	43
2.8 Conclusions.....	44
2.9 References for Chapter 2.....	45
Chapter 3. Chemo-, regio-, and stereoselective copper(II)-catalyzed boron addition to acetylenic esters and amides in aqueous media.....	50
3.1 Contributions.....	50
3.2 Abstract.....	51
3.3 Introduction.....	52
3.4 Optimizing the $\beta$ -borylation of ethyl 2-butynoate with pinB-Bdan.....	55
3.5 Substrate scope for the $\beta$ -borylation of alkynoates with pinB-Bdan.....	58
3.6 Preparation of alkynamides.....	60
3.7 Re-optimization of solvent systems.....	62

3.8	Substrate scope for the $\beta$ -borylation of alkynamides .....	63
3.9	Conclusions .....	67
3.10	References for Chapter 3 .....	67
Chapter 4. Borylation of propargylic alcohols using a bimetallic catalyts system: an unexpected diboration route to vinyl, allyl diboronate esters .....		76
4.1	Contributions .....	76
4.2	Abstract.....	77
4.3	Introduction .....	78
4.4	Optimization of reaction conditions for the diboration of 2-butynol .....	80
4.5	Stability studies.....	87
4.6	Preparation of propargylic alcohols.....	89
4.7	Substrate scope for the diboration of propargylic alcohols .....	91
4.8	Mechanistic investigations and proposed mechanism.....	94
4.9	Conclusions .....	96
4.10	References for Chapter 4 .....	97
Chapter 5. Experimental .....		103
5.1	General methods .....	103
5.2	Instrumentation.....	104
5.3	Synthetic procedures and characterization of products for Chapter 2.....	105
5.4	Synthetic procedures and characterization of products for Chapter 3.....	117
5.5	Synthetic procedures and characterization of products for Chapter 4.....	133
5.6	General procedures for stability studies .....	146
5.7	References for Chapter 5 .....	148
Appendix.....		152

## List of Figures

Figure 1.1. General structures of common organoboron compounds.....	1
Figure 1.2. Commonly encountered boronic acid derivatives.....	3
Figure 1.3. Allylation transition states.....	11
Figure 1.4. Interaction of Velcade <sup>®</sup> inside the 26S proteasome.....	12
Figure 1.5. Prodrug Ninlaro <sup>®</sup> and its active form.....	12
Figure 1.6. Interaction of Kerydin <sup>®</sup> with tRNA synthetase.....	13
Figure 1.7. Mode of action for Eucrisa <sup>®</sup> .....	14
Figure 2.1. Structures of alkynoates synthesized.....	38
Figure 2.2. Protodeboration of pyridin-2-ylboronic acid.....	42
Figure 3.1. Structure of surfactant, TPGS-750-M.....	57
Figure 3.2. Structures of alkynamides synthesized.....	62
Figure 4.1. Structures of ligands used in Table 4.2.....	84
Figure 4.2. Stability of 4.5a in solution over time.....	88
Figure 4.3. Decomposition of 4.5a on column stationary phases.....	89
Figure 4.4. <sup>1</sup> H NMR illustrating the decomposition of 4.5a on silica.....	89
Figure 4.5. Structures of propargylic alcohols synthesized.....	91

## List of Schemes

Scheme 1.1. Boronic acid in equilibrium with the $sp^3$ -hybridized species.....	2
Scheme 1.2. Synthesis of diethanolamine derivatives from pinacol ester 1.6.....	4
Scheme 1.3. Oxidation of organoboron compounds.....	6
Scheme 1.4. Catalytic cycle for the Suzuki–Miyaura cross-coupling reaction. ....	7
Scheme 1.5. Cu(II)-catalyzed Chan–Lam coupling reaction.....	9
Scheme 1.6. Versatility of organoboron compounds to form carbon–carbon and carbon–heteroatom bonds.....	10
Scheme 2.1. (a) Metal- and ligand-free borylation of terminal alkynes and (b) copper-catalyzed carbonylation.....	34
Scheme 2.2. Strategies toward $\beta$ -boryl- $\alpha,\beta$ -unsaturated esters.....	35
Scheme 2.3. Synthesis of alkynoates.....	38
Scheme 2.4. $\beta$ -Borylation of alkynoates bearing heteroatoms.....	41
Scheme 2.5. Chemoselectivity of the reaction.....	42
Scheme 2.6. Proposed catalytic cycle for the formation of $\beta$ -borylated unsaturated esters.....	44
Scheme 3.1. Chemoselective Suzuki–Miyaura cross-coupling.....	53
Scheme 3.2. Incorporation of the 1,8-diaminonaphthalene protecting group.....	53
Scheme 3.3. $\beta$ -Borylation of $\alpha,\beta$ -unsaturated carbonyl compounds.....	54
Scheme 3.4. Approaches to Bdan vinylboronates.....	55
Scheme 3.5. Method to synthesize pinB-Bdan.....	56
Scheme 3.6. Methods employed to synthesize alkynamides.....	61
Scheme 4.1. Borylation of propargylic carbonates and propargylic alcohols.....	79
Scheme 4.2. Synthesis of vinyl, allyl diboronates using (a) symmetrical and (b) unsymmetrical diboron reagents.....	80

Scheme 4.3. Methods to synthesize propargylic alcohols. ....	90
Scheme 4.4. Borylation of tertiary propargylic alcohols. ....	94
Scheme 4.5. Synthesis of compounds used in mechanistic studies. ....	95
Scheme 4.6. Borylation reactions with proposed intermediates. ....	95
Scheme 4.7. Proposed catalytic cycle for the borylation of propargylic alcohols. ....	96



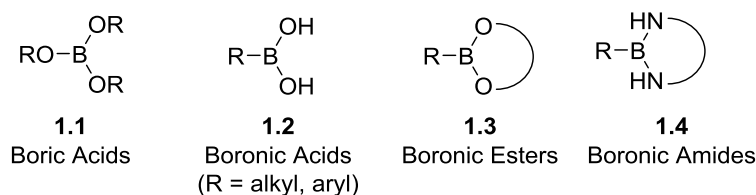
## List of Tables

Table 2.1. Optimization of reaction conditions for the borylation of alkynoates using B <sub>2</sub> pin <sub>2</sub> ....	37
Table 2.2. Copper(II)-catalyzed aqueous β-borylation of alkynoates using B <sub>2</sub> pin <sub>2</sub> . .....	39
Table 3.1. Optimization of reaction conditions using an unsymmetrical diboron reagent. ....	57
Table 3.2. Boryl conjugate addition to substituted alkynoates with pinB-Bdan. ....	59
Table 3.3. Screening of solvent systems for the borylation of Weinreb amides. ....	63
Table 3.4. Boryl conjugate addition to Weinreb amides and substituted alkynamides. ....	64
Table 4.1. Base and additive screenings for the borylation of propargylic alcohols. ....	81
Table 4.2. Screening of ligands for the borylation of propargylic alcohols. ....	83
Table 4.3. Screening catalysts for the borylation of propargylic alcohols.....	85
Table 4.4. Screening solvents and temperatures for the borylation of propargylic alcohols.....	86
Table 4.5. Diboration of propargylic alcohols with B <sub>2</sub> pin <sub>2</sub> . ....	92

## Chapter 1. Synthetic versatility of organoboron compounds

### 1.1 Structures, properties, and characteristics of boronic acids and boronic acid derivatives

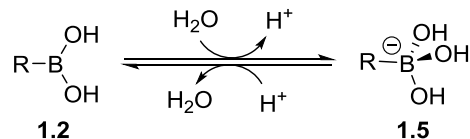
While boric acid is commonly found in minerals, boronic acids are not naturally occurring; therefore, it was not until Frankland and Duppa isolated the first boronic acid from triethyl borate in 1859 that their properties were explored.<sup>1-2</sup> Boronic acids have the general formula  $\text{RB}(\text{OH})_2$ , where R is any carbon substituent (Figure 1.1). It was revealed that the trivalent boron atom is  $\text{sp}^2$ -hybridized in its ground state with a trigonal planar geometry. The Lewis acidic properties of boron are correlated to its empty p-orbital and 6 valence electrons.<sup>3</sup> In



**Figure 1.1.** General structures of common organoboron compounds.

turn, this makes boron electron deficient and able to accept electrons. In order to satisfy its octet, boron can coordinate to Lewis bases and other nucleophiles through its empty p-orbital (Scheme 1.1). As an anion, the boron center is  $\text{sp}^3$ -hybridized and adopts a tetrahedral geometry. This reversible Lewis acid–base interaction has been exploited in a number of synthetic transformations and in targeting enzymes and proteasomes.<sup>3</sup>

Compared to their carbon analogues, boronic acids have greater stability in part due to the lone pairs on the adjacent oxygen atoms that donate electron density into the empty p-orbital.



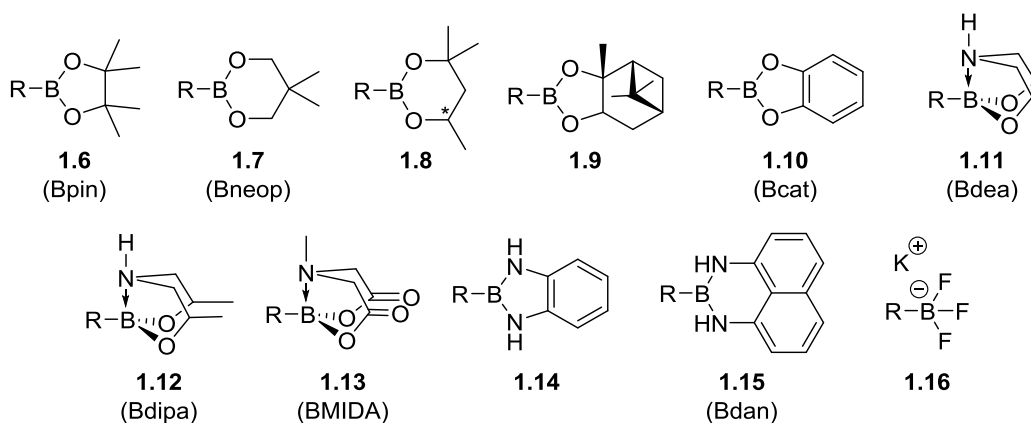
**Scheme 1.1.** Boronic acid in equilibrium with the sp<sup>3</sup>-hybridized species.

This additional electron density shortens the B–O bond (1.35–1.38 Å) giving it partial double bond character and a slightly restricted rotation.<sup>3</sup> It is estimated that protecting the boronic acid to form the boronic ester further shortens the B–O bond length (1.28–1.35 Å).<sup>3-5</sup> Interestingly, the B–O bond in tricoordinate boron compounds is stronger than the corresponding C–O bond (125–130 kcal/mol vs 92 kcal/mol); however, the B–C bond is 8 kcal/mol weaker and as much as 0.05 Å longer than the typical C–C bond (85 kcal/mol and 1.54 Å) making it easier to derivatize as a synthetic intermediate.<sup>6-7</sup>

Over an extended period of time, boronic acids are generally non-toxic to humans in small quantities and environmentally benign, as they degrade to boric acid.<sup>8-9</sup> In low concentrations, some boronic acids and boronic acid derivatives have been shown to be beneficial for biological functions.<sup>10-11</sup> Furthermore, they can be easily handled in air for short periods of time without any precautions or Schlenk techniques. In comparison to aryl and alkenyl boronic acids, aliphatic, vinyl, and heterocyclic boronic acids are less stable and therefore more susceptible to oxidation over time.<sup>12</sup> To minimize or prevent decomposition to the corresponding boric acid, they are often stored under an inert atmosphere. Alternatively, boronic acids can be protected as the corresponding ester or amide derivatives (Figure 1.2). This alters the stability and reactivity of the boron compound as well as methods for purification.

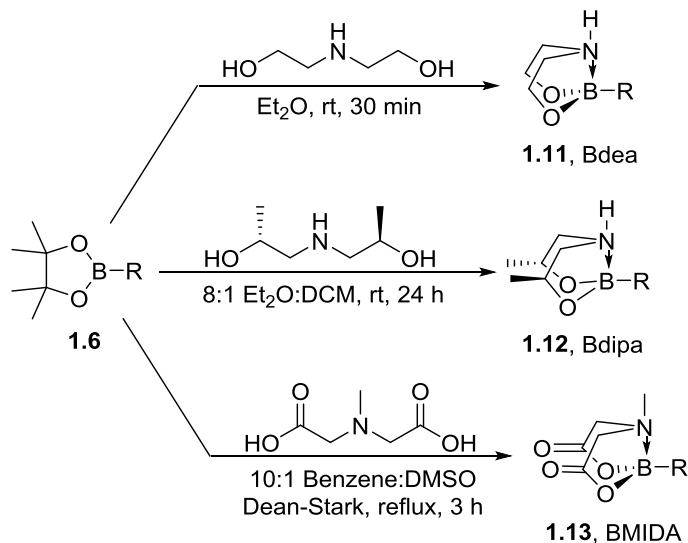
A variety of methods have been reported for the protection of boronic acids. Boronic esters **1.6–1.10** can generally be synthesized by reacting the boronic acid with the corresponding

diol.<sup>13</sup> While protecting the boronic acid offers greater long-term stability, it also decreases reactivity due to the increase in steric bulk and loss of the hydroxyl groups.<sup>3, 14</sup> Furthermore, boronic esters **1.6–1.10** are less Lewis acidic than boronic acids, the pinacol moiety **1.6** being the least Lewis acidic. The decreased Lewis acidity is attributed to the alkyl groups donating electron density into the boron center more effectively.<sup>15</sup> In comparison, the electron density that is withdrawn by the neighboring aryl ring makes the catechol boronate **1.10** more Lewis acidic.<sup>16</sup> The majority of  $sp^2$ -hybridized boronic esters are achiral; however, the more expensive chiral boron moieties, hexyleneglycol boronic ester **1.8** and (+)-pinanediol boronic ester **1.9**, can be introduced.<sup>17-18</sup>



**Figure 1.2.** Commonly encountered boronic acid derivatives.

Diethanolamine derivatives **1.11–1.13** represent an alternative to  $sp^2$ -hybridized protecting groups. They can readily be synthesized from pinacol ester **1.6** using diethanolamine, diisopropanolamine, or methyliminodiacetic acid (Scheme 1.2).<sup>19-20</sup> The nitrogen atom internally coordinates to the empty p-orbital of boron and rehybridizes the boron center to  $sp^3$  hybridization with a distorted tetrahedral geometry, as confirmed by X-ray crystal structures.<sup>21-22</sup> The dative B–N bond causes a distinct chemical shift in  $^{11}\text{B}$  NMR ( $\delta$  8–14 ppm) compared to boronic acids and esters ( $\delta$  25–35 ppm).<sup>21, 23-24</sup> Not only does the occupied p-orbital increased



**Scheme 1.2.** Synthesis of diethanolamine derivatives from pinacol ester **1.6**.

stability, but it also decreases the Lewis acidity relative to boronic esters. The increased electron density reduces the probability of hydrolysis and oxidation; however, deprotection of **1.11** can effortlessly be achieved in  $\leq 20$  minutes with 0.1 M HCl, a process that is further accelerated by heat.<sup>25</sup> On the other hand, **1.13** is stable under weakly acidic conditions but is readily deprotected in the presence of 0.1 M NaOH or a 1:2 aqueous  $\text{NaHCO}_3\text{:MeOH}$  mixture.<sup>19, 26-27</sup>

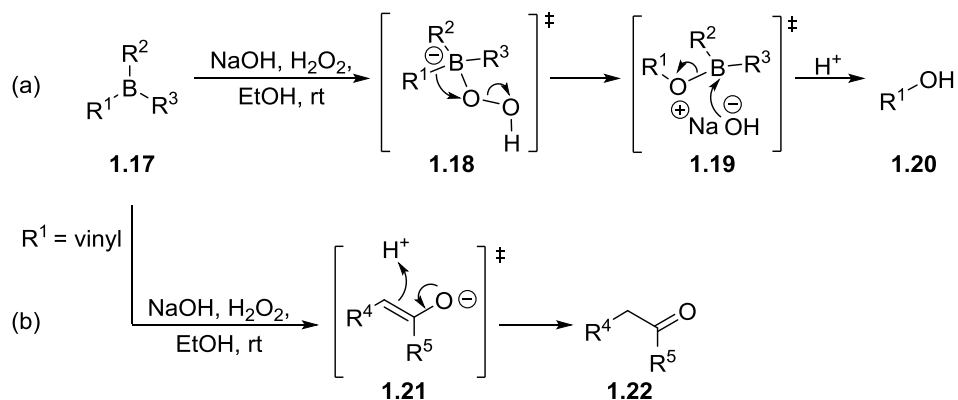
Organoboronamides serve as another useful class of air- and moisture-stable boronic acid derivatives. As a result of the adjacent nitrogen atoms donating electron density into the boron center, the Lewis acidity is drastically diminished.<sup>28</sup> In turn, this renders the boronic acid derivatives inert to most conditions. Specifically, **1.14** and **1.15** are unreactive towards both weakly acidic and basic conditions but are rapidly cleaved with  $\text{H}_2\text{SO}_4$  or HCl.<sup>3, 29-30</sup> Although the reactivity of boronamides is drastically different from boronic esters, they are indistinguishable by  $^{11}\text{B}$  NMR, as is observed with diborated compounds bearing both pinacol and 1,8-diaminonaphthalene groups.<sup>14, 31</sup>

Organotrifluoroborates are another class of protecting group that masks the boronic acid functionality. Treatment with  $\text{KHF}_2$  or a 3:2 KF:tartric acid mixture readily forms the  $\text{sp}^3$ -hybridized tetrahedral species **1.16** that can easily be purified by recrystallization.<sup>32</sup> This is ideal for large scale pharmaceutical reactions. Formation of the trifluoroborate salt is favored due to the strong B–F bond (157.5 kcal/mol), which is substantially stronger than the B–O bond (129.9 kcal/mol).<sup>6</sup> Work conducted independently by Lennox<sup>33</sup> and Liu<sup>34</sup> revealed that the rate of hydrolysis and hydrolytic conditions are dependent upon the unique structure of the trifluoroborate compound.

## 1.2 Organoboron compounds as synthetic intermediates

The synthetic versatility of boronic acids and boronic acid derivatives has been shown by their use as synthetic intermediates to form carbon–carbon and carbon–heteroatom bonds, which by alternative approaches would be problematic. The first transformation of boronic acids was discovered in 1956 by H.C. Brown, a Nobel Prize winner, when he reported the oxidation of alkyl boronic acids with NaOH and  $\text{H}_2\text{O}_2$  in EtOH to synthesize the corresponding alcohols (Scheme 1.3a).<sup>35</sup> The use of  $\text{NaBO}_3$  has also been shown to be effective in oxidizing organoboron reagents.<sup>36</sup> The enol formed from the oxidation of vinyl boronic acids or boronate esters tautomerizes to the more stable ketone or aldehyde (Scheme 1.3b).

Another significant breakthrough in boron chemistry arose with the discovery of the Suzuki–Miyaura cross-coupling reaction in which Akira Suzuki shared the Nobel Prize in chemistry with Richard Heck and Ei-ichi Negishi in 2010.<sup>37</sup> This palladium-catalyzed cross-coupling reaction produces new carbon–carbon bonds by reacting various organoboron compounds and organic halides in the presence of a base. Extensive literature details a four step

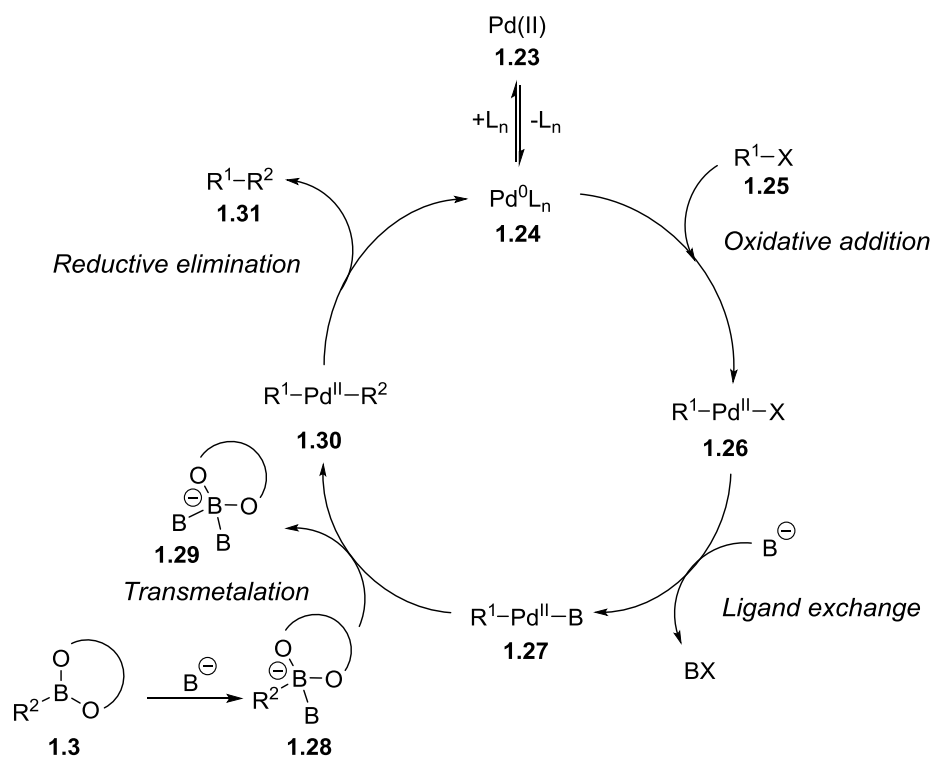


**Scheme 1.3.** Oxidation of organoboron compounds.

catalytic cycle beginning with the oxidative addition of organohalide **1.25** to the Pd(0) active catalyst (Scheme 1.4).<sup>38</sup> Exchange of the halogen ligand with the base forms complex **1.27** which upon transmetalation with the  $sp^3$ -hybridized anionic boron species generates Pd(II) intermediate **1.30**. Reductive elimination of the desired product **1.31** regenerates the active catalyst. Commonly observed side products from this cross-coupling includes protodeboration, oxidation, and homocoupling products.<sup>39</sup>

Typically, air- and moisture-free reaction conditions are crucial to successfully employing the traditional Suzuki–Miyaura cross-coupling reaction. In recent years the reaction conditions, metal catalysts, and ligands have been altered to allow coupling reactions to be conducted in aqueous media<sup>40-43</sup> or under solvent-less conditions.<sup>44</sup> These improvements have made the reaction more environmentally friendly and economical than reaction with organometallic reagents.<sup>45</sup>

The cross-coupling reaction commonly employs boronic acids and boronate esters because of their commercial availability and ability to easily form the tetrahedral species needed to undergo the transmetalation step.<sup>14</sup> Unfortunately, the less Lewis acidic boronamides **1.14**–



**Scheme 1.4.** Catalytic cycle for the Suzuki–Miyaura cross-coupling reaction.

**1.15** are unable to form the tetrahedral species rendering them unreactive towards cross-coupling reactions.<sup>31</sup> Despite being sp<sup>3</sup>-hybridized, the *N*-coordinated organoboronate esters **1.11–1.13** and trifluoroborates **1.16** are inert to traditional coupling conditions; however, these boron compounds can serve as efficient reagents by first hydrolyzing the protecting group *in-situ* to reveal the more reactive boronic acid, which is the actual coupling partner.<sup>19, 46-50</sup>

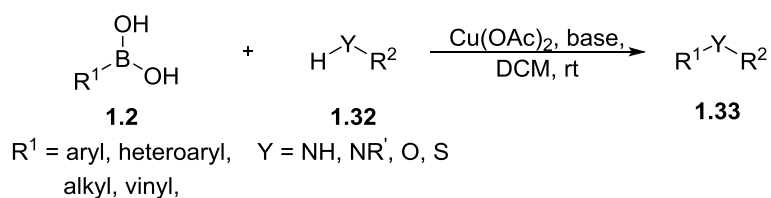
Amongst the myriad of Suzuki–Miyaura cross-coupling protocols reported, the majority utilize vinyl or aryl organoboronate esters. Recent literature has shown that the coupling can successfully be used with chiral secondary and tertiary organoboron compounds to stereospecifically synthesize quaternary centers.<sup>51-53</sup> The major challenge associated with coupling chiral organoboron compounds is the suppression of the common β-hydride elimination



product.<sup>54</sup> Based on the mechanism, retention or inversion of the chiral center is suggested to occur during the oxidative addition or transmetalation step.<sup>55-57</sup>

The versatility of the reaction has been shown not only with the reaction solvents and diverse organoboron compounds employed but also in the variety of organic halides that have been studied. Reactivity of the organohalide is based upon the leaving group ability and strength of the carbon–halogen bond (I > OTf > Br >> Cl); therefore, it is not surprising that aryl chlorides make for difficult cross-coupling partners.<sup>58-59</sup> It was established that in order for the unreactive aryl chlorides to oxidatively add to the palladium(0) complex, the addition of phosphine ligands and electron withdrawing groups on the aryl ring are essential.<sup>60</sup> Other substrates that have been a challenge to cross-couple include unprotected haloimidazoles,<sup>61</sup> halogenated electron-rich aminopyrazoles,<sup>62</sup> and nitrofluorarenes.<sup>63</sup>

In 1998, almost 20 years after the discovery of the Suzuki–Miyaura cross-coupling reaction, an alternative organoboron cross-coupling reaction was disclosed. Separate reports by Chan,<sup>64</sup> Lam,<sup>65</sup> and Evans<sup>66</sup> detailed a simple Cu(II)-catalyzed *N*- and *O*-arylation of aryl boronic acids with aryl amines, heteroaryl amines, amides, and alcohols in the presence of an amine base and atmospheric oxygen as an oxidant (Scheme 1.5). Recent reports have disclosed that the more reactive substituted thiols are also excellent cross-coupling partners.<sup>67-69</sup> Problematic substrates including vinyl boronic acids,<sup>70</sup> alkyl boronic acids,<sup>71</sup> and aliphatic amines<sup>72</sup> require catalytic amounts of copper or an additional oxidant. Further optimization by Quach and Batey have demonstrated that the reaction can successfully be conducted under base-free conditions.<sup>73</sup> Additionally, it has been shown that the boronate esters and trifluoroborates will undergo cross-coupling; however, protecting groups are generally not required due to the wide functional group tolerance and mild reaction conditions.<sup>74-75</sup> While the Buchwald–Hartwig cross-coupling reaction



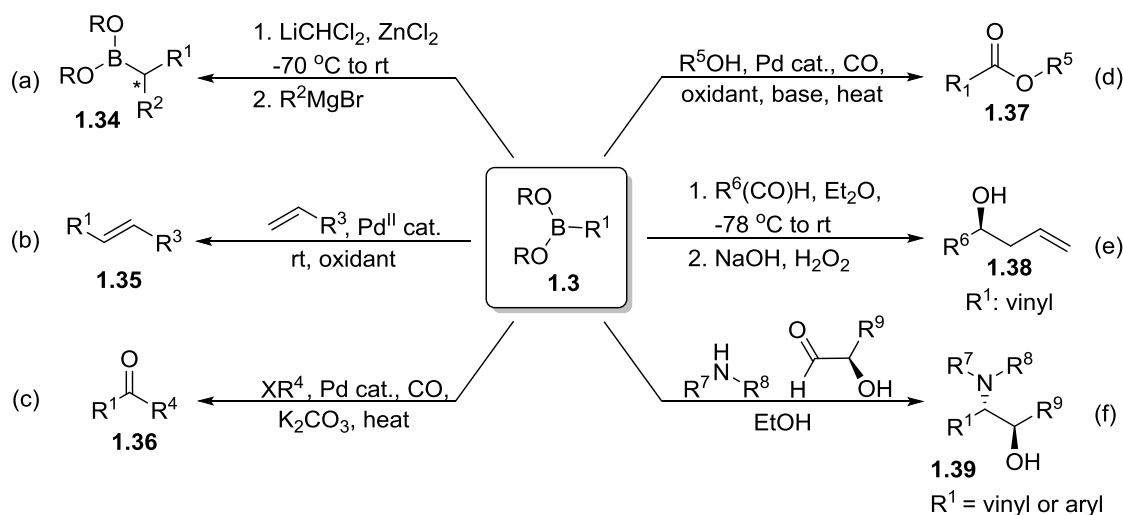
**Scheme 1.5.** Cu(II)-catalyzed Chan–Lam coupling reaction.

cross-coupling reaction can efficiently synthesize similar substrates, the Chan-Lam coupling-reaction has been considered an appealing alternative since the reaction is conducted open-to-air with an inexpensive copper(II) catalyst.

While the aforementioned reactions show the versatility of organoboron compounds, the functionality of these reagents is not limited to these few transformations. Several other carbon–carbon and carbon–heteroatom forming reactions have been researched in depth and are illustrated in Scheme 1.6. The asymmetric homologation reaction introduces chirality into the molecule while simultaneously forming a new carbon–carbon bond with the addition of a Grignard reagent or nucleophile to the  $\alpha$ -chloro boronic ester intermediate (Scheme 1.6a).<sup>76-77</sup> While this approach has shown promise in the total synthesis of biologically active products, it is limited by the availability of organoboron compounds and functional groups that are stable under basic organometallic conditions.<sup>78-80</sup> Alternatively, the Pd(II)-catalyzed oxidative Heck coupling reaction of boronate esters and olefins allows for the formation of alkenes using either  $\text{Cu(OAc)}_2$  or oxygen as an oxidant (Scheme 1.6b).<sup>81-82</sup> In contrast to the Suzuki–Miyaura cross-coupling reaction and Heck reaction, the oxidative Heck coupling requires a Pd(II) catalyst and proceeds through an initial transmetalation step with the oxidant being used to regenerate the Pd(II) catalyst.<sup>83</sup>

Until the work by Ishiyama *et al.* in 1993, diaryl ketones were commonly prepared with

Friedel–Crafts acylation.<sup>84-85</sup> The carbonylation of boronic acids and organic halides with CO allows for the installation of a carbonyl group to form unsymmetrical ketones under milder reaction conditions (Scheme 1.6c).<sup>38, 86-87</sup> Base and solvent optimizations are crucial in preventing the formation of the direct coupling product.<sup>38</sup> This procedure has subsequently led to the alkoxy-carbonylation coupling for the synthesis of esters (Scheme 1.6d).<sup>88-90</sup>

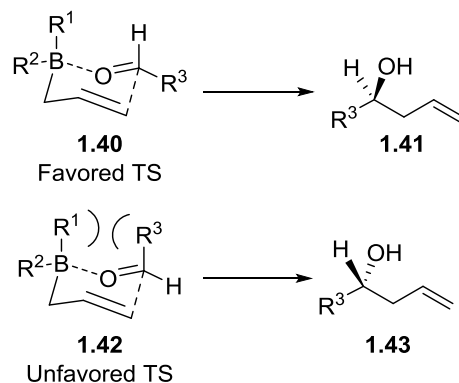


**Scheme 1.6.** Versatility of organoboron compounds to form carbon–carbon and carbon–heteroatom bonds.

Another procedure for the introduction of a carbon–oxygen bond includes the asymmetric allylation of aldehydes or ketones and allyl organoboron compounds to synthesize homoallylic alcohols in high enantiomeric excess (Scheme 1.6e).<sup>91-92</sup> The enantioselectivity can be explained by a 6-membered chair-like transition state that favors the aldehyde substituent being in the equatorial position to prevent 1,3-diaxial steric interactions (Figure 1.3).<sup>93</sup>

Alternative synthetic applications that utilize vinyl and arylboronic acids include the Petasis borono-Mannich reaction. Initial reports from Petasis and Akritopoulou in 1993 detailed the addition of vinyl or aryl boronic acids to amines and aldehydes to form allylic and arylamines without the use of a strong base or transition metal.<sup>94</sup> Further studies indicated that higher yields

where often obtained when employing vinyl boronic acids and secondary amines.<sup>95-96</sup> Over time, this protocol has become known for the synthesis of  $\alpha$ -amino acids and biological agents.<sup>97-101</sup>

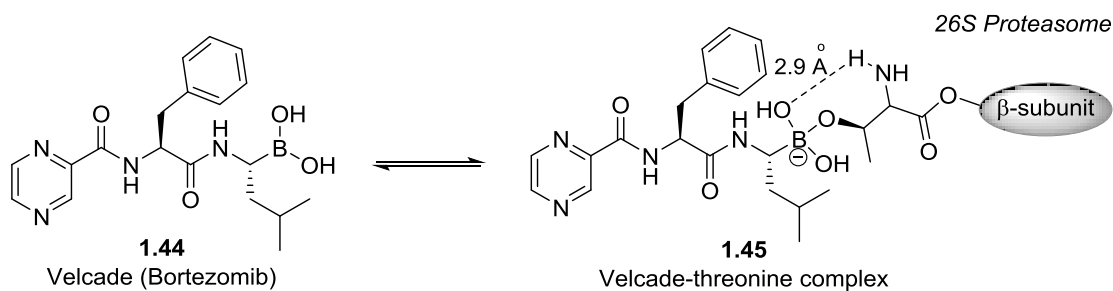


**Figure 1.3.** Allylation transition states.

### 1.3 Therapeutic applications of organoboron compounds

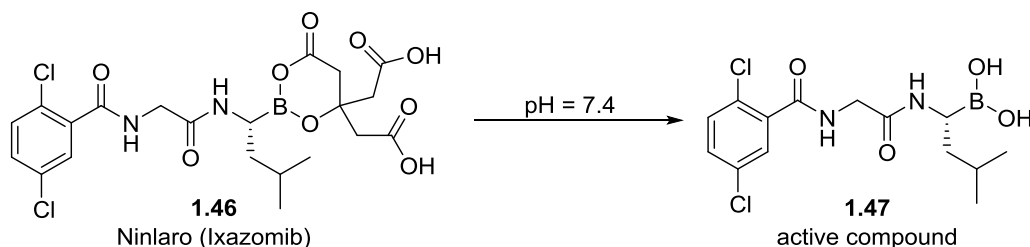
In addition to being used as synthetic intermediates, organoboron compounds have also shown promise in therapeutic applications. The empty p-orbital of boron and its ability to form strong reversible covalent bonds with oxygen nucleophiles (130–125 kcal/mol) favors the incorporation of boron into therapeutic agents. In 2003, Velcade<sup>®</sup> **1.44** was marketed by Millennium Pharmaceuticals, now owned by Takeda Pharmaceuticals, as the first FDA approved boron containing therapeutic agent.<sup>102-103</sup> This dipeptide boronic acid analogue is a proteasome inhibitor used to slow down the progression of relapsed multiple myeloma, mantle cell lymphoma, and other cancer cell types.<sup>102</sup> It has been shown to affect the ubiquitin-proteasome pathway by reversibly binding to the *N*-terminal threonine residue of the  $\beta$ -subunit that is found in the 20S core of the 26S proteasome (Figure 1.4).<sup>104-106</sup> Inhibition of the 26S proteasome causes an accumulation of proteins leading to cell apoptosis.<sup>107</sup> Velcade<sup>®</sup> has a  $K_i$  of  $6.2 \times 10^{-4}$   $\mu\text{M}$ ; however, the aldehyde analogue has a  $K_i$  of 0.6  $\mu\text{M}$  which indicates that incorporation of the boronic acid into the molecule allows for better inhibition of target enzyme.<sup>108</sup> Selectivity

studies have shown that Velcade<sup>®</sup> is selective for the 26S proteasome when compared to other serine proteases including  $\beta$ -lactamase,<sup>109-110</sup> thrombin,<sup>111-112</sup> and elastase,<sup>113-115</sup> which are known targets of boronic acid complexes.



**Figure 1.4.** Interaction of Velcade<sup>®</sup> inside the 26S proteasome.

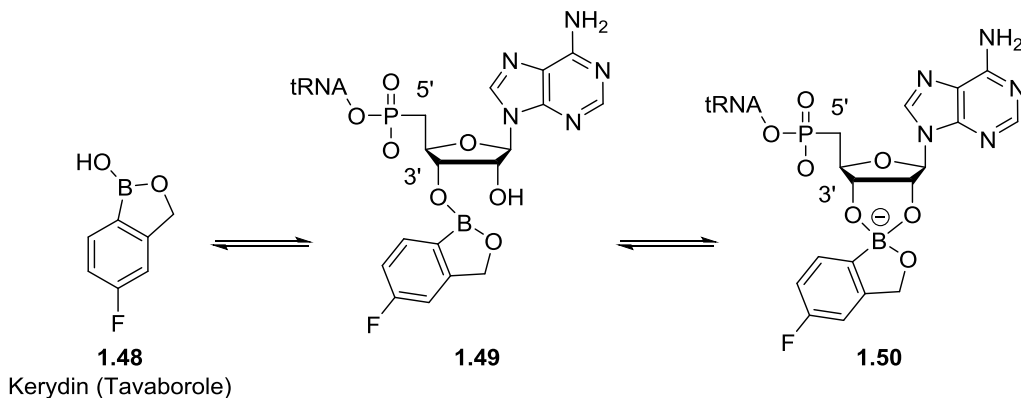
Similar to Velcade<sup>®</sup>, Ninlaro<sup>®</sup> **1.46** contains a dipeptide backbone and is used to slow down the progression of multiple myeloma by the same mode of action; however, despite its potency, this therapeutic agent is used in combination with lenalidomide and dexamethasone for better inhibition.<sup>116-118</sup> Additionally, Ninlaro<sup>®</sup> is the first oral boron-containing therapeutic agent and prodrug. Hydrolysis of the citrate protected boron moiety under physiological conditions reveals the boronic acid and active compound **1.47** (Figure 1.5).<sup>119-120</sup> While there is no improvement in the  $K_i$  compared to Velcade<sup>®</sup>, this inhibitor has reduced toxicity and improved selectivity for the  $\beta$ -subunit of the 26S proteasome.<sup>118, 121</sup>



**Figure 1.5.** Prodrug Ninlaro<sup>®</sup> and its active form.

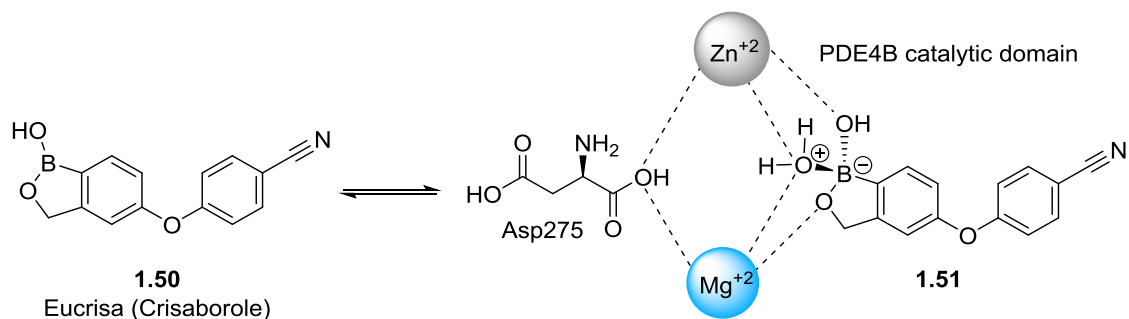
Benzoxaboroles represent another important class of boron-containing therapeutic agents.

Kerydin<sup>®</sup> **1.48** is a topical medication marketed in 2014 as a treatment for fungal infections of the nail and instead of incorporating a boronic acid it contains a benzoxaborole moiety.<sup>122-123</sup> This therapeutic agent has a unique mechanism in that it blocks protein synthesis in the editing site and forms a reversible complex with the 2' and 3' hydroxyl groups of leucyl-aminoacyl transfer RNA (tRNA) synthetase leading to cellular apoptosis (Figure 1.6).<sup>124-125</sup>



**Figure 1.6.** Interaction of Kerydin<sup>®</sup> with tRNA synthetase.

Further screening studies of benzoxaborole derivatives led to the discovery of Eucrisa<sup>®</sup> **1.51**, which is the most recent FDA approved boron-containing therapeutic agent. As a topical treatment for psoriasis and atopic dermatitis, Eucrisa<sup>®</sup> inhibits the phosphodiesterase-4 (PDE4) enzyme ( $IC_{50} = 0.8 \pm 0.3 \mu M$ ).<sup>126-127</sup> Modeling studies attributed its potency to the formation of an anionic tetrahedral intermediate with a water molecule in the active site of the PDE4B enzyme and coordination to two metal ions (Figure 1.7).<sup>128</sup> Inhibition of this enzyme prevents hydrolysis of cyclic AMP, a signaling molecule that suppresses the release of proinflammatory mediators.<sup>129</sup> While other potent boronic acids and boronic acid derivatives have been reported, none of these compounds have gone to clinical trials due to their toxicity or lack of selectivity.<sup>130-132</sup>



**Figure 1.7.** Mode of action for Eucrisa<sup>®</sup>.

## 1.4 Dissertation overview

Chapter 1 details the general characteristics, properties, and structures of common organoboron moieties. Methods to introduce alternative protecting groups have been discussed in addition to the stability, general bond strengths, and chemical shifts of organoboron compounds. The application of organoboron compounds as synthetic intermediates is incorporated with an emphasis on the number of diverse reactions that can be used to synthesize new carbon–carbon and carbon–heteroatom bonds. Using organoboron compounds as therapeutic agents is also discussed as well as their mechanism of action.

A copper(II)-catalyzed aqueous borylation protocol of alkynoates and the symmetrical diboron reagent,  $\text{B}_2\text{pin}_2$ , is described in Chapter 2. The  $\beta$ -borylated and (*Z*)-stereoisomer was selectively obtained under mild reaction conditions. A catalytic cycle has been proposed based on information gathered from the previous aqueous  $\beta$ -borylation protocol of ethylenic esters.

In Chapter 3, the open-to-air aqueous  $\beta$ -borylation protocol was altered so that it could be conducted in the presence of an unsymmetrical diboron reagent, pinB-Bdan. Optimization of the reaction conditions improved the solubility of the diboron reagent and provided the products in

moderate to excellent yields. Activation of the more Lewis acidic pinacol moiety ensured that the 1,8-diaminonaphthalene moiety was chemoselectively transferred to the  $\beta$ -carbon.

Chapter 4 details the novel synthesis of vinyl and allyl boronate esters from unactivated propargylic alcohol species by creating a leaving group *in situ*. Both the yield and selectivity were greatly improved by using a bimetallic catalytic system and a boronic acid additive at room temperature. The regio- and stereoselectivity of the products were assigned based on nOe experiments. NMR studies revealed the low isolated yields were due to the instability of the diborated products on silica during purification. Finally, a catalytic cycle is proposed based on the mechanistic studies.

Chapter 5 provides the supplemental information for Chapters 2-4 including the general procedures, instrumentation, experimental procedures, and product characterization for products synthesized by the author.

## 1.5 References for Chapter 1

1. Frankland, E.; Duppa, B., On Boric Ethide. *Proc. R. Soc. London* **1859**, *10*, 568.
2. Matteson, D. S., *Stereodirected Synthesis with Organoboranes*. 1st ed.; Springer-Verlang Berlin Heidelberg, 1995.
3. Hall, D. G., *Boronic Acids: Preparation, Applications in Organic Synthesis, Medicine and Materials*. 2nd ed.; Wiley-VCH: Weinheim, Germany, 2011.
4. Lappert, M. F., Organic Compounds of Boron. *Chem. Rev.* **1956**, *56*, 959.
5. Coulson, C. A.; Dingle, T. W., The B–O Bond Lengths in Boron-Oxygen Compounds. *Acta Crystallogr., Sect. B* **1968**, *24*, 153.



6. Sana, M.; Leroy, G.; Wilante, C., Enthalpies of Formation and Bond Energies in Lithium, Beryllium, and Boron Derivatives. A Theoretical Attempt for Data Rationalization. *Organometallics* **1991**, *10*, 264.
7. Allen, F. H.; Kennard, O.; Watson, D. G.; Brammer, L.; Orpen, A. G.; Taylor, R., Tables of Bond Lengths Determined by X-Ray and Neutron Diffraction. Part 1. Bond Lengths in Organic Compounds. *J. Chem. Soc., Perkin Trans. 2* **1987**, S1.
8. Benderdour, M.; Bui-Van, T.; Dicko, A.; Belleville, F., In Vivo and in Vitro Effects on Boron and Boronated Compounds. *J. Trace Elem. Med. Biol.* **1998**, *12*, 2.
9. DeFrancesco, H.; Dudley, J.; Coca, A., Boron Chemistry: An Overview. In *Boron Reagents in Synthesis* [Online] American Chemical Society: 2016; pp 1. <http://dx.doi.org/10.1021/bk-2016-1236.ch001> (accessed July 16, 2017)
10. Hunt, C. D., Dietary Boron: Progress in Establishing Essential Roles in Human Physiology. *J. Trace Elem. Med. Biol.* **2012**, *26*, 157.
11. Hosmane, N. S., Boron for Living: Health and Nutrition. In *Boron Science: New Technologies and Applications*, 1st ed.; CRC press: Boca Raton, Florida, 2011; pp 73.
12. Knapp, D. M.; Gillis, E. P.; Burke, M. D., A General Solution for Unstable Boronic Acids: Slow-Release Cross-Coupling from Air-Stable Mida Boronates. *J. Am. Chem. Soc.* **2009**, *131*, 6961.
13. Kuivila, H. G.; Keough, A. H.; Soboczenski, E. J., Areneboronates from Diols and Polyols. *J. Org. Chem.* **1954**, *19*, 780.
14. Lennox, A. J. J.; Lloyd-Jones, G. C., Selection of Boron Reagents for Suzuki-Miyaura Coupling. *Chem. Soc. Rev.* **2014**, *43*, 412.

15. Sivaev, I. B.; Bregadze, V. I., Lewis Acidity of Boron Compounds. *Coord. Chem. Rev.* **2014**, *270*, 75.
16. Dang, L.; Zhao, H.; Lin, Z., Understanding the Higher Reactivity of B<sub>2</sub>cat<sub>2</sub> versus B<sub>2</sub>pin<sub>2</sub> in Copper(I)-Catalyzed Alkene Diboration Reactions. *Organometallics* **2008**, *27*, 1178.
17. Matteson, D. S., Asymmetric Synthesis with Boronic Esters. *Acc. Chem. Res.* **1988**, *21*, 294.
18. Blandin, V.; Chavant, P. Y., Preparations and Applications of Hexyleneglycol Organoboronic Esters. In *Boron: Sensing, Synthesis and Supramolecular Self-Assembly* [Online], The Royal Society of Chemistry: 2016; pp 61. <http://dx.doi.org/10.1039/9781782622123-00061> (accessed July 6, 2017).
19. Gillis, E. P.; Burke, M. D., A Simple and Modular Strategy for Small Molecule Synthesis: Iterative Suzuki–Miyaura Coupling of B-Protected Haloboronic Acid Building Blocks. *J. Am. Chem. Soc.* **2007**, *129*, 6716.
20. Mancilla, T.; Contreras, R.; Wrackmeyer, B., New Bicyclic Organoboronic Esters Derived from Iminodiacetic Acids. *J. Organomet. Chem.* **1986**, *307*, 1.
21. Gao, M.; Thorpe, S. B.; Kleeberg, C.; Slebodnick, C.; Marder, T. B.; Santos, W. L., Structure and Reactivity of a Preactivated sp<sup>2</sup>–sp<sup>3</sup> Diboron Reagent: Catalytic Regioselective Boration of α,β-Unsaturated Conjugated Compounds. *J. Org. Chem.* **2011**, *76*, 3997.
22. Gao, M.; Thorpe, S. B.; Santos, W. L., sp<sup>2</sup>–sp<sup>3</sup> Hybridized Mixed Diboron: Synthesis, Characterization, and Copper-Catalyzed β-Boration of α,β-Unsaturated Conjugated Compounds. *Org. Lett.* **2009**, *11*, 3478.

23. Mancilla, T.; Zamudio-Rivera, L. S.; Hiram, I. B.; Santillan, R.; Farfán, N., Synthesis and Characterization of New (N→B) Phenyl Substituted [*N*-Benzyliminodiacetate-*O,O',N*]boranes. *Arch. Org. Chem.* **2005**, *6*, 366.
24. Metola, P.; Chapin, B. M.; Anslyn, E. V., <sup>11</sup>B NMR and Its Uses in Structural Characterization of Boronic Acids and Boronate Esters. In *Boron: Sensing, Synthesis and Supramolecular Self-Assembly* [Online], The Royal Society of Chemistry: 2016; pp 44. <http://dx.doi.org/10.1039/9781782622123-00044> (accessed online June 28, 2017)
25. Sun, J.; Perfetti, M. T.; Santos, W. L., A Method for the Deprotection of Alkylpinacolyl Boronate Esters. *J. Org. Chem.* **2011**, *76*, 3571.
26. Gillis, E. P.; Burke, M. D., Multistep Synthesis of Complex Boronic Acids from Simple Mida Boronates. *J. Am. Chem. Soc.* **2008**, *130*, 14084.
27. Lee, S. J.; Gray, K. C.; Paek, J. S.; Burke, M. D., Simple, Efficient, and Modular Syntheses of Polyene Natural Products via Iterative Cross-Coupling. *J. Am. Chem. Soc.* **2008**, *130*, 466.
28. Cid, J.; Carbó, J. J.; Fernández, E., A Clear-Cut Example of Selective Bpin-Bdan Activation and Precise Bdan Transfer on Boron Conjugate Addition. *Chem. - Eur. J.* **2014**, *20*, 3616.
29. Noguchi, H.; Hojo, K.; Suginome, M., Boron-Masking Strategy for the Selective Synthesis of Oligoarenes via Iterative Suzuki–Miyaura Coupling. *J. Am. Chem. Soc.* **2007**, *129*, 758.
30. Iwadate, N.; Suginome, M., Synthesis of β-Protected β-Styrylboronic Acids via Iridium-Catalyzed Hydroboration of Alkynes with 1,8-Naphthalenediaminoborane Leading to Iterative Synthesis of Oligo(phenylenevinylene)s. *Org. Lett.* **2009**, *11*, 1899.
31. Verma, A.; Snead, R. F.; Dai, Y.; Slebodnick, C.; Yang, Y.; Yu, H.; Yao, F.; Santos, W. L.,

- Substrate-Assisted, Transition Metal-Free Diboration of Alkynamides with Mixed Diboron: Regio- and Stereoselective Access to *Trans*-1,2-Vinyldiboronates. *Angew. Chem. Int. Ed.* **2017**, *129*, 5193.
32. Churches, Q. I.; Hooper, J. F.; Hutton, C. A., A General Method for Interconversion of Boronic Acid Protecting Groups: Trifluoroborates as Common Intermediates. *J. Org. Chem.* **2015**, *80*, 5428.
33. Lennox, A. J.; Lloyd-Jones, G. C., Organotrifluoroborate Hydrolysis: Boronic Acid Release Mechanism and an Acid-Base Paradox in Cross-Coupling. *J. Am. Chem. Soc.* **2012**, *134*, 7431.
34. Liu, Z.; Chao, D.; Li, Y.; Ting, R.; Oh, J.; Perrin, D. M., From Minutes to Years: Predicting Organotrifluoroborate Solvolysis Rates. *Chem. - Eur. J.* **2015**, *21*, 3924.
35. Brown, H. C.; Rao, B. C. S., A New Technique for the Conversion of Olefins into Organoboranes and Related Alcohols. *J. Am. Chem. Soc.* **1956**, *78*, 5694.
36. Kabalka, G. W.; Shoup, T. M.; Goudgaon, N. M., Sodium Perborate: A Mild and Convenient Reagent for Efficiently Oxidizing Organoboranes. *J. Org. Chem.* **1988**, *54*, 1989.
37. Miyaura, N.; Yamada, K.; Suzuki, A., A New Stereospecific Cross-Coupling by the Palladium-Catalyzed Reaction of 1-Alkenylboranes with 1-Alkenyl or 1-Alkynyl Halides. *Tetrahedron Lett.* **1979**, *20*, 3437.
38. Miyaura, N.; Suzuki, A., Palladium-Catalyzed Cross-Coupling Reactions of Organoboron Compounds. *Chem. Rev.* **1995**, *95*, 2457.
39. Lennox, A. J. J.; Lloyd-Jones, G. C., The Slow-Release Strategy in Suzuki–Miyaura Coupling. *Isr. J. Chem.* **2010**, *50*, 664.

40. Casalnuovo, A. L.; Calabrese, J. C., Palladium-Catalyzed Alkylations in Aqueous Media. *J. Am. Chem. Soc.* **1990**, *112*, 4324.
41. Bussolari, J. C.; Reborn, D. C., Preparation of 5-Aryl Furfurals and Aryl Thiophene-2-Carboxaldehydes via Palladium-Catalyzed C–C Bond Formation in Aqueous Media. *Org. Lett.* **1999**, *1*, 965.
42. Badone, D.; Baroni, M.; Cardamone, R.; Ielmini, A.; Guzzi, U., Highly Efficient Palladium-Catalyzed Boronic Acid Coupling Reactions in Water: Scope and Limitations. *J. Org. Chem.* **1997**, *62*, 7170.
43. Alonso, F.; Beletskaya, I. P.; Yus, M., Non-Conventional Methodologies for Transition-Metal Catalysed Carbon-carbon Coupling: A Critical Overview. Part 2: The Suzuki Reaction. *Tetrahedron* **2008**, *64*, 3047.
44. Asachenko, A. F.; Sorochkina, K. R.; Dzhevakov, P. B.; Topchiy, M. A.; Nechaev, M. S., Suzuki–Miyaura Cross-Coupling under Solvent-Free Conditions. *Adv. Synth. Cat.* **2013**, *355*, 3553.
45. Crudden, C. M.; Glasspoole, B. W.; Lata, C. J., Expanding the Scope of Transformations of Organoboron Species: Carbon-Carbon Bond Formation with Retention of Configuration. *Chem. Commun.* **2009**, 6704.
46. Molander, G. A.; Canturk, B.; Kennedy, L. E., Scope of the Suzuki-Miyaura Cross-Coupling Reactions of Potassium Heteroaryltrifluoroborates. *J. Org. Chem.* **2008**, *74*, 973.
47. Molander, G. A., Organotrifluoroborates: Another Branch of the Mighty Oak. *J. Org. Chem.* **2015**, *80*, 7837.
48. Darses, S.; Genet, J.-P., Potassium Organotrifluoroborates: New Perspectives in Organic Synthesis. *Chem. Rev.* **2008**, *108*, 288.

49. Hiebel, G. A. M.-A., Synthesis of Amidomethyltrifluoroborates and Their Use in Cross-Coupling Reactions. *Org. Lett.* **2010**, *12*, 4876.
50. Li, J.; Grillo, A. S.; Burke, M. D., From Synthesis to Function via Iterative Assembly of N-Methyliminodiacetic Acid Boronate Building Blocks. *Acc. Chem. Res.* **2015**, *48*, 2297.
51. Odachowski, M.; Bonet, A.; Essafi, S.; Conti-Ramsden, P.; Harvey, J. N.; Leonori, D.; Aggarwal, V. K., Development of Enantiospecific Coupling of Secondary and Tertiary Boronic Esters with Aromatic Compounds. *J. Am. Chem. Soc.* **2016**, *138*, 9521.
52. Imao, D.; Glasspoole, B. W.; Laberge, V. S.; Crudden, C. M., Cross Coupling Reactions of Chiral Secondary Organoboronic Esters with Retention of Configuration. *J. Am. Chem. Soc.* **2009**, *131*, 5024.
53. Sandrock, D. L.; Jean-Gérard, L.; Chen, C.-y.; Dreher, S. D.; Molander, G. A., Stereospecific Cross-Coupling of Secondary Alkyl  $\beta$ -Trifluoroboratoamides. *J. Am. Chem. Soc.* **2010**, *132*, 17108.
54. Jana, R.; Pathak, T. P.; Sigman, M. S., Advances in Transition Metal (Pd, Ni, Fe)-Catalyzed Cross-Coupling Reactions Using Alkyl-Organometallics as Reaction Partners. *Chem. Rev.* **2011**, *111*, 1417.
55. Leonori, D.; Aggarwal, V. K., Stereospecific Couplings of Secondary and Tertiary Boronic Esters. *Angew. Chem., Int. Ed.* **2015**, *54*, 1082.
56. Cherney, A. H.; Kadunce, N. T.; Reisman, S. E., Enantioselective and Enantiospecific Transition Metal-Catalyzed Cross-Coupling Reactions of Organometallic Reagents to Construct C–C Bonds. *Chem. Rev.* **2015**, *115*, 9587.
57. Awano, T.; Ohmura, T.; Suginome, M., Inversion or Retention? Effects of Acidic Additives on the Stereochemical Course in Enantiospecific Suzuki–Miyaura Coupling of  $\alpha$ -

- (Acetylamino)benzylboronic Esters. *J. Am. Chem. Soc.* **2011**, *133*, 20738.
58. Wolfe, J. P.; Buchwald, S. L., A Highly Active Catalyst for the Room-Temperature Amination and Suzuki Coupling of Aryl Chlorides. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413.
59. Littke, A. F.; Fu, G. C., Palladium-Catalyzed Coupling Reactions of Aryl Chlorides. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176.
60. Littke, A. F.; Fu, G. C., A Convenient and General Method for Pd-Catalyzed Suzuki Cross-Couplings of Aryl Chlorides and Arylboronic Acids. *Angew. Chem. Int. Ed.* **1998**, *37*, 3387.
61. Tan, J.; Chen, Y.; Li, H.; Yasuda, N., Suzuki-Miyaura Cross-Coupling Reactions of Unprotected Haloimidazoles. *J. Org. Chem.* **2014**, *79*, 8871.
62. Jedinák, L. s.; Zátopková, R. t.; Zemánková, H.; Šustková, A.; Cankař, P., The Suzuki–Miyaura Cross-Coupling Reaction of Halogenated Aminopyrazoles: Method Development, Scope, and Mechanism of Dehalogenation Side Reaction. *J. Org. Chem.* **2017**, *82*, 157.
63. Widdowson, D. A.; Wilhelm, R., Palladium-Catalyzed Suzuki Reactions of Fluoroarenes. *Chem. Commun.* **2003**, 578.
64. Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P., New N- and O-Arylations with Phenylboronic Acids and Cupric Acetate. *Tetrahedron Lett.* **1998**, *39*, 2933.
65. Lam, P. Y. S.; Clarkt, C. G.; Saubernt, S.; Adamst, J.; Winters, M. P.; Chan, D. M. T.; Combst, A., New Aryl/Heteroaryl C-N Bond Cross-Coupling Reactions via Arylboronic Acid/Cupric Acetate Arylation. *Tetrahedron Lett.* **1998**, *39*, 2941.

66. Evans, D. A.; Katz, J. L.; West, T. R., Synthesis of Diaryl Ethers through the Copper-Promoted Arylation of Phenols with Arylboronic Acids. An Expedient Synthesis of Thyroxine. *Tetrahedron Lett.* **1998**, *39*, 2937.
67. Rao, K. S.; Wu, T.-S., Chan–Lam Coupling Reactions: Synthesis of Heterocycles. *Tetrahedron* **2012**, *68*, 7735.
68. Ley, S. V.; Thomas, A. W., Modern Synthetic Methods for Copper-Mediated C(aryl)–O, C(aryl)–N, and C(aryl)–S Bond Formation. *Angew. Chem. Int. Ed.* **2003**, *42*, 5400.
69. Xu, H.-J.; Zhao, Y.-Q.; Feng, T.; Feng, Y.-S., Chan–Lam-Type S-Arylation of Thiols with Boronic Acids at Room Temperature. *J. Org. Chem.* **2012**, *77*, 2878.
70. Shade, R. E.; Hyde, A. M.; Olsen, J.-C.; Merlic, C. A., Copper-Promoted Coupling of Vinyl Boronates and Alcohols: A Mild Synthesis of Allyl Vinyl Ethers. *J. Am. Chem. Soc.* **2010**, *132*, 1202.
71. Rossi, S. A.; Shimkin, K. W.; Xu, Q.; Mori-Quiroz, L. M.; Watson, D. A., Selective Formation of Secondary Amides via the Copper-Catalyzed Cross-Coupling of Alkylboronic Acids with Primary Amides. *Org. Lett.* **2013**, *15*, 2314.
72. Mahapatra, S.; Halfen, J. A.; Tolman, W. B., Mechanistic Study of the Oxidative N-Dealkylation Reactions of Bis( $\mu$ -oxo)dicopper Complexes. *J. Am. Chem. Soc.* **1996**, *118*, 11575.
73. Quach, T. D.; Batey, R. A., Ligand- and Base-Free Copper(II)-Catalyzed C–N Bond Formation: Cross-Coupling Reactions of Organoboron Compounds with Aliphatic Amines and Anilines. *Org. Lett.* **2003**, *5*, 4397.



74. Huang, F.; Quach, T. D.; Batey, R. A., Copper-Catalyzed Nondecarboxylative Cross Coupling of Alkenyltrifluoroborate Salts with Carboxylic Acids or Carboxylates: Synthesis of Enol Esters. *Org. Lett.* **2013**, *15*, 3150.
75. Vantourout, J. C.; Law, R. P.; Isidro-Llobet, A.; Atkinson, S. J.; Watson, A. J. B., Chan–Evans–Lam Amination of Boronic Acid Pinacol (Bpin) Esters: Overcoming the Aryl Amine Problem. *J. Org. Chem.* **2016**, *81*, 3942.
76. Matteson, D. S., Boronic Esters in Asymmetric Synthesis. *J. Org. Chem.* **2013**, *78*, 10009.
77. Matteson, D. S.; Ray, R., Directed Chiral Synthesis with Pinanediol Boronic Esters. *J. Am. Chem. Soc.* **1980**, *102*, 7590.
78. Eppe, G.; Didier, D.; Marek, I., Stereocontrolled Formation of Several Carbon–Carbon Bonds in Acyclic Systems. *Chem. Rev.* **2015**, *115*, 9175.
79. Robinson, A.; Aggarwal, V. K., Asymmetric Total Synthesis of Solandelactone E: Stereocontrolled Synthesis of the 2-Ene-1,4-Diol Core through a Lithiation–Borylation–Allylation Sequence. *Angew. Chem. Int. Ed.* **2010**, *49*, 6673.
80. Davoli, P.; Fava, R.; Morandi, S.; Spaggiari, A.; Prati, F., Enantioselective Total Synthesis of (–)-Microcarpalide. *Tetrahedron* **2005**, *61*, 4427.
81. Dieck, H. A.; Heck, R. F., Palladium-Catalyzed Conjugated Diene Synthesis from Vinylic Halides and Olefinic Compounds. *J. Org. Chem.* **1975**, *40*, 1083.
82. Jung, Y. C.; Mishra, R. K.; Yoon, C. H.; Jung, K. W., Oxygen-Promoted Pd(II) Catalysis for the Coupling of Organoboron Compounds and Olefins. *Org. Lett.* **2003**, *5*, 2231.
83. Lee, A.-L., Enantioselective Oxidative Boron Heck Reactions. *Org. Biomol. Chem.* **2016**, *14*, 5357.

84. Ishiyama, T.; Kizaki, H.; Miyaura, N.; Suzuki, A., Synthesis of Unsymmetrical Biaryl Ketones via Palladium-Catalyzed Carbonylative Cross-Coupling Reaction of Arylboronic Acids with Iodoarenes. *Tetrahedron Lett.* **1993**, *34*, 7595.
85. Olah, G. A., *Friedel-Crafts Chemistry*. John Wiley & Sons: Hoboken, NJ, 1973.
86. Ishiyama, T.; Kizaki, H.; Hayashi, T.; Suzuki, A.; Miyaura, N., Palladium-Catalyzed Carbonylative Cross-Coupling Reaction of Arylboronic Acids with Aryl Electrophiles: Synthesis of Biaryl Ketones. *J. Org. Chem.* **1998**, *63*, 4726.
87. Neumann, H.; Brennfürher, A.; Beller, M., A General Synthesis of Diarylketones by Means of a Three-Component Cross-Coupling of Aryl and Heteroaryl Bromides, Carbon Monoxide, and Boronic Acids. *Chem. - Eur. J.* **2008**, *14*, 3645.
88. Liu, Q.; Li, G.; He, J.; Liu, J.; Li, P.; Lei, A., Palladium-Catalyzed Aerobic Oxidative Carbonylation of Arylboronate Esters under Mild Conditions. *Angew. Chem. Int. Ed.* **2010**, *49*, 3371.
89. Cho, C. S.; Ohe, T.; Uemura, S., Palladium(0)-Catalyzed Carbonylation of Aryl and Alkenyl Boronic Acids with Carbon Monoxide Leading to Esters and Ketones. Transformation of a C–B Bond to a C–CO Bond. *J. Organomet. Chem.* **1995**, *496*, 221.
90. Sharma, P.; Rohilla, S.; Jain, N., Palladium Catalyzed Carbonylative Coupling for Synthesis of Arylketones and Arylesters using Chloroform as the Carbon Monoxide Source. *J. Org. Chem.* **2017**, *82*, 1105.
91. Mikhailov, B. M.; Bubnov, Y. N., Reaction of Triallylboron with Carbonyl Compounds. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1964**, *13*, 1774.
92. Burgos, C. H.; Canales, E.; Matos, K.; Soderquist, J. A., Asymmetric Allyl- and

- Crotylboration with the Robust, Versatile, and Recyclable 10-TMS-9-Borabicyclo[3.3.2]decanes. *J. Am. Chem. Soc.* **2005**, *127*, 8044.
93. Denmark, S. E.; Weber, E. J., On the Stereochemistry of Allylmetal–Aldehyde Condensations. *Helv. Chim. Acta* **1983**, *66*, 1655.
94. Petasis, A. N.; Akritopoulou, I., The Boronic Acid Mannich Reaction: A New Method for the Synthesis of Geometrically Pure Allylamines. *Tetrahedron Lett.* **1993**, *34*, 583.
95. Candeias, N. R.; Montalbano, F.; Cal, P. M. S. D.; Gois, P. M. P., Boronic Acids and Esters in the Petasis-Borono Mannich Multicomponent Reaction. *Chem. Rev.* **2010**, *110*, 6169.
96. Southwood, T. J.; Curryb, M. C.; Hutton, C. A., Factors Affecting the Efficiency and Stereoselectivity of  $\alpha$ -Amino Acid Synthesis by the Petasis Reaction. *Tetrahedron* **2006**, *62*, 236.
97. Petasis, N. A.; Zavialov, I. A., Highly Stereocontrolled One-Step Synthesis of *Anti*- $\alpha$ -Amino Alcohols from Organoboronic Acids, Amines, and  $\beta$ -Hydroxy Aldehydes. *J. Am. Chem. Soc.* **1998**, *120*, 11798.
98. Petasis, N. A.; Zavialov, I. A., A New and Practical Synthesis of  $\alpha$ -Amino Acids from Alkenyl Boronic Acids *J. Am. Chem. Soc.* **1997**, *119*, 445.
99. Stuetz, A.; Petranyi, G., Synthesis and Antifungal Activity of (*E*)-*N*-(6,6-Dimethyl-2-Hepten-4-ynyl)-*N*-Methyl-1-Naphthalenemethanamin (SF 86-327) and Related Allylamine Derivatives with Enhanced Oral Activity. *J. Med. Chem.* **1984**, *27*, 1539.
100. Horie, M.; Tsuchiya, Y.; Hayashi, M.; Iida, Y.; Iwasawa, Y.; Nagata, Y.; Sawasaki, Y.; Fukuzumi, H.; Kitani, K.; Kamei, T., NB-598: A Potent Competitive Inhibitor of Squalene Epoxidase. *J. Biol. Chem.* **1990**, *165*, 18075.

101. Ghosal, P.; Shaw, A. K., A Chiron Approach to Aminocytitols by Petasis-Borono-Mannich Reaction: Formal Synthesis of (+)-Conduramine E and (-)-Conduramine E. *J. Org. Chem.* **2012**, *77*, 7627.
102. Baker, S. J.; Ding, C. Z.; Akama, T.; Zhang, Y.-K.; Hernandez, V.; Xia, Y., Theraptic Potential of Boron-Containing Compounds. *Future Med. Chem.* **2009**, *1*, 1275.
103. Bross, P. F.; Kane, R.; Farrell, A. T.; Abraham, S.; Benson, K.; Brower, M. E.; Bradley, S.; Gobburu, J. V.; Goheer, A.; Lee, S.-L.; Leighton, J.; Liang, C. Y.; Lostritto, R. T.; McGuinn, W. D.; Morse, D. E.; Rahman, A.; Rosario, L. A.; Verbois, S. L.; Williams, G.; Wang, Y.-C.; Pazdur, R., Approval Summary for Bortezomib for Injection in the Treatment of Multiple Myeloma. *Clin. Cancer Res.* **2004**, *10*, 3954.
104. Rentsch, A.; Landsberg, D.; Brodmann, T.; Bulow, L.; Girbig, A.-K.; Kalesse, M., Synthesis and Pharmacology of Proteasome Inhibitors. *Angew. Chem., Int. Ed.* **2013**, *52*, 5450.
105. Adams, J., The Development of Proteasome Inhibitors as Anticancer Drugs. *Cancer Cell* **2004**, *5*, 417.
106. Groll, M.; Berkers, C. R.; Ploegh, H. L.; Ovaas, H., Crystal Structure of the Boronic Acid-Based Proteasome Inhibitor Bortezomib in Complex with the Yeast 20S Proteasome. *Structure* *14*, 451.
107. Kale, A. J.; Moore, B. S., The Molecular Mechanism of Acquired Proteasome Inhibitor Resistance. *J. Med. Chem.* **2012**, *55*, 10317.
108. Adams, J.; Behnke, M.; Chen, S.; Cruickshank, A. A.; Dick, L. R.; Grenier, L.; Klunder, J. M.; Ma, Y.-T.; Plamondon, L.; Stein, R. L., Potent and Selective Inhibitors of the Proteasome: Dipeptidyl Boronic Acids. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 333.

109. Chen, Y.; Shoichet, B.; Bonnet, R., Structure, Function, and Inhibition Along the Reaction Coordinate of CTX-M  $\beta$ -Lactamases. *J. Am. Chem. Soc.* **2005**, *127*, 5423.
110. Baker, S. J.; Tomshob, J. W.; Benkovicc, S. J., Boron-Containing Inhibitors of Synthetases. *Chem. Soc. Rev.* **2011**, *40*, 4279.
111. Kettner, C.; Mersinger, L.; Knabbn, R., The Selective Inhibition of Thrombin by Peptides of Boroarginine. *J. Biol. Chem.* **1990**, *265*, 18289.
112. Spencer, J.; Burd, A. P.; Goodwin, C. A.; Mérette, S. A. M.; Scully, M. F.; Adatia, T.; Deadman, J. J., Synthesis of Ortho-Modified Mercapto- and Piperazino-Methyl-Phenylboronic Acid Derivatives. *Tetrahedron* **2002**, *58*, 1551.
113. Berry, S. C.; Fink, A. L.; Shenvi, A. B.; Kettne, C. A., Interaction of Peptide Boronic Acids with Elastase: Circular Dichroism Studies. *Proteins* **1988**, *4*, 205.
114. Kettner, C. A.; Shenvi, A. B., Inhibition of the Serine Proteases Leukocyte Elastase, Pancreatic Elastase, Cathepsine G, and Chymotrypsin by Peptide Boronic Acids. *J. Biol. Chem.* **1984**, *259*, 15106.
115. Smoum, R.; Rubinstein, A.; Dembitsky, V. M.; Srebnik, M., Boron Containing Compounds as Protease Inhibitors. *Chem. Rev.* **2012**, *112*, 4156.
116. Offidani, M.; Corvatta, L.; Caraffa, P.; Gentili, S.; Maracci, L.; Leoni, P., An Evidence-Based Review of Ixazomib Citrate and Its Potential in the Treatment of Newly Diagnosed Multiple Myeloma. *OncoTargets Ther.* **2014**, *7*, 1793.
117. Kupperman, E.; Lee, E. C.; Cao, Y.; Bannerman, B.; Fitzgerald, M.; Berger, A.; Yang, J. Y. Y.; Hales, P.; Bruzzese, F.; Liu, J.; Blank, J.; Garcia, K.; Tsu, C.; Dick, L.; Fleming, P.; Yu, L.; Manfredi, M.; Rolfe, M.; Bolen, J., Evaluation of the Proteasome Inhibitor MLN9708 in Preclinical Models of Human Cancer. *Cancer Res.* **2010**, *70*, 1970.

118. Raedler, L. A., Ninlaro (Ixazomib): First Oral Proteasome Inhibitor Approved for the Treatment of Patients with Relapsed or Refractory Multiple Myeloma. *Am. Health Drug Benefits* **2016**, *9*, 102.
119. Muz, B.; Ghazarian, R. N.; Ou, M.; Luderer, M. J.; Kusdono, H. D.; Azab, A. K., Spotlight on Ixazomib: Potential in the Treatment of Multiple Myeloma. *Drug Des., Dev. Ther.* **2016**, *10*, 217.
120. Al-Salama, Z. T.; Garnock-Jones, K. P.; Scott, L. J., Ixazomib: A Review in Relapsed and/or Refractory Multiple Myeloma. *Targeted Oncol.* **2017**, *4*.
121. Park, J.; Park, E.; Jung, C.-K.; Kang, S.-W.; Kim, B. G.; Jung, Y.; Kim, T. H.; Lim, J.-Y.; Lee, S.-E.; Min, C.-K.; Won, K.-A., Oral Proteasome Inhibitor with Strong Preclinical Efficacy in Myeloma Models. *BMC Cancer* **2016**, *16*, 247.
122. Adamczyk-Woźniak, A.; Borys, K. M.; Sporzyński, A., Recent Developments in the Chemistry and Biological Applications of Benzoxaboroles. *Chem. Rev.* **2015**, *115*, 5224.
123. Baker, S. J.; Zhang, Y.-K.; Akama, T.; Lau, A.; Zhou, H.; Hernandez, V.; Mao, W.; Alley, M. R. K.; Sanders, V.; Plattner, J. J., Discovery of a New Boron-Containing Antifungal Agent, 5-Fluoro-1,3-Dihydro-1-Hydroxy-2,1-Benzoxaborole (AN2690), for the Potential Treatment of Onychomycosis. *J. Med. Chem.* **2006**, *49*, 4447.
124. Rock, F. L.; Mao, W.; Yaremchuk, A.; Tukalo, M.; Crépin, T.; Zhou, H.; Zhang, Y.-K.; Hernandez, V.; Akama, T.; Baker, S. J.; Plattner, J. J.; Shapiro, L.; Martinis, S. A.; Benkovic, S. J.; Cusack, S.; Alley, M. R. K., An Antifungal Agent Inhibits an Aminoacyl-tRNA Synthetase by Trapping tRNA in the Editing Site. *Science* **2007**, *316*, 1759.
125. Elewski, B. E.; Aly, R.; Baldwin, S. L.; González Soto, R. F.; Rich, P.; Weisfeld, M.; Wiltz, H.; Zane, L. T.; Pollak, R., Efficacy and Safety of Tavaborole Topical Solution, 5%,

- a Novel Boron-Based Antifungal Agent, for the Treatment of Toenail Onychomycosis: Results from 2 Randomized Phase-III Studies. *J. Am. Acad. Dermatol.* **2015**, *73*, 62.
126. Akama, T.; Baker, S. J.; Zhang, Y.-K.; Hernandez, V.; Zhou, H.; Sanders, V.; Freund, Y.; Kimura, R.; Maples, K. R.; Plattner, J. J., Discovery and Structure–Activity Study of a Novel Benzoxaborole Anti-Inflammatory Agent (AN2728) for the Potential Topical Treatment of Psoriasis and Atopic Dermatitis. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2129.
127. Dong, C.; Virtucio, C.; Zemska, O.; Baltazar, G.; Zhou, Y.; Baia, D.; Jones-Iatauro, S.; Sexton, H.; Martin, S.; Dee, J.; Mak, Y.; Meewan, M.; Rock, F.; Akama, T.; Jarnagin, K., Treatment of Skin Inflammation with Benzoxaborole Phosphodiesterase Inhibitors: Selectivity, Cellular Activity, and Effect on Cytokines Associated with Skin Inflammation and Skin Architecture Changes. *J. Pharmacol. Exp. Ther.* **2016**, *358*, 413.
128. Freund, Y. R.; Akama, T.; Alley, M. R. K.; Antunes, J.; Dong, C.; Jarnagin, K.; Kimura, R.; Nieman, J. A.; Maples, K. R.; Plattner, J. J.; Rock, F.; Sharma, R.; Singh, R.; Sanders, V.; Zhou, Y., Boron-Based Phosphodiesterase Inhibitors Show Novel Binding of Boron to PDE4 Bimetal Center. *FEBS Lett.* **2012**, *586*, 3410.
129. Zane, L. T.; Chanda, S.; Jarnagin, K.; Nelson, D. B.; Spelman, L.; Gold, L. F. S., Crisaborole and Its Potential Role in Treating Atopic Dermatitis: Overview of Early Clinical Studies. *Immunotherapy* **2016**, *8*, 853.
130. Zhang, Y.-K.; Plattner, J. J.; Akama, T.; Baker, S. J.; Hernandez, V. S.; Sanders, V.; Freund, Y.; Kimura, R.; Bu, W.; Hold, K. M.; Lu, X.-S., Design and Synthesis of Boron-Containing PDE4 Inhibitors Using Soft-Drug Strategy for Potential Dermatologic Anti-Inflammatory Application. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2270.

131. Baker, S. J.; Akama, T.; Zhang, Y.-K.; Sauro, V.; Pandit, C.; Singh, R.; Kully, M.; Khan, J.; Plattner, J. J.; Benkovic, S. J.; Lee, V.; Maples, K. R., Identification of a Novel Boron-Containing Antibacterial Agent (AN0128) with Anti-Inflammatory Activity, for the Potential Treatment of Cutaneous Diseases. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5963.
132. Hofer, A.; Kovacs, G.; Zappatini, A.; Leuenberger, M.; Hediger, M. A.; Lochner, M., Design, Synthesis and Pharmacological Characterization of Analogs of 2-Aminoethyl Diphenylborinate (2-APB), a Known Store-Operated Calcium Channel Blocker, for Inhibition of TRPV6-Mediated Calcium Transport. *Bioorg. Med. Chem.* **2013**, *21*, 3202.



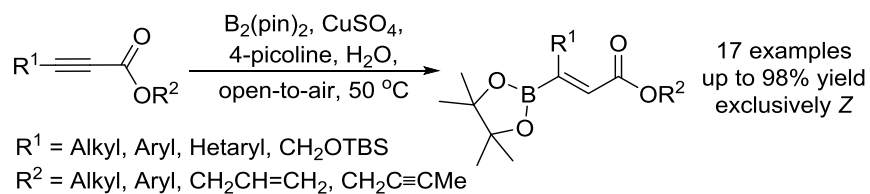
## Chapter 2. Copper(II)-catalyzed $\beta$ -borylation of acetylenic esters in water

### 2.1 Contributions

The work described in this chapter was conducted in collaboration with Joseph Calderone. The author is solely responsible for the synthesis of the alkynoates, borylation of substrates **2.10c-d** and **2.10j-r**, and all necessary characterization. Optimization of borylation conditions and borylation of substrates **2.10a-b** and **2.10e-i** were duplicated by Joseph Calderone. The final manuscript was prepared in collaboration with Dr. Webster L. Santos. This work has been published in *Synthesis* and is available online [Peck, C. L.; Calderone, J. A.; Santos, W. L. Copper(II)-Catalyzed  $\beta$ -Borylation of Acetylenic Esters in Water. *Synthesis*, **2015**, 47, 2242. Reproduced (adapted) with permission from Thieme.]

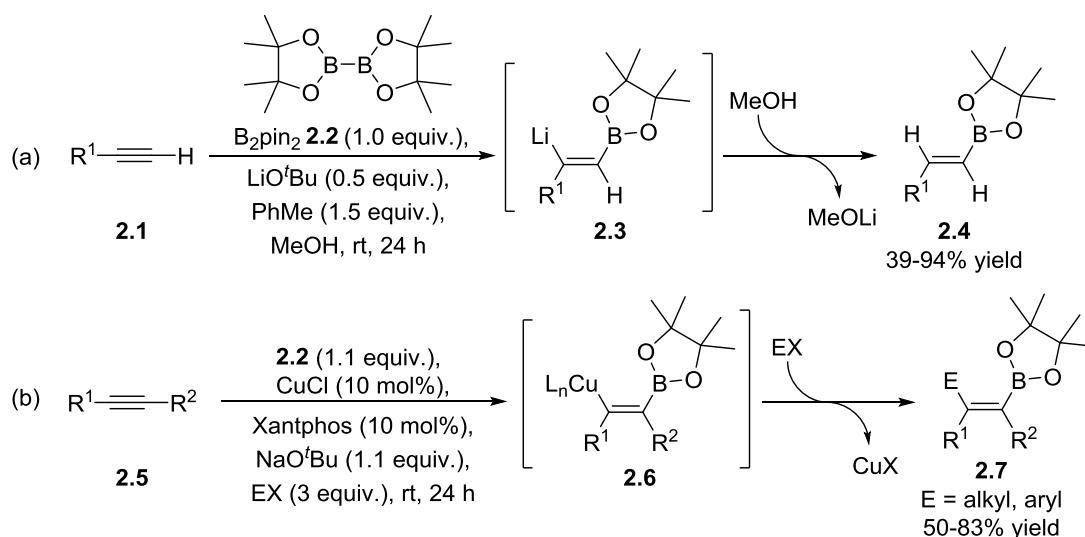
## 2.2 Abstract

An efficient and simple method for the  $\beta$ -borylation of alkynoates has been developed. In the presence of bis(pinacolato)diboron ( $B_2pin_2$ ) and catalytic amounts of both copper(II) and 4-picoline, substituted alkynoates undergo borylation in a regio-, stereo-, and chemoselective fashion. The reaction is performed under mild conditions with water as a solvent and open-to-air to exclusively afford (*Z*)- $\beta$ -boryl- $\alpha,\beta$ -unsaturated esters using a broad substrate scope.



## 2.3 Introduction

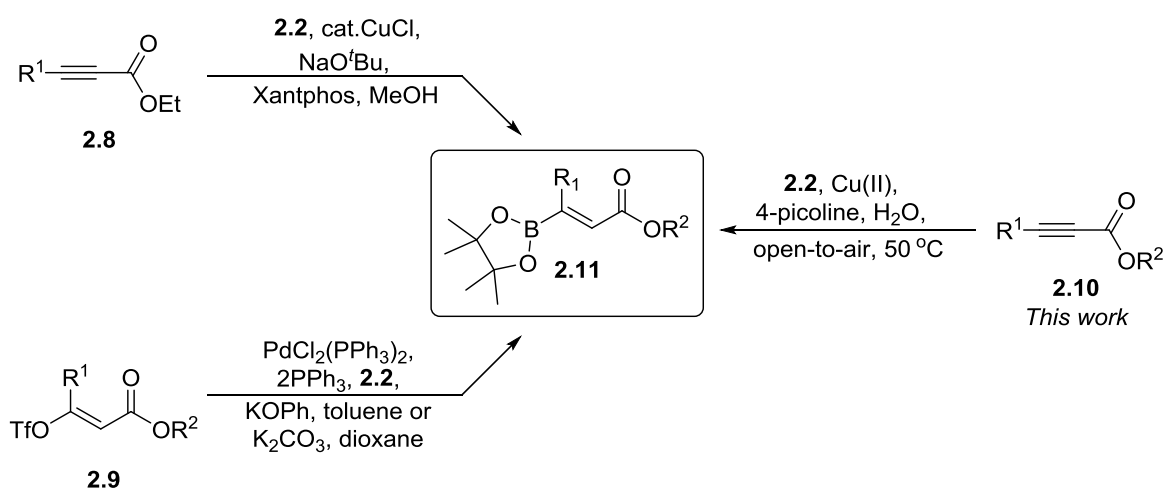
Vinylboronic acids and their derivatives are vital synthetic intermediates for the Suzuki–Miyaura cross-coupling reaction as well as synthetic handles for transformations into other functional groups.<sup>1-5</sup> As such, various avenues have been explored to afford these versatile boron intermediates in a straightforward manner. Most noticeably,  $\alpha$ - or  $\beta$ -vinylboronates can be readily synthesized by borylating symmetrical or unsymmetrical internal alkynes using  $B_2pin_2$  and various transition metal catalysts, specifically palladium,<sup>6</sup> silver,<sup>7</sup> iron,<sup>8-9</sup> and copper.<sup>10-16</sup> Furthermore, Wen *et al.* disclosed an environmentally friendly transition metal-free protocol employing open-to-air conditions in MeOH; unfortunately, the study provided a limited substrate scope.<sup>17</sup> Recently, Hong *et al.* improved upon this method by developing a transition metal-free and ligand-free protocol for the borylation of terminal alkynes (Scheme 2.1a).<sup>18</sup> Alternatively, alkynes can undergo a three-component copper-catalyzed carboborylation reaction to facilitate the formation of tetrasubstituted vinylboronates (Scheme 2.1b).<sup>19-22</sup> This reaction has been



**Scheme 2.1.** (a) Metal- and ligand-free borylation of terminal alkynes and (b) copper-catalyzed carbonylation

proposed to occur through the formation of a borylcuprate intermediate **2.6** followed by trapping with an alkyl or aryl electrophile.

Although the borylation of alkynes serves as an efficient method to access vinylboronates, only a limited number of methods for the borylation of alkynoates have been reported (Scheme 2.2).<sup>23-26</sup> In 2003, Ishiyama *et al.* reported a palladium-catalyzed cross-coupling of vinyl triflates to afford  $\beta$ -boryl- $\alpha,\beta$ -unsaturated carbonyl compounds.<sup>27</sup> Subsequently, Lee *et al.* disclosed copper(I)-catalyzed borylation conditions employing alkynoates and B<sub>2</sub>pin<sub>2</sub> as the boron source.<sup>12</sup> No product formation was detected without the presence of the methanol additive to protonate the proposed boryl-copper intermediate. Subsequent Cu(I)-catalyzed protocols have been reported.<sup>13, 28</sup> Unfortunately, these methods have shortcomings ranging from a limited substrate scope to poor *E*- and *Z*-stereoselectivity. Furthermore, the reactions must be conducted under inert atmospheric conditions because of the air- and moisture-sensitivity of the catalytic systems. In recent years, synthetic protocols that utilize boronic acid derivatives and employ environmentally friendly conditions have been



**Scheme 2.2.** Strategies toward  $\beta$ -boryl- $\alpha,\beta$ -unsaturated esters.

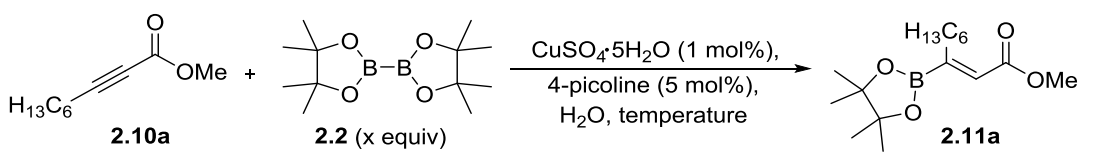
reported, eliminating the necessity for organic solvents.<sup>29-30</sup> In contrast, complementary processes that generate boronic acid derivatives using copper as a catalyst in an aqueous environment are emerging.<sup>31-35</sup> Our laboratory previously reported a copper(II)-catalyzed borylation protocol of  $\alpha,\beta$ -unsaturated esters and ketones using water as the solvent and under atmospheric conditions.<sup>36</sup> This method was later extended to the silylation of alkynes bearing ketones, aldehydes, esters, and amides using suginome's reagent (pinB-SiMe<sub>2</sub>Ph).<sup>37</sup> Because of our interest in this area, we aimed to develop a catalytic system that could be used to conduct borylation reactions in aqueous media.

#### 2.4 Optimizing the $\beta$ -borylation of alkynoates with B<sub>2</sub>pin<sub>2</sub>

To explore the prospect of expanding our previous aqueous  $\beta$ -borylation protocol, we re-examined reaction conditions that generated  $\beta$ -boryl-unsaturated ketones.<sup>36</sup> Optimization reactions revealed that a variety of commercially available amine bases afforded good conversions, with 4-picoline giving a >99.5% conversion. Although copper(I) catalysts were ineffective, signifying copper(I) is not the active species in the reaction, CuSO<sub>4</sub> afforded the best conversion. This may have been due to its superior solubility in aqueous media. We employed these conditions to methyl non-2-ynoate **2.10a**, which served as the model substrate because of its borderline aqueous solubility and commercial availability. Fortunately, standard conditions afforded vinylboronate **2.11a** in a 59% yield (Table 2.1, entry 1). Nuclear Overhauser effect (nOe) studies of the crude and purified product indicated exclusive formation of the (*Z*)-product. An increase in reaction time did not significantly affect the reaction yield (entry 2). However, changing the number of equivalents of B<sub>2</sub>pin<sub>2</sub> to 1.5 resulted in an improved reaction yield (entry 3). We also screened the effect of temperature on the reaction and to our delight a 76% yield was obtained at 50 °C. Unfortunately, conducting the reaction above 50 °C resulted in a slightly

decreased yield. Running control reactions in the absence of CuSO<sub>4</sub> and 4-picoline did not afford the desired product indicating that they are essential in providing the corresponding (Z)-β-boryl-α,β-unsaturated ester (entries 7 and 8). The screening study revealed that B<sub>2</sub>pin<sub>2</sub> (1.5 equiv), CuSO<sub>4</sub> (1 mol%), and 4-picoline (5 mol%) in water at 50 °C were the optimal conditions.

**Table 2.1.** Optimization of reaction conditions for the borylation of alkynoates using B<sub>2</sub>pin<sub>2</sub>.<sup>a</sup>



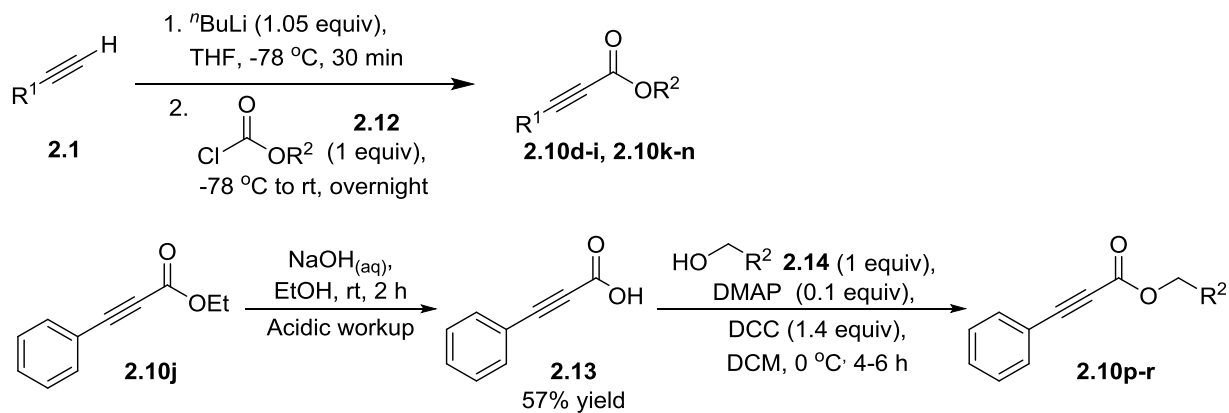
Entry	Time (h)	B <sub>2</sub> pin <sub>2</sub> (equiv)	Temperature (°C)	Yield (%) <sup>b</sup>
1	4	1.3	rt	59
2	6.5	1.3	rt	61
3	6.5	1.5	rt	67
4	4.5	1.5	40	70
<b>5</b>	<b>3</b>	<b>1.5</b>	<b>50</b>	<b>76</b>
6	6.5	1.5	60	67
7	3	1.5	rt	n.r. <sup>c</sup>
8	3	1.5	rt	n.r. <sup>d</sup>

<sup>a</sup> General procedure: methyl non-2-ynoate (**2.10a**, 1.0 equiv), B<sub>2</sub>pin<sub>2</sub> (1.3-1.5 equiv), 4-picoline (5 mol%), and 1 mL solvent were added to a 1 dram vial and stirred. <sup>b</sup> Isolated yield. <sup>c</sup> In the absence of Cu(SO<sub>4</sub>). <sup>d</sup> In the absence of 4-picoline. n.r. = no reaction.

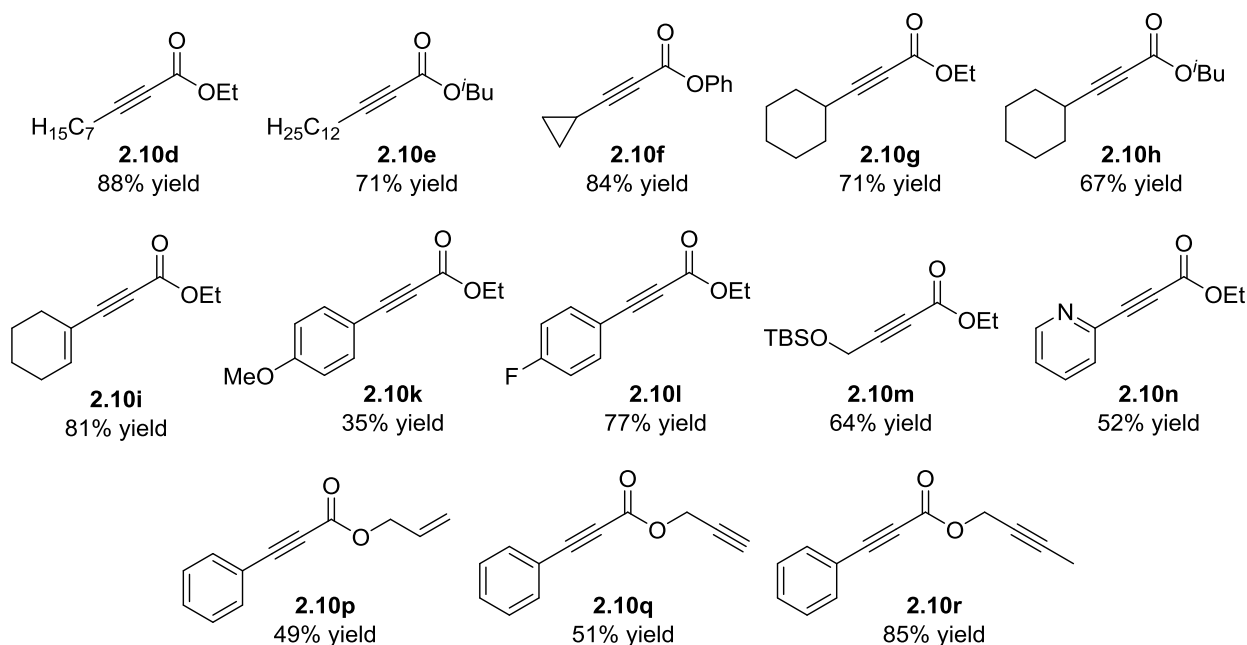
## 2.5 Preparation of alkynoates

Only a limited number of alkynoates were commercially available; therefore, the remaining substrates had to be synthesized following one of two methods (Scheme 2.3). The majority of substrates were synthesized following Lee *et al.*'s literature protocol.<sup>12</sup> Deprotonation of terminal alkyne **2.1** using butyllithium followed by addition of chloroformate

**2.12** provided the corresponding alkynoates **2.10d-i** and **2.10k-n** in moderate to good yields. Alternatively, base-catalyzed hydrolysis of commercially available alkynoate **2.10j** yields 3-phenylpropionic acid **2.13** in a 57% yield. Fisher esterification of carboxylic acid **2.13** with propargylic alcohol **2.14** was used to synthesize the desired alkynoates **2.10p-r**. Figure 2.1 depicts all of the alkynoates that were synthesized.



**Scheme 2.3.** Synthesis of alkynoates.



**Figure 2.1.** Structures of alkynoates synthesized.

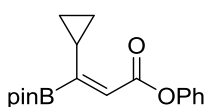
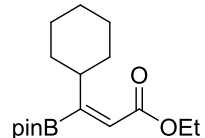
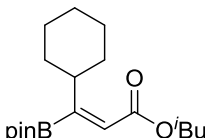
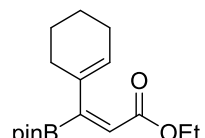
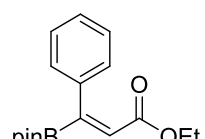
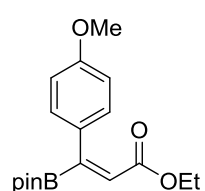
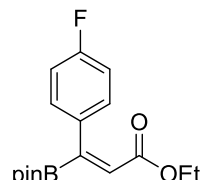
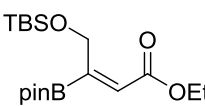
## 2.6 Substrate scope for the copper(II)-catalyzed $\beta$ -borylation of alkynoates

With optimized conditions and alkynoates in hand, the scope of the reaction with various alkynoates was explored (Table 2.2). Aliphatic alkyl groups including methyl (**2.10b**), propyl (**2.10c**), hexyl (**2.10a**), and heptyl (**2.10d**) were efficient substrates, affording the corresponding (Z)- $\beta$ -boryl- $\alpha,\beta$ -unsaturated esters **2.11a-d** in good to excellent yields (entries 1–4). The use of a dodecyl-bearing substituent resulted in no reaction (entry 5). Attempts to improve the reaction using biphasic conditions and increased temperatures were unsuccessful. However, substrates with a cyclopropyl or larger cyclohexyl group with either ethyl or isobutyl ester moieties were borylated in excellent yields (entries 6–8). Furthermore, cyclohexenyne **2.10i** was borylated regioselectively on the  $\beta$ -position to generate  $\alpha,\beta,\gamma,\delta$ -unsaturated diene **2.11i** in a 98% yield. Aryl substitutions were also tolerated. For example, substrates bearing phenyl (**2.10j**), electron

**Table 2.2.** Copper(II)-catalyzed aqueous  $\beta$ -borylation of alkynoates using  $B_2pin_2$ .<sup>a</sup>

Entry	Product	<b>2.11</b>	Time (h) <sup>b</sup>	Yield (%) <sup>c,d</sup>
1		<b>2.11a</b>	3	76
2		<b>2.11b</b>	2	96 <sup>e,f</sup>
3		<b>2.11c</b>	4	84
4		<b>2.11d</b>	2	85
5		<b>2.11e</b>	–	n.r.

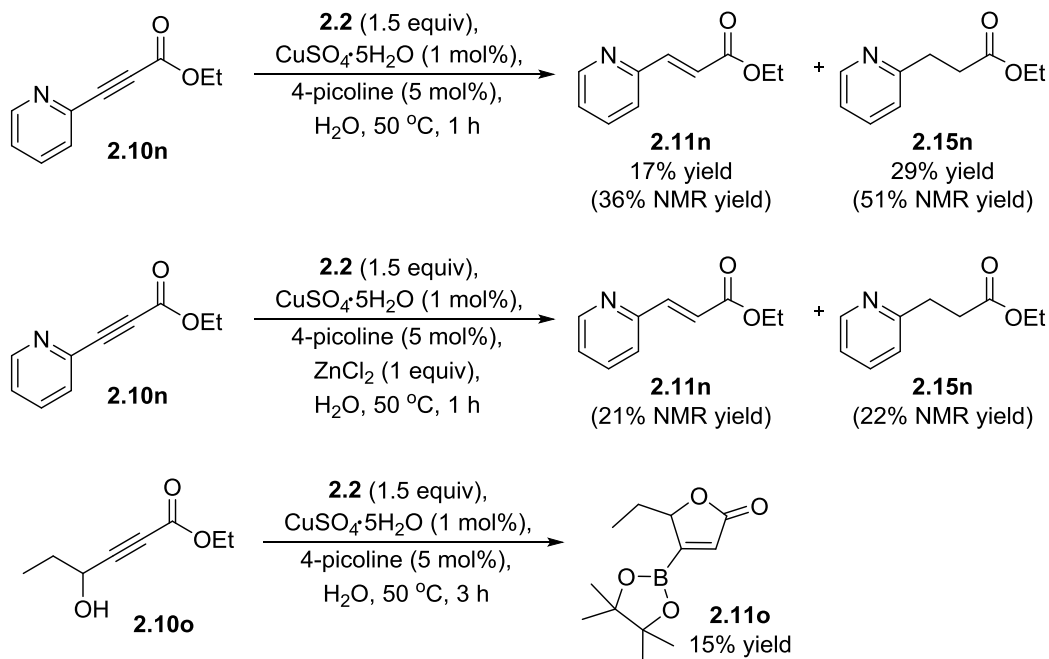


Entry	Product	2.11	Time (h) <sup>b</sup>	Yield (%) <sup>c,d</sup>
6		<b>2.11f</b>	4	85
7		<b>2.11g</b>	3	76
8		<b>2.11h</b>	6	70
9		<b>2.11i</b>	22	98
10		<b>2.11j</b>	4	95 <sup>e,g</sup>
11		<b>2.11k</b>	20	91
12		<b>2.11l</b>	24	90 <sup>e</sup>
13		<b>2.11m</b>	3	84

<sup>a</sup> General procedure: alkyne **2.10** (1.0 equiv), B<sub>2</sub>pin<sub>2</sub> (1.5 equiv), 4-picoline (5 mol%), and 1 mL solvent were added to a 1 dram vial and stirred at 50 °C. <sup>b</sup> Reaction completion based on consumption of starting material. <sup>c</sup> Isolated yield. <sup>d</sup> Yields are an average of two or more reactions. <sup>e</sup> The reaction was performed at room temperature. <sup>f</sup> B<sub>2</sub>pin<sub>2</sub> (1.1 equiv) was used. <sup>g</sup> B<sub>2</sub>pin<sub>2</sub> (1.3 equiv) was used. n.r. = no reaction.

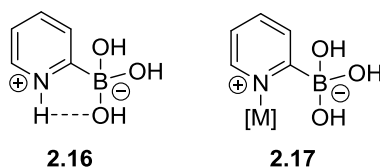
donating methoxy (**2.10k**) or electron withdrawing fluorine (**2.10l**) groups yielded the corresponding borylated products in excellent yields (entries 10–12). Finally, *tert*-butyldimethylsilyl-protected alcohol **2.10m** gave product **2.11m** in 84% yield, confirming the good functional group compatibility of the reaction conditions.

To assess the limitations of the reaction, 2-pyridyl substituted substrate **2.10n** was subjected to our optimized conditions (Scheme 2.4). In this case, the resulting products underwent protodeboration: mono- and diboration followed by spontaneous protodeboration generated semihydrogenated **2.11n** and fully reduced **2.15n**. Surprisingly, the double bond geometry of **2.11n** was found to be *E*, possibly a result of isomerization leading to the more stable *trans* isomer. NMR studies with pyridin-2-ylboronic acid in water revealed that zwitterionic boronate **2.16** is extremely reactive and likely to undergo aqueous protodeboration.<sup>38</sup>



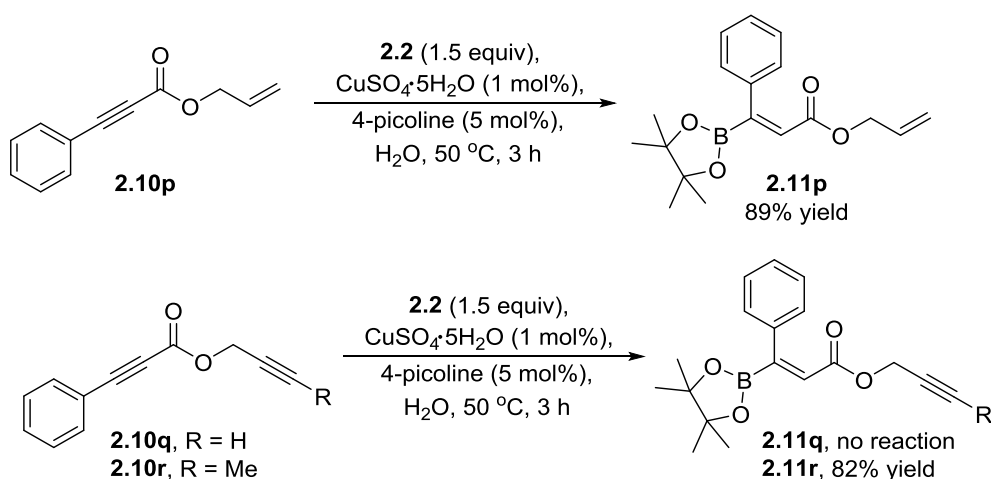
**Scheme 2.4.**  $\beta$ -Borylation of alkynoates bearing heteroatoms.

However, protodeboration can be suppressed by the addition of metal additives (Figure 2.2). Unfortunately, the addition of  $\text{ZnCl}_2$  (1.0 equiv) still did not afford the desired  $\beta$ -borylated product. However, it was confirmed that the formation of the protodeborylated product and fully reduced product had decreased. Whereas TBS-protected **2.10m** was readily borylated, the corresponding propargylic alcohol **2.10o** underwent  $\beta$ -borylation; only the cyclized butenolide **2.11o** was isolated in low yield.



**Figure 2.2.** Protodeboration of pyridin-2-ylboronic acid.

The selective borylation on the  $\beta$ -position of enyne **2.10i** prompted us to further explore the selectivity of the reaction (Scheme 2.5). Given that copper(I)-catalyzed borylations of non-activated alkenes and alkynes have been reported, it was unclear whether a copper(II) catalyst system was sufficiently selective in the presence of competing functional groups. Thus, 3-

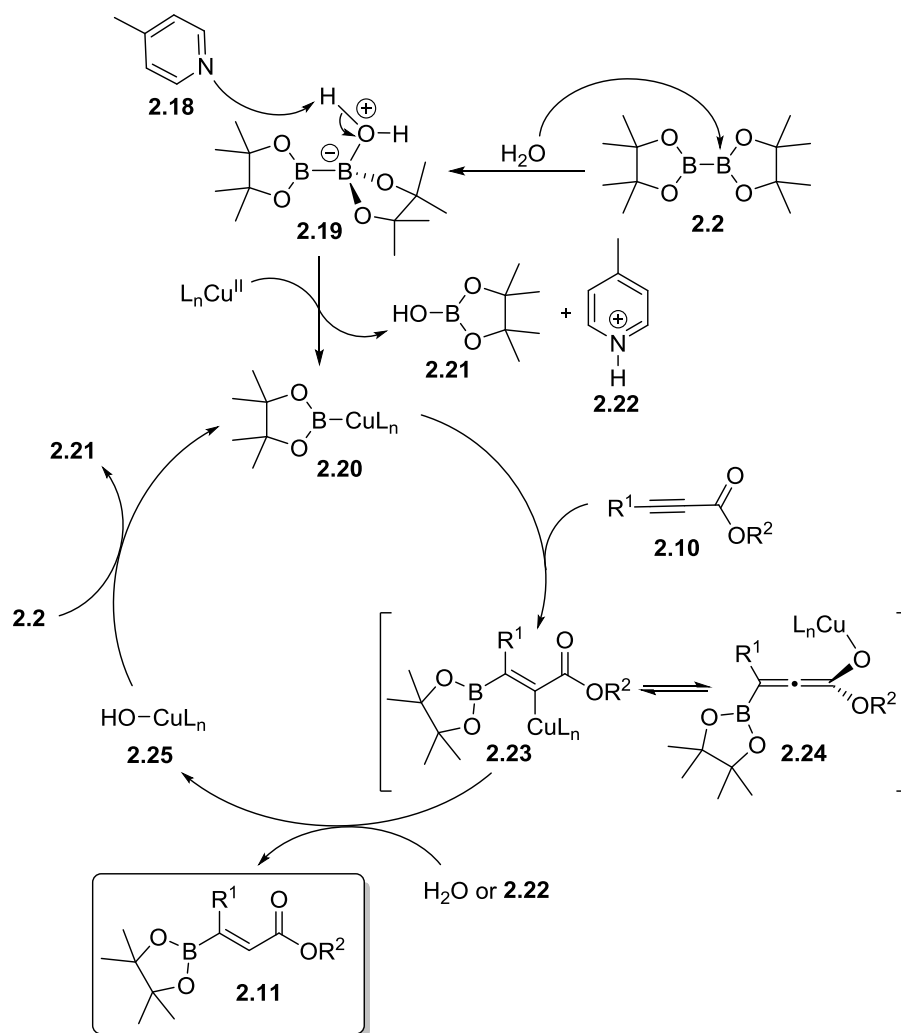


**Scheme 2.5.** Chemoselectivity of the reaction.

phenylpropionate substrates containing allyl (**2.10p**) or propargyl (**2.10q-r**) groups were synthesized. When subjected to the borylation conditions, product **2.11p** was isolated in an excellent yield. Unfortunately, incorporation of a propargyl terminal alkyne did not afford the product; however, it is suspected this is the result of copper inserting into the C-H bond.<sup>39-40</sup> Fortunately, the incorporation of a methyl group designed to block this interaction allowed **2.10r** to be borylated in an 82% yield. Exquisite reactivity at the more activated alkyne was observed with these substrates, demonstrating the chemoselectivity of the reaction.

## 2.7 Proposed mechanism

A proposed catalytic cycle to account for the formation of  $\beta$ -borated- $\alpha,\beta$ -unsaturated esters **2.11** using copper(II) catalytic conditions is shown in Scheme 2.6. Based on previous experimental results conducted in our laboratory using  $\alpha,\beta$ -unsaturated carbonyl compounds, we propose that H<sub>2</sub>O binds to the empty p-orbital of boron to generate the sp<sup>2</sup>-sp<sup>3</sup> hybridized Lewis acid-base adduct **2.19**.<sup>36, 41</sup> Formation of the activated diboron reagent causes the B-B bond to lengthen, making it weaker and therefore easier to break. The addition of 4-picoline helps facilitate transmetalation to generate boryl-copper species **2.20**. 3,4-Conjugate addition of **2.20** to acetylenic ester **2.10** occurs in a *syn*-fashion to form organocuprate **2.23**, which is in equilibrium with the corresponding enolate **2.24**. During this step, the regioselectivity of the reaction is governed by the electrophilic  $\beta$ -carbon of the acetylenic ester. Protonation of intermediates **2.23** and **2.24** with either the solvent or the more acidic protonated 4-picoline will result in the formation of the desired borylated product. Regeneration of the active copper species occurs through a copper-alkoxide intermediate **2.25** and a second diboron reagent.



**Scheme 2.6.** Proposed catalytic cycle for the formation of  $\beta$ -borylated unsaturated esters.

## 2.8 Conclusions

In summary, we have developed a simple, mild, and efficient copper(II)-catalyzed borylation method for alkynoates. The reaction is performed open-to-air and utilizes water as the reaction medium to afford (*Z*)- $\beta$ -borylated products exclusively. Furthermore, alkynoates were transformed chemoselectively into the desired products in the presence of competing functional groups. Further investigations of the substrate scope and application of the method are underway.

## 2.9 References for Chapter 2

1. Beletskaya, I.; Moberg, C., Element–Element Additions to Unsaturated Carbon–Carbon Bonds Catalyzed by Transition Metal Complexes. *Chem. Rev.* **2006**, *106*, 2320.
2. Brown, J. M.; Nguyen, B. N., *Stereoselective Synthesis I: Stereoselective Reactions of Carbon–Carbon Double Bonds*. Thieme: Stuttgart, Germany, 2011.
3. Burks, H. E.; Morken, J. P., Catalytic Enantioselective Diboration, Disilation and Silaboration: New Opportunities for Asymmetric Synthesis. *Chem. Commun.* **2007**, 4717.
4. Hall, D. G., *Boronic Acids: Preparation, Applications in Organic Synthesis, Medicine and Materials*. 2nd ed.; Wiley-VCH: 2011.
5. Takaya, J.; Iwasawa, N., Catalytic, Direct Synthesis of Bis(boronate) Compounds. *ACS Catal.* **2012**, *2*, 1993.
6. Ojha, D. P.; Prabhu, K. R., Pd-Catalyzed Hydroborylation of Alkynes: A Ligand Controlled Regioselectivity Switch for the Synthesis of  $\alpha$ - or  $\beta$ -Vinylboronates. *Org. Lett.* **2016**, *18*, 432.
7. Yoshida, H.; Kageyuki, I.; Takaki, K., Silver-Catalyzed Highly Regioselective Formal Hydroboration of Alkynes. *Org. Lett.* **2014**, *16*, 3512.
8. Rawat, V. S.; Sreedhar, B., Iron-Catalyzed Borylation Reactions of Alkynes: An Efficient Synthesis of E-Vinyl Boronates. *Synlett* **2014**, *8*, 1132.
9. Khan, A.; Asiri, A. M.; Kosa, S. A.; Garcia, H.; Grirrane, A., Catalytic Stereoselective Addition to Alkynes: Borylation or Silylation Promoted by Magnesia-Supported Iron Oxide and *Cis*-Diboration or Silaboration by Supported Platinum Nanoparticles. *J. Catal.* **2015**, *329*, 401.

10. Mohan, B.; Park, K. H., Superparamagnetic Copper Ferrite Nanoparticles Catalyzed Aerobic, Ligand-Free, Regioselective Hydroboration of Alkynes: Influence of Synergistic Effect. *Appl. Catal., A* **2016**, *519*, 78.
11. Kim, H. R.; Yun, J., Highly Regio- and Stereoselective Synthesis of Alkenylboronic Esters by Copper-Catalyzed Boron Additions to Disubstituted Alkynes. *Chem. Commun.* **2011**, *47*, 2943.
12. Lee, J.-E.; Kwon, J.; Yun, J., Copper-Catalyzed Addition of Diboron Reagents to  $\alpha,\beta$ -Acetylenic Esters: Efficient Synthesis of  $\beta$ -Boryl- $\alpha,\beta$ -Ethylenic Esters. *Chem. Commun.* **2008**, 733.
13. Tai, C. C.; Yu, M. S.; Chen, Y. L.; Chuang, W. H.; Lin, T. H.; Yap, G. P.; Ong, T. G., Synthesis of a Guanidine NHC Complex and Its Application in Borylation Reactions. *Chem. Commun.* **2014**, *50*, 4344.
14. Jang, H.; Zhugralin, A. R.; Lee, Y.; Hoveyda, A. H., Highly Selective Methods for Synthesis of Internal  $\alpha$ -Vinylboronates Through Efficient NHC-Cu-Catalyzed Hydroboration of Terminal Alkynes. Utility in Chemical Synthesis and Mechanistic Basis for Selectivity. *J. Am. Chem. Soc.* **2011**, *133*, 7859.
15. Yuan, W.; Ma, S., CuCl-K<sub>2</sub>CO<sub>3</sub>-Catalyzed Highly Selective Borylcupration of Internal Alkynes-Ligand Effect. *Org. Biomol. Chem.* **2012**, *10*, 7266.
16. Liu, S.; Zeng, X.; Xu, B., Cu(II)-Catalyzed Regioselective Borylation of Alkynes and Alkenes. *Tetrahedron Lett.* **2016**, *57*, 3706.
17. Wen, K.; Chen, J.; Gao, F.; Bhadury, P. S.; Fan, E.; Sun, Z., Metal-Free Catalytic Hydroboration of Multiple Bonds in Methanol using *N*-Heterocyclic Carbenes under Open Atmosphere. *Org. Biomol. Chem.* **2013**, *11*, 6350.

18. Hong, S.; Zhang, W.; Liu, M.; Yao, Z.-J.; Deng, W., Transition Metal-Free Hydroboration of Terminal Alkynes Activated by Base. *Tetrahedron Lett.* **2016**, *57*, 1.
19. Bidal, Y. D.; Lazreg, F.; Cazin, C. S. J., Copper-Catalyzed Regioselective Formation of Tri- and Tetrasubstituted Vinylboronates in Air. *ACS Catal.* **2014**, *4*, 1564.
20. Alfaro, R.; Parra, A.; Alemán, J.; García Ruano, J. L.; Tortosa, M., Copper(I)-Catalyzed Formal Carboboration of Alkynes: Synthesis of Tri- and Tetrasubstituted Vinylboronates. *J. Am. Chem. Soc.* **2012**, *134*, 15165.
21. Itoh, T.; Shimizu, Y.; Kanai, M., Ligand-Enabled, Copper-Catalyzed Regio- and Stereoselective Synthesis of Trialkylsubstituted Alkenylboronates from Unactivated Internal Alkynes. *J. Am. Chem. Soc.* **2016**, *138*, 7528.
22. Yoshida, H.; Kageyuki, I.; Takaki, K., Copper-Catalyzed Three-Component Carboboration of Alkynes and Alkenes. *Org. Lett.* **2013**, *15*, 952.
23. Ishiyama, T.; Matsuda, N.; Murata, M.; Ozawa, F.; Suzuki, A.; Miyaura, N., Platinum(0)-Catalyzed Diboration of Alkynes with Tetrakis(alkoxo)diborons: An Efficient and Convenient Approach to *Cis*-Bis(boryl)alkenes. *Organometallics* **1996**, *15*, 713.
24. Anderson, K. M.; Lesley, M. J.; Norman, N. C.; Orpen, A. G.; Starbuck, J., The Platinum-Catalyzed Diboration of Alkynes Using 1,2-B<sub>2</sub>Cl<sub>2</sub>(NMe<sub>2</sub>)<sub>2</sub>: Formation of 1-Azonia-2-Borata-5-Borole Derivatives. *New J. Chem.* **1999**, *23*, 1053.
25. Thomas, R. L.; Souza, F. E. S.; Marder, T. B., Highly Efficient Monophosphine Platinum Catalysts for Alkyne Diboration. *J. Chem. Soc., Dalton Trans.* **2001**, 1650.
26. Cuenca, A. B.; Shishido, R.; Ito, H.; Fernandez, E., Transition Metal-Free B-B and B-Interelement Reactions with Organic Molecules. *Chem. Soc. Rev.* **2017**, *46*, 415.



27. Ishiyama, T.; Takagi, J.; Kamon, A.; Miyaura, N., Palladium-Catalyzed Cross-Coupling Reaction of Bis(pinacolato)diboron with Vinyl Triflates  $\beta$ -Substituted by a Carbonyl Group: Efficient Synthesis of  $\beta$ -Boryl- $\alpha,\beta$ -Unsaturated Carbonyl Compounds and Their Synthetic Utility. *J. Organomet. Chem.* **2003**, *687*, 284.
28. Semba, K.; Fujihara, T.; Terao, J.; Tsuji, Y., Copper-Catalyzed Highly Regio- and Stereoselective Directed Hydroboration of Unsymmetrical Internal Alkynes: Controlling Regioselectivity by Choice of Catalytic Species. *Chem. - Eur. J.* **2012**, *18*, 4179.
29. Isley, N. A.; Gallou, F.; Lipshutz, B. H., Transforming Suzuki–Miyaura Cross-Couplings of MIDA Boronates into a Green Technology: No Organic Solvents. *J. Am. Chem. Soc.* **2013**, *135*, 17707.
30. Lipshutz, B. H.; Moser, R.; Voigtritter, K. R., Miyaura Borylations of Aryl Bromides in Water at Room Temperature. *Isr. J. Chem.* **2010**, *50*, 691.
31. Chea, H. S., H. S.; Yun, J., Ligandless Copper-Catalyzed  $\beta$ -Boration of  $\alpha,\beta$ -Unsaturated Compounds in Aqueous Solution. *J. Bull. Korean Chem. Soc.* **2010**, *21* (3), 551.
32. Kitanosono, T.; Kobayashi, S., Asymmetric Boron Conjugate Additions to Enones in Water Catalyzed by Copper(0). *Asian J. Org. Chem.* **2013**, *2*, 961.
33. Kobayashi, S.; Xu, P.; Endo, T.; Ueno, M.; Kitanosono, T., Chiral Copper(II)-Catalyzed Enantioselective Boron Conjugate Additions to  $\alpha,\beta$ -Unsaturated Carbonyl Compounds in Water. *Angew. Chem., Int. Ed.* **2012**, *51*, 12763.
34. Stavber, G.; Časar, Z., Basic  $\text{CuCO}_3$ /Ligand as a New Catalyst for 'on Water' Borylation of Michael Acceptors, Alkenes and Alkynes: Application to the Efficient Asymmetric Synthesis of  $\beta$ -Alcohol Type Sitagliptin Side Chain. *Appl. Organomet. Chem.* **2013**, *27*, 159.

35. Stavber, G.; Časar, Z., Cu(II)- and Cu(0)-Catalyzed Mono Borylation of Unsaturated Hydrocarbons with B<sub>2</sub>pin<sub>2</sub>: Entering into the Water. *ChemCatChem* **2014**, *6*, 2162.
36. Thorpe, S. B.; Calderone, J. A.; Santos, W. L., Unexpected Copper(II) Catalysis: Catalytic Amine Base Promoted β-Borylation of α,β-Unsaturated Carbonyl Compounds in Water. *Org. Lett.* **2012**, *14*, 1918.
37. Calderone, J. A.; Santos, W. L., Copper(II)-Catalyzed Silylation of Activated Alkynes in Water: Diastereodivergent Access to E- or Z-β-Silyl-α,β-Unsaturated Carbonyl and Carboxyl Compounds. *Angew. Chem., Int. Ed.* **2014**, *53*, 4154.
38. Cox, P. A.; Leach, A. G.; Campbell, A. D.; Lloyd-Jones, G. C., Protodeboration of Heteroaromatic, Vinyl, and Cyclopropyl Boronic Acids: pH-Rate Profiles, Autocatalysis, and Disproportionation. *J. Am. Chem. Soc.* **2016**, *138*, 9145.
39. Díaz-Requejo, M. M.; Belderráin, T. R.; Nicasio, M. C.; Trofimenko, S.; Pérez, P. J., Intermolecular Copper-Catalyzed Carbon-Hydrogen Bond Activation via Carbene Insertion. *J. Am. Chem. Soc.* **2002**, *124*, 896.
40. Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L., Catalytic Carbene Insertion into C-H Bonds. *Chem. Rev.* **2010**, *110*, 704.
41. Gao, M.; Thorpe, S. B.; Kleeberg, C.; Slobodnick, C.; Marder, T. B.; Santos, W. L., Structure and Reactivity of a Preactivated sp<sup>2</sup>-sp<sup>3</sup> Diboron Reagent: Catalytic Regioselective Boration of α,β-Unsaturated Conjugated Compounds. *J. Org. Chem.* **2011**, *76*, 3997.

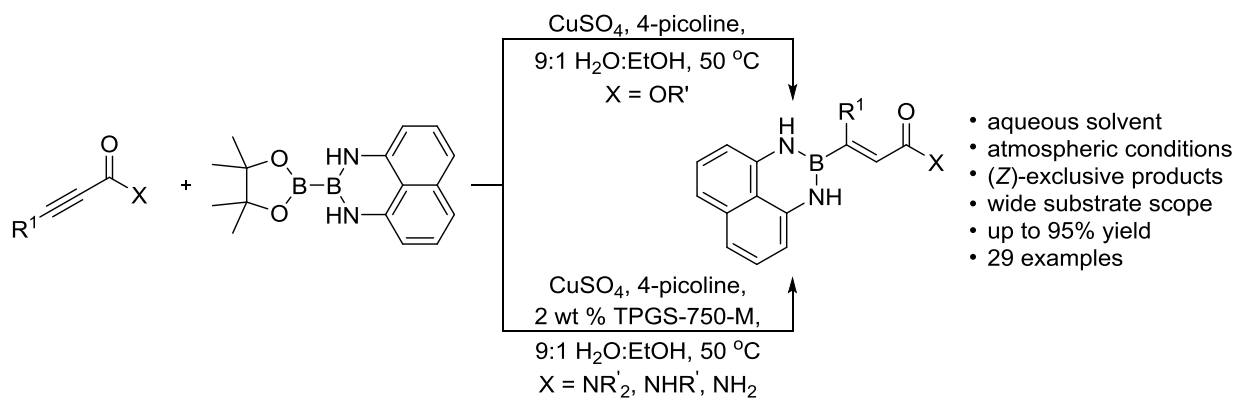
## Chapter 3. Chemo-, regio-, and stereoselective copper(II)-catalyzed boron addition to acetylenic esters and amides in aqueous media

### 3.1 Contributions

The work described in this chapter was conducted in collaboration with Dr. Amanda Nelson and Sean Rafferty. Alkynoates were synthesized by Sean Rafferty. The alkynoate optimization and substrate scope was conducted by Dr. Amanda Nelson and duplicated by Sean Rafferty. The author is solely responsible for the synthesis and characterization of the alkynamides and characterization of the  $\beta$ -boryl  $\alpha,\beta$ -unsaturated amides. The alkynamide optimization and substrate scope was run by the author and duplicated by Dr. Amanda Nelson. The final manuscript was prepared in collaboration with Dr. Amanda Nelson. The author contributed greatly to the revision of the manuscript. This work has been published in *The Journal of Organic Chemistry* and is available online. [Reprinted (adapted) with permission from Nelson, A. K.; Peck, C. L.; Rafferty, S. M.; Santos, W. L. Chemo-, Regio-, and Stereoselective Copper(II)-Catalyzed Boron Addition to Acetylenic Esters and Amides in Aqueous Media. *J. Org. Chem.* **2016**, *81*, 4269. Copyright 2017 American Chemical Society]

### 3.2 Abstract

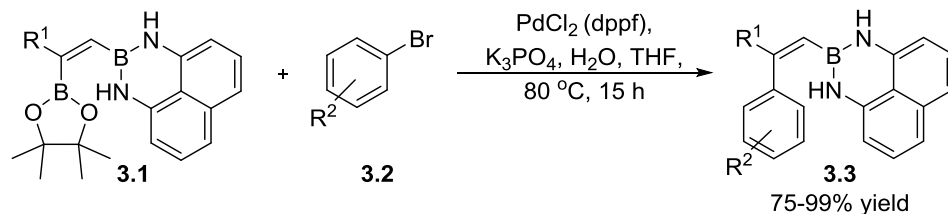
Aqueous conditions were developed for conducting an open-to-air, copper(II)-catalyzed addition of pinB-Bdan to alkynoates and alkynamides. The simple and mild  $\beta$ -borylation protocol proceeds in a remarkably chemo-, regio-, and stereoselective fashion to afford 1,8-diaminonaphthalene protected (*Z*)- $\beta$ -boryl enoates and primary, secondary, and tertiary enamides in good to excellent yields. These reactions demonstrate a high tolerance towards a variety of alkyl, aryl, and heteroatom functional groups and provide convenient access to a diverse range of vinylboronic acid derivatives.



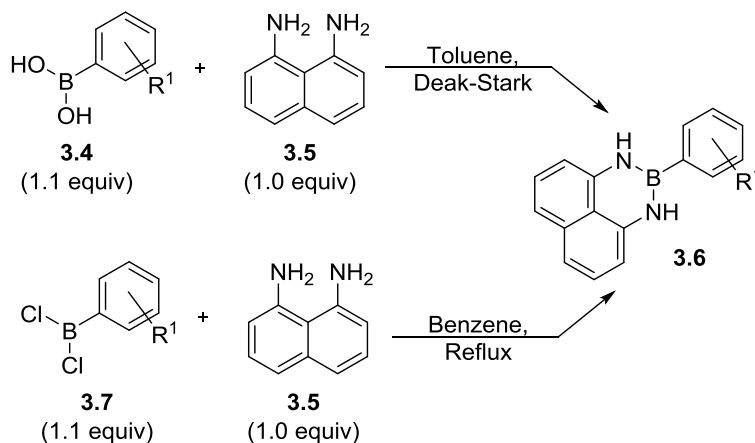
### 3.3 Introduction

Vinylboronic acids and their derivatives serve as valuable intermediates in organic synthesis, particularly with Suzuki–Miyaura cross-coupling reactions to form carbon–carbon bonds.<sup>1-4</sup> As a consequence, efficient and economical methods for their preparation are essential. Access to these derivatives via borylation of alkynes with boron sources such as pinacolborane (HBpin) and bis(pinacolato)diboron ( $B_2pin_2$ ) is well established including uncatalyzed,<sup>5</sup> transition metal-catalyzed,<sup>6-7</sup> and acid/base-catalyzed processes.<sup>8-10</sup> However, some of these methods have disadvantages such as the use of organic solvents and precious transition metals, including platinum or palladium, and the production of toxic byproducts. Among the class of vinylboronic acid derivatives, routes to conjugated vinylboronates bearing carbonyl groups are severely limited, and methods toward primary and secondary amides are nonexistent.<sup>11-12</sup> Because of the utility of vinylboronic acids, the development of simple, efficient, and sustainable methods for their installation are important.

Among the myriad of protecting groups for boron, the pinacol (pin) moiety is a standout, popular choice because of its compatibility with numerous reaction conditions. However, the 1,8-diaminonaphthyl group (dan), an alternative boron ligand, is emerging as an orthogonal protecting group.<sup>13-19</sup> This moiety is attractive because of its robustness and compatibility, and it allows for fine-tuning of the reactivity of the boron center. For example, chemoselective transformations of Bpin derivatives occur in the presence of the Bdan group due to the difference in Lewis acidity (Scheme 3.1).<sup>13-14, 17-18, 20-23</sup> Therefore, novel methods to introduce Bdan into organic substrates efficiently are valuable. Traditionally, condensation of 1,8-diaminonaphthalene

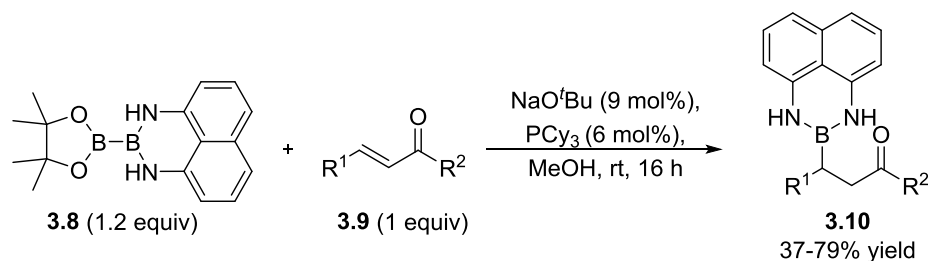


**Scheme 3.1.** Chemoselective Suzuki–Miyaura cross-coupling.



**Scheme 3.2.** Incorporation of the 1,8-diaminonaphthalene protecting group.

(**3.5**) and the substrate bearing a boronic acid or boron dichloride moiety allows for the introduction of the Bdan moiety; however, methods for direct incorporation are preferred (Scheme 3.2).<sup>24-26</sup> In particular, a differentially protected diboron reagent, pinB–Bdan (**3.8**) has been particularly useful for the incorporation of the Bdan substituent.<sup>22-23, 27-33</sup> For example, the elegant work by Cid *et al.* reported the organocatalytic addition of **3.8** to  $\alpha,\beta$ -unsaturated carbonyl compounds **3.9** (Scheme 3.3).<sup>27</sup> DFT studies were run to compare the reactivity of the activated adducts and it confirmed the Bpin moiety has a higher nucleophilic character. The decreased Lewis acidity of the Bdan moiety is a result of the adjacent nitrogen atoms donating electron density into the empty p-orbital on the boron center. In turn, this leads to the selective activation of Bpin and the chemoselective transfer of the Bdan moiety. Further, Gravel *et al.* pioneered a method to incorporate Bdan onto the vinylic  $\beta$ -carbon of esters (Scheme 3.4, top).<sup>34</sup>

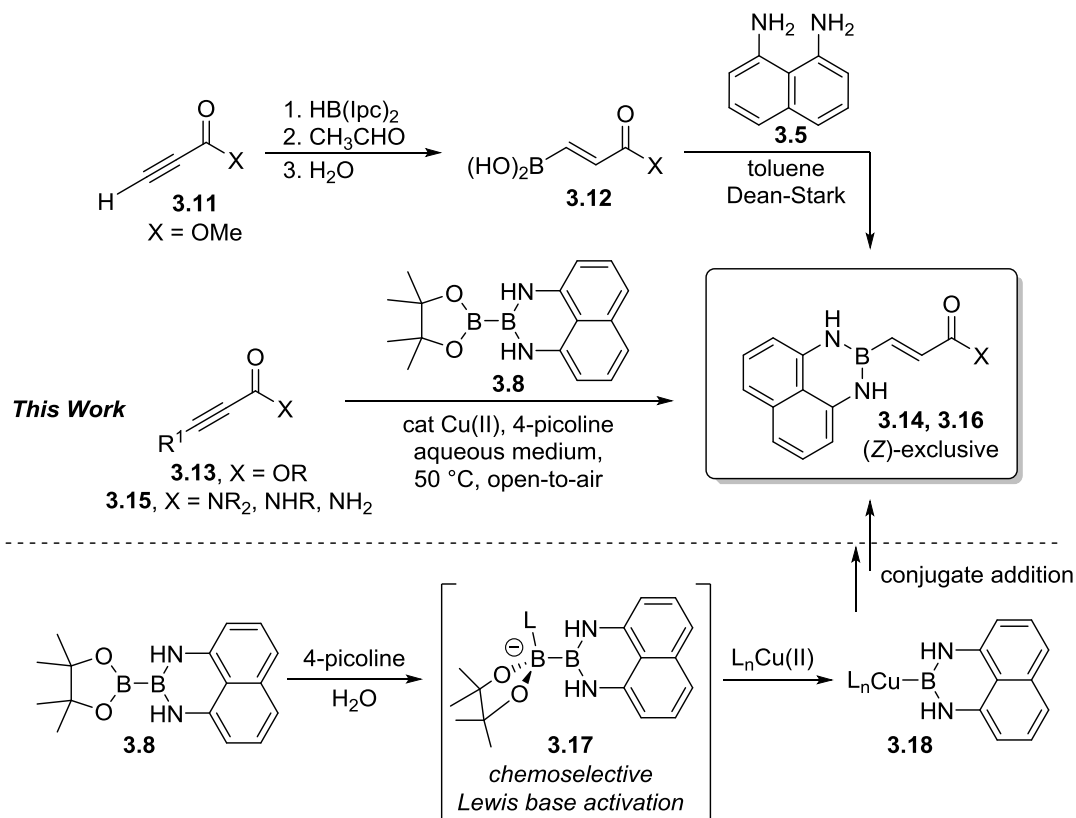


**Scheme 3.3.**  $\beta$ -Borylation of  $\alpha,\beta$ -unsaturated carbonyl compounds.

This multistep procedure, however, was limited to esters containing no substituents on the  $\beta$ -carbon. Regardless, the copper-catalyzed enantioselective conjugate borylation,<sup>17</sup> alkylation,<sup>15</sup> and reduction<sup>35</sup> reactions developed demonstrate the utility of these compounds as synthetic intermediates.

Given our interest in developing sustainable methods for the borylation of activated carbon-carbon bonds<sup>36-37</sup> and the paucity of borylation reactions in water,<sup>38-43</sup> we set out to contribute a simple, efficient, and environmentally friendly process for the addition of Bdan to acetylenic carbonyl groups. Water is a notably enticing solvent of choice partly due to its cost-effectiveness and because it is not flammable or toxic. Further, we wanted to capitalize on our initial finding that earth abundant and air stable copper(II) efficiently catalyzes the borylation of  $\alpha,\beta$ -unsaturated carbonyls, affording an environmentally and user-friendly method.<sup>36, 44</sup> The seminal work of Lawson *et al.*,<sup>45</sup> outlining the platinum-catalyzed borylation of  $\alpha,\beta$ -unsaturated ketones, propelled other transition metal-catalyzed and metal-free investigations on  $\beta$ -borylation reactions.<sup>46-51</sup> Inspired by these contributions, we report the development of an efficient and aqueous-based method for generating structurally diverse 1,8-diaminonaphthalene protected  $\beta$ -boryl- $\alpha,\beta$ -unsaturated carbonyl compounds, including primary and secondary amides (Scheme 3.4). In this strategy, we capitalize on the chemoselective activation of the more Lewis acidic

boron by activating it with a Lewis base, either water or 4-picoline, to form an  $sp^2$ - $sp^3$  diboron intermediate **3.17**, thereby facilitating the efficient transfer of Bdan.<sup>36, 52-55</sup>

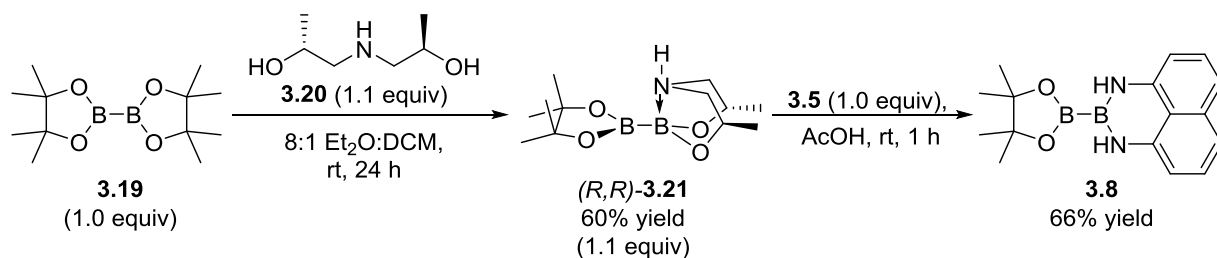


**Scheme 3.4.** Approaches to Bdan vinylboronates.

### 3.4 Optimizing the $\beta$ -borylation of ethyl 2-butynoate with pinB-Bdan

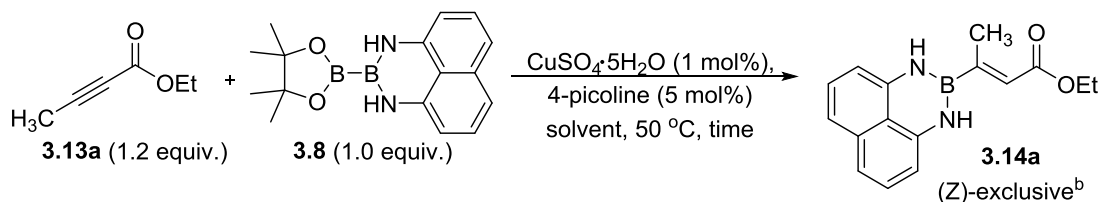
Preliminary studies utilized commercially available 2-butynoate (**3.13a**) and the previously established aqueous borylation protocol of alkynoates with B<sub>2</sub>pin<sub>2</sub>.<sup>9</sup> The unsymmetrical diboron reagent **3.8** was synthesized according to Guo *et al.*'s two-step protocol, which proceeds through an  $sp^2$ - $sp^3$  hybridized diboron reagent (*R,R*)-**3.21** (Scheme 3.5).<sup>23</sup> Under these previous conditions, no reaction was observed likely due to the insolubility of the pinB-Bdan diboron reagent in water (Table 3.1, entry 1). Addition of an environmentally benign





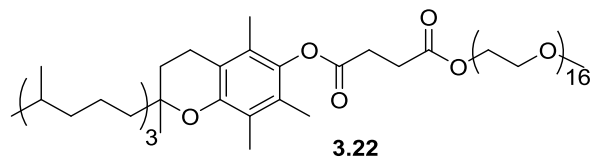
**Scheme 3.5.** Method to synthesize pinB-Bdan.

alcohol such as ethanol or 2-propanol promoted solubility (entries 2-7). As such, the reaction proceeds smoothly to provide the (*Z*)- $\beta$ -boryl- $\alpha,\beta$ -unsaturated ester **3.14a** as a single regio- and stereoisomer, which was verified by nuclear Overhauser effect (nOe) experiments. The expected chemoselective transfer of Bdan to the  $\beta$ -carbon was observed as a consequence of the difference in Lewis acidity of each boron center, allowing the conjugate addition of the 1,8-diaminonaphthyl boryl-copper complex **3.18** (Scheme 3.4). The optimal percentage of alcohol in the aqueous solvent system was determined by monitoring the percent conversion over time (entries 2-5). We observed a high conversion after 6 hours with 5% ethanol (entry 2). However, complete conversion was achieved in a shorter period of time when the ethanol additive was increased to 10% (entry 3). Higher percentages of the ethanol additive had a negative effect on the rate of conversion, requiring 6 hours to reach completion (entries 4-5). Unlike the copper(I)-catalyzed borylation reaction developed by Mun *et al.*,<sup>56</sup> in which a methanol additive increased the rate of the reaction, no reaction was observed in this case (entry 6). Under these conditions, **3.8** was insoluble and unable to participate in the reaction. 2-Propanol, on the other hand, was an adequate additive (entry 7). Next, we explored the use of a nanomicellar surfactant, 2 wt % TPGS-750-M (**3.22**),<sup>57-58</sup> as an adequate alternative aqueous reaction medium and found these conditions to be similar to those for the 10% ethanol mixture (entries 8, 9). In comparison, no

**Table 3.1.** Optimization of reaction conditions using an unsymmetrical diboron reagent.<sup>a</sup>

Entry	Solvent	Time (h)	Conversion, % <sup>c</sup> (Yield, %)
1	H <sub>2</sub> O	6	0
2	5% EtOH/H <sub>2</sub> O	6	93
<b>3</b>	<b>10% EtOH/H<sub>2</sub>O</b>	<b>4</b>	<b>100 (86)</b>
4	15% EtOH/H <sub>2</sub> O	6	100
5	20% EtOH/H <sub>2</sub> O	6	100
6	10% MeOH/H <sub>2</sub> O	6	0
7	10% <i>i</i> PrOH/H <sub>2</sub> O	4	100 (85)
8	2 wt % TPGS-750-M/H <sub>2</sub> O	6	94
9	10% EtOH, 2 wt % TPGS-750-M/H <sub>2</sub> O	6	100 (86)
10	10% EtOH/H <sub>2</sub> O	1	0 <sup>d</sup>
11	10% EtOH/H <sub>2</sub> O	1	0 <sup>e</sup>

<sup>a</sup> General procedure: pinB–Bdan (**3.8**, 1.0 equiv.), 2-butyne (**3.13a**, 1.2 equiv.), 4-picoline (5 mol%),  $\text{CuSO}_4$  (1 mol%), and 1 mL of solvent were added to a 1 dram vial and stirred. <sup>b</sup> Exclusive stereochemistry was obtained, as determined by GC-MS of the crude mixture and confirmed by nOe experiments. <sup>c</sup> Conversion determined by monitoring the consumption of pinB–Bdan with GC-MS. <sup>d</sup> In the absence of  $\text{Cu}(\text{SO}_4)$ . <sup>e</sup> In the absence of 4-picoline.

**Figure 3.1.** Structure of surfactant, TPGS-750-M.

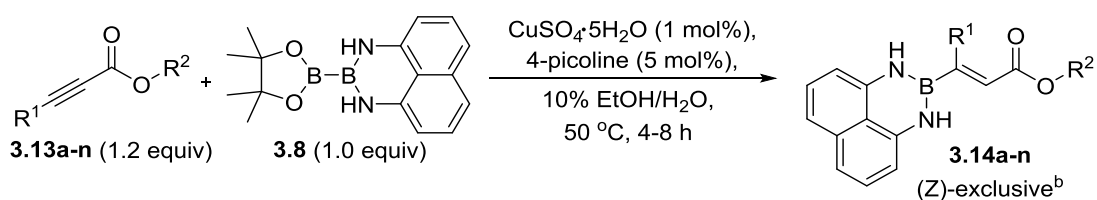
improvement to the yield was observed with the addition of the surfactant to the EtOH/H<sub>2</sub>O mixture. As expected, the copper(II) catalyst and 4-picoline were needed for the efficient

conversion into product (entries 10, 11). We opted to utilize copper(II) instead of copper (I) sources such as CuCl because of solubility issues in water and oxidation to copper(II) upon exposure to air.<sup>36</sup> Therefore, the simpler reaction conditions were determined to be optimal (entry 3).

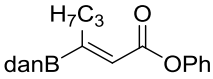
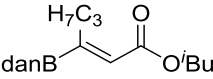
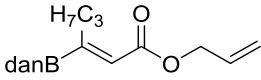
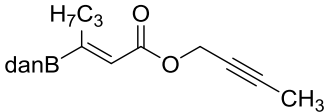
### 3.5 Substrate scope for the $\beta$ -borylation of alkynoates with pinB-Bdan

Under these optimized conditions, the functional group tolerance and scope of the reaction was examined (Table 3.2). Overall, the borylation reaction rapidly installed the Bdan functional unit onto the  $\beta$ -carbon regio- and stereoselectively, providing the (*Z*)-stereoisomer in all cases. Various alkyl chains ranging from methyl to heptyl substituents on the R<sup>1</sup> position provided the products in high yields with short reaction times (**3.14a-d**). The more sterically hindered *tert*-butyl substituent affected neither the yield nor the selectivity of the product (**3.14e**). Next, we examined various cyclic rings and obtained high yields for cyclopropyl (**3.14f**) and cyclohexyl (**3.14h**) substituents. Unfortunately, the borylated product for ethyl 3-cyclopentyl-propionate (**3.14g**) was only obtained in a 48% yield. Regioselectivity for the  $\beta$ -borylation was demonstrated by applying the reaction conditions to the conjugated cyclohex-3-en-1-yne ester (**3.13i**) to give the (*Z*)- $\alpha,\beta,\gamma,\delta$ -unsaturated diene in a 78% yield. When R<sup>1</sup> contained an ether substituent, the borylation proceeded smoothly to give **3.14j** in a 77% yield. Next, we probed substituent tolerance in the R<sup>2</sup> position and found that substrates containing sterically bulky substituents, such as a phenyl ring and branched isobutyl group, were readily borylated to provide good yields of the respective (*Z*)- $\beta$ -boryl- $\alpha,\beta$ -unsaturated esters (**3.14k-l**). Finally, we demonstrated the chemoselectivity of this reaction by examining unsaturation at the R<sup>2</sup> position. The borylation of hexynoate derivatives bearing allyl (**3.13m**) and propargyl (**3.13n**) groups

**Table 3.2.** Boryl conjugate addition to substituted alkynoates with pinB-Bdan.<sup>a</sup>



Entry	Product	<b>3.14</b>	Time (h) <sup>c</sup>	Yield (%) <sup>d</sup>
1		<b>3.14a</b>	4	86
2		<b>3.14b</b>	4	79
3		<b>3.14c</b>	4	88
4		<b>3.14d</b>	4	82
5		<b>3.14e</b>	6	81
6		<b>3.14f</b>	4	83
7		<b>3.14g</b>	8	48
8		<b>3.14h</b>	4	72
9		<b>3.14i</b>	8	78
10		<b>3.14j</b>	4	77

Entry	Product	<b>3.14</b>	Time (h) <sup>c</sup>	Yield (%) <sup>d</sup>
11		<b>3.14k</b>	4	79
12		<b>3.14l</b>	8	85
13		<b>3.14m</b>	6	82
14		<b>3.14n</b>	6	73

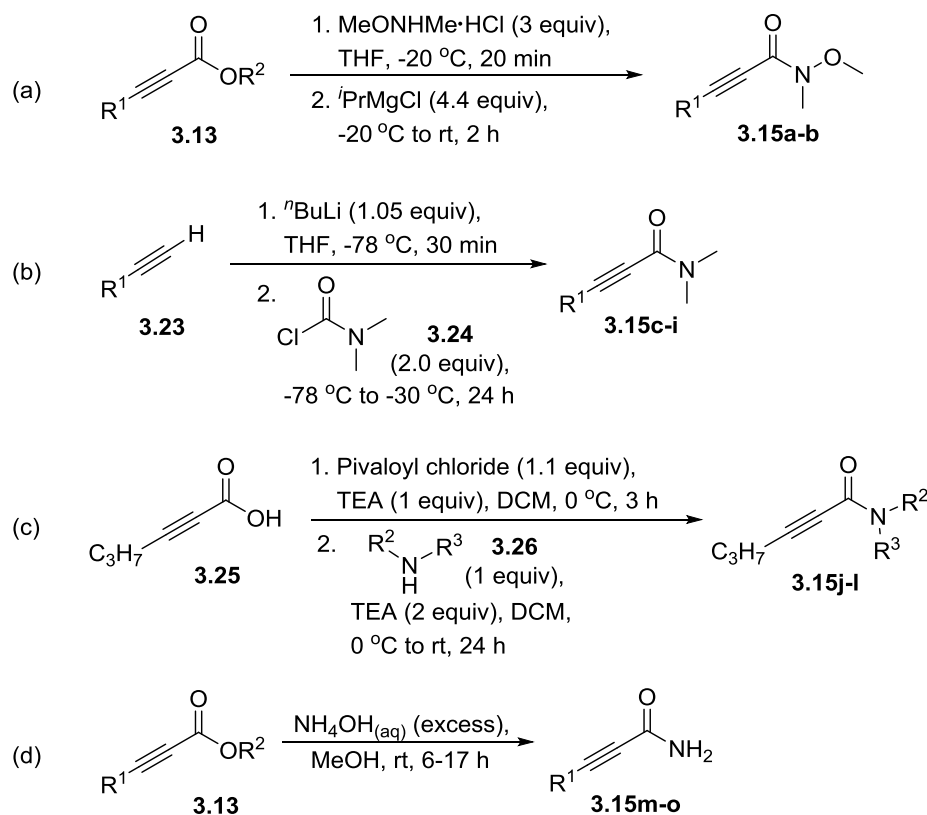
<sup>a</sup> General procedure: pinB–Bdan (**3.8**, 1.0 equiv.), alkynoate (**3.13a-n**, 1.2 equiv.), 4-picoline (5 mol%), CuSO<sub>4</sub> (1 mol%), and 1 mL of 10% EtOH/H<sub>2</sub>O were added to a 1 dram vial and stirred. <sup>b</sup> Exclusive stereochemistry was obtained, as determined by GC-MS of the crude material and confirmed by nOe experiments of the isolated product. <sup>c</sup> Conversion determined by monitoring the consumption of pinB–Bdan with GC-MS. <sup>d</sup> Yields are an average of two or more reactions.

resulted in high yields of the β-borylated products, thus verifying that the reaction occurs exclusively at the more activated alkyne.

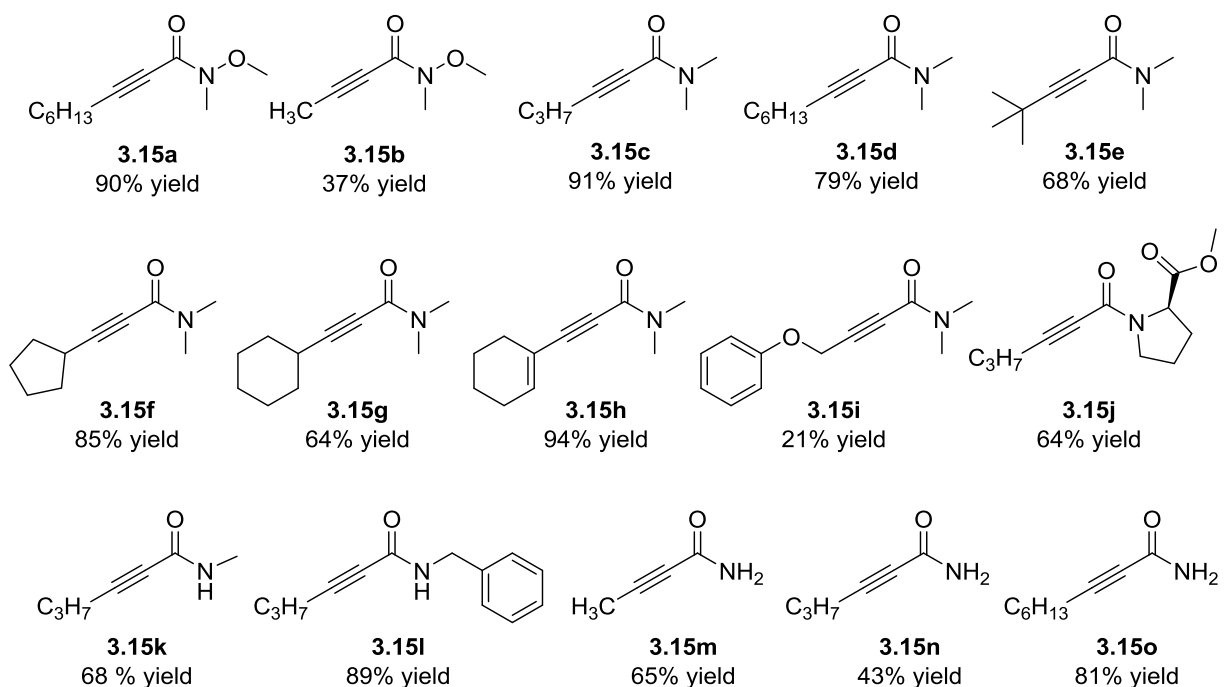
### 3.6 Preparation of alkynamides

Prompted by the great success of the alkynoate substrates, we sought to expand the substrate scope to include alkynamides derivatives. Unfortunately, the majority of alkynamides were not commercially available; therefore, sterics and electronics on the alkyne and amide functionality had to be precisely introduced using multiple protocols (Scheme 3.6). Coincidentally, Linstadt *et al.* have recently established a quick and efficient synthetic protocol for the synthesis of Weinreb amides **3.15a-b** by reacting commercially available alkynoate **3.13** in the presence of *N,O*-dimethylhydroxylamine hydrochloride and isopropyl magnesium chloride (Scheme 3.6a).<sup>57</sup> Furthermore, the protocol for the synthesis of alkynoates was altered by using

dimethylcarbonyl chloride (**3.24**) to afford a series of *N,N'*-dimethylamide substrates **3.15c-i** in up to a 94% yield (Scheme 3.6b).<sup>12</sup> To vary the amide functionality, hex-2-ynoic acid (**3.24**) was treated with pivaloyl chloride to afford a good leaving group and subsequent addition of the deprotonated amide **3.26** afforded tertiary amide **3.15j** and secondary amides **3.15k-l** in moderate to good yields (Scheme 3.6c).<sup>57</sup> Finally, a base-catalyzed hydrolysis reaction using ammonium hydroxide provided the desired alkyl substituted carboxamides **3.15m-o** following recrystallizing in varying yields (43–81% yield) (Scheme 3.6d).<sup>57</sup> All of the alkynamides synthesized are presented in Figure 3.2.



**Scheme 3.6.** Methods employed to synthesize alkynamides.



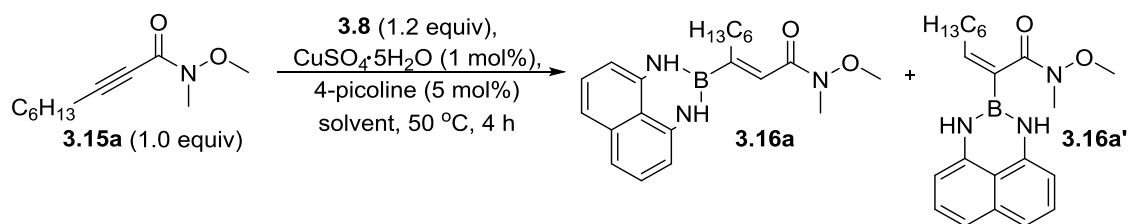
**Figure 3.2.** Structures of alkyne amides synthesized.

### 3.7 Re-optimization of solvent systems

Amides have received minimal attention as substrates due to their inherently low reactivity towards 1,4-conjugate additions.<sup>59-62</sup> In fact, methods to access (*Z*)- $\beta$ -boryl- $\alpha,\beta$ -unsaturated amides directly are not available. However, it has been suggested that alkyne amides and alkynoates undergo 3,4-*syn* addition reactions.<sup>62</sup> Therefore, to test whether we can effectively borylate alkyne amides we used our previously optimized conditions for borylating alkynoates. Gratifyingly, Weinreb amide **3.15a** reacted readily under our 10% ethanol aqueous conditions to provide the desired product **3.16a** in an 82% yield (Table 3.3, entry 1). To our surprise, a slight amount of the  $\alpha$ -borylated product **3.16a'** was detected by <sup>1</sup>H NMR and confirmed by nOe in the crude reaction mixture. The formation of the  $\alpha$ -borylated product was likely a result of the boron in the boryl-copper complex coordinating to the oxygen atom of the Weinreb amide, directing the boron to the  $\alpha$ -position. After determining we were successfully

able to borylate Weinreb amides, we re-examined the use of a surfactant to pursue an increase in the reaction yield. When ethanol was replaced by the 2 wt % TPGS-750-M surfactant (**3.22**), a drastically lower yield was obtained (entry 2). However, in contrast to the alkynoate optimization results, when ethanol was employed in conjunction with the surfactant, an excellent yield of **3.16a** was obtained (88% yield, entry 3). As expected, the reaction remained stereoselective for the (*Z*)-isomer and maintained a high regioselectivity for the  $\beta$ -borylated product.

**Table 3.3.** Screening of solvent systems for the borylation of Weinreb amides.<sup>a, b</sup>



Entry	Solvent	Ratio <b>3.16a</b> : <b>3.16a'</b>	Yield (%) <sup>c,d</sup>
1	10% EtOH/H <sub>2</sub> O	99:1	82
2	2 wt % TPGS-750-M/H <sub>2</sub> O	98:2	61
<b>3</b>	<b>10% EtOH, 2 wt % TPGS-750-M/H<sub>2</sub>O</b>	<b>98:2</b>	<b>88</b>

<sup>a</sup> General procedure: pinB–Bdan (**3.8**, 1.2 equiv), alkynamide (**3.15a**, 1.0 equiv), 4-picoline (5 mol%), CuSO<sub>4</sub> (1 mol%), and 1 mL of solvent were added to a 1 dram vial and stirred. <sup>b</sup> Stereochemistry was determined by <sup>1</sup>H HMR of the crude material and confirmed by nOe experiments of the isolated product. <sup>c</sup> Isolated yields are of a single product,  $\beta$ -borylated product **3.16a**. <sup>d</sup> Yields are an average of two reactions.

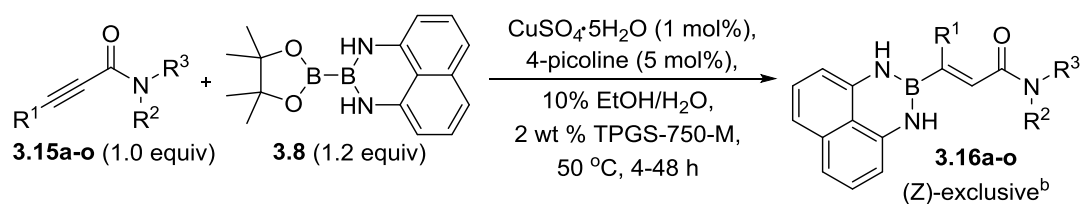
### 3.8 Substrate scope for the $\beta$ -borylation of alkynamides

As the addition of the 2 wt % TPGS-750-M surfactant (**3.22**) improved the yield, we continued to use this aqueous-based media to explore the scope and limitations of alkynamide

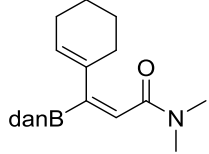
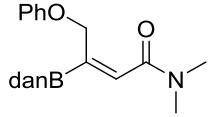
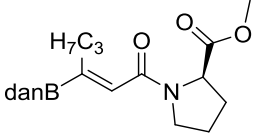
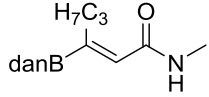
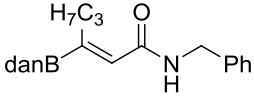
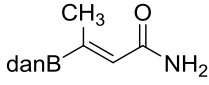
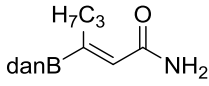
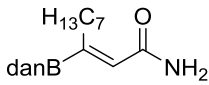


substrates (Table 3.4). A comparable but slightly lower yield was obtained when the alkyl chain of the Weinreb amide was reduced from a hexyl (**3.16a**) to a methyl substituent (**3.16b**). Furthermore, although the reaction was highly regioselective for the  $\beta$ -borylated product, a slightly higher amount of the  $\alpha$ -borylated product was observed than with the hexyl substituent ( $\alpha:\beta = 10:90$ ). The Weinreb amide derivatives were the only substrates in which the  $\alpha$ -borylated

**Table 3.4.** Boryl conjugate addition to Weinreb amides and substituted alkynamides.<sup>a</sup>



Entry	Product	<b>3.16</b>	Time (h) <sup>c</sup>	Yield (%) <sup>d</sup>
1		<b>3.16a</b>	4	91 <sup>e,f</sup>
2		<b>3.16b</b>	10	85 <sup>e,g</sup>
3		<b>3.16c</b>	15	76
4		<b>3.16d</b>	10	86
5		<b>3.16e</b>	48	71
6		<b>3.16f</b>	12	89
7		<b>3.16g</b>	15	93

Entry	Product	<b>3.16</b>	Time (h) <sup>c</sup>	Yield (%) <sup>d</sup>
8		<b>3.16h</b>	28	79
9		<b>3.16i</b>	15	82
10		<b>3.16j</b>	9	92
11		<b>3.16k</b>	12	76
12		<b>3.16l</b>	12	96
13		<b>3.16m</b>	15	41
14		<b>3.16n</b>	16	90
15		<b>3.16o</b>	9	93

<sup>a</sup> General procedure: pinB–Bdan (**3.8**, 1.2 equiv), alkynamide (**3.15a-o**, 1.0 equiv), 4-picoline (5 mol%), CuSO<sub>4</sub> (1 mol%), and 1 mL of 10% EtOH/H<sub>2</sub>O, 2 wt % TPGS-750-M were added to a 1 dram vial and stirred. <sup>b</sup> Exclusive stereochemistry was obtained, as determined by GC-MS of the crude material and confirmed by nOe experiments of the isolated product. <sup>c</sup> Conversion determined by monitoring the consumption of pinB–Bdan with GC-MS. <sup>d</sup> Averaged from two or more experiments. <sup>e</sup> Isolated yields are of a single product, β-borylated product. <sup>f</sup> Ratio of α:β borylated product 2:98. <sup>g</sup> Ratio of α:β borylated product 10:90.

product was observed.

A series of *N,N'*-dimethylamide substrates were synthesized to explore further the effects

of substitutions on the alkyne. Substrates with aliphatic substituents on the R<sup>1</sup> position, such as propyl (**3.15c**) or hexyl (**3.15d**) groups, undergo  $\beta$ -borylations in good yields. The branched *tert*-butyl derivative also gave the desired product **3.16e** stereoselectively. Although this reaction does not reach completion after 48 hours, a good yield (71%) was still obtained. Additionally, the borylation of amides containing cyclic R<sup>1</sup> substituents proceeded smoothly and provided the desired products in excellent yields (**3.16f-h**). Even 3-cyclopentyl-*N,N'*-dimethylpropiolamide (**3.15f**) afforded the borylation product in a 89% yield, which was surprising given that the ester equivalent was low yielding. The conjugated cyclohex-3-en-1-yne substituted *N,N'*-dimethylpropiolamide (**3.15h**) was regioselectively borylated at the  $\beta$ -position, providing the (*Z*)- $\alpha,\beta,\gamma,\delta$ -unsaturated diene **3.16h** in a 79% yield. Borylation of the methylene phenyl ether (**3.15i**) also proceeded smoothly. Finally, we demonstrated that the steric bulk of the tertiary amide was well tolerated with an alkynamide derivative of D-proline (**3.15j**). This substrate readily underwent  $\beta$ -borylation to give the desired product **3.16j** in an excellent yield (92%) and with retention of the chiral center. A polarimeter was used to determine the optical rotation and ultimately the chirality of the product which was compared to the starting material.

The acidic hydrogen of the amide functional group was also tolerated under these mild conditions, as evidenced by **3.16k-o**. Hirano *et al.* reported a Ni-catalyzed  $\beta$ -borylation of *N,N'*-dimethylamide derivatives and Weinreb amides; however, to the best of our knowledge, borylation of secondary and primary amides have never been reported.<sup>63</sup> In our case, the secondary amides were regio- and stereoselectively borylated in good to excellent yields (**3.16k-l**). When the steric demand of the amide substituent was increased from a methyl (**3.15k**) to a benzyl (**3.15l**) group, the borylation proceeded nearly quantitatively (96% yield, **3.16l**). Moreover, the less reactive carboxamides readily underwent borylation as well (**3.15m-o**).

Excellent yields were obtained when the R<sup>1</sup> position was substituted with a propyl (**3.16m**) or hexyl (**3.16n**) alkyl chain while a modest yield was obtained for a methyl substituent (**3.16o**). Interestingly, a trend of increasing product yield as the R<sup>1</sup> substituent became larger was observed, presumably as a consequence of the solubility of the starting material. No other aqueous solvent systems were tested in an attempt to increase the yield of **3.16m**.

### 3.9 Conclusions

In summary, we have developed a mild and efficient copper(II)-catalyzed  $\beta$ -borylation of alkynoates and alkynamides using unsymmetrical diboron reagent **3.8**. We demonstrated the chemoselective transfer of the less Lewis acidic Bdan moiety and notably borylated inherently unreactive secondary and primary amides. The reaction was carried out under environmentally friendly conditions, which were open-to-air and in an aqueous media. Catalytic amounts of an inexpensive, air stable copper(II) catalyst and a commercially available amine base also makes this approach cost-effective.

### 3.10 References for Chapter 3

1. Miyaura, N.; Suzuki, A., Palladium-Catalyzed Cross-Coupling Reactions of Organoboron Compounds. *Chem. Rev.* **1995**, *95*, 2457.
2. Mkhaliid, I. A. I.; Coapes, R. B.; Edes, S. N.; Coventry, D. N.; Souza, F. E. S.; Thomas, R. L.; Hall, J. J.; Bi, S.-W.; Lin, Z.; Marder, T. B., Rhodium-Catalyzed Dehydrogenative Borylation of Alkenes: Vinylboronates via C-H Activation. *Dalton Trans.* **2008**, 1055.
3. Hall, D. G., *Boronic Acids: Preparation, Applications in Organic Synthesis, Medicine and Materials*. 2nd ed.; Wiley-VCH: Weinheim, Germany, 2011.

4. Lennox, A. J. J.; Lloyd-Jones, G. C., Selection of Boron Reagents for Suzuki-Miyaura Coupling. *Chem. Soc. Rev.* **2014**, *43*, 412.
5. Tucker, C. E.; Davidson, J.; Knochel, P., Mild and Stereoselective Hydroborations of Functionalized Alkynes and Alkenes using Pinacolborane. *J. Org. Chem.* **1992**, *57*, 3482.
6. Beletskaya, I.; Pelter, A., Hydroborations Catalyzed by Transition Metal Complexes. *Tetrahedron* **1997**, *53*, 4957.
7. Yoshida, H., Borylation of Alkynes Under Base/Coinage Metal Catalysis: Some Recent Developments. *ACS Catal.* **2016**, *6*, 1799.
8. Wen, K.; Chen, J.; Gao, F.; Bhadury, P. S.; Fan, E.; Sun, Z., Metal-Free Catalytic Hydroboration of Multiple Bonds in Methanol using *N*-Heterocyclic Carbenes Under Open Atmosphere. *Org. Biomol. Chem.* **2013**, *11*, 6350.
9. Barbeyron, R.; Benedetti, E.; Cossy, J.; Vasseur, J.-J.; Arseniyadis, S.; Smietana, M., Recent Developments in Alkyne Borylations. *Tetrahedron* **2014**, *70*, 8431.
10. Ho, H. E.; Asao, N.; Yamamoto, Y.; Jin, T., Carboxylic Acid-Catalyzed Highly Efficient and Selective Hydroboration of Alkynes with Pinacolborane. *Org. Lett.* **2014**, *16*, 4670.
11. Ishiyama, T.; Takagi, J.; Kamon, A.; Miyaura, N., Palladium-Catalyzed Cross-Coupling Reaction of Bis(pinacolato)diboron with Vinyl Triflates  $\beta$ -Substituted by a Carbonyl Group: Efficient Synthesis of  $\beta$ -Boryl- $\alpha,\beta$ -Unsaturated Carbonyl Compounds and Their Synthetic Utility. *J. Organomet. Chem.* **2003**, *687*, 284.
12. Lee, J.-E.; Kwon, J.; Yun, J., Copper-Catalyzed Addition of Diboron Reagents to  $\alpha,\beta$ -Acetylenic Esters: Efficient Synthesis of  $\beta$ -Boryl- $\alpha,\beta$ -Ethylenic Esters. *Chem. Commun.* **2008**, 733.
13. Noguchi, H.; Hojo, K.; Suginome, M., Boron-Masking Strategy for the Selective Synthesis

- of Oligoarenes via Iterative Suzuki–Miyaura Coupling. *J. Am. Chem. Soc.* **2007**, *129*, 758.
14. Iwadate, N.; Suginome, M., Synthesis of B-Protected  $\beta$ -Styrylboronic Acids via Iridium-Catalyzed Hydroboration of Alkynes with 1,8-Naphthalenediaminatoborane Leading to Iterative Synthesis of Oligo(phenylenevinylene)s. *Org. Lett.* **2009**, *11*, 1899.
  15. Lee, J. C. H.; Hall, D. G., Chiral Boronate Derivatives via Catalytic Enantioselective Conjugate Addition of Grignard Reagents on 3-Boronyl Unsaturated Esters and Thioesters. *J. Am. Chem. Soc.* **2010**, *132*, 5544.
  16. Iannazzo, L.; Vollhardt, K. P. C.; Malacria, M.; Aubert, C.; Gandon, V., Alkynylboronates and -Boramides in Co(I)- and Rh(I)-Catalyzed [2+2+2] Cycloadditions: Construction of Oligoaryls through Selective Suzuki Couplings. *Eur. J. Org. Chem.* **2011**, *43*, 3283.
  17. Lee, J. C. H.; McDonald, R.; Hall, D. G., Enantioselective Preparation and Chemoselective Cross-Coupling of 1,1-Diboron Compounds. *Nat. Chem.* **2011**, *3*, 894.
  18. Feng, X.; Jeon, H.; Yun, J., Regio- and Enantioselective Copper(I)-Catalyzed Hydroboration of Borylalkenes: Asymmetric Synthesis of 1,1-Diborylalkanes. *Angew. Chem., Int. Ed.* **2013**, *52*, 3989.
  19. Yoshida, H.; Takemoto, Y.; Takaki, K., Direct Synthesis of Boron-Protected Alkenyl- and Alkylborons via Copper-Catalyzed Formal Hydroboration of Alkynes and Alkenes. *Asian J. Org. Chem.* **2014**, *3*, 1204.
  20. Noguchi, H.; Shioda, T.; Chou, C.-M.; Suginome, M., Differentially Protected Benzenediboronic Acids: Divalent Cross-Coupling Modules for the Efficient Synthesis of Boron-Substituted Oligoarenes. *Org. Lett.* **2008**, *10*, 377.
  21. Iwadate, N.; Suginome, M., Synthesis of Masked Haloareneboronic Acids via Iridium-

- Catalyzed Aromatic C–H Borylation with 1,8-Naphthalenediaminatoborane (HBdan). *J. Organomet. Chem.* **2009**, *694*, 1713.
22. Iwadate, N.; Suginome, M., Differentially Protected Diboron for Regioselective Diboration of Alkynes: Internal-Selective Cross-Coupling of 1-Alkene-1,2-Diboronic Acid Derivatives. *J. Am. Chem. Soc.* **2010**, *132*, 2548.
  23. Guo, X.; Nelson, A. K.; Slebodnick, C.; Santos, W. L., Regio- and Chemoselective Diboration of Allenes with Unsymmetrical Diboron: Formation of Vinyl and Allyl Boronic Acid Derivatives. *ACS Catal.* **2015**, *5*, 2172.
  24. Caserio, J. F.; Cavallo, J.; Wagner, R., Preparation of 8-Bora-7,9-Diazaro-Peri-Naphthene and Derivatives. *J. Org. Chem.* **1961**, *26*, 2157.
  25. Slabber, C. A.; Grimmer, C. D.; Robinson, R. S., Solution-State  $^{15}\text{N}$  NMR and Solid-State Single-Crystal XRD Study of Heterosubstituted Diazaboroles and Borinines Prepared via an Effective and Simple Microwave-Assisted Solvent-Free Synthesis. *J. Org. Chem.* **2013**, *78*, 122.
  26. Kaupp, G.; Naimi-Jamal, M. R.; Stepanenko, V., Waste-Free and Facile Solid-State Protection of Diamines, Anthranilic Acid, Diols, and Polyols with Phenylboronic Acid. *Chem. - Eur. J.* **2003**, *9*, 4156.
  27. Cid, J.; Carbó, J. J.; Fernández, E., A Clear-Cut Example of Selective Bpin-Bdan Activation and Precise Bdan Transfer on Boron Conjugate Addition. *Chem. - Eur. J.* **2014**, *20*, 3616.
  28. Yoshida, H.; Takemoto, Y.; Takaki, K., A Masked Diboron in Cu-Catalyzed Borylation Reaction: Highly Regioselective Formal Hydroboration of Alkynes for Synthesis of Branched Alkenylborons. *Chem. Commun.* **2014**, *50*, 8299.

29. Cuenca, A. B.; Cid, J.; Garcia-Lopez, D.; Carbo, J. J.; Fernandez, E., Unsymmetrical 1,1-Diborated Multisubstituted  $sp^3$ -Carbons Formed via a Metal-Free Concerted-Asynchronous Mechanism. *Org. Biomol. Chem.* **2015**, *13*, 9659.
30. Miralles, N.; Cid, J.; Cuenca, A. B.; Carbo, J. J.; Fernandez, E., Mixed Diboration of Alkenes in a Metal-Free Context. *Chem. Commun.* **2015**, *51*, 1693.
31. Sakae, R.; Hirano, K.; Miura, M., Ligand-Controlled Regiodivergent Cu-Catalyzed Aminoboration of Unactivated Terminal Alkenes. *J. Am. Chem. Soc.* **2015**, *137*, 6460.
32. Sakae, R.; Hirano, K.; Sato, T.; Miura, M., Copper-Catalyzed Stereoselective Aminoboration of Bicyclic Alkenes. *Angew. Chem., Int. Ed.* **2015**, *54*, 613.
33. Xu, L.; Li, P., Direct Introduction of a Naphthalene-1,8-Diamino Boryl [B(dan)] Group by a Pd-Catalyzed Selective Boryl Transfer Reaction. *Chem. Commun.* **2015**, *51*, 5656.
34. Gravel, M.; Touré, B. B.; Hall, D. G., Practical Procedure for the Preparation of Functionalized (*E*)-1-Alkenylboronic Acids Including the Unprecedented 1-Alkoxy carbonyl Derivatives *Org. Prep. Proced. Int.* **2004**, *36*, 573.
35. Ding, J.; Lee, J. C. H.; Hall, D. G., Stereoselective Preparation of  $\beta$ -Aryl- $\beta$ -Boronyl Enoates and Their Copper-Catalyzed Enantioselective Conjugate Reduction. *Org. Lett.* **2012**, *14*, 4462.
36. Thorpe, S. B.; Calderone, J. A.; Santos, W. L., Unexpected Copper(II) Catalysis: Catalytic Amine Base Promoted  $\beta$ -Borylation of  $\alpha,\beta$ -Unsaturated Carbonyl Compounds in Water. *Org. Lett.* **2012**, *14*, 1918.
37. Peck, C. L.; Calderone, J. A.; Santos, W. L., Copper(II)-Catalyzed  $\beta$ -Borylation of Acetylenic Esters in Water. *Synthesis* **2015**, *47*, 2242.



38. Chea, H. S., H. S.; Yun, J., Ligandless Copper-Catalyzed  $\beta$ -Boration of  $\alpha$ ,  $\beta$ -Unsaturated Compounds in Aqueous Solution. *Bull. Korean Chem. Soc.* **2010**, *21*, 551.
39. Kobayashi, S.; Xu, P.; Endo, T.; Ueno, M.; Kitanosono, T., Chiral Copper(II)-Catalyzed Enantioselective Boron Conjugate Additions to  $\alpha,\beta$ -Unsaturated Carbonyl Compounds in Water. *Angew. Chem., Int. Ed.* **2012**, *51*, 12763.
40. Kitanosono, T.; Kobayashi, S., Asymmetric Boron Conjugate Additions to Enones in Water Catalyzed by Copper(0). *Asian J. Org. Chem.* **2013**, *2*, 961.
41. Kitanosono, T.; Xu, P.; Kobayashi, S., Heterogeneous and Homogeneous Chiral Cu(II) Catalysis in Water: Enantioselective Boron Conjugate Additions to Dienones and Dienoesters. *Chem. Commun.* **2013**, *49*, 8184.
42. Stavber, G.; Časar, Z., Basic  $\text{CuCO}_3$ /Ligand as a New Catalyst for 'on Water' Borylation of Michael Acceptors, Alkenes and Alkynes: Application to the Efficient Asymmetric Synthesis of  $\beta$ -Alcohol Type Sitagliptin Side Chain. *Appl. Organomet. Chem.* **2013**, *27*, 159.
43. Yao, Z.-J.; Hong, S.; Zhang, W.; Liu, M.; Deng, W., Copper-Catalyzed Regioselective Hydroboration of Terminal Alkynes in Aqueous Medium. *Tetrahedron Lett.* **2016**, *57*, 910.
44. Thorpe, S. B.; Guo, X.; Santos, W. L., Regio- and Stereoselective Copper-Catalyzed  $\beta$ -Borylation of Allenates by a Preactivated Diboron. *Chem. Commun.* **2011**, *47*, 424.
45. G. Lawson, Y.; J. Gerald Lesley, M.; C. Norman, N.; R. Rice, C.; B. Marder, T., Platinum-Catalyzed 1,4-Diboration of  $\alpha,\beta$ -Unsaturated Ketones. *Chem. Commun.* **1997**, 2051.
46. Stavber, G.; Časar, Z., Cu(II)- and Cu(0)-Catalyzed Mono Borylation of Unsaturated Hydrocarbons with  $\text{B}_2\text{pin}_2$ : Entering into the Water. *ChemCatChem* **2014**, *6*, 2162.

47. Gulyás, H.; Bonet, A.; Pubill-Ulldemolins, C.; Solé, C.; Cid, J.; Fernández, E., Nucleophilic Boron Strikes Back. *Pure Appl. Chem.* **2012**, *84*, 2219.
48. Calow, A. D. J.; Whiting, A., Catalytic Methodologies for the  $\beta$ -Boration of Conjugated Electron Deficient Alkenes. *Org. Biomol. Chem.* **2012**, *10*, 5485.
49. Schiffner, J. A.; Müther, K.; Oestreich, M., Enantioselective Conjugate Borylation. *Angew. Chem., Int. Ed.* **2010**, *49*, 1194.
50. Mantilli, L.; Mazet, C., Copper-Catalyzed Asymmetric  $\beta$ -Boration of  $\alpha,\beta$ -Unsaturated Carbonyl Derivatives. *ChemCatChem* **2010**, *2*, 501.
51. Lillo, V.; Bonet, A.; Fernandez, E., Asymmetric Induction on  $\alpha$ -Boration of  $\alpha,\beta$ -Unsaturated Compounds: An Inexpensive Approach. *Dalton Trans.* **2009**, 2899.
52. Pietsch, S.; Neeve, E. C.; Apperley, D. C.; Bertermann, R.; Mo, F.; Qiu, D.; Cheung, M. S.; Dang, L.; Wang, J.; Radius, U.; Lin, Z.; Kleeberg, C.; Marder, T. B., Synthesis, Structure, and Reactivity of Anionic  $sp^2$ - $sp^3$  Diboron Compounds: Readily Accessible Boryl Nucleophiles. *Chem. - Eur. J.* **2015**, *21*, 7082.
53. Dewhurst, R. D.; Neeve, E. C.; Braunschweig, H.; Marder, T. B.,  $sp^2$ - $sp^3$  Diboranes: Astounding Structural Variability and Mild Sources of Nucleophilic Boron for Organic Synthesis. *Chem. Commun.* **2015**, *51*, 9594.
54. Gao, M.; Thorpe, S. B.; Kleeberg, C.; Slebodnick, C.; Marder, T. B.; Santos, W. L., Structure and Reactivity of a Preactivated  $sp^2$ - $sp^3$  Diboron Reagent: Catalytic Regioselective Boration of  $\alpha,\beta$ -Unsaturated Conjugated Compounds. *J. Org. Chem.* **2011**, *76*, 3997.
55. Gao, M.; Thorpe, S. B.; Santos, W. L.,  $sp^2$ - $sp^3$  Hybridized Mixed Diboron: Synthesis,

- Characterization, and Copper-Catalyzed  $\beta$ -Boration of  $\alpha,\beta$ -Unsaturated Conjugated Compounds. *Org. Lett.* **2009**, *11*, 3478.
56. Mun, S.; Lee, J.-E.; Yun, J., Copper-Catalyzed  $\beta$ -Boration of  $\alpha,\beta$ -Unsaturated Carbonyl Compounds: Rate Acceleration by Alcohol Additives. *Org. Lett.* **2006**, *8*, 4887.
57. Linstadt, R. T. H.; Peterson, C. A.; Lippincott, D. J.; Jette, C. I.; Lipshutz, B. H., Stereoselective Silylcupration of Conjugated Alkynes in Water at Room Temperature. *Angew. Chem., Int. Ed.* **2014**, *53*, 4159.
58. Lipshutz, B. H.; Ghorai, S., Transitioning Organic Synthesis from Organic Solvents to Water. What's Your E Factor? *Green Chem.* **2014**, *16*, 3660.
59. Chea, H.; Sim, H.-S.; Yun, J., Copper-Catalyzed Conjugate Addition of Diboron Reagents to  $\alpha,\beta$ -Unsaturated Amides: Highly Reactive Copper-1,2-Bis(diphenylphosphino)benzene Catalyst System. *Adv. Synth. Catal.* **2009**, *351*, 855.
60. Wu, H.; Radomkit, S.; O'Brien, J. M.; Hoveyda, A. H., Metal-Free Catalytic Enantioselective C–B Bond Formation: (Pinacolato)boron Conjugate Additions to  $\alpha,\beta$ -Unsaturated Ketones, Esters, Weinreb Amides, and Aldehydes Promoted by Chiral N-Heterocyclic Carbenes. *J. Am. Chem. Soc.* **2012**, *134*, 8277.
61. Molander, G. A.; Wisniewski, S. R.; Hosseini-Sarvari, M., Synthesis and Suzuki–Miyaura Cross-Coupling of Enantioenriched Secondary Potassium  $\beta$ -Trifluoroboratoamides: Catalytic, Asymmetric Conjugate Addition of Bisboronic Acid and Tetrakis(dimethylamino)diboron to  $\alpha,\beta$ -Unsaturated Carbonyl Compounds. *Adv. Synth. Catal.* **2013**, *355*, 3037.
62. Calderone, J. A.; Santos, W. L., Copper(II)-Catalyzed Silylation of Activated Alkynes in

Water: Diastereodivergent Access to E- or Z- $\beta$ -Silyl- $\alpha,\beta$ -Unsaturated Carbonyl and Carboxyl Compounds. *Angew. Chem., Int. Ed.* **2014**, 53 (16), 4154.

63. Hirano, K.; Yorimitsu, H.; Oshima, K., Nickel-Catalyzed  $\beta$ -Boration of  $\alpha,\beta$ -Unsaturated Esters and Amides with Bis(pinacolato)diboron. *Org. Lett.* **2007**, 9, 5031.

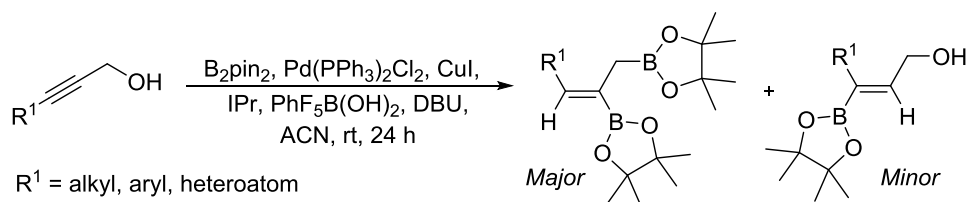
## **Chapter 4. Borylation of propargylic alcohols using a bimetallic catalytic system: an unexpected diboration route to vinyl, allyl diboronate esters**

### **4.1 Contributions**

All of the work described in this chapter, including substrate synthesis, optimization, borylation reactions, purification procedures, characterization, and mechanistic studies were performed by the author. The manuscript was written exclusively by the author in preparation for publication in a peer reviewed journal. The final manuscript was corrected by Dr. Webster L. Santos.

## 4.2 Abstract

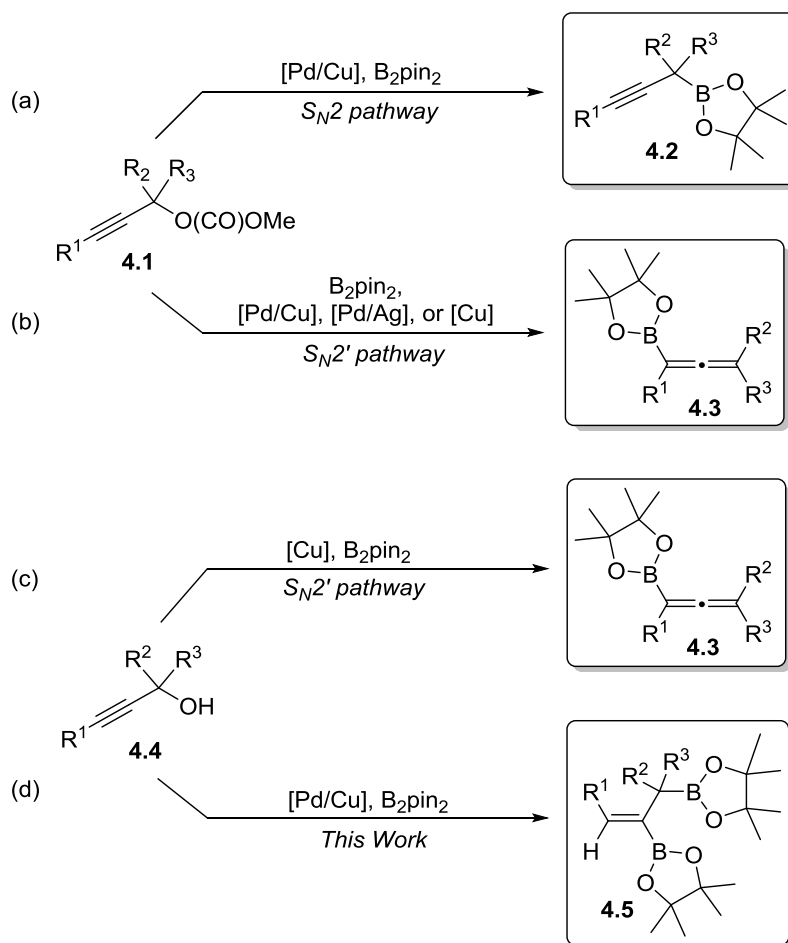
A novel protocol for the borylation of unactivated propargylic alcohol species has been achieved using a bimetallic palladium and copper catalytic system. The corresponding vinyl, allyl diboronate esters are preferentially formed over the *syn* addition product in up to a 99:1 ratio. This borylation protocol is compatible with a range of functional groups. Furthermore, mechanistic studies with potential reaction intermediates were conducted to help elucidate a plausible catalytic cycle.



### 4.3 Introduction

Highly decorated organoboron compounds are of great value in modern organic synthesis as intermediates in cross-coupling reactions as well as transformations to other functional groups.<sup>1-8</sup> Numerous transition metal-catalyzed borylation protocols utilizing activated propargylic substrates have been reported, which are useful precursors to access high value  $\alpha$ - or  $\beta$ -vinyl boronic acid derivatives.<sup>9-12</sup> Despite this, only a limited number of these methods employ propargylic alcohol protected substrates.<sup>13-16</sup> Recently, the seminal work of Zhao *et al.* demonstrated that a carbonate leaving group can alternately afford propargylic boronate ester **4.2** or allenyl boronate ester **4.3** (Figure 4.1a-b).<sup>17</sup> Depending on the bimetallic conditions, a formal  $S_N2$  or  $S_N2'$  pathway proceeds to efficiently afford an allenyl or propargylic boronic acid derivative. Unfortunately, other leaving groups such as phosphonate and acetate were shown to be less effective, therefore limiting the application of this method. Although the acetate leaving group provided marginal yields, it was required in combination with a silver co-catalyst for the borylation of terminal alkynes in order to prevent Glaser coupling.<sup>18-20</sup> Alternatively, Ito *et al.* reported a protocol for the formation of allenyl boronate esters utilizing a Cu(I)-catalyzed phosphine complex (Scheme 4.1b).<sup>21</sup>

Comparatively, Mao *et al.* developed a method for the synthesis of allenyl boronates using unprotected propargylic alcohol species (Figure 4.1c).<sup>22</sup> Although problematic, activation of the  $sp^3$ -hybridized C-O bond of the propargylic alcohol was successfully achieved by the addition of  $Ti(O^iPr)_4$ . Inspired by this work, we report the unanticipated formation of vinyl, allyl diboronate esters from propargylic alcohols without a preactivated leaving group. To

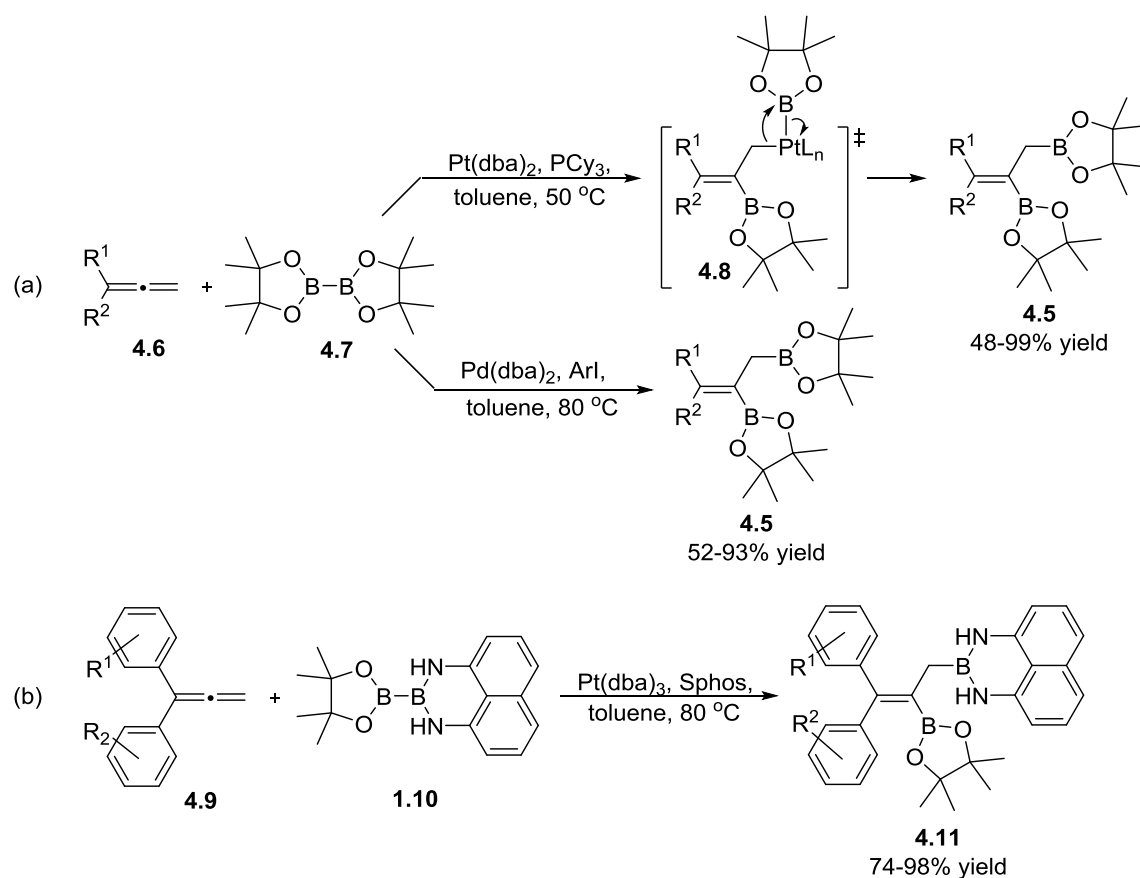


**Scheme 4.1.** Borylation of propargylic carbonates and propargylic alcohols.

the best of our knowledge, the formation of these vinyl, allyl diboronate ester products have previously only been achieved using a Pt- or Pd-catalyzed diboration of allenes (Scheme 4.2).<sup>23-</sup>

<sup>25</sup> The use of both symmetrical and unsymmetrical diboron reagents was effective when employing these approaches. Compared to allenes, the use of propargylic alcohol species to synthesize these diborated products is preferred as they are more commercially available as well as easier to handle and purify. While other organoboron reagents ( $PhMe_2Si-B(OR)_2$  and  $Me_3Sn-B(NR_2)_2$ ) have also been used to synthesize similar products,<sup>26-30</sup> the use of propargylic alcohol species to synthesize vinyl, allyl diboronate esters is unprecedented.





**Scheme 4.2.** Synthesis of vinyl, allyl diboronates using (a) symmetrical and (b) unsymmetrical diboron reagents.

#### 4.4 Optimization of reaction conditions for the diboration of 2-butynol

Preliminary studies were initiated with commercially available 2-butynol (**4.4a**) and a bimetallic catalytic system. To our surprise, initial conditions employing  $\text{Pd}(\text{PPh}_3)_4$ ,  $\text{CuI}$ ,  $\text{B}_2\text{pin}_2$  (**4.7**), and pyridine in THF at 50 °C afforded vinyl, allyl diboronate product **4.5a** in a 4% yield (Table 4.1, entry 1). Under these conditions, the *syn* addition product **4.12a** was observed as a minor byproduct. The expected propargyl or allenyl boronate products were not detected. The stereochemistry and conformation of each product was readily confirmed by nuclear Overhauser effect (nOe) experiments and  $^1\text{H}$  NMR experiments. While the strength of the base was not a

factor in the reaction outcome, the more sterically hindered base, DBU, was found to favor the vinyl, allyl diboronate product **4.5a** and increased the yield to 15% (entries 2–5).

We postulated that activation of the hydroxyl group was crucial to effectively generating

**Table 4.1.** Base and additive screenings for the borylation of propargylic alcohols.<sup>a</sup>

Entry	Base	Additive (x mol%)	Ratio <b>4.5a</b> : <b>4.12a</b> <sup>b</sup>	Yield <b>4.5a</b> (%) <sup>c</sup>
1	Pyridine	–	85:15	(4)
2	TEA	–	>1:99	(>1)
3	DBU	–	75:25	(15)
4	NaOH	–	18:82	(7)
5	NaO <sup>t</sup> Bu	–	28:72	(8)
6	DBU	PhF <sub>5</sub> B(OH) <sub>2</sub> (100)	65:35	(7)
7	DBU	PhF <sub>5</sub> B(OH) <sub>2</sub> (20)	89:11	(14)
8	DBU	PhF <sub>5</sub> B(OH) <sub>2</sub> (10)	86:14	20
<b>9</b>	<b>DBU</b>	<b>PhF<sub>5</sub>B(OH)<sub>2</sub> (5)</b>	<b>90:10</b>	<b>22</b>
10	DBU	Ti(O <sup>i</sup> Pr) <sub>4</sub> (5)	88:12	11
11	DBU	FeCl <sub>3</sub> (5)	90:10	17
12	DBU	AlCl <sub>3</sub> (5)	76:24	7
13	DBU	TMSCl (5)	71:29	14

<sup>a</sup> Reaction conditions: In an Ar purged flask, Pd(PPh<sub>3</sub>)<sub>3</sub> (0.024 mmol) and CuI (0.024 mmol) were premixed in THF (1.5 mL) for 30 min. **4.4a** (0.484 mmol) and base (0.484 mmol) were added before cannulating in a solution of B<sub>2</sub>pin<sub>2</sub> (0.968 mmol) and additive (0.024 mmol) in THF (0.5 mL). <sup>b</sup> Ratios determined by GC analysis of crude mixture and stereochemistry was confirmed by nOe experiments. <sup>c</sup> GC yields determined with benzophenone as an internal standard. Isolated yields shown in parenthesis.

a leaving group *in-situ*; therefore, Lewis acids and transition metals that have been shown to be successful in Friedel–Crafts reactions of allylic alcohols were explored in future reactions (entries 6–13).<sup>22, 31–33</sup> The formation of **4.5a** was shown to be more efficient when using catalytic amounts rather than stoichiometric amounts of the additive, with 5 mol% additive giving the best results (entries 6–9). Unfortunately, pentafluorophenylboronic acid was the only additive that improved the yield (entries 9–13).

Bidentate and monodentate ligands with a range of natural bite angles ( $\beta_n$ ) and cone angles ( $\theta$ ) were also surveyed in an attempt to increase the yield while maintaining excellent selectivity (Table 4.2). Notably, the larger natural bite angle of Xantphos (**4.13**,  $\beta_n = 107^\circ$ ) was preferred to dppp (**4.17**,  $\beta_n = 91^\circ$ ) (entries 1–5).<sup>34–35</sup> With the exception of (*R,R*)-QuinoxP\* (**4.16**), all bidentate phosphine ligands favored the formation of **4.5a** in greater than a 90:10 ratio. When employing bidentate nitrogen-containing ligands, an increase in the yield was observed in some instances, including those in which bpy (**4.18**) and 4,4'-di-*tert*-butyl-2,2'-bpy (**4.19**) were used (entries 6–10). Unfortunately, low yields and poor selectivities were observed when employing bidentate ketone **4.23** and tridentate ligand **4.24** (entries 11, 12).

The reactivity of the metal center and product selectivity can be altered by modifying the electronic properties and steric bulk of the monodentate phosphine ligands.<sup>36–39</sup> Although a moderate selectivity was maintained with all of the monodentate phosphine ligands, the yields were not improved regardless of the cone angle (entries 13–18). *N*-heterocyclic carbenes (NHCs) have been known to form strong, stabilizing bonds with metal catalysts (entries 19–21).<sup>40–44</sup> Some of the most commonly used NHCs in borylation reactions and cross-coupling reactions were tested with our reaction conditions. Unfortunately, ICy (**4.31**) and IMes (**4.32**)

decreased the yield of the vinyl and allyl boronate ester **4.5a** and afforded poor selectivities.<sup>45-48</sup>

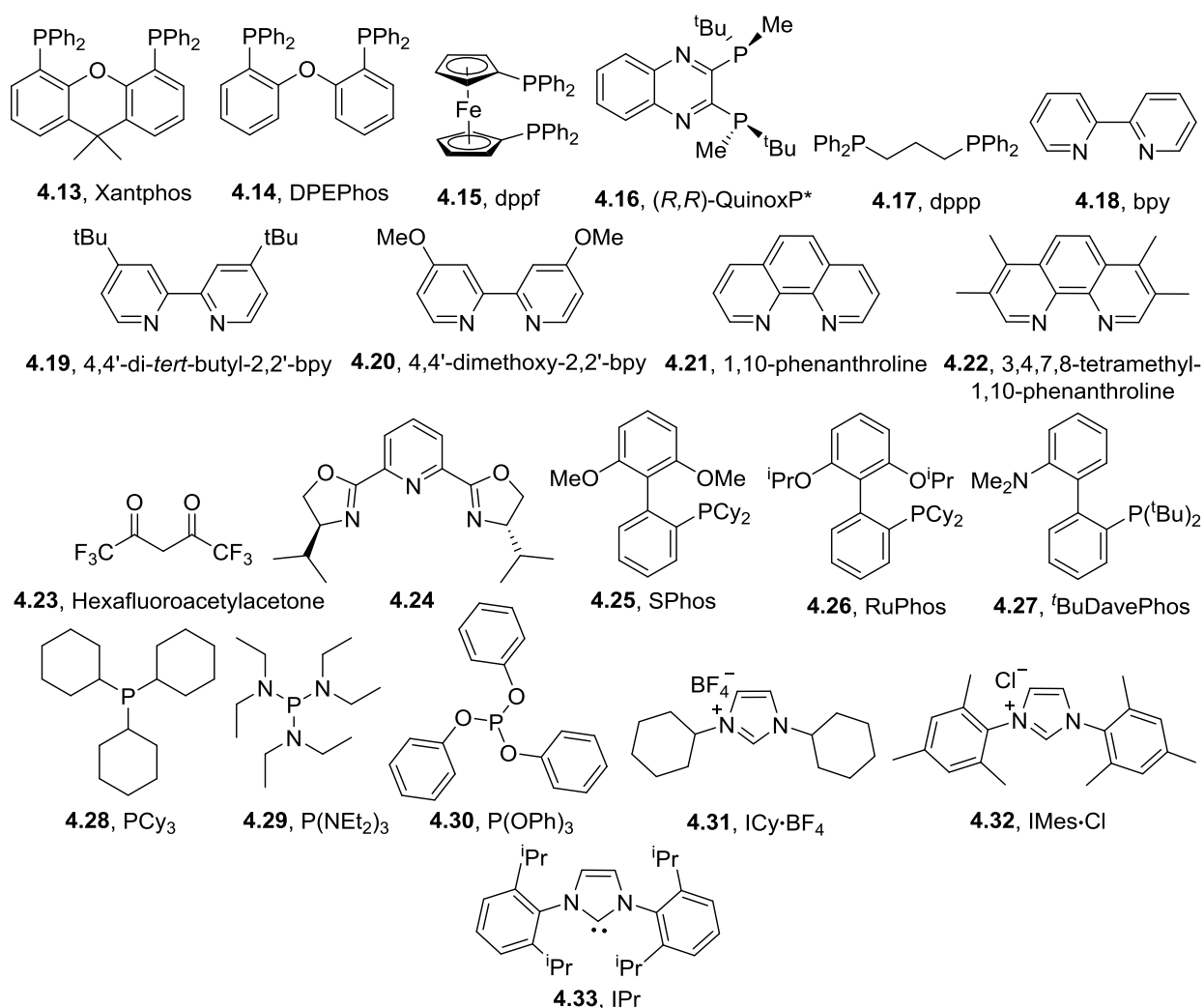
Comparatively, the bulkier NHC ligand, IPr (**4.33**) gave the best yield of all ligands and a 98:2 product ratio.

**Table 4.2.** Screening of ligands for the borylation of propargylic alcohols.<sup>a</sup>

Entry	Ligand	Ratio <b>4.5a</b> : <b>4.12a</b> <sup>b</sup>	Yield <b>4.5a</b> (%) <sup>c</sup>
1	Xantphos ( <b>4.13</b> )	100:0	29
2	DPEPhos ( <b>4.14</b> )	100:0	7
3	dppf ( <b>4.15</b> )	>99:1	15
4	( <i>R,R</i> )-QuinoxP* ( <b>4.16</b> )	61:39	2
5	dppp ( <b>4.17</b> )	100:0	2
6	bpy ( <b>4.18</b> )	>99:1	32
7	4,4'-di- <i>tert</i> -butyl-2,2'-bpy ( <b>4.19</b> )	94:6	32
8	4,4'-dimethoxy-2,2'-bpy ( <b>4.20</b> )	90:10	21
9	1,10-phenanthroline ( <b>4.21</b> )	70:30	3
10	3,4,7,8-tetramethyl-1,10-phenanthroline ( <b>4.22</b> )	84:16	7
11	Hexafluoroacetylacetone ( <b>4.23</b> )	73:27	11
12	<b>4.24</b>	61:39	2
13	SPhos ( <b>4.25</b> )	100:0	4
14	RuPhos ( <b>4.26</b> )	>99:1	12
15	<sup>t</sup> BuDavePhos ( <b>4.27</b> )	85:15	19
16	PCy <sub>3</sub> ( <b>4.28</b> )	80:20	16
17	P(NEt <sub>2</sub> ) <sub>3</sub> ( <b>4.29</b> )	94:6	21
18	P(OPh) <sub>3</sub> ( <b>4.30</b> )	97:3	10
19	ICy·BF <sub>4</sub> ( <b>4.31</b> )	64:36	2 <sup>d</sup>

Entry	Ligand	Ratio <b>4.5a</b> : <b>4.12a</b> <sup>b</sup>	Yield <b>4.5a</b> (%) <sup>c</sup>
20	IMes·Cl ( <b>4.32</b> )	83:17	9 <sup>d</sup>
<b>21</b>	<b>IPr</b> ( <b>4.33</b> )	<b>98:2</b>	<b>37</b>

<sup>a</sup> Reaction conditions: In an Ar purged flask, Pd(PPh<sub>3</sub>)<sub>4</sub> (0.024 mmol), CuI (0.024 mmol), and ligand (0.053 mmol) were premixed in THF (1.5 mL) for 30 min. **4.4a** (0.484 mmol) and DBU (0.484 mmol) were added before cannulating in a solution of B<sub>2</sub>pin<sub>2</sub> (0.968 mmol) and PhF<sub>5</sub>B(OH)<sub>2</sub> (0.024 mmol) in THF (0.5 mL). <sup>b</sup> Ratios determined by GC analysis of crude mixture and stereochemistry was confirmed by nOe experiments. <sup>c</sup> GC yields determined with benzophenone as an internal standard. <sup>d</sup> Ligand deprotonated with NaO<sup>t</sup>Bu (1 equiv.).



**Figure 4.1.** Structures of ligands used in Table 4.2.

In addition to using IPr, the individual ligands on the catalysts can also alter the reactivity of the metal center (Table 4.3). The majority of the palladium catalysts were ineffective, except for the air-stable palladium(II) catalyst, Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>, which gave identical results to the air- and moisture-sensitive palladium(0) catalyst, Pd(PPh<sub>3</sub>)<sub>4</sub> (entries 1–7). On the other hand, a clear trend was observed in regards to the copper catalysts that were tested (entries 2, 8–10). Hard–soft

**Table 4.3.** Screening catalysts for the borylation of propargylic alcohols.<sup>a</sup>

Reaction scheme showing the borylation of propargylic alcohol **4.4a** (1 equiv) using a palladium catalyst (5 mol%), copper catalyst (5 mol%), IPr (11 mol%), B<sub>2</sub>pin<sub>2</sub> (2 equiv), DBU (1 equiv), PhF<sub>5</sub>B(OH)<sub>2</sub> (5 mol%), and THF at 50 °C for 24 h. The products are a mixture of **4.5a** and **4.12a**.

Entry	Palladium Catalyst	Copper Catalyst	Ratio <b>4.5a</b> : <b>4.12a</b> <sup>b</sup>	Yield <b>4.5a</b> (%) <sup>c</sup>
1	Pd(PPh <sub>3</sub> ) <sub>4</sub>	CuI	98:2	37
2	<b>Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub></b>	<b>CuI</b>	<b>98:2</b>	<b>37</b>
3	Pd(OAc) <sub>2</sub>	CuI	70:30	<1
4	Pd(TFA) <sub>2</sub>	CuI	30:70	<1
5	Pd(ACN) <sub>2</sub> (BF <sub>4</sub> ) <sub>2</sub>	CuI	100:0	<1
6	Pd(dppf) <sub>2</sub> Cl <sub>2</sub>	CuI	97:3	6
7	Pd <sub>2</sub> (dba) <sub>3</sub>	CuI	68:31	<1
8	Pd(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub>	CuCl	100:0	<1
9	Pd(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub>	CuBr	100:0	26
10	Pd(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub>	CuCN	100:0	32
11	Pd(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub>	Cu(Oac) <sub>2</sub>	100:0	<1
12	Pd(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub>	Cu(acac) <sub>2</sub>	100:0	<1

<sup>a</sup> Reaction conditions: In an Ar purged flask, palladium catalyst (0.024 mmol), copper catalyst (0.024 mmol), and IPr (0.053 mmol) were premixed in THF (1.5 mL) for 30 min. **4.4a** (0.484 mmol) and DBU (0.484 mmol) were added before cannulating in a solution of B<sub>2</sub>pin<sub>2</sub> (0.968 mmol) and PhF<sub>5</sub>B(OH)<sub>2</sub> (0.024 mmol) in THF (0.5 mL). <sup>b</sup> Ratios determined by GC analysis of crude mixture and stereochemistry was confirmed by nOe experiments. <sup>c</sup> GC yields determined with benzophenone as an internal standard.

acid–base theory dictates that soft metal acids, such as copper(I), react favorably with soft bases.<sup>49-50</sup> In accordance with this, the softer halides, I<sup>-</sup> and CN<sup>-</sup>, afforded better yields. Catalyst solubility and a counterion effect may also play a role, considering the most soluble copper catalyst gave the best results and the least soluble catalyst was ineffective. Moreover, all copper(II) catalysts were unsuccessful in producing the desired product, indicating that copper(I) is likely the active catalyst.

Once all of the reagents were screened, we turned our efforts to examining the reaction solvent and temperature (Table 4.4). It was established that polar aprotic solvent such as ACN and DCM were more efficient than nonpolar solvents (entries 1–11). Unfortunately, a 1:1 mixture of the best polar aprotic solvents negatively affected the selectivity and yield (entry 12). Polar protic solvents were avoided as they would hinder the formation of the leaving group *in-situ*. Conducting the reaction at room temperature compared to heating was shown to be crucial

**Table 4.4.** Screening solvents and temperatures for the borylation of propargylic alcohols.<sup>a</sup>

Entry	Solvent	Temperature (°C)	Ratio <b>4.5a</b> : <b>4.12a</b> <sup>b</sup>	Yield <b>4.5a</b> (%) <sup>c</sup>
1	THF	50	98:2	37
2	DCM	50	94:6	44
3	DMF	50	71:29	11
4	ACN	50	93:7	49
5	DMA	50	86:14	19
6	1:1 DCM:ACN	50	83:17	21
7	Toluene	50	98:2	16

Entry	Solvent	Temperature (°C)	Ratio <b>4.5a:4.12a</b> <sup>b</sup>	Yield <b>4.5a</b> (%) <sup>c</sup>
8	1,4-dioxane	50	67:36	14
9	Benzene	50	71:29	17
10	MTBE	50	99:1	<1
11	Cyclohexane	50	31:68	15
<b>12</b>	<b>ACN</b>	<b>rt</b>	<b>96:4</b>	<b>68 (36)</b>
13	ACN	reflux	89:11	53
14	ACN	rt	n.r.	n.r. <sup>d</sup>
15	ACN	rt	0:100	0 <sup>e</sup>
16	ACN	rt	n.r.	n.r. <sup>f</sup>
17	ACN	rt	n.r.	n.r. <sup>g</sup>

<sup>a</sup> Reaction conditions: In an Ar purged flask, Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (0.024 mmol), CuI (0.024 mmol), and IPr (0.053 mmol) were premixed in solvent (1.5 mL) for 30 min. **4.4a** (0.484 mmol) and DBU (0.484 mmol) were added before cannulating in a solution of B<sub>2</sub>pin<sub>2</sub> (0.968 mmol) and PhF<sub>5</sub>B(OH)<sub>2</sub> (0.024 mmol) in solvent (0.5 mL). <sup>b</sup> Ratios determined by GC analysis of crude mixture and stereochemistry was confirmed by nOe experiments. <sup>c</sup> GC yields determined with benzophenone as an internal standard. Isolated yields shown in parenthesis. <sup>d</sup> pinB–Bdan used as the diboron reagent. <sup>e</sup> Reaction run in the absence of palladium. <sup>f</sup> Reaction run in the absence of copper. <sup>g</sup> Reaction run in the absence of DBU. n.r. = no reaction.

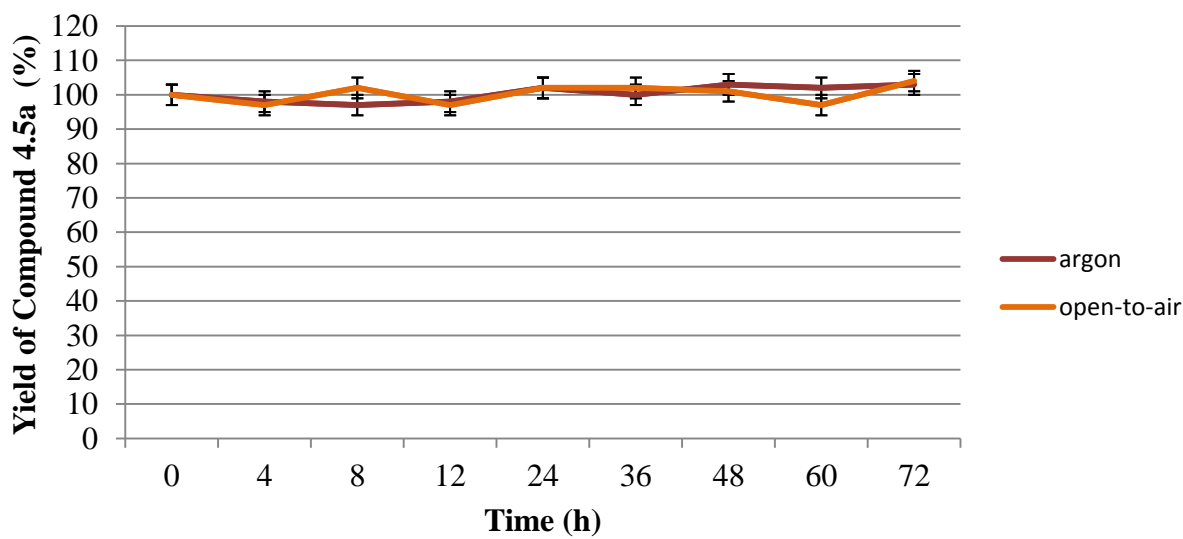
in the formation of the diborated product **4.5a** (entries 12, 13). While B<sub>2</sub>pin<sub>2</sub> (**4.7**) was shown to be reactive in the borylation of 2-butyne (**4.4a**), the unsymmetrical diboron reagent pinB–Bdan (**4.10**) was unreactive (entry 14). Optimal reaction conditions afforded the vinyl, allyl diboronate product **4.5a** in a 68% yield after 24 hours at room temperature; unfortunately, only a 36% isolated yield was obtained. As expected, control reactions indicated the importance of the catalysts and base (entries 15–17).

## 4.5 Stability studies



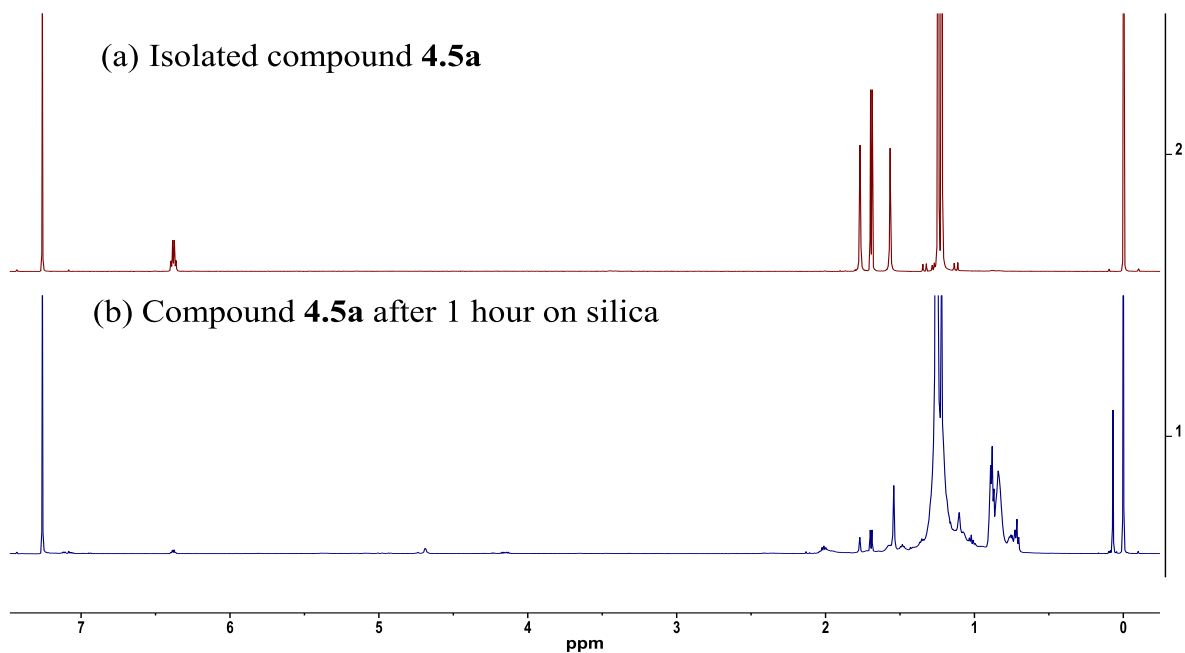
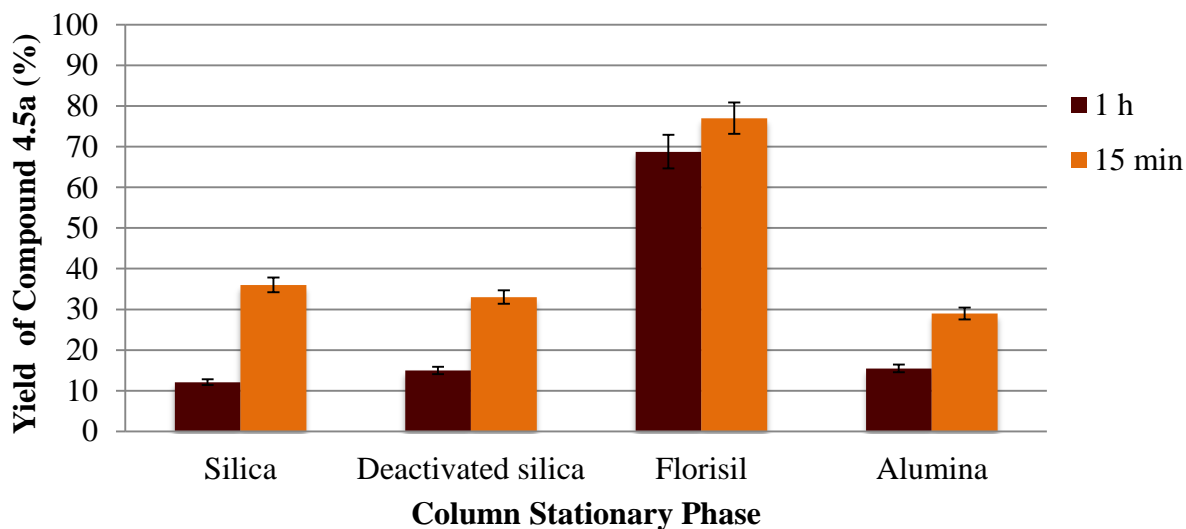
In an effort to understand why the isolated yields were significantly lower than the GC yields, two stability studies were conducted. Over the period of 3 days, compound **4.5a** was analyzed by  $^1\text{H}$  NMR to determine potential decomposition (Figure 4.1). Results indicated that regardless of whether the compound was stored under argon or open-to-air, no decomposition was observed. Alternatively, we looked into the possibility of the product decomposing during purification (Figure 4.2). When isolated compound **4.5a** was combined with silica for 1 hour, the product had decomposed significantly (Figure 4.3). Other stationary

**Figure 4.2.** Stability of **4.5a** in solution over time.



phases were explored as alternatives. Unfortunately, deactivated silica and alumina provided similar results. Despite minimal product decomposition being observed when using florisil, we were unable to use it for purification. The vinyl and allyl borate products are not UV active and must be observed using  $\text{KMnO}_4$  stain; unfortunately, florisil TLC plates don't stain effectively, making it difficult to find an ideal solvent system for purification. Regardless of this, it was noticed that purifying the product in less than 15 minutes was crucial to limiting decomposition.

**Figure 4.3.** Decomposition of **4.5a** on column stationary phases.

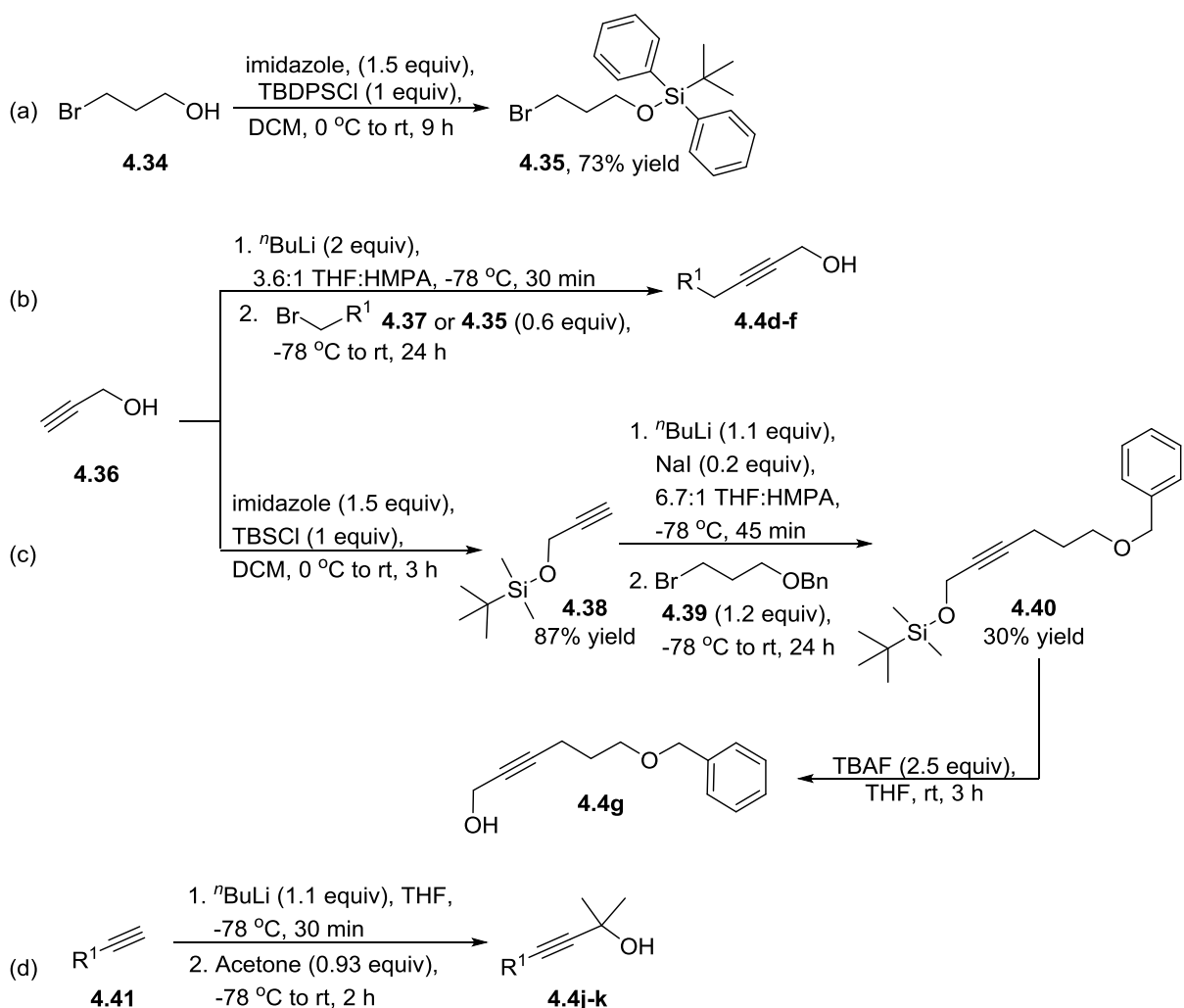


**Figure 4.4.** <sup>1</sup>H NMR illustrating the decomposition of **4.5a** on silica.

#### 4.6 Preparation of propargylic alcohols

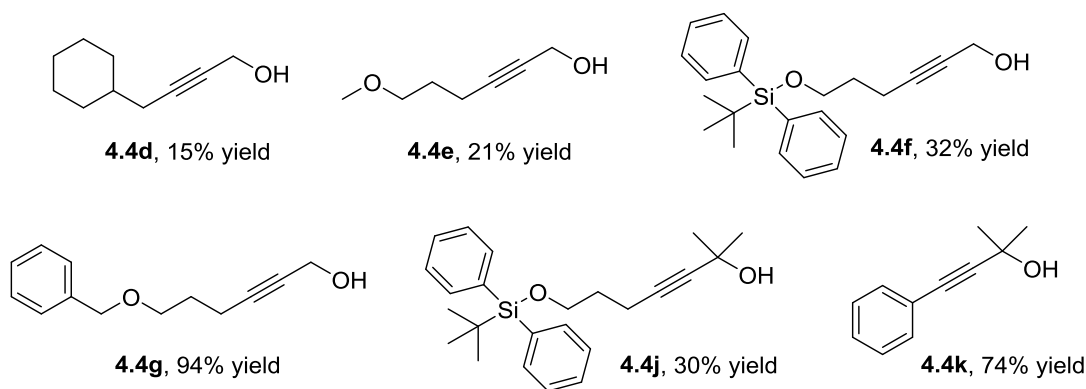
Only propargylic alcohols bearing alkyl or aryl substituents were commercially available; therefore, the remaining propargylic alcohols were synthesized according to multiple procedures

(Scheme 4.3). While the majority of the propargylic bromide intermediates utilized in the synthesis of propargylic alcohols **4.4d-f** were commercially available, 3-bromo-1-propanol had to be protected using imidazole and *tert*-butyl(chloro)diphenylsilane to synthesize compound **4.35** (Scheme 4.3a).<sup>51</sup> Formation of the organolithium species from propargylic alcohol **4.36** and butyllithium followed by nucleophilic substitution with the propargylic bromide intermediates yielded **4.4d-j** in low yields due to formation of the disubstituted product (Scheme 4.3b).<sup>52</sup> Unfortunately, the benzyl protected ether **4.4g** was unable to be synthesized



**Scheme 4.3.** Methods to synthesize propargylic alcohols.

following this method as the disubstituted product was exclusively formed, even when carefully controlling the equivalence of the bromide substituent. Therefore, **4.36** was protected as its *tert*-butyldimethylsilyl ether before performing this reaction to synthesize **4.40**. Deprotection of intermediate **4.40** with TBAF readily formed propargylic alcohol **4.4g** in a 94% yield (Scheme 4.3c). Finally, addition of *n*-butyllithium and acetone to terminal alkyne **4.41** afforded the desired tertiary propargylic alcohol species **4.4j-k** (Scheme 4.3d). Figure 4.4 illustrates the propargylic alcohol species that were synthesized.

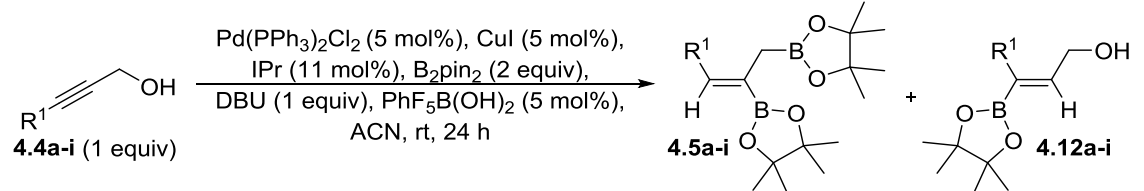


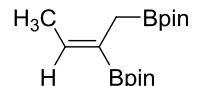
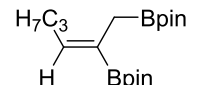
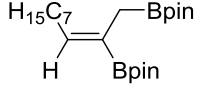
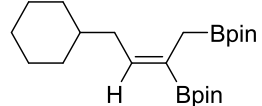
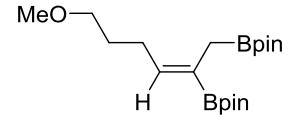
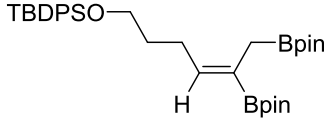
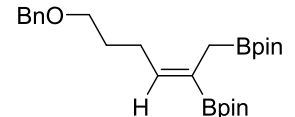
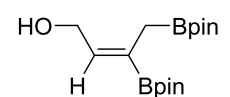
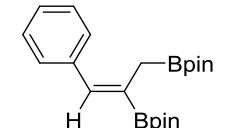
**Figure 4.5.** Structures of propargylic alcohols synthesized.

#### 4.7 Substrate scope for the diboration of propargylic alcohols

With the optimal conditions determined (Table 4.6, entry 12) and substrates synthesized, we applied these borylation conditions to unreactive propargylic alcohol species to investigate the scope and limitations of the reaction. As shown in Table 4.5, commercially available aliphatic propargylic alcohols species containing methyl (**4.4a**) and propyl (**4.4b**) substituents were efficiently borylated in good yields with excellent selectivities (entries 1, 2). The longer heptyl (**4.4c**) substituent resulted in a slight decreased yield (41% GC yield, entry 3). Unfortunately, only a 29% yield was observed with cyclohexylbut-2-yn-1-ol (**4.4d**) along with a

**Table 4.5.** Diboration of propargylic alcohols with B<sub>2</sub>pin<sub>2</sub>.<sup>a</sup>



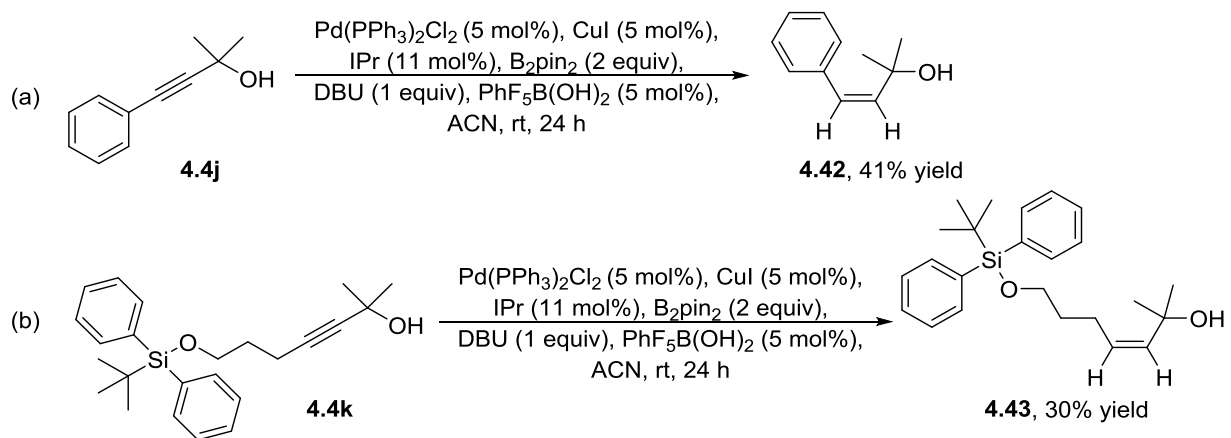
Entry	Major Product	4.5	Ratio 4.5:4.12 <sup>b</sup>	Yield 4.5 (%) <sup>c,d</sup>
1		<b>4.5a</b>	96:4	68 (36)
2		<b>4.5b</b>	94:6	76 (19)
3		<b>4.5c</b>	94:6	41 (35)
4		<b>4.5d</b>	87:13	29 (14)
5		<b>4.5e</b>	91:9	28 (14)
6		<b>4.5f</b>	95:5	54 (28)
7		<b>4.5g</b>	90:10	59 (24)
8		<b>4.5h</b>	–	n.d. <sup>e</sup>
9		<b>4.5i</b>	99:1	11 (7)

<sup>a</sup> Reaction conditions: In an Ar purged flask, Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (0.024 mmol), CuI (0.024 mmol), and IPr (0.053 mmol) were premixed in ACN (1.5 mL) for 30 min. **4.4a-i** (0.484 mmol) and DBU (0.484 mmol) were added before cannulating in a solution of B<sub>2</sub>pin<sub>2</sub> (0.968 mmol) and PhF<sub>5</sub>B(OH)<sub>2</sub> (0.024 mmol) in ACN (0.5 mL). <sup>b</sup> Ratios determined by GC analysis of crude mixture and stereochemistry was confirmed by nOe experiments. <sup>c</sup> GC yields determined with benzophenone as an internal standard. Isolated yields shown in parenthesis. <sup>d</sup> Yields are an average of two or more experiments. <sup>e</sup> 10% GC yield of **4.5a** and 5% isolated yield. n.d. = not detected.

marginal decrease in the product ratio (entry 4). The presence of residual starting material indicates that the steric bulk of the cyclohexyl group may be inhibiting product formation. A few other negligible by-products that were detected using GC-MS could not be identified.

Furthermore, a series of ether linkers were tested to expand the scope of the reaction (entries 5–7). Although borylating the methoxy protected alcohol substrate (**4.4e**) resulted in a lower yield, the *tert*-butyldiphenylsilyl protecting group (**4.4f**) was more efficient, affording a 54% GC yield. Additionally, the propargylic alcohols bearing the benzyl ether (**4.4g**) was well tolerated, producing vinyl, allyl diboronate **4.5g** in a 59% yield.

To further explore the functional group tolerance of the reaction, but-2-yne-2,4-diol (**4.4h**) was subjected to the reaction conditions (entry 8). Instead of isolating the desired product **4.5h**, product **4.5a** was formed in a low yield. It is postulated that both hydroxyl groups become activated to generate the triborated product, which undergoes spontaneously protodeboronation. In general, aryl substituents (**4.4i**) had a negative impact on the reaction yield despite attempts to improve it, including increased reaction times and biphasic solvents (entry 9). As no additional substrates bearing substituents on the aryl ring were tested, it was uncertain whether decreased reactivity was a result of steric hindrance or an electronic effect. An additional limitation of this protocol was evident when borylating tertiary propargylic alcohol species (**4.4j, k**, Scheme 4.4). Instead of producing the vinyl and allyl boronate product, the reaction exclusively formed the *cis* reduced products **4.42** and **4.43**.



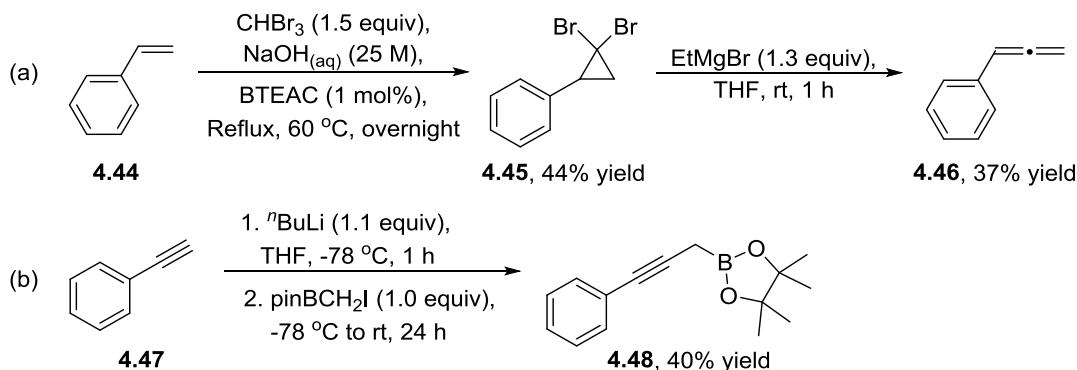
**Scheme 4.4.** Borylation of tertiary propargylic alcohols.

## 4.8 Mechanistic investigations and proposed mechanism

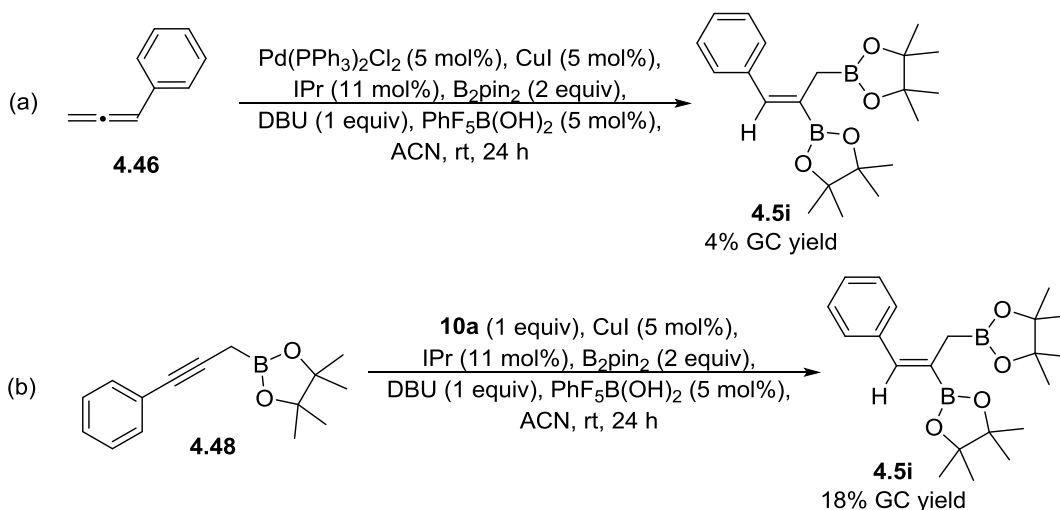
To help elucidate the mechanism, two intermediates were synthesized to determine whether the reaction proceeds through an allene intermediate that is then diborated or a propargyl boronate that undergoes *syn* addition (Scheme 4.5). (2,2'-Dibromocyclopropyl)benzene intermediate **4.45** was synthesized through an  $\alpha$ -elimination and cyclopropanation reaction of styrene with bromoform. A metal-halogen exchange reaction between **4.45** and ethylmagnesium bromide formed a Grignard complex that upon collapsing furnished phenylallene **4.46** (Scheme 4.5a). Alternatively, a substitution reaction with organolithium species and 2-(iodomethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane generated propargyl boronate **4.48** (Scheme 4.5b).

These intermediates were then borylated with the optimized bimetallic-catalyzed conditions (Scheme 4.6). Minimal product formation, <5% GC yield of **4.5i**, was detected when borylating phenylallene **4.46**. This indicated that this intermediate and pathway is not likely to occur. Taking into consideration previous literature on the borylation of carbonate protected propargylic alcohol species, it was suspected that the reaction may be proceeding through a propargyl boronate intermediate. To investigate this hypothesis, **4.48**

was subjected to the reaction conditions that afforded the diborated product **4.5i** in a 18% GC yield. On the bases of these results, a potential mechanism has been proposed (Scheme 4.7).



**Scheme 4.5.** Synthesis of compounds used in mechanistic studies.

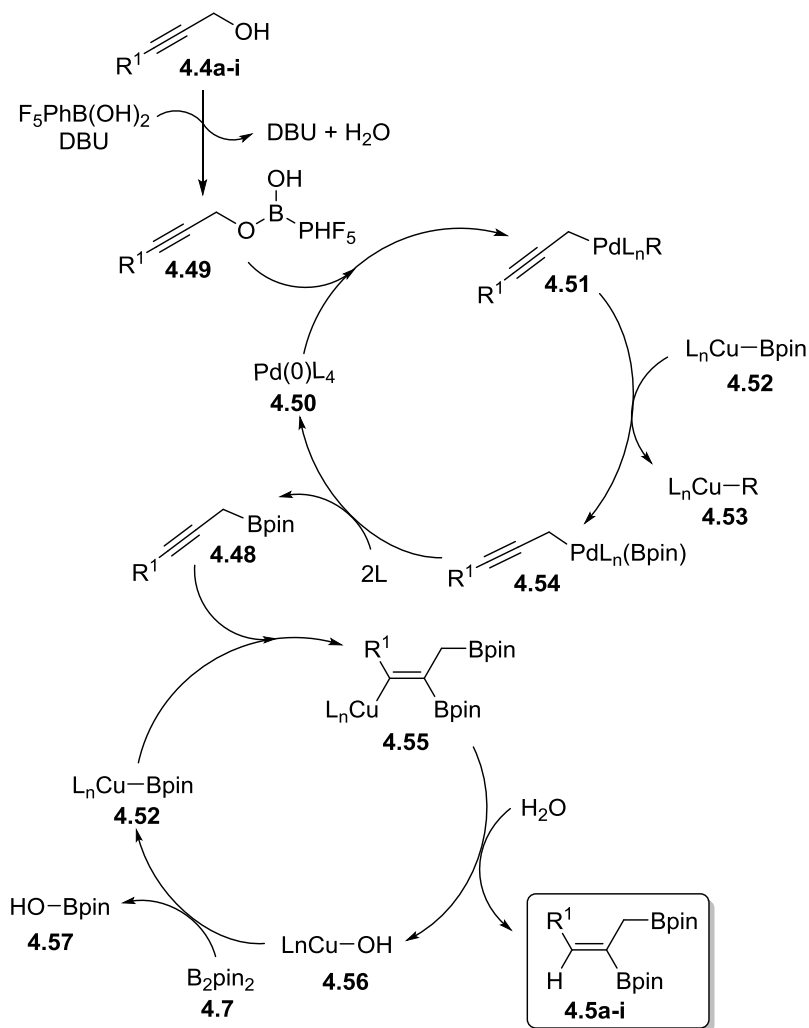


**Scheme 4.6.** Borylation reactions with proposed intermediates.

Reacting propargylic alcohols **4.4a-i** with pentafluorophenyl boronic acid additive and DBU can generate the proposed leaving group *in-situ*. Formation of Pd(II) intermediate **4.5i** can occur through the oxidative addition of the Pd(0) complex to **4.49**. Following this, transmetalation with boryl-copper species **4.52** can generate Pd-boronate intermediate **4.54**. Reductive elimination can form propargyl boronate intermediate **4.48** and regenerate the active Pd(0) catalyst. The *syn* addition of an additional boryl-copper species to the propargyl boronate



**4.48** can form the diborated copper complex **4.55**. Protonation with a proton source will produce the desired diborated products **4.5a-i**. Afterwards, the diboron reagent **4.7** can regenerate the boryl-copper species to be reused throughout the cycle.



**Scheme 4.7.** Proposed catalytic cycle for the borylation of propargylic alcohols.

## 4.9 Conclusions

In summary, a simple and mild palladium- and copper-catalyzed protocol for the diboration of propargylic alcohol species has been developed. This method is an alternative to literature protocols for synthesizing vinyl, allyl diboronates. Most notably, the reaction

furnished the diborated product as the major product in each case. The corresponding products were afforded in varying yields. Stability studies confirmed that significant product decomposition occurs during purification. Furthermore, we synthesized potential reaction intermediates to help propose a plausible mechanism.

#### 4.10 References for Chapter 4

1. Dembitsky, V. M.; Abu Ali, H.; Srebnik, M., Recent Chemistry of the Diboron Compounds. In *Adv. Organomet. Chem.* [Online] West, R.; Hill, A., Eds. Academic Press: 2004; pp 193. [https://doi.org/10.1016/S0065-3055\(03\)51005-X](https://doi.org/10.1016/S0065-3055(03)51005-X)
2. Beletskaya, I.; Moberg, C., Element–Element Additions to Unsaturated Carbon–Carbon Bonds Catalyzed by Transition Metal Complexes. *Chem. Rev.* **2006**, *106*, 2320.
3. Ding, C.-H.; Hou, X.-L., Catalytic Asymmetric Propargylation. *Chem. Rev.* **2011**, *111*, 1914.
4. Hall, D. G., *Boronic Acids: Preparation, Applications in Organic Synthesis, Medicine and Materials*. 2nd ed.; Wiley-VCH: Weinheim, Germany, 2011.
5. Lennox, A. J. J.; Lloyd-Jones, G. C., Selection of Boron Reagents for Suzuki-Miyaura Coupling. *Chem. Soc. Rev.* **2014**, *43*, 412.
6. Miyaura, N.; Suzuki, A., Palladium-Catalyzed Cross-Coupling Reactions of Organoboron Compounds. *Chem. Rev.* **1995**, *95*, 2457.
7. Neeve, E. C.; Geier, S. J.; Mkhaliid, I. A.; Westcott, S. A.; Marder, T. B., Diboron Compounds: From Structural Curiosity to Synthetic Workhorse. *Chem. Rev.* **2016**, *116*, 9091.
8. Xu, L.; Li, P., Direct Introduction of a Naphthalene-1,8-Diamino Boryl [B(dan)] Group by a Pd-Catalyzed Selective Boryl Transfer Reaction. *Chem. Commun.* **2015**, *51*, 5656.

9. Yoshida, H., Borylation of Alkynes Under Base/Coinage Metal Catalysis: Some Recent Developments. *ACS Catal.* **2016**, *6*, 1799.
10. Itoh, T.; Shimizu, Y.; Kanai, M., Ligand-Enabled, Copper-Catalyzed Regio- and Stereoselective Synthesis of Trialkylsubstituted Alkenylboronates from Unactivated Internal Alkynes. *J. Am. Chem. Soc.* **2016**, *138*, 7528.
11. Jang, H.; Zhugralin, A. R.; Lee, Y.; Hoveyda, A. H., Highly Selective Methods for Synthesis of Internal  $\alpha$ -Vinylboronates Through Efficient NHC-Cu-Catalyzed Hydroboration of Terminal Alkynes. Utility in Chemical Synthesis and Mechanistic Basis for Selectivity. *J. Am. Chem. Soc.* **2011**, *133*, 7859.
12. Semba, K.; Fujihara, T.; Terao, J.; Tsuji, Y., Copper-Catalyzed Highly Regio- and Stereoselective Directed Hydroboration of Unsymmetrical Internal Alkynes: Controlling Regioselectivity by Choice of Catalytic Species. *Chem. - Eur. J.* **2012**, *18*, 4179.
13. Moure, A. L.; Carretero, J. C., Regiocontrolled Cu(I)-Catalyzed Borylation of Propargylic-Functionalized Internal Alkynes. *J. Am. Chem. Soc.* **2012**, *134*, 7219.
14. Moure, A. L.; Mauleón, P.; Arrayás, R. G.; Carretero, J. C., Formal Regiocontrolled Hydroboration of Unbiased Internal Alkynes via Borylation/Allylic Alkylation of Terminal Alkynes. *Org. Lett.* **2013**, *15*, 2054.
15. Park, J. K.; Ondrusek, B. A.; McQuade, T., Regioselective Catalytic Hydroboration of Propargylic Species using Cu(I)-NHC Complexes. *Org. Lett.* **2012**, *14*, 4790.
16. Yuan, W.; Ma, S., CuCl-K<sub>2</sub>CO<sub>3</sub>-Catalyzed Highly Selective Borylcupration of Internal Alkynes-Ligand Effect. *Org. Biomol. Chem.* **2012**, *10*, 7266.
17. Zhao, T. S. N.; Yang, Y.; Lessing, T.; Szabó, K. J., Borylation of Propargylic Substrates by

- Bimetallic Catalysis. Synthesis of Allenyl, Propargylic, and Butadienyl Bpin Derivatives. *J. Am. Chem. Soc.* **2014**, *136*, 7563.
18. Zhu, Y.; Shi, Y., A Facile Copper(I)-Catalyzed Homocoupling of Terminal Alkynes to 1,3-Diyne with Diaziridinone Under Mild Conditions. *Org. Biomol. Chem.* **2013**, *11*, 7451.
  19. Alonso, F.; Yus, M., Heterogeneous Catalytic Homocoupling of Terminal Alkynes. *ACS Catal.* **2012**, *2*, 1441.
  20. Sindhu, K. S.; Anilkumar, G., Recent Advances and Applications of Glaser Coupling Employing Greener Protocols. *RCS Adv.* **2014**, *4*, 27867.
  21. Ito, H.; Sasaki, Y.; Sawamura, M., Copper(I)-Catalyzed Substitution of Propargylic Carbonates with Diboron: Selective Synthesis of Multisubstituted Allenylboronates. *J. Am. Chem. Soc.* **2008**, *130*, 15774.
  22. Mao, L.; Szabó, K. J.; Marder, T. B., Synthesis of Benzyl-, Allyl-, and Allenyl-Boronates via Copper-Catalyzed Borylation of Alcohols. *Org. Lett.* **2017**, *19*, 1204.
  23. Guo, X.; Nelson, A. K.; Slebodnick, C.; Santos, W. L., Regio- and Chemoselective Diboration of Allenes with Unsymmetrical Diboron: Formation of Vinyl and Allyl Boronic Acid Derivatives. *ACS Catal.* **2015**, *5* (4), 2172.
  24. Ishiyama, T.; Kitano, T.; Miyaura, N., Platinum(0)-Catalyzed Diboration of Allenes with Bis(pinacolato)diboron. *Tetrahedron Lett.* **1998**, *39*, 2357.
  25. Yang, F.-Y.; Cheng, C.-H., Unusual Diboration of Allenes Catalyzed by Palladium Complexes and Organic Iodides: A New Efficient Route to Diboronic Compounds. *J. Am. Chem. Soc.* **2001**, *123*, 761.
  26. Onozawa, S.-y.; Hatanaka, Y.; Tanaka, M., Palladium-Catalyzed Borylsilylation and Borylstannylative Dimerization of 1,2-Dienes. *Chem. Commun.* **1999**, 1863.

27. Chang, K.-J.; Rayabarapu, D. K.; Yang, F.-Y.; Cheng, C.-H., Unusual Palladium-Catalyzed Silaboration of Allenes Using Organic Iodides as Initiators: Mechanism and Application. *J. Am. Chem. Soc.* **2005**, *127*, 126.
28. Ohmura, T.; Suginome, M., Asymmetric Silaboration of Terminal Allenes Bearing  $\alpha$ -Stereogenic Centers: Stereoselection Based on Reagent Control. *Org. Lett.* **2006**, *8*, 2503.
29. Suginome, M.; Ohmura, T.; Miyake, Y.; Mitani, S.; Ito, Y.; Murakami, M., Enantioface-Selective Palladium-Catalyzed Silaboration of Allenes via Double Asymmetric Induction. *J. Am. Chem. Soc.* **2003**, *125*, 11174.
30. Suginome, M.; Ohmori, Y.; Ito, Y., Palladium-Catalyzed Regioselective Silaboration of 1,2-Dienes. *J. Organomet. Chem.* **2000**, *611*, 403.
31. Cao, Z.-C.; Luo, F.-X.; Shi, W.-J.; Shi, Z.-J., Direct Borylation of Benzyl Alcohol and Its Analogues in the Absence of Bases. *Org. Chem. Front.* **2015**, *2*, 1505.
32. McCubbin, J. A.; Hosseini, H.; Krokhin, O. V., Boronic Acid Catalyzed Friedel–Crafts Reactions of Allylic Alcohols with Electron-Rich Arenes and Heteroarenes. *J. Org. Chem.* **2010**, *75*, 959.
33. Ricardo, C. L.; Mo, X.; McCubbin, J. A.; Hall, D. G., A Surprising Substituent Effect Provides a Superior Boronic Acid Catalyst for Mild and Metal-Free Direct Friedel–Crafts Alkylations and Prenylations of Neutral Arenes. *Chem. - Eur. J.* **2015**, *21*, 4218.
34. Dierkes, P.; van Leeuwen, P., The Bite Angle Makes the Difference: A Practical Ligand Parameter for Diphosphine Ligands. *J. Chem. Soc., Dalton Trans.* **1999**, 1519.
35. Leeuwen, P. W. N. M.; Kamer, P. C. J.; Reek, J. N. H.; Dierkes, P., Ligand Bite Angle Effects in Metal-Catalyzed C–C Bond Formation. *Chem. Rev.* **2000**, *100*, 2741.

36. Bilbrey, J. A.; Kazez, A. H.; Locklin, J.; Allen, W. D., Exact Ligand Cone Angles. *J. Comput. Chem.* **2013**, *34*, 1189.
37. Müller, T. E.; Mingos, D. M. P., Determination of the Tolman Cone Angle from Crystallographic Parameters and a Statistical Analysis using the Crystallographic Data Base. *Transition Met. Chem.* **1995**, *20*, 533.
38. DeSanto, J. T.; Mosbo, J. A.; Storhoff, B. N.; Bock, P. L.; Bloss, R. E., Phosphorus-Ligand Cone Angles. Consequences of Alternate Definitions and Use of MINDO/3 Calculations. *Inorg. Chem.* **1980**, *19*, 3086.
39. Tolman, C. A., Steric Effects of Phosphorus Ligands in Organometallic Chemistry and Homogeneous Catalysis. *Chem. Rev.* **1977**, *77*, 313.
40. Alfaro, R.; Parra, A.; Alemán, J.; García Ruano, J. L.; Tortosa, M., Copper(I)-Catalyzed Formal Carboboration of Alkynes: Synthesis of Tri- and Tetrasubstituted Vinylboronates. *J. Am. Chem. Soc.* **2012**, *134*, 15165.
41. Konnick, M. M.; Guzei, I. A.; Stahl, S. S., Characterization of Peroxo and Hydroperoxo Intermediates in the Aerobic Oxidation of *N*-Heterocyclic Carbene Coordinated Palladium(0). *J. Am. Chem. Soc.* **2004**, *126*, 10212.
42. Weskamp, T.; Böhm, V. P. W.; Herrmann, W. A., Combining *N*-Heterocyclic Carbenes and Phosphines: Improved Palladium(II) Catalysts for Aryl Coupling Reactions. *J. Organomet. Chem.* **1999**, *585*, 348.
43. Wanzlick, H. W., Aspects of Nucleophilic Carbene Chemistry. *Angew. Chem., Int. Ed.* **1962**, *1*, 75.
44. Weskamp, T.; Böhm, V. P. W.; Herrmann, W. A., *N*-Heterocyclic Carbenes: State of the Art in Transition-Metal-Complex Synthesis. *J. Organomet. Chem.* **2000**, *600*, 12.

45. Zhang, C.; Huang, J.; Trudell, M. L.; Nolan, S. P., Palladium–Imidazol-2-Ylidene Complexes as Catalysts for Facile and Efficient Suzuki Cross-Coupling Reactions of Aryl Chlorides with Arylboronic Acids. *J. Org. Chem.* **1999**, *64*, 3804.
46. Lebel, H.; Janes, M. K.; Charette, A. B.; Nolan, S. P., Structure and Reactivity of “Unusual” *N*-Heterocyclic Carbene (NHC) Palladium Complexes Synthesized from Imidazolium Salts. *J. Am. Chem. Soc.* **2004**, *126*, 5046.
47. Fortman, G. C.; Nolan, S. P., *N*-Heterocyclic Carbene (NHC) Ligands and Palladium in Homogeneous Cross-Coupling Catalysis: A Perfect Union. *Chem. Soc. Rev.* **2011**, *40*, 5451.
48. Böhm, V. P. W.; Gstöttmayr, C. W. K.; Weskamp, T.; Herrmann, W. A., *N*-Heterocyclic Carbenes: Part 26. *N*-Heterocyclic Carbene Complexes of Palladium(0): Synthesis and Application in the Suzuki Cross-Coupling Reaction. *J. Organomet. Chem.* **2000**, *595*, 186.
49. Pearson, R. G., Hard and Soft Acids and Bases. *J. Am. Chem. Soc.* **1963**, *85*, 3533.
50. Pearson, R. G., Hard and Soft Acids and Bases, HSAB, Part 1: Fundamental Principles. *J. Chem. Educ.* **1968**, *45*, 581.
51. Du, Y.; Zheng, J.-F.; Wang, Z.-G.; Jiang, L.-J.; Ruan, Y.-P.; Huang, P.-Q., A Concise, Protection-Free and Divergent Approach for the Enantioselective Syntheses of Two Pheromonal Epoxide Components of the Fall Webworm Moth and Other Species. *J. Org. Chem.* **2010**, *75*, 4619.
52. Yoneda, N.; Fukata, Y.; Asano, K.; Matsubara, S., Asymmetric Synthesis of Spiroketal with Aminothiourea Catalysts. *Angew. Chem., Int. Ed.* **2015**, *54*, 15497.

## Chapter 5. Experimental

### 5.1 General methods

Unless otherwise noted, all reactions in Chapters 2–4 were conducted under a nitrogen or argon atmosphere using oven-dried glassware. All  $\beta$ -borylation reactions in Chapter 2–3 were performed open-to-air in a 1 dram vial. All  $\beta$ -borylation reactions were duplicated at least twice. Deionized (DI) water was used from the house DI water system without degassing or further purification. Nuclease-free water was purchased from Qiagen and used as received. Tetrahydrofuran, dichloromethane, acetonitrile, toluene, and *N,N*-dimethylformamide for Chapter 4 were obtained from an Innovative Technology Pure Solv-MD solvent purification system and further degassed by bubbling  $N_2$  for at least 10 minutes. Additional solvents used in Chapters 4 were purchased with sure-seal tops and used as received. Symmetrical diboron reagent bis(pinacolato)diboron ( $B_2pin_2$ ) was donated from AllylChem or purchased from Boron Molecular and used as received while unsymmetrical diboron reagent 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-naphtho[1,8-de][1,3,2]diazaborinine (pinB–Bdan) was synthesized according to the literature.<sup>1</sup> All other commercially available catalysts, substrates, and reagents were purchased and used as received. TLC analyses were performed using EMD silica gel 60 F<sub>254</sub> plates, Agela Technologies silica gel MF254 plates, or Silicycle Aluminium backed silica gel F-254 plates. Visualization of developed plates were observed under UV light (254 nm) and with permanganate or phosphomolybdic acid stains. Gas chromatography (GC) yields were determined by constructing calibration curves with benzophenone as an internal standard.



## 5.2 Instrumentation

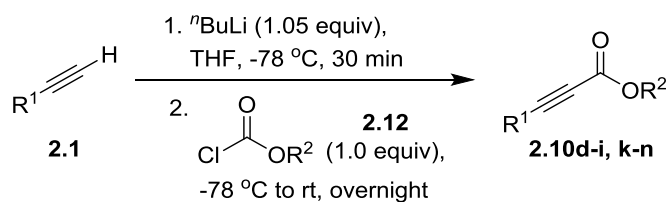
$^1\text{H}$  NMR spectra were recorded on a Bruker Avance II 500 MHz, Bruker Avance 600 MHz, Agilent MR 400 MHz, or Agilent DD2 400 MHz spectrometer. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ( $\text{CDCl}_3$ : 7.26 ppm,  $(\text{CD}_2)_3\text{CO}$ : 2.05 ppm,  $(\text{CD}_3)_2\text{SO}$ : 2.50 ppm). Data is reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, qt = quartet of triplets, tt = triplet of triplets, br = broad), coupling constants (Hz), and integration.  $^{13}\text{C}$  NMR spectra were recorded on a Bruker Avance II 126 MHz, Bruker Avance III 151 MHz, Agilent MR 101 MHz or Agilent D2 101 MHz spectrometer. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ( $\text{CDCl}_3$ : 77.16 ppm,  $(\text{CD}_3)_2\text{SO}$ : 39.52 ppm,  $(\text{CD}_3)_2\text{CO}$ : 29.84 ppm). The carbon directly attached to the boron may not be observed due to quadrupolar relaxation. In the diborated products, the primary carbon on both boron atoms may overlap and be observed as a single signal.  $^{11}\text{B}$  NMR spectra were recorded on an Agilent DD2 128 MHz or Varian Inova 128 MHz spectrometer. Chemical shifts are reported in ppm using boron trifluoride diethyl etherate as an external standard ( $\text{BF}_3\text{O}(\text{C}_2\text{H}_5)_2$ : 0 ppm). High resolution mass spectra (HRMS) were performed on an Agilent LC-ESI-TOF. Ionization techniques implemented are reported as electron spray ionization (+ESI) or mixed extraction ion chromatography (+mixed EIC), a mixture of ESI and atmospheric pressure chemical ionization (APCI). GC analyses were performed on an Agilent 789B Series system coupled to an Agilent 5977A Mass Selective Detector and an Agilent 7693 autosampler. Melting and boiling points were measured on a Büchi Melting Point B-540. Optical rotation was determined using a JASCO P-2000 Polarimeter. All spectral data for published compounds including  $^1\text{H}$ ,  $^{13}\text{C}$ ,  $^{11}\text{B}$ , and NOESY can

be found online at [10.1021/acs.joc.6b00648](https://doi.org/10.1021/acs.joc.6b00648) for Chapter 2 or [10.1055/s-0034-1380524](https://doi.org/10.1055/s-0034-1380524) for Chapter 3. Spectral data for all unpublished compounds are included in the Appendix.

### 5.3 Synthetic procedures and characterization of products for Chapter 2

#### **General procedure for the synthesis of acetylenic esters 2.10d-i and 2.10k-n (general procedure A):**

Dry THF and **2.1** (300  $\mu$ L, 1.0 equiv) are added to an oven dried nitrogen purged flask. The flask is cooled to  $-78$   $^{\circ}$ C using a dry ice-acetone cold bath. Next, butyllithium (769  $\mu$ L of 2.5 M in hexanes, 1.05 equiv) is added dropwise to the flask and allowed to stir for 30 minutes. To the flask, chloroformate **2.12** (175  $\mu$ L, 1.0 equiv) is slowly added. The reaction is held at  $-78$   $^{\circ}$ C for 6–8 hours and allowed to warm to room temperature overnight. After 24 hours, the reaction was quenched with DI water and hexanes. The organic layer was washed with DI water ( $3 \times 10$  mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo*. Column chromatography was used to purify the product, eluting with hexanes and EtOAc to yield the title compounds.



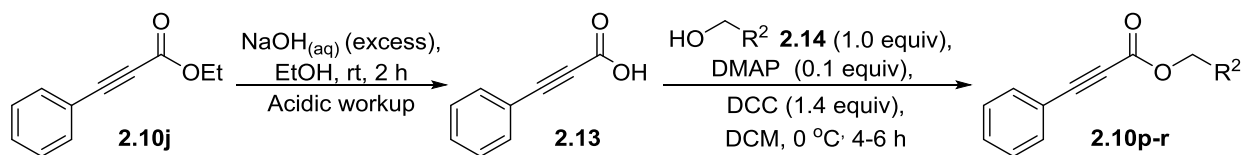
#### **General procedure for the synthesis of carboxylic acid 2.13 (general procedure B):**

An aqueous NaOH solution (639 mg, 1.1 equiv, 0.24 M) in DI water (66.4 mL) was added slowly to a stirring solution of **2.10j** (2.5 g, 1.0 equiv) in ethanol (113 mL) at room temperature. After 2 hours, the reaction mixture was diluted with DI water (100 mL) and washed with DCM ( $2 \times 50$  mL). The aqueous phase was acidified with 10% HCl and extracted with DCM ( $3 \times 50$  mL). The combined extracts were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and

concentrated *in vacuo*. The solid was dissolved in a minimal amount of DCM then hexanes was slowly added until crystals began precipitating. The crude solution was sealed and stored at 5 °C overnight. The precipitate was filtered, washed with cold hexanes, and dried on high vacuum to yield the final product **2.13** as white crystals.

**General procedure for the synthesis of acetylenic esters 2.10p-r (general procedure C):**

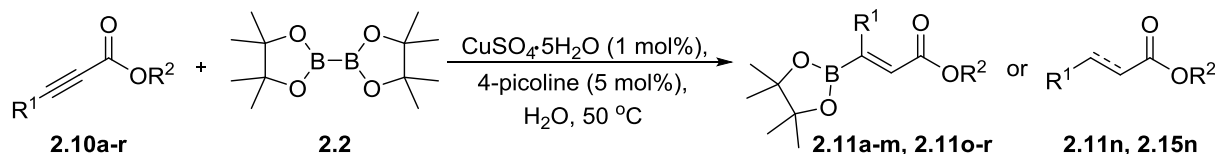
A solution of DMAP (28 mg, 0.1 equiv) in dry DCM was added to a mixture of **2.13** (500 mg, 1.5 equiv) and alcohol **2.14** (132 mg, 1.0 equiv) in DCM. The solution was cooled to 0 °C and stirred for 15 minutes prior to the addition of DCC (659 mg, 1.4 equiv). After stirring for 4–6 hours, the reaction mixture was filtered through a short plug of silica, which was rinsed with hexanes. The filtrate was concentrated *in vacuo* and purified by column chromatography eluting with hexanes and EtOAc.



**General procedure for the  $\beta$ -borylation of 2.10a-r using B<sub>2</sub>pin<sub>2</sub> (general procedure D):**

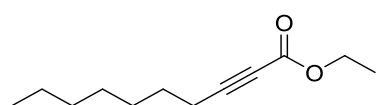
In a 1 dram vial, **2.10a-r** (88 mg, 1.0 equiv, 0.521 mmol), 4-picoline (2.55  $\mu$ L, 0.05 equiv), half of the B<sub>2</sub>pin<sub>2</sub> (198 mg total, 1.5 equiv), and 1 mL of 1.3 mg/mL CuSO<sub>4</sub> stock solution (0.01 equiv) are mixed and stirred vigorously at 50 °C. The remaining diboron was added over a period of 10 minutes. Once the reaction was complete according to TLC, the reaction was quenched with hexanes. The aqueous layer was extracted with hexanes (3  $\times$  10 mL), collecting the organic layer each time. The hexanes layer was washed with DI water (5  $\times$  10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Column chromatography was

used to purify the product, eluting with hexanes and EtOAc.



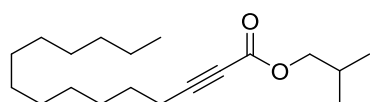
### Characterization of acetylenic esters **2.10d-i** and **2.10k-n**:

#### Ethyl dec-2-ynoate (**2.10d**):



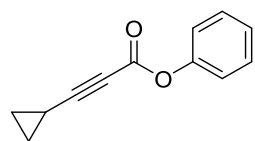
Compound **2.10d** was synthesized according to general procedure A and isolated in an 88% yield as a yellow liquid (bp  $256.5\text{ }^\circ C$ ). TLC  $R_f = 0.63$  (90:10 Hex:EtOAc);  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$  4.21 (q,  $J = 7.2$  Hz, 2H), 2.32 (t,  $J = 7.2$  Hz, 2H), 1.61–1.53 (m, 2H), 1.43–1.35 (m, 2H), 1.30 (t, 3H), 1.29–1.23 (m, 6H), 0.91–0.84 (t, 3H);  $^{13}C$  NMR (101 MHz,  $CDCl_3$ ):  $\delta$  154.0, 89.7, 73.3, 61.9, 31.8, 29.0, 28.8, 27.7, 22.7, 18.8, 14.21, 14.20; HRMS (+ Mixed EIC): Calcd for  $C_{12}H_{20}O_2$   $[M+H]^+$ : 197.1536; Found: 197.1544.

#### Isobutyl pentadec-2-ynoate (**2.10e**):



Compound **2.10e** was synthesized according to general procedure A and isolated in a 71% yield as a yellow liquid. TLC  $R_f = 0.68$  (90:10 Hex:EtOAc).  $^1H$  and  $^{13}C$  NMR spectra are consistent with the literature.<sup>2</sup>

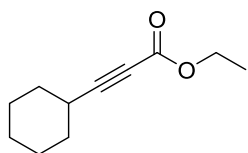
#### Phenyl 3-cyclopropylpropiolate (**2.10f**):



Compound **2.10f** was synthesized according to general procedure A and isolated in an 84% yield as a colorless liquid (bp  $>270\text{ }^\circ C$  (decomp)). TLC  $R_f = 0.43$  (90:10 Hex:EtOAc);  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$  7.40–7.35 (m, 2H), 7.26–7.22 (m, 1H), 7.14–7.10 (m, 2H), 1.48–1.40 (m, 1H), 1.02–0.95 (m,

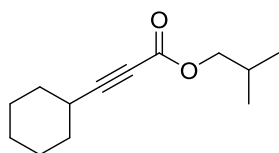
4H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  152.1, 150.3, 129.6, 126.4, 121.6, 96.2, 68.3, 9.6, -0.3; HRMS (+Mixed EIC): Calcd for  $\text{C}_{12}\text{H}_{10}\text{O}_2$   $[\text{M}+\text{H}]^+$ : 187.0754; Found: 187.0753.

#### Ethyl 3-cyclohexylpropiolate (2.10g):



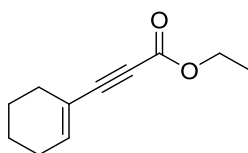
Compound **2.10g** was synthesized according to general procedure A and isolated in a 71% yield as a colorless oil. TLC  $R_f$  = 0.58 (90:10 Hex:EtOAc).  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra are consistent with the literature.<sup>3</sup>

#### Isobutyl 3-cyclohexylpropiolate (2.10h):



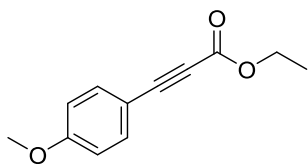
Compound **2.10h** was synthesized according to general procedure A and isolated in a 67% yield as a yellow oil (bp 280 °C). TLC  $R_f$  = 0.63 (90:10 Hex:EtOAc);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  3.93 (d,  $J$  = 6.8 Hz, 2H), 2.56–2.47 (m, 1H), 2.03–1.93 (m, 1H), 1.89–1.80 (m, 2H), 1.76–1.67 (m, 2H), 1.57–1.47 (m, 3H), 1.37–1.28 (m, 3H), 0.95 (d,  $J$  = 6.7 Hz, 6H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  154.2, 92.8, 73.0, 71.7, 31.4, 28.9, 27.6, 25.6, 24.6, 19.0; HRMS (+Mixed EIC): Calcd for  $\text{C}_{13}\text{H}_{20}\text{O}_2$   $[\text{M}+\text{H}]^+$ : 209.1536; Found: 209.1527.

#### Ethyl 3-(cyclohex-1-en-1-yl)propiolate (2.10i):



Compound **2.10i** was synthesized according to general procedure A and isolated in an 81% yield as a yellow liquid (bp 151.8 °C). TLC  $R_f$  = 0.66 (90:10 Hex:EtOAc);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.47–6.43 (m, 1H), 4.24 (q,  $J$  = 7.1 Hz, 2H), 2.19–2.11 (m, 4H), 1.69–1.57 (m, 4H), 1.31 (t,  $J$  = 7.1 Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  154.5, 142.2, 118.6, 88.5, 78.8, 61.9, 28.3, 26.1, 22.1, 21.2, 14.2; HRMS (+Mixed EIC): Calcd for  $\text{C}_{11}\text{H}_{14}\text{O}_2$   $[\text{M}+\text{H}]^+$ : 179.1067; Found: 179.1062.

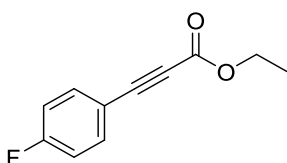
### Ethyl 3-(4-methoxyphenyl)propiolate (2.10k):



literature.<sup>4</sup>

Compound **2.10k** was synthesized according to general procedure A and isolated in a 35% yield as a yellow liquid. TLC  $R_f = 0.34$  (90:10 Hex:EtOAc).  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra are consistent with the

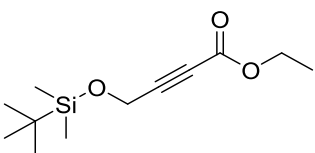
### Ethyl 3-(4-fluorophenyl)propiolate (2.10l):



literature.<sup>4</sup>

Compound **2.10l** was synthesized according to general procedure A and isolated in a 77% yield as a white solid. TLC  $R_f = 0.52$  (90:10 Hex:EtOAc).  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra are consistent with the

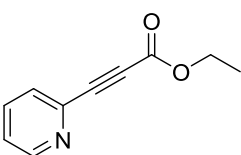
### Ethyl 4-((tert-butyldimethylsilyl)oxy)but-2-ynoate (2.10m):



literature.<sup>2</sup>

Compound **2.10m** was synthesized according to general procedure A and isolated in a 64% yield as a light brown liquid. TLC  $R_f = 0.59$  (90:10 Hex:EtOAc).  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra are consistent with

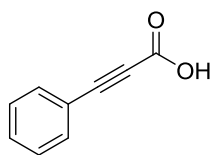
### Ethyl 3-(pyridine-2-yl)propiolate (2.10n):



Compound **2.10n** was synthesized according to general procedure A and isolated in a 52% yield as a brown solid. TLC  $R_f = 0.35$  (80:20 Hex:EtOAc).  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra are consistent with the literature.<sup>5</sup>

## Characterization of carboxylic acid 2.13:

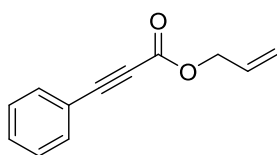
### 3-phenylpropionic acid (2.13):



Compound **2.13** was synthesized according to general procedure B and isolated in a 56% yield as white crystals. TLC  $R_f = 0.46$  (70:30 Hex:EtOAc).  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra are consistent with literature.<sup>6</sup>

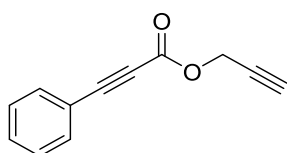
### Characterization of acetylenic esters 2.10p-r:

#### **Allyl 3-phenylpropiolate (2.10p):**



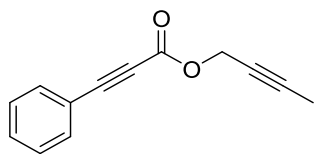
Compound **2.10p** was synthesized according to general procedure C and isolated in a 49% yield as a colorless oil. TLC  $R_f = 0.62$  (90:10 Hex:EtOAc).  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra are consistent with the literature.<sup>7</sup>

#### **Prop-2-yn-1-yl 3-phenylpropiolate (2.10q):**



Compound **2.10q** was synthesized according to general procedure C and isolated in a 51% yield as a light yellow solid (mp 35.0–35.5 °C). TLC  $R_f = 0.50$  (90:10 Hex:EtOAc);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.62–7.57 (m, 2H), 7.50–7.43 (m, 1H), 7.42–7.35 (m, 2H), 4.83 (d,  $J = 2.5$  Hz, 2H), 2.55 (t,  $J = 2.5$  Hz, 1H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  153.2, 133.3, 131.1, 128.8, 119.4, 87.8, 80.0, 75.92, 75.90, 53.4; HRMS (+ESI): Calcd for  $\text{C}_{12}\text{H}_9\text{O}_2$   $[\text{M}+\text{H}]^+$ : 185.0524 ; Found 184.0589.

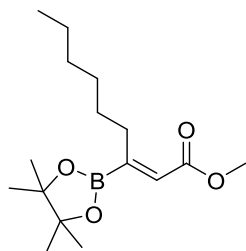
#### **But-2-yn-1-yl 3-phenylpropiolate (2.10r):**



Compound **2.10r** was synthesized according to general procedure C and isolated in an 85% yield as a colorless oil. TLC  $R_f = 0.57$  (90:10 Hex:EtOAc).  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra are consistent with literature.<sup>6</sup>

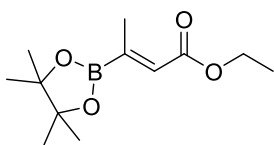
### Characterization of $\beta$ -borylated $\alpha,\beta$ -unsaturated esters 2.11a-m, 2.11o-p, and 2.11r:

**Methyl (Z)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)non-2-enoate (2.11a):**



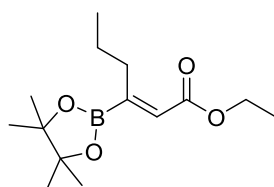
Compound **2.11a** was synthesized according to general procedure D and isolated in a 76% yield as a colorless oil (bp 299 °C). TLC  $R_f$  = 0.56 (90:10 Hex:EtOAc);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.39 (s, 1H), 3.70 (s, 3H), 2.66 (t, 2H), 1.46–1.37 (m, 2H), 1.37–1.27 (m, 6H), 1.27 (s, 12H), 0.87 (t, 3H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  166.6, 129.3, 84.2, 51.2, 31.9, 30.2, 29.7, 29.5, 24.8, 22.4, 14.2;  $^{11}\text{B}$  NMR (128 MHz,  $\text{CDCl}_3$ ):  $\delta$  30.1; HRMS (+Mixed EIC): Calcd for  $\text{C}_{16}\text{H}_{29}\text{BO}_4$   $[\text{M}+\text{H}]^+$ : 297.2275, Found: 297.2248.

**Ethyl (Z)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-2-enoate (2.11b):**



Compound **2.11b** was synthesized according to general procedure D and isolated in a 96% yield as a colorless oil. TLC  $R_f$  = 0.45 (90:10 Hex:EtOAc).  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra are consistent with literature.<sup>8</sup>

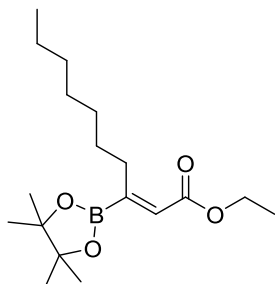
**Ethyl (Z)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-2-enoate (2.11c):**



Compound **2.11c** was synthesized according to general procedure D and isolated in an 84% yield as a pale yellow oil (bp 281 °C). TLC  $R_f$  = 0.65 (90:10 Hex:EtOAc);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.41 (s, 1H), 4.16 (q,  $J$  = 7.1 Hz, 2H), 2.64 (t, 2H), 1.50–1.41 (m, 2H), 1.27 (t, 3H), 1.26 (s, 12H), 0.93 (t,  $J$  = 7.4 Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  166.1, 130.0, 84.0, 59.8, 31.9, 24.7, 22.9, 14.3, 14.2;  $^{11}\text{B}$  NMR (128 MHz,  $\text{CDCl}_3$ ):  $\delta$  29.9; HRMS (ESI+): Calcd for  $\text{C}_{14}\text{H}_{25}\text{BO}_4$   $[\text{M}+\text{H}]^+$ : 269.18; Found: 269.08.

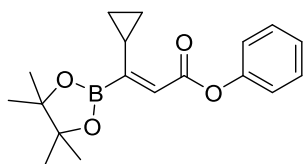
**Ethyl (Z)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)dec-2-enoate (2.11d):**





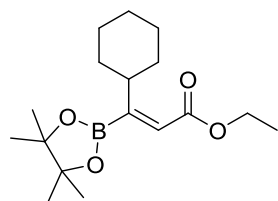
Compound **2.11d** was synthesized according to general procedure D and isolated in an 85% yield as a pale yellow liquid (bp 232 °C). TLC  $R_f$  = 0.72 (90:10 Hex:EtOAc);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.39 (s, 1H), 4.16 (q,  $J$  = 7.2 Hz, 2H), 2.65 (t, 2H), 1.46–1.37 (m, 2H), 1.36–1.21 (m, 23H), 0.87 (t, 2H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  166.2, 129.9, 84.1, 59.9, 32.0, 30.2, 29.8, 29.9, 29.4, 24.9, 22.8, 14.4, 14.3;  $^{11}\text{B}$  NMR (128 MHz,  $\text{CDCl}_3$ ):  $\delta$  30.2; HRMS (ESI+): Calcd for  $\text{C}_{18}\text{H}_{33}\text{BO}_4$   $[\text{M}+\text{H}]^+$ : 325.2546, Found: 325.2560.

**Phenyl (Z)-3-cyclopropyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)acrylate (2.11f):**



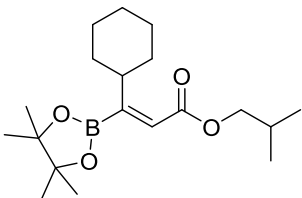
Compound **2.11f** was synthesized according to general procedure D and isolated in an 85% yield as a white solid (mp 107.1–108.4 °C). TLC  $R_f$  = 0.57 (90:10 Hex:EtOAc);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.41–7.35 (m, 2H), 7.24–7.19 (m, 1H), 7.14–7.10 (m, 2H), 6.56 (s, 1H), 3.15–3.05 (m, 1H), 1.27 (s, 12H), 1.06–1.01 (m, 2H), 0.93–0.88 (m, 2H);  $^{13}\text{C}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  165.0, 150.9, 129.4, 126.7, 125.7, 121.9, 84.2, 24.8, 14.3, 9.2;  $^{11}\text{B}$  NMR (128 MHz,  $\text{CDCl}_3$ ):  $\delta$  29.1; HRMS (+Mixed EIC): Calcd for  $\text{C}_{18}\text{H}_{23}\text{BO}_4$   $[\text{M}+\text{H}]^+$ : 315.1762, Found: 315.1765.

**Ethyl (Z)-3-cyclohexyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)acrylate (2.11g):**



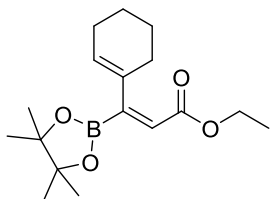
Compound **2.11g** was synthesized according to general procedure D and isolated in a 76% yield as a pale yellow oil. TLC  $R_f$  = 0.50 (90:10 Hex:EtOAc).  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra are consistent with literature.<sup>8</sup>

**Isobutyl (Z)-3-cyclohexyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)acrylate (2.11h):**



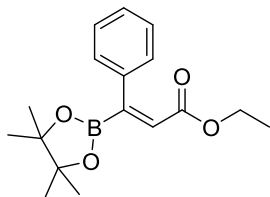
Compound **2.11h** was synthesized according to general procedure D and isolated in a 70% yield as a colorless oil (bp 338 °C). TLC  $R_f = 0.64$  (90:10 Hex:EtOAc);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.24 (s, 1H), 3.89 (d,  $J = 6.6$  Hz), 3.44–3.34 (m, 1H), 2.00–1.89 (m, 1H), 1.76–1.63 (m, 4H), 1.61–1.43 (m, 6H), 1.28 (s, 12H), 0.95 (d, 6H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  166.5, 127.8, 83.9, 70.3, 40.2, 31.5, 27.9, 26.4, 26.1, 24.9, 19.3;  $^{11}\text{B}$  NMR (128 MHz,  $\text{CDCl}_3$ ):  $\delta$  30.3; HRMS (ESI+): Calcd for  $\text{C}_{19}\text{H}_{33}\text{BO}_4$   $[\text{M}+\text{H}]^+$ : 337.2561, Found: 337.2545.

**Ethyl (Z)-3-(cyclohex-1-en-1-yl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)acrylate (2.11i):**



Compound **2.11i** was synthesized according to general procedure D and isolated in a 98% yield as a yellow oil. (bp >220 °C (decomp)). TLC  $R_f = 0.53$  (90:10 Hex:EtOAc);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.31 (s, 1H), 5.46–5.42 (m, 1H), 4.14 (q,  $J = 7.1$  Hz, 2H), 2.02–2.15 (m, 4H), 1.71–1.64 (m, 2H), 1.63–1.56 (m, 2H), 1.26 (s, 12H), 1.25 (t,  $J = 7.1$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  167.1, 137.6, 130.1, 123.7, 84.2, 60.2, 28.1, 25.5, 24.8, 22.8, 22.1, 14.4;  $^{11}\text{B}$  NMR (128 MHz,  $\text{CDCl}_3$ ):  $\delta$  30.0; HRMS (+Mixed EIC): Calcd for  $\text{C}_{17}\text{H}_{27}\text{BO}_4$   $[\text{M}+\text{H}]^+$ : 307.2070, Found: 307.2075.

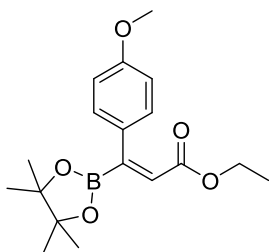
**Ethyl (Z)-3-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)acrylate (2.11j):**



Compound **2.11j** was synthesized according to general procedure D and isolated in a 95% yield as a yellow oil (bp 192 °C). TLC  $R_f = 0.31$  (90:10 Hex:EtOAc);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.32–7.23 (m, 3H), 7.22–7.18 (m, 2H), 6.64 (s, 1H), 4.02 (q,  $J = 7.1$  Hz, 2H),

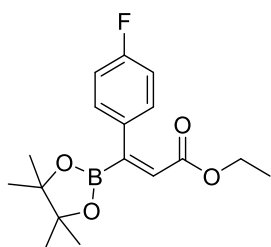
1.27 (s, 12H), 1.06 (t,  $J = 7.1$ , 3H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  166.5, 138.8, 132.4, 128.1, 127.8, 127.4, 84.6, 60.3, 24.9, 14.0;  $^{11}\text{B}$  NMR (128 MHz,  $\text{CDCl}_3$ ):  $\delta$  29.7; HRMS (ESI+): Calcd for  $\text{C}_{17}\text{H}_{23}\text{BO}_4$   $[\text{M}+\text{H}]^+$ : 303.1765; Found: 303.1740.

**Ethyl (Z)-3-(4-methoxyphenyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)acrylate (2.11k):**



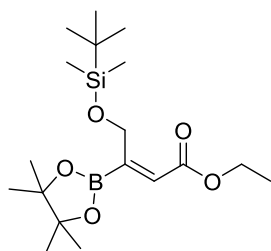
Compound **2.11k** was synthesized according to general procedure D and isolated in a 91% yield as a yellow liquid (bp 308 °C). TLC  $R_f = 0.34$  (90:10 Hex:EtOAc);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.23–7.19 (m, 2H), 6.87–6.83 (m, 2H), 6.58 (s, 1H), 4.07 (q,  $J = 7.1$  Hz, 2H), 3.80 (s, 3H), 1.29 (s, 12H), 1.14 (t,  $J = 7.1$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  166.7, 159.3, 131.2, 130.8, 129.8, 113.3, 84.6, 60.3, 55.3, 24.9, 14.2;  $^{11}\text{B}$  NMR (128 MHz,  $\text{CDCl}_3$ ):  $\delta$  30.5; HRMS (+Mixed EIC): Calcd for  $\text{C}_{18}\text{H}_{25}\text{BO}_5$   $[\text{M}+\text{H}]^+$ : 333.1868, Found: 333.1875.

**Ethyl (Z)-3-(4-fluorophenyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)acrylate (2.11l):**



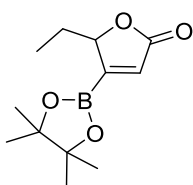
Compound **2.11l** was synthesized according to general procedure D and isolated in a 90% yield as a pale yellow solid (mp 58.2 - 60.4 °C). TLC  $R_f = 0.43$  (90:10 Hex:EtOAc);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.23–7.17 (m, 2H), 7.03–6.97 (m, 2H), 6.65 (s, 1H), 4.06 (q,  $J = 7.1$  Hz, 2H), 1.28 (s, 12H), 1.12 (t,  $J = 7.1$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  166.3, 163.6 ( $^1J_{\text{CF}} = 247$  Hz), 161.2 ( $^1J_{\text{CF}} = 247$  Hz), 134.53 ( $^4J_{\text{CF}} = 3.4$  Hz), 134.50 ( $^4J_{\text{CF}} = 3.4$  Hz), 132.5, 129.99 ( $^3J_{\text{CF}} = 8.1$  Hz), 129.91 ( $^3J_{\text{CF}} = 8.1$  Hz), 114.9 ( $^2J_{\text{CF}} = 21.5$  Hz), 114.6 ( $^2J = 21.5$  Hz), 84.7, 60.4, 24.9, 14.1;  $^{11}\text{B}$  NMR (128 MHz,  $\text{CDCl}_3$ ):  $\delta$  29.6; HRMS (+Mixed EIC): Calcd for  $\text{C}_{17}\text{H}_{22}\text{BFO}$   $[\text{M}+\text{H}]^+$ : 321.1695, Found: 321.167.

**Ethyl (Z)-4-((tert-butyldimethylsilyl)oxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-2-enoate (2.11m):**



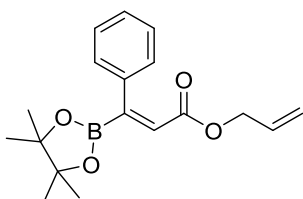
Compound **2.11m** was synthesized according to general procedure D and isolated in an 84% yield as a pale yellow liquid. (bp 291 °C). TLC  $R_f = 0.53$  (90:10 Hex:EtOAc);  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.19 (t,  $J = 2.0$  Hz), 4.82 (d,  $J = 2.0$  Hz, 2H), 4.16 (q,  $J = 7.1$  Hz, 2H), 1.28 (s, 12H), 1.26 (t,  $J = 7.1$  Hz, 3H), 0.90 (s, 9H), 0.07 (s, 6H);  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  165.9, 126.8, 84.2, 62.2, 60.2, 26.2, 24.9, 18.6, 14.4, -5.1;  $^{11}\text{B NMR}$  (128 MHz,  $\text{CDCl}_3$ ):  $\delta$  30.3; HRMS (ESI+): Calcd for  $\text{C}_{18}\text{H}_{35}\text{BO}_5\text{Si}$   $[\text{M}+\text{H}]^+$ : 371.2420, Found: 371.2384.

**5-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)furan-2(5H)-one (2.11o):**



Compound **2.11o** was synthesized according to general procedure D and isolated in a 15% yield as a white solid (mp 65.9–68.1 °C). TLC  $R_f = 0.19$  (70:30 Hex:EtOAc);  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ): 6.49 (d,  $J = 2.1$  Hz, 1H), 5.11 (m, 1H), 2.07 (m, 1H), 1.63 (m, 1H), 1.30 (s, 12H), 0.94 (t,  $J = 7.4$  Hz, 3H);  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  151.4, 131.9, 87.2, 85.0, 26.2, 25.0, 24.7, 9.2;  $^{11}\text{B NMR}$  (128 MHz,  $\text{CDCl}_3$ ):  $\delta$  28.39; HRMS (Mixed + EIC): Calcd for  $\text{C}_{12}\text{H}_{19}\text{BO}_4$   $[\text{M}+\text{H}]^+$ : 239.1449, Found: 239.1458.

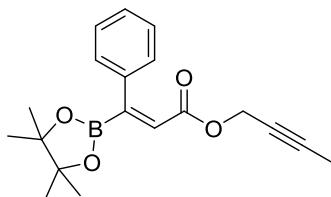
**Allyl (Z)-3-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)acrylate (2.11p):**



Compound **2.11p** was synthesized according to general procedure D and was isolated in an 89% yield as a colorless liquid (bp >277 °C (decomp)). TLC  $R_f = 0.52$  (90:10 Hex:EtOAc);  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.34–7.27 (m, 3H); 7.24–7.20 (m, 2H), 6.68 (s, 1H), 5.74 (m, 1H), 5.18–5.10 (m, 2H), 4.49 (dt,  $J = 5.6, 1.4$  Hz, 2H), 1.28 (s, 12H);  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  165.8, 138.5, 131.8,

131.6, 127.9, 127.7, 127.3, 118.1, 84.5, 64.9, 24.7;  $^{11}\text{B}$  NMR (128 MHz,  $\text{CDCl}_3$ ):  $\delta$  29.8; HRMS (ESI+): Calcd for  $\text{C}_{18}\text{H}_{23}\text{BO}_4$   $[\text{M}+\text{H}]^+$ : 315.1762, Found: 315.1758.

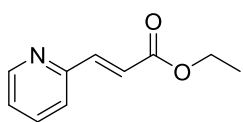
**But-2-yn-1-yl (Z)-3-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)acrylate (2.11r):**



Compound **2.11r** was synthesized according to general procedure D and isolated in an 82% yield as a white solid (mp 89.7–91.9 °C). TLC  $R_f$  = 0.55 (90:10 Hex:EtOAc);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.34–7.27 (m, 2H), 7.26–7.21(m, 2H), 6.68 (s, 1H), 4.57 (q,  $J$  = 2.4 Hz, 2H), 1.82 (t,  $J$  = 2.4 Hz, 3H), 1.28 (s, 12H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  165.4, 138.3, 131.1, 128.2, 127.8, 127.6, 84.7, 83.2, 73.1, 52.7, 24.9, 3.8;  $^{11}\text{B}$  NMR (128 MHz,  $\text{CDCl}_3$ ):  $\delta$  30.1; HRMS (ESI+): Calcd for  $\text{C}_{19}\text{H}_{23}\text{BO}_4$   $[\text{M}+\text{H}]^+$ : 327.1762, Found: 327.175.

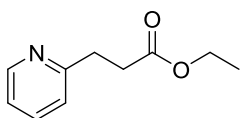
**Characterization of reduced products 2.11n and 2.15n:**

**Ethyl (E)-3-(pyridin-2-yl)acrylate (2.11n):**



Compound **2.11n** was synthesized according to general procedure D and isolated in a 17% yield as a colorless liquid. TLC  $R_f$  = 0.66 (1:1 Hex:EtOAc).  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra are consistent with literature.<sup>9</sup>

**Ethyl 3-(pyridin-2-yl)propanoate (2.15n):**

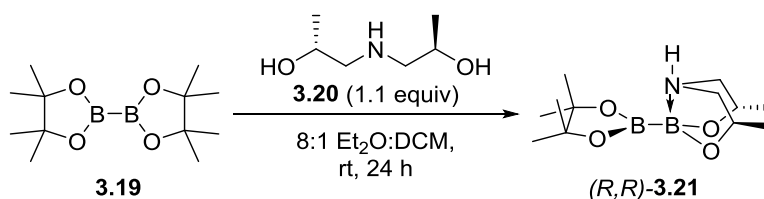


Compound **2.15n** was synthesized according to general procedure D and isolated in a 29% yield as a colorless liquid. TLC  $R_f$  = 0.17 (1:1 Hex:EtOAc).  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra are consistent with literature.<sup>10</sup>

## 5.4 Synthetic procedures and characterization of products for Chapter 3

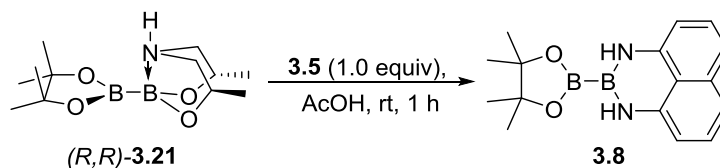
### General procedure for the synthesis of (R,R)-3.21 (general procedure E):

To an argon purged flask containing bis(pinacolato)diboron **3.19** (5 g, 1.0 equiv) and (2*R*,2'*R*)-1,1'-azanediylbis(propan-2-ol) (*R,R*)-**3.20** (2.88 g, 1.1 equiv) Et<sub>2</sub>O (33.3 mL) and DCM (4.17 mL) were added in an 8:1 ratio (0.525 M) to give a white suspension. The reaction was stirred at room temperature for 24 hours under argon. The reaction mixture was filtered and washed with Et<sub>2</sub>O (5 × 30 mL) to obtain the final product as a white solid.



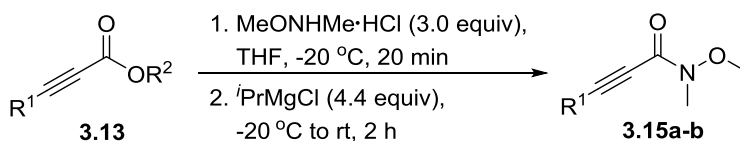
### General procedure for the synthesis of 3.8 (general procedure F):

Diboron (*R,R*)-**3.21** (0.56 g, 1.1 equiv) and 1,8-diaminonaphthalene **3.5** (0.299 g, 1.0 equiv) were added to a nitrogen purged 25 mL round bottom flask. Acetic acid (6.50 ml, 0.3 M) was added and the reaction was stirred at room temperature for 1 hour. The mixture was concentrated *in vacuo* and diluted with EtOAc (30 mL). The solution was washed with DI water (4 × 20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated *in vacuo*. Column chromatography was used to purify the product, eluting with hexanes and EtOAc to yield the title compound as a white solid.



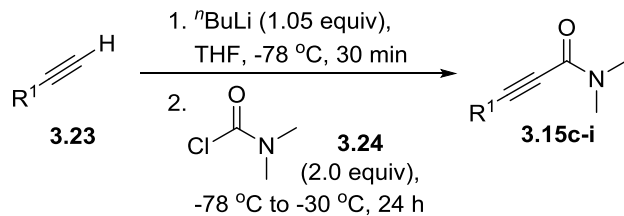
### General procedure for the synthesis of Weinreb amides 3.15a-b (general procedure G):

Dry THF (27.2 mL, 0.2 M), acetylenic ester **3.13** (1.0 mL, 1.0 equiv), and *N,O*-dimethylhydroxylamine HCl (997 mg, 3.0 equiv) were added to an oven dried nitrogen purged flask. The flask was cooled to  $-20\text{ }^{\circ}\text{C}$  and kept cold for 1 hour prior to the dropwise addition of isopropyl magnesium chloride (12.0 mL of 2 M in diethyl ether, 4.4 equiv). Consumption of the starting material was monitored by TLC. The reaction was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$ . The mixture was extracted with  $\text{Et}_2\text{O}$  ( $3 \times 10\text{ mL}$ ). The combined extracts were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo*. The products were purified using column chromatography, eluting with hexanes and EtOAc.



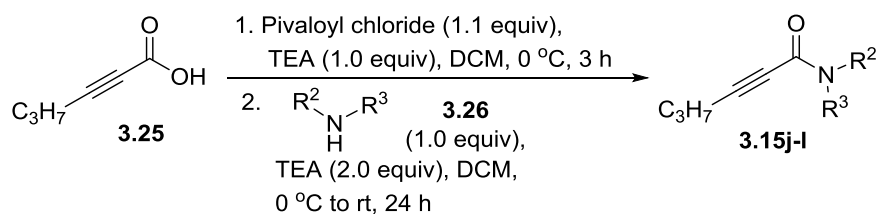
**General procedure for the synthesis of dimethyl amides 3.15c-i (general procedure H):**

Dry THF (10 mL, 0.5 M) and terminal alkyne **3.23** (500 mg, 1.0 equiv) were added to an oven dried nitrogen purged flask. The flask was cooled to  $-78\text{ }^{\circ}\text{C}$  followed by the dropwise addition of butyllithium (1.8 mL of 2.5 M in hexanes, 1.05 equiv). After stirring for 30 minutes, this solution was transferred dropwise via cannula to a separate nitrogen dried flask containing dry THF (10 mL) and dimethylcarbamic chloride (0.84 mL, 9.07 mmol 2.0 equiv). The reaction temperature was held at  $-78\text{ }^{\circ}\text{C}$  for 6 hours and allowed to warm to room temperature overnight. The reaction was quenched with DI water and extracted with hexanes ( $5 \times 5\text{ mL}$ ). The organic layer was then washed with DI water ( $5 \times 10\text{ mL}$ ), dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo*. Column chromatography was used to purify the products, eluting with hexanes and  $\text{Et}_2\text{O}$  (**3.15c**) or hexanes and EtOAc (**3.15d-i**).



**General procedure for the synthesis of secondary and tertiary amides 3.15j-l (general procedure I):**

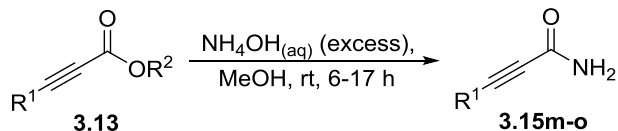
Dry DCM (45.3 mL, 0.1 M) and hexynoic acid **3.25** (0.50 mL, 1.0 equiv) were added to an oven dried nitrogen purged flask and cooled to  $0\text{ }^{\circ}\text{C}$ . TEA (0.63 mL, 1.0 equiv) was added dropwise to the flask and allowed to stir for 15 minutes before the dropwise addition of pivaloyl chloride (0.61 mL, 1.1 equiv). The consumption of starting material was monitored by TLC. TEA (917 mg, 2.0 equiv) was added dropwise to a separate nitrogen dried flask containing dry DCM (45.3 mL, 0.1 M) and amine **3.26** (585 mg, 1.0 equiv). The solution was stirred at room temperature for 1 hour prior to being added dropwise to the initial flask via cannula. The reaction mixture was allowed to warm to room temperature overnight. The reaction was quenched with DI water. Subsequently, the products were extracted with DCM ( $3 \times 10\text{ mL}$ ). The organic layer was then washed with DI water ( $2 \times 10\text{ mL}$ ), 10% NaOH ( $3 \times 10\text{ mL}$ ), brine, dried with  $\text{Na}_2\text{SO}_4$ , and concentrated *in vacuo*. Column chromatography was used to purify the products, eluting with hexane and EtOAc. The resulting products were  $>97\%$  pure and used as is for the  $\beta$ -borylation reaction.





**General procedure for the synthesis of carboxamides 3.15m-o (general procedure J):**

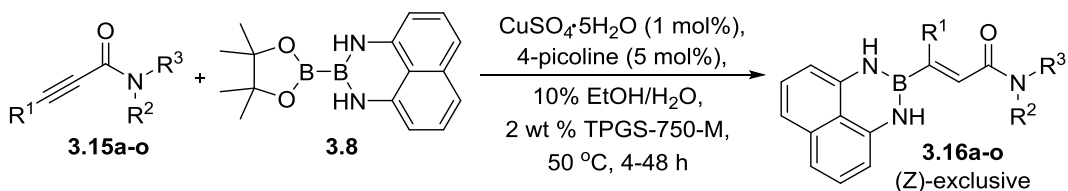
Ester **3.13** (600 mg, 1.0 equiv) and MeOH (28.5 mL, 0.1 M) were added to an oven dried nitrogen purged flask. To the reaction mixture, an excess of 28–30% ammonium hydroxide (36.8 mL, 75 equiv) was added dropwise and allowed to stir at room temperature. The progress of the reaction was followed by TLC. The crude reaction mixture was concentrated *in vacuo* to provide an off-white colored solid. The mixture was dissolved in EtOAc (10 mL) and rinsed with DI water (3 × 10 mL). The combined extracts were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The solid was dissolved in a minimal amount of Et<sub>2</sub>O at room temperature then hexanes was added slowly until the solution became cloudy. The crude solution was sealed and stored at 5 °C overnight. The precipitate was filtered, washed with cold hexanes, and dried on high vacuum to yield the final product **3.15m-o**.



**General procedure for the  $\beta$ -borylation of acetylenic amides using (pin)B-B(dan) (general procedure K):**

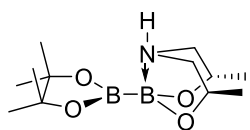
In a 1 dram vial, (pin)B-B(dan) **3.8** (183 mg, 1.2 equiv), 4-picoline (2.55  $\mu$ L, 0.05 equiv), amide **3.15a-o** (103 mg, 1.0 equiv) were added. Afterwards, 0.5 mL of 2.6 mg/mL CuSO<sub>4</sub> stock solution (prepared with aqueous 2 wt % TPGS-750-M), 0.4 mL aqueous 2 wt % TPGS-750-M, and 0.1 mL 200 proof ethanol (9:1 ratio, 0.52 M) were added down the sides of the vial. The reaction was heated to 50 °C and stirred vigorously. The reaction was monitored for completion by TLC. In some cases, the product and acetylenic amide exhibited the same R<sub>f</sub>; therefore, GC-MS was used to determine the consumption of the starting material in these cases. After the

reaction was complete, the reaction was quenched with EtOAc. The product was extracted using EtOAc (3 × 10 mL). The combined extracts were then washed with DI water (5 × 10 mL) and brine. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Column chromatography was used to purify the borylated product, eluting with hexanes and EtOAc (**3.15a-1**) or Et<sub>2</sub>O and EtOAc (**3.15m-o**).



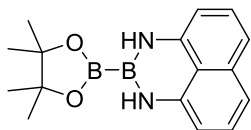
### Characterization of diborated compounds (*R,R*)**3.21** and **3.8**:

**(4*R*,8*R*)-4,8-dimethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,6,2-dioxazaborocane (3.21):**



Compound (*R,R*)-**3.21** was synthesized according to general procedure E and isolated in a 60% yield as a white solid. TLC  $R_f = 0.0$  (100% EtOAc). <sup>1</sup>H and <sup>13</sup>C NMR spectra are consistent with the literature.<sup>1</sup>

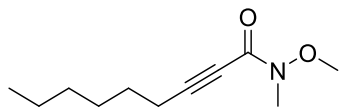
**2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-naphtho[1,8-de][1,3,2]diazaborinine (3.8):**



Compound **3.8** was synthesized according to general procedure F and isolated in a 66% yield as a white solid. TLC  $R_f = 0.30$  (90:10 Hex:EtOAc). <sup>1</sup>H and <sup>13</sup>C NMR spectra are consistent with the literature.<sup>1</sup>

### Characterization of acetylenic amides **3.15a-o**:

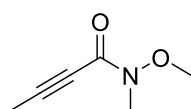
***N*-Methoxy-*N*-methylnon-2-ynamide (3.15a):**



the literature.<sup>11</sup>

Compound **3.15a** was synthesized according to general procedure G and isolated in a 90% yield as a light yellow oil. TLC  $R_f = 0.40$  (80:20 Hex:EtOAc).  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra are consistent with

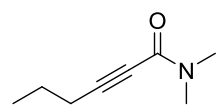
***N*-Methoxy-*N*-methylbut-2-ynamide (3.15b):**



$^1\text{H}$  and  $^{13}\text{C}$  NMR spectra are consistent with the literature.<sup>12</sup>

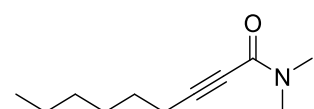
Compound **3.15b** was synthesized according to general procedure G and isolated in a 55% yield as a colorless oil. TLC  $R_f = 0.34$  (60:40 Hex:EtOAc).

***N,N*-Dimethylhex-2-ynamide (3.15c):**



Compound **3.15c** was synthesized according to general procedure H and isolated in a 91% yield as a pale yellow oil (bp  $>210\text{ }^\circ\text{C}$  (decomp)). TLC  $R_f = 0.26$  (70:30 Hex:EtOAc);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.19 (s, 3H), 2.95 (s, 3H), 2.33 (t,  $J = 7.1$  Hz, 2H), 1.66–1.55 (m, 2H), 1.01 (t,  $J = 7.3$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  155.0, 93.1, 74.3, 38.5, 34.2, 21.5, 21.0, 13.7; HRMS (ESI<sup>+</sup>): Calcd for  $\text{C}_8\text{H}_{14}\text{NO}$   $[\text{M}+\text{H}]^+$ : 140.1070, Found 140.1075.

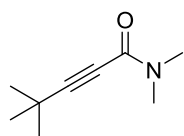
***N,N*-Dimethylnon-2-ynamide (3.15d):**



literature.<sup>13</sup>

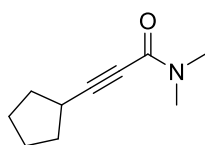
Compound **3.15d** was synthesized according to general procedure H and isolated in a 78% yield as a yellow oil. TLC  $R_f = 0.18$  (1:1 Hex:EtOAc).  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra are consistent with the

***N,N*-4,4-Tetramethylpent-2-ynamide (3.15e):**



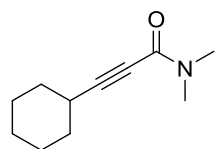
Compound **3.15e** was synthesized according to general procedure H and isolated in a 68% yield as an off-white solid (mp 64.0 – 64.8 °C). TLC  $R_f$  = 0.39 (60:40 Hex:EtOAc);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.17 (s, 3H), 2.94 (s, 3H), 1.27 (s, 9H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  155.0, 100.3, 72.7, 38.5, 34.2, 30.3, 27.8; HRMS (ESI+): Calcd for  $\text{C}_9\text{H}_{16}\text{NO}$   $[\text{M}+\text{H}]^+$ : 154.1226, Found 154.1222.

### 3-Cyclopentyl-*N,N*-dimethylpropiolamide (3.15f):



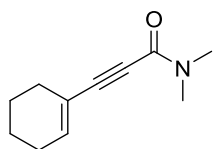
Compound **3.15f** was synthesized according to general procedure H and isolated in an 85% yield as a light brown liquid (bp >250 °C (decomp)). TLC  $R_f$  = 0.34 (60:40 Hex:EtOAc);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.16 (s, 3H), 2.93 (s, 3H), 2.80–2.70 (m 1H), 2.00–1.88 (m, 2H), 1.77–1.62 (m, 4H), 1.61–1.53 (m, 2H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  155.0, 97.1, 73.6, 38.4, 34.1, 33.3, 30.1, 25.1; HRMS (ESI+): Calcd for  $\text{C}_{10}\text{H}_{16}\text{NO}$   $[\text{M}+\text{H}]^+$ : 166.1226, Found 166.1227.

### 3-Cyclohexyl-*N,N*-dimethylpropiolamide (3.15g):



Compound **3.15g** was synthesized according to general procedure H and isolated in a 64% yield as a white solid (mp 51.0–51.8 °C). TLC  $R_f$  = 0.35 (60:40 Hex:EtOAc);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.19 (s, 3H), 2.96 (s, 3H), 2.61–2.49 (m, 1H), 1.89–1.64 (m, 4H), 1.57–1.30 (m, 6H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  155.0, 96.7, 74.0, 38.5, 34.1, 31.8, 29.2, 25.8, 24.8; HRMS (ESI+): Calcd for  $\text{C}_{11}\text{H}_{18}\text{NO}$   $[\text{M}+\text{H}]^+$ : 180.1383, Found 180.1387.

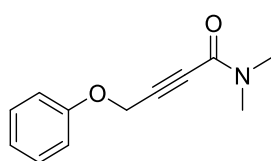
### 3-(Cyclohex-1-en-1-yl)-*N,N*-dimethylpropiolamide (3.15h):



Compound **3.15h** was synthesized according to general procedure H and isolated in a 94% yield as an off-white solid (mp 41.6–42.6 °C). TLC  $R_f$  = 0.36 (60:40 Hex:EtOAc);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.36–6.31 (m,

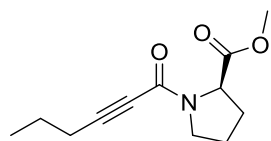
1H), 3.18 (s, 3H), 2.97 (s, 3H), 2.18–2.09 (m, 4H), 1.68–1.54 (m, 4H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 155.1, 139.8, 119.2, 92.4, 79.5, 38.5, 34.2, 28.5, 26.0, 22.1, 21.3; HRMS (ESI+): Calcd for C<sub>11</sub>H<sub>15</sub>NO [M+H]<sup>+</sup>: 178.1226, Found 178.1224.

***N,N*-Dimethyl-4-phenoxybut-2-ynamide (3.15i):**



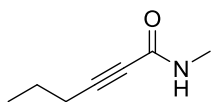
Compound **3.15i** was synthesized according to general procedure H and isolated in a 21% yield as a yellow oil (bp <180 °C (decomp)). TLC R<sub>f</sub> = 0.41 (1:1 Hex:EtOAc); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.33–7.27 (m, 2H), 7.03–6.95 (m, 2H), 4.85 (s, 2H), 3.07 (s, 3H), 2.94 (s, 3H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 157.4, 153.7, 129.7, 122.0, 115.1, 86.0, 79.9, 55.9, 38.3, 34.2; HRMS (ESI+): Calcd for C<sub>13</sub>H<sub>14</sub>NO<sub>2</sub> [M+H]<sup>+</sup>: 204.1019, Found 204.1023.

**Methyl hex-2-ynoyl-D-prolinate (3.15j):**



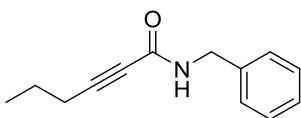
Compound **3.15j** was synthesized according to general procedure I and isolated in a 64% yield (1:1 mixture of rotamers) as a colorless viscous oil (bp >235 °C (decomp)). TLC R<sub>f</sub> = 0.44 (60:40 Hex:EtOAc); In the characterization, the second rotamer is designated by \* and the overlapping rotamer peaks are designated by †; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 4.63 (dd, *J* = 8.7, 3.2 Hz, 1H), 4.50\* (dd, *J* = 8.7, 3.8 Hz, 1H), 3.84–3.54<sup>†</sup> (m, 10H), 2.33 (t, *J* = 7.0 Hz, 2H), 2.28\* (t, *J* = 7.0 Hz, 2H), 2.25–2.19 (m, 1H), 2.14–1.89<sup>†</sup> (m, 7H), 1.66–1.51<sup>†</sup> (m, 4H), 1.02 (t, *J* = 7.3 Hz, 3H), 0.98\* (t, *J* = 7.3 Hz, 3H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 172.4, 172.0\*, 153.1, 152.9\*, 92.3, 92.1\*, 74.8, 74.7\*, 60.7, 57.9\*, 52.3, 52.2\*, 48.4, 45.7\*, 30.6, 29.7\*, 24.1, 23.1\*, 21.2, 21.1\*, 20.7, 20.6\*, 13.4, 13.3\*; HRMS (ESI+): Calcd for C<sub>12</sub>H<sub>18</sub>NO<sub>3</sub> [M+H]<sup>+</sup>: 224.1281, Found 224.1297.

***N*-Methylhex-2-ynamide (3.15k):**



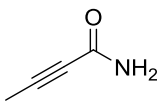
Compound **3.15k** was synthesized according to general procedure I and isolated in a 68% yield (9:1 mixture of rotamers) as a white solid. TLC  $R_f = 0.41$  (60:40 Hex:EtOAc).  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra are consistent with the literature.<sup>14</sup>

#### **N-Benzylhex-2-ynamide (3.15l):**



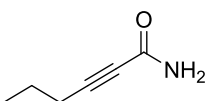
Compound **3.15l** was synthesized according to general procedure I and isolated in a 53% yield (9:1 mixture of rotamers) as a white solid (mp 44.2–45.1 °C). TLC  $R_f = 0.29$  (80:20 Hex:EtOAc). In the characterization, the minor rotamer is designated by \* and the overlapping rotamer peaks are designated by †;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.39–7.26† (m, 10H), 6.06 (br s, 1H), 6.00\* (br s, 1H), 4.60\* (d,  $J = 6.6$  Hz, 2H), 4.47 (d,  $J = 5.9$  Hz, 2H), 2.33\* (t,  $J = 7.1$  Hz, 2H), 2.26 (t,  $J = 7.1$  Hz, 2H), 1.57† (m,  $J = 7.2$  Hz, 4H), 0.99 (t,  $J = 7.3$  Hz, 3H), 0.98\* (t,  $J = 7.3$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  153.6†, 137.7\*, 137.5, 128.9\*, 128.8, 128.0, 127.9\*, 127.8, 127.2\*, 87.9†, 75.6†, 47.4\*, 43.9, 21.4, 21.3\*, 21.0\*, 20.7, 13.7, 13.6\*; HRMS (ESI+): Calcd for  $\text{C}_{13}\text{H}_{16}\text{NO}$   $[\text{M}+\text{H}]^+$ : 202.1226, Found 202.1234.

#### **But-2-ynamide (3.15m):**



Compound **3.15m** was synthesized according to general procedure J and isolated in a 65% yield as off-white crystals. TLC  $R_f = 0.48$  (1:1 Hex:EtOAc).  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra are consistent with the literature.<sup>15</sup>

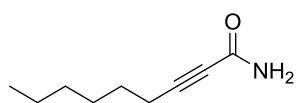
#### **Hex-2-ynamide (3.15n):**



Compound **3.15n** was synthesized according to general procedure J and isolated in a 43% yield as white crystals (mp 80.5–81.5 °C). TLC  $R_f = 0.28$  (1:1 Hex:EtOAc);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.33 (br s, 1H), 5.80 (br s, 1H), 2.29–2.23 (m,

2H), 1.63–1.51 (m, 2H), 1.02–0.95 (m, 3H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  155.3, 89.0, 75.1, 21.3, 20.7, 13.6; HRMS (ESI+): Calcd for  $\text{C}_6\text{H}_{10}\text{NO}$   $[\text{M}+\text{H}]^+$ : 112.0757, Found 112.0755.

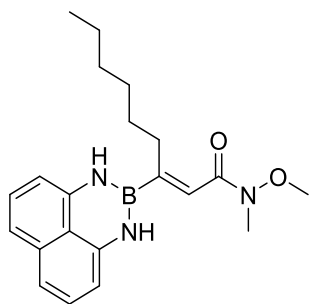
### Non-2-ynamide (3.15o):



Compound **3.15o** was synthesized according to general procedure J and isolated in an 81% yield as white crystals. TLC  $R_f = 0.40$  (1:1 Hex:EtOAc).  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra are consistent with the literature.<sup>13</sup>

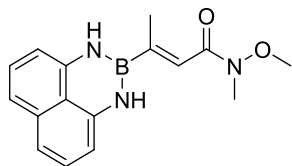
### Characterization of $\beta$ -borylated $\alpha,\beta$ -unsaturated amides 3.16a-o:

#### **(Z)-N-Methoxy-N-methyl-3-(1*H*-naphtho[1,8-*de*][1,3,2]diazaborinin-2(3*H*)-yl)non-2-enamide (3.16a):**



Compound **3.16a** was synthesized according to general procedure K and isolated in a 95% yield as a yellow solid (mp 85.6 – 86.5 °C).  $\alpha$ -borylated product **3.16a'** was detected by  $^1\text{H}$  NMR and NOESY. Ratio of **3.16a**:**3.16a'** was determined by  $^1\text{H}$  NMR integrations. TLC  $R_f = 0.39$  (60:40 Hex:EtOAc);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.12 (dd,  $J = 8.3, 7.2$  Hz, 2H), 7.04 (dd,  $J = 8.3$  Hz,  $^4J = 1.0$  Hz, 2H), 6.57 (br s, 1H), 6.37 (dd,  $J = 7.2$  Hz,  $^4J = 1.0$  Hz, 2H), 5.79 (br s, 2H), 3.71 (s, 3H), 3.26 (s, 3H), 2.67–2.60 (m, 2H), 1.54–1.44 (m, 2H), 1.42–1.35 (m, 2H), 1.33–1.25 (m, 4H), 0.89–0.84 (m, 3H);  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  167.6, 153.4 (br), 140.8, 136.5, 127.7, 124.6 (br), 120.1, 118.1, 106.2, 61.7, 32.3 (br), 31.9, 31.0, 30.1, 29.8, 22.8, 14.2;  $^{11}\text{B}$  NMR (128 MHz,  $\text{CDCl}_3$ )  $\delta$  28.98; HRMS (ESI+): Calcd for  $\text{C}_{21}\text{H}_{29}\text{BN}_3\text{O}_2$   $[\text{M}+\text{H}]^+$ : 366.2347, Found 366.2361. Note:  $\beta$ -carbon observed as a broad signal with a 3 second delay

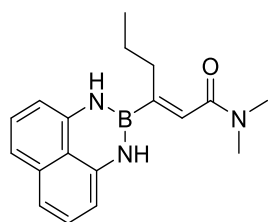
**(Z)-N-Methoxy-N-methyl-3-(1*H*-naphtho[1,8-*de*][1,3,2]diazaborinin-2(3*H*)-yl)but-2-enamide (3.16b):**



Compound **3.16b** was synthesized according to general procedure K and isolated in an 81% yield as a yellow solid (mp 99.2–100.1 °C).  $\alpha$ -borylated product **3.16b'** was detected by  $^1\text{H}$  NMR and NOESY.

Ratio of **3.16b**:**3.16b'** was determined by  $^1\text{H}$  NMR integrations. TLC  $R_f = 0.24$  (60:40 Hex:EtOAc).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.12 (dd,  $J = 8.3, 7.3$  Hz, 2H), 7.04 (dd,  $J = 8.3$  Hz,  $^4J = 1.0$  Hz, 2H), 6.63 (br s, 1H), 6.37 (dd,  $J = 7.3$  Hz,  $^4J = 1.0$  Hz, 2H), 5.86 (br s, 2H), 3.71 (s, 3H), 3.27 (s, 3H), 2.20 (s, 3H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  167.6, 147.3 (br), 140.8, 136.4, 127.7, 125.5, 120.1, 118.1, 106.2, 61.8, 32.2 (br), 16.7;  $^{11}\text{B}$  NMR (128 MHz,  $\text{CDCl}_3$ )  $\delta$  28.69; HRMS (ESI+): Calcd for  $\text{C}_{16}\text{H}_{19}\text{BN}_3\text{O}_2$   $[\text{M}+\text{H}]^+$ : 296.1565. Note:  $\beta$ -carbon observed as a broad signal with a 3 second delay

**(Z)-N,N-Dimethyl-3-(1*H*-naphtho[1,8-*de*][1,3,2]diazaborinin-2(3*H*)-yl)hex-2-enamide (3.16c):**



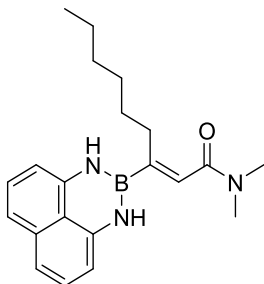
Compound **3.16c** was synthesized according to general procedure K and isolated in a 76% yield as a beige solid (mp 197.3–198.3 °C). TLC  $R_f = 0.33$  (1:1 Hex:EtOAc).  $^1\text{H}$  NMR (400 MHz,  $(\text{CD}_3)_2\text{CO}$ )  $\delta$  7.37 (br s, 2H), 7.05 (dd,  $J = 8.3, 7.4$  Hz, 2H), 6.94 (dd,  $J = 8.3$  Hz,  $^4J = 1.0$  Hz, 2H), 6.54 (s, 1H), 6.50 (dd,  $J = 7.4$  Hz,  $^4J = 1.0$  Hz, 2H), 3.04 (s, 3H), 2.93 (s, 3H), 2.43 – 2.37 (m, 2H), 1.53 – 1.42 (m, 2H), 0.88 (t,  $J = 7.4$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz,  $(\text{CD}_3)_2\text{CO}$ )  $\delta$  167.0, 142.1, 136.5, 130.5, 127.5, 120.2, 116.8, 105.7, 36.8, 33.3, 32.4, 22.8, 13.6;  $^{11}\text{B}$  NMR (128 MHz,  $(\text{CD}_3)_2\text{CO}$ )  $\delta$  28.94; HRMS (ESI+): Calcd for  $\text{C}_{18}\text{H}_{23}\text{BN}_3\text{O}$   $[\text{M}+\text{H}]^+$ : 309.1929, Found



309.1938.

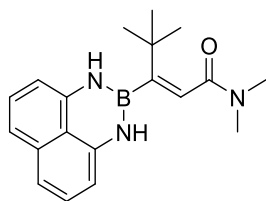
**(Z)-N,N-Dimethyl-3-(1H-naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-yl)non-2-enamide**

**(3.16d):**



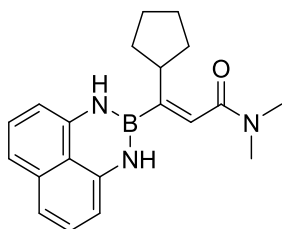
Compound **3.16d** was synthesized according to general procedure K and isolated in an 86% yield as a beige solid (mp 50.4–51.2 °C). TLC  $R_f = 0.28$  (60:40 Hex:EtOAc);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.11 (dd,  $J = 8.3, 7.3$  Hz, 2H), 7.03 (dd,  $J = 8.3$  Hz,  $^4J = 1.0$  Hz, 2H), 6.37–6.33 (m, 3H, Ar-H), 5.76 (br s, 2H), 3.04 (s, 3H), 3.02 (s, 3H), 2.35–2.29 (m, 2H), 1.50–1.39 (m, 2H), 1.37–1.23 (m, 6H), 0.89–0.83 (m, 3H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  168.9, 140.9, 136.4, 129.6, 127.7, 120.0, 117.9, 106.1, 38.0, 34.5, 31.8, 31.5, 29.8, 29.7, 22.7, 14.2;  $^{11}\text{B}$  NMR (128 MHz,  $\text{CDCl}_3$ )  $\delta$  28.92; HRMS (ESI+): Calcd for  $\text{C}_{21}\text{H}_{29}\text{BN}_3\text{O}$   $[\text{M}+\text{H}]^+$ : 350.2398, Found 350.2420.

**(Z)-N,N-4,4-Tetramethyl-3-(1H-naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-yl)pent-2-enamide (3.16e):**



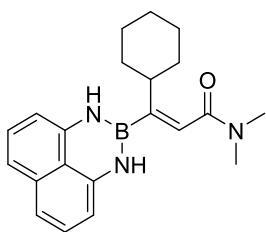
Compound **3.16e** was synthesized according to general procedure K and isolated in a 71% yield as a beige solid (mp >195 °C (decomp)). TLC  $R_f = 0.23$  (1:1 Hex:EtOAc);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.11 (dd,  $J = 8.3, 7.2$  Hz, 2H), 7.03 (dd,  $J = 8.3$  Hz,  $^4J = 1.0$  Hz, 2H), 6.32 (dd,  $J = 7.2$  Hz,  $^4J = 1.0$  Hz, 2H), 5.97 (s, 1H), 5.68 (br s, 2H), 3.07 (s, 3H), 2.97 (s, 3H), 1.22 (s, 9H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  170.8, 140.9, 136.3, 127.7, 127.0, 119.7, 117.9, 106.0, 38.5, 36.6, 34.3, 30.6;  $^{11}\text{B}$  NMR (128 MHz,  $\text{CDCl}_3$ )  $\delta$  29.67; HRMS (ESI+): Calcd for  $\text{C}_{19}\text{H}_{25}\text{BN}_3\text{O}$   $[\text{M}+\text{H}]^+$ : 322.2085, Found 322.2081.

**(Z)-3-Cyclopentyl-N,N-dimethyl-3-(1H-naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-yl)acrylamide (3.16f):**



Compound **3.16f** was synthesized according to general procedure K and isolated in an 89% yield as a beige solid (mp >185 °C (decomp)). TLC  $R_f$  = 0.25 (1:1 Hex:EtOAc);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.11 (dd,  $J$  = 8.3, 7.3 Hz, 2H), 7.03 (dd,  $J$  = 8.3 Hz,  $^4J$  = 0.9 Hz, 2H), 6.32 (dd,  $J$  = 7.3 Hz,  $^4J$  = 0.9 Hz, 2H), 6.20 (s, 1H), 5.75 (br s, 2H), 3.05 (s, 3H), 3.01 (s, 3H), 3.00–2.90 (m, 1H), 1.99–1.85 (m, 2H), 1.76–1.55 (m, 4H), 1.51–1.39 (m, 2H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  169.1, 140.8, 136.3, 128.7, 127.7, 119.9, 118.0, 106.1, 43.0, 38.3, 34.5, 33.3, 25.8;  $^{11}\text{B}$  NMR (128 MHz,  $\text{CDCl}_3$ )  $\delta$  29.35; HRMS (ESI+): Calcd for  $\text{C}_{20}\text{H}_{25}\text{BN}_3\text{O}$   $[\text{M}+\text{H}]^+$ : 334.2085, Found 334.2086.

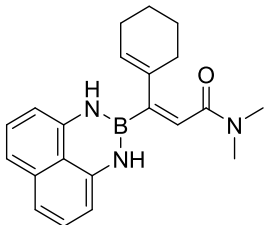
**(Z)-3-Cyclohexyl-N,N-dimethyl-3-(1H-naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-yl)acrylamide (3.16g):**



Compound **3.16g** was synthesized according to general procedure K and isolated in a 93% yield as a white solid (mp 175.2–177.5 °C). TLC  $R_f$  = 0.43 (1:1 Hex:EtOAc);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.11 (dd,  $J$  = 8.3, 7.3 Hz, 2H), 7.03 (dd,  $J$  = 8.3 Hz,  $^4J$  = 1.0 Hz, 2H), 6.33 (dd,  $J$  = 7.3 Hz,  $^4J$  = 1.0 Hz, 2H), 6.13 (s, 1H), 5.68 (br s, 2H), 3.05 (s, 3H), 3.01 (s, 3H), 2.66–2.56 (m, 1H), 1.80–1.64 (m, 5H), 1.40–1.11 (m, 5H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  168.8, 140.8, 136.4, 127.66, 127.67, 119.8, 118.0, 106.0, 42.2, 38.2, 34.5, 33.1, 26.3, 26.1;  $^{11}\text{B}$  NMR (128 MHz,  $\text{CDCl}_3$ )  $\delta$  29.45; HRMS (ESI+): Calcd for  $\text{C}_{21}\text{H}_{27}\text{BN}_3\text{O}$   $[\text{M}+\text{H}]^+$ : 348.2242, Found 348.2247.

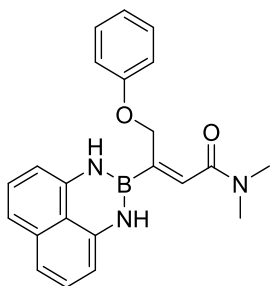
**(Z)-3-(Cyclohex-1-en-1-yl)-N,N-dimethyl-3-(1H-naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-**

**yl)acrylamide (3.16h)**



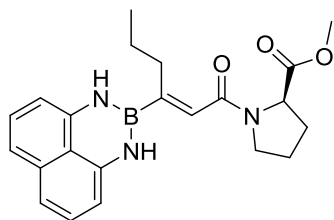
Compound **3.16h** was synthesized according to general procedure K and isolated in an 83% yield as a light brown solid (mp >155 °C (decomp)). TLC  $R_f = 0.21$  (1:1 Hex:EtOAc);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.11 (dd,  $J = 8.3, 7.3$  Hz, 2H), 7.02 (dd,  $J = 8.3$  Hz,  $^4J = 1.0$  Hz, 2H), 6.33 (dd,  $J = 7.3$  Hz,  $^4J = 1.0$  Hz, 2H), 6.21 (s, 1H), 5.78 (br s, 2H), 5.65–5.62 (m, 1H), 3.02 (s, 3H), 2.98 (s, 3H), 2.15–2.08 (m, 4H), 1.71–1.59 (m, 4H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  169.5, 141.0, 137.7, 136.4, 128.3, 127.7, 126.6, 120.0, 117.9, 106.1, 38.2, 34.4, 28.3, 25.7, 23.0, 22.1;  $^{11}\text{B}$  NMR (128 MHz,  $\text{CDCl}_3$ )  $\delta$  28.66; HRMS (ESI<sup>+</sup>): Calcd for  $\text{C}_{21}\text{H}_{25}\text{BN}_3\text{O}$   $[\text{M}+\text{H}]^+$ : 346.2085, Found 346.2090.

**(Z)-N,N-Dimethyl-3-(1H-naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-yl)-4-phenoxybut-2-enamide (3.16i):**



Compound **3.16i** was synthesized according to general procedure K and isolated in an 82% yield as a beige solid (mp >153 °C (decomp)). TLC  $R_f = 0.29$  (20:1  $\text{Et}_2\text{O}:\text{EtOAc}$ );  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.31–7.24 (m, 2H), 7.11 (dd,  $J = 8.3, 7.3$  Hz, 2H), 7.03 (dd,  $J = 8.3$  Hz,  $^4J = 1.0$  Hz, 2H), 7.00–6.94 (m, 1H), 6.94–6.89 (m, 2H), 6.65 (t,  $^4J = 1.3$  Hz, 1H), 6.38 (br s, 2H), 6.35 (dd,  $J = 7.3$  Hz,  $^4J = 1.0$  Hz, 2H), 4.94 (d,  $^4J = 1.3$  Hz, 2H), 3.03 (s, 6H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  167.7, 158.3, 141.0, 136.5, 132.2, 129.8, 127.7, 121.4, 120.2, 117.9, 114.8, 106.2, 68.4, 38.1, 34.8;  $^{11}\text{B}$  NMR (128 MHz,  $\text{CDCl}_3$ )  $\delta$  28.42; HRMS (ESI<sup>+</sup>): Calcd for  $\text{C}_{22}\text{H}_{23}\text{BN}_3\text{O}_2$   $[\text{M}+\text{H}]^+$ : 372.1878, Found 372.1886.

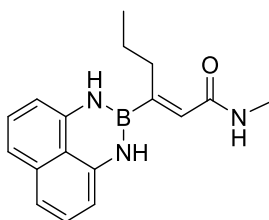
**Methyl (Z)-(3-(1H-naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-yl)hex-2-enoyl)-D-prolinate (3.16j):**



Compound **3.16j** was synthesized according to general procedure K and isolated in a 92% yield (76:24 mixture of rotamers) as a yellow solid (mp 149.9–151.4 °C). TLC  $R_f = 0.40$  (1:1 Hex:EtOAc);  $[\alpha]_D +35.7$  ( $c$  0.0386, MeOH). In the

characterization, minor rotamer is designated by \* and the overlapping rotamer peaks are designated by †.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.11† (dd,  $J = 8.3, 7.3$  Hz, 4H), 7.03† (dd,  $J = 8.3$  Hz,  $^4J = 0.8$  Hz, 4H), 6.38–6.33† (m, 5H), 6.21\* (s, 1H), 5.95 (br s, 2H), 5.87\* (br s, 2H), 4.57 (dd,  $J = 8.4, 4.0$  Hz, 1H), 4.42\* (dd,  $J = 8.4, 3.5$  Hz, 1H), 3.75–3.60† (m, 8H), 3.57–3.45† (m, 2H), 2.57–1.92† (m, 12H) 1.57–1.44† (m, 4H), 0.98–0.92† (m, 6H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  173.1\*, 172.9, 166.9\*, 166.6, 150.3† (br), 140.9, 140.9\*, 136.4†, 128.4\*, 128.2, 127.7†, 120.1†, 118.0\*, 117.9, 106.2\*, 106.1, 60.1\*, 58.5, 52.7\*, 52.3, 47.7, 46.1\*, 33.1\*, 32.9, 31.5\*, 29.4, 25.0, 23.2, 23.1\*, 23.0\*, 14.5\*, 14.4;  $^{11}\text{B}$  NMR (128 MHz,  $\text{CDCl}_3$ )  $\delta$  29.79; HRMS (ESI+): Calcd for  $\text{C}_{22}\text{H}_{27}\text{BN}_3\text{O}_3$   $[\text{M}+\text{H}]^+$ : 392.2140, Found 392.2102. Note:  $\beta$ -carbon observed as a broad signal with a 3 second delay

**(Z)-N-Methyl-3-(1*H*-naphtho[1,8-*de*][1,3,2]diazaborinin-2(3*H*)-yl)hex-2-enamide (3.16k):**

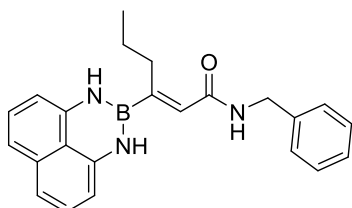


Compound **3.16k** was synthesized according to general procedure K and isolated in a 77% yield as a yellow solid (mp >157 °C (decomp)).

TLC  $R_f = 0.27$  (1:1 Hex:EtOAc);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.11 (dd,  $J = 8.3, 7.3$  Hz, 2H), 7.03 (dd,  $J = 8.3$  Hz,  $^4J = 0.8$  Hz, 2H), 6.34 (dd,  $J = 7.3$  Hz,  $^4J = 0.8$  Hz, 2H), 6.11 (s, 1H), 5.76 (br s, 2H), 5.60 (s, 1H), 2.88 (d,  $J = 4.9$  Hz, 3H), 2.72–2.65 (m, 2H), 1.56–1.45 (m, 2H), 0.97 (t,  $J = 7.3$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  167.5, 140.8, 136.3, 128.3, 127.7, 120.0, 118.0, 106.2, 32.2, 26.2, 23.4, 14.4;  $^{11}\text{B}$  NMR

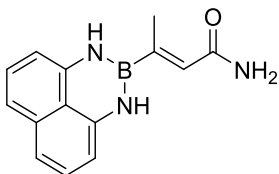
(128 MHz, CDCl<sub>3</sub>)  $\delta$  28.83; HRMS (ESI<sup>+</sup>): Calcd for C<sub>17</sub>H<sub>21</sub>BN<sub>3</sub>O [M+H]<sup>+</sup>: 294.1772, Found 294.1772.

**(Z)-N-Benzyl-3-(1H-naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-yl)hex-2-enamide (3.16l):**



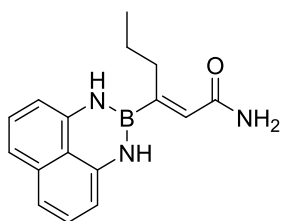
Compound **3.16l** was synthesized according to general procedure K and isolated in a 96% yield as a yellow solid (mp 113.5–114.8 °C). TLC R<sub>f</sub> = 0.18 (80:20 Hex:EtOAc); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.26–7.39 (m, 5H), 7.10 (dd, *J* = 8.3, 7.3 Hz, 2H), 7.03 (dd, *J* = 8.3 Hz, <sup>4</sup>*J* = 0.8 Hz, 2H), 6.33 (dd, *J* = 7.3 Hz, <sup>4</sup>*J* = 0.8 Hz, 2H), 6.13 (s, 1H), 5.88 (t, *J* = 5.7 Hz, 1H), 5.76 (br s, 2H), 4.50 (d, *J* = 5.7 Hz, 2H), 2.74–2.69 (m, 2H), 1.58–1.46 (m, 2H), 0.97 (t, *J* = 7.3 Hz, 3H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  166.4, 140.8, 138.3, 136.4, 128.9, 128.1, 128.0, 127.72, 127.71, 120.1, 118.1, 106.2, 43.6, 32.4, 23.5, 14.5; <sup>11</sup>B NMR (128 MHz, CDCl<sub>3</sub>)  $\delta$  29.14. HRMS (ESI<sup>+</sup>): Calcd for C<sub>23</sub>H<sub>25</sub>BN<sub>3</sub>O [M+H]<sup>+</sup>: 370.2085, Found 370.2086.

**(Z)-3-(1H-Naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-yl)but-2-enamide (3.16m):**



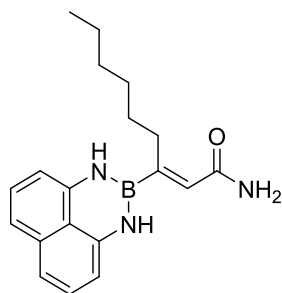
Compound **3.16m** was synthesized according to general procedure K and isolated in a 46% yield as a yellow solid (mp 164.8–165.6 °C). TLC R<sub>f</sub> = 0.47 (1:1 Et<sub>2</sub>O:EtOAc); <sup>1</sup>H NMR (400 MHz, (CD<sub>3</sub>)<sub>2</sub>SO)  $\delta$  7.89 (s, 2H), 7.31 (s, 1H), 7.04 (dd, *J* = 8.3, 7.4 Hz, 2H), 6.95 (s, 1H), 6.87 (dd, *J* = 8.3, <sup>4</sup>*J* = 0.9 Hz, 2H), 6.50 (dd, *J* = 7.4, <sup>4</sup>*J* = 0.9 Hz, 2H), 6.34 (q, <sup>4</sup>*J* = 1.6 Hz, 1H), 2.16 (d, <sup>4</sup>*J* = 1.6 Hz, 3H); <sup>13</sup>C NMR (101 MHz, (CD<sub>3</sub>)<sub>2</sub>SO)  $\delta$  168.4, 142.2, 135.9, 130.4, 127.6, 119.8, 116.3, 105.6, 16.2; <sup>11</sup>B NMR (128 MHz, (CD<sub>3</sub>)<sub>2</sub>SO)  $\delta$  30.04; HRMS (ESI<sup>+</sup>): Calcd for C<sub>14</sub>H<sub>15</sub>BN<sub>3</sub>O [M+H]<sup>+</sup>: 252.1303, Found 252.129.

**(Z)-3-(1*H*-Naphtho[1,8-*de*][1,3,2]diazaborinin-2(3*H*)-yl)hex-2-enamide (3.16n):**



Compound **3.16n** was synthesized according to general procedure K and isolated in a 90% yield as a yellow solid (mp 133.5–134.3 °C). TLC  $R_f = 0.23$  (2:1 Et<sub>2</sub>O:EtOAc); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.12 (dd,  $J = 8.3, 7.3$  Hz, 2H), 7.04 (dd,  $J = 8.3$  Hz,  $^4J = 1.0$  Hz, 2H), 6.35 (dd,  $J = 7.3$  Hz,  $^4J = 1.0$  Hz, 2H), 6.18 (t,  $^4J = 0.9$  Hz, 1H), 5.78 (s, 2H), 5.59 (br d,  $J = 34.8$  Hz, 2H), 2.72 – 2.68 (m, 2H), 1.57 – 1.45 (m, 2H), 0.97 (t,  $J = 7.3$  Hz, 3H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  168.3, 140.7, 136.4, 127.7, 127.2, 120.1, 118.2, 106.3, 32.4, 23.3, 14.5; <sup>11</sup>B NMR (128 MHz, CDCl<sub>3</sub>)  $\delta$  29.07; HRMS (ESI+): Calcd for C<sub>16</sub>H<sub>19</sub>BN<sub>3</sub>O [M+H]<sup>+</sup>: 280.1616, Found 280.1621.

**(Z)-3-(1*H*-Naphtho[1,8-*de*][1,3,2]diazaborinin-2(3*H*)-yl)non-2-enamide (3.16o):**



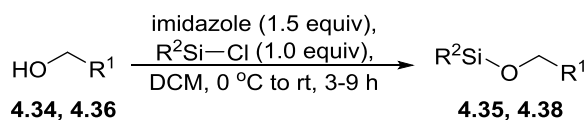
Compound **3.16o** was synthesized according to general procedure K and isolated in a 93% yield as a yellow solid (mp 98.6–99.3 °C). TLC  $R_f = 0.33$  (2:1 Et<sub>2</sub>O:EtOAc); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.12 (dd,  $J = 8.3, 7.2$  Hz, 2H), 7.04 (dd,  $J = 8.3$  Hz,  $^4J = 1.0$  Hz, 2H), 6.35 (dd,  $J = 7.2$  Hz,  $^4J = 1.0$  Hz, 2H), 6.16 (t,  $^4J = 0.93$  Hz, 1H), 5.80 (br s, 2H), 5.63 (br d,  $J = 55.2$  Hz, 2H), 2.74–2.69 (m, 2H), 1.51–1.22 (m, 8H), 0.90–0.83 (m, 3H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  168.7, 140.8, 136.4, 127.7, 127.0, 120.1, 118.1, 106.2, 31.8, 30.4, 30.1, 29.7, 22.7, 14.2; <sup>11</sup>B NMR (128 MHz, CDCl<sub>3</sub>)  $\delta$  28.97; HRMS (ESI+): Calcd for C<sub>19</sub>H<sub>25</sub>BN<sub>3</sub>O [M+H]<sup>+</sup>: 322.2085, Found 322.2080.

## 5.5 Synthetic procedures and characterization of products for Chapter 4

### General procedure for the synthesis of alcohol protected intermediates 4.35 and 4.38

**(general procedure L):**

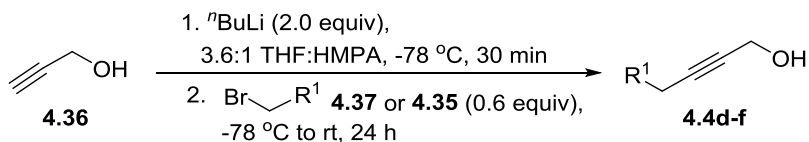
Dry DCM (7.92 mL, 0.705 M total) was added to a nitrogen purged flask containing alcohol **4.34** or **4.36** (0.8 g, 1.0 equiv). The flask was cooled to 0 °C before the addition of imidazole (570 mg, 1.5 equiv) which was dissolved in dry DCM (6 mL). After 10 minutes, *tert*-butyl(chloro)diphenylsilane (1.45 mL, 1.0 equiv) or *tert*-butyldimethylsilyl chloride (1.56 g dissolved in 1.92 mL DCM, 1.0 equiv) was added to the reaction dropwise. The mixture was allowed to warm up to room temperature. The progress of the reaction was followed by TLC. The aqueous phase was extracted with DCM (3 × 25 mL). The combined organic phases were washed with DI water (1 × 25 mL), brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Column chromatography was used to purify the product, eluting with hexanes and EtOAc to yield the desired compound. Note: Compound **4.38** is volatile under reduced pressure.



**General procedure for the synthesis of propargylic alcohols 4.4d-f (general procedure M):**

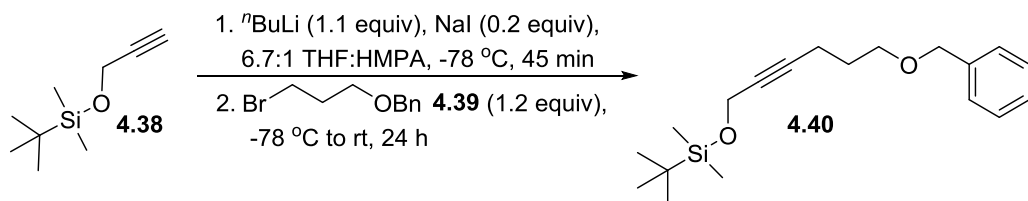
Prop-2-yn-1-ol **4.36** (0.5 mL, 1.0 equiv) was added to a nitrogen purged flask followed by dry THF:HMPA (3.6:1 ratio, 17.3 mL, 0.5 M). The flask was cooled to -78 °C before the dropwise addition of butyllithium (6.93 mL of 2.5 M in hexanes, 2.0 equiv) over a period of 10 minutes. The reaction was stirred at -78 °C for 45 minutes before **4.37** or **4.35** (0.581 mL, 0.6 equiv) was added dropwise. The solution was allowed to slowly warm up to room temperature overnight. The reaction was quenched by adding sat. NH<sub>4</sub>Cl. The aqueous layer was washed with Et<sub>2</sub>O (3 × 10 mL), brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Column

chromatography was used to purify the product, eluting with hexanes and EtOAc to yield the desired compounds.



**General procedure for the synthesis of TBS protected propargylic alcohol 4.40 (general procedure N):**

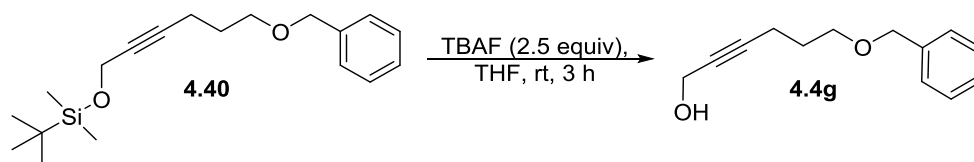
*Tert*-butyldimethyl(prop-2-yn-1-yloxy)silane **4.38** (0.5 g, 1.0 equiv) was added to a nitrogen purged flask followed by dry THF:HMPA (6.67:1 ratio, 8.2 mL, 0.306 M total). The flask was cooled to  $-78 \text{ }^\circ\text{C}$  before the dropwise addition of butyllithium (1.29 mL of 2.5 M in hexanes, 1.1 equiv) over a period of 10 minutes. The reaction was stirred at  $-78 \text{ }^\circ\text{C}$  for 45 minutes. Afterwards, NaI (88 mg, 0.2 equiv) dissolved in dry THF:HMPA (6.67:1 ratio, 1.4 mL) and ((3-bromopropoxy)methyl)benzene **4.39** (0.65 mL, 1.2 equiv) were added dropwise. The solution was allowed to slowly warm up to room temperature overnight. After 24 hours, the reaction was quenched by adding sat.  $\text{NH}_4\text{Cl}$ . The aqueous layer was washed with  $\text{Et}_2\text{O}$  ( $3 \times 20$  mL), brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo*. Column chromatography was used to purify the product, eluting with hexanes and  $\text{Et}_2\text{O}$  to yield the title compound.



**General procedure for the deprotection of 4.40 to synthesize propargylic alcohol 4.4g (general procedure O):**

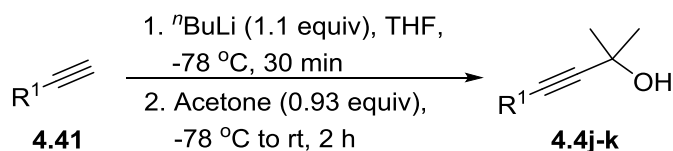


In an oven dried flask, ((6-(benzyloxy)hex-2-yn-1-yl)oxy)(tert-butyl)dimethylsilane **4.40** (205 mg, 1.0 equiv) was dissolved in dry THF (2.14 mL, 0.3 M) followed by the addition of tetrabutylammonium fluoride (1.6 mL of 1 M in THF, 2.5 equiv). The reaction was stirred at ambient temperature for 3 hours. Once the reaction is complete, the crude mixture was dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Column chromatography was used to purify the product, eluting with hexanes and EtOAc to yield the title compound.



**General procedure for the synthesis of tertiary propargylic alcohols 4.4j-k (general procedure P):**

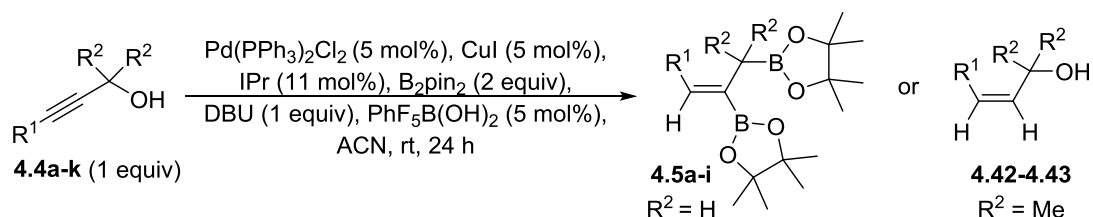
Dry THF (6.3 mL, 0.575 M) was added to a nitrogen purged flask containing alkyne **4.41** (0.4 mL, 1.0 equiv). The flask was cooled to  $-78\text{ }^{\circ}\text{C}$  before the dropwise addition of *n*-butyllithium (1.45 mL of 2.5 M in hexanes, 1.1 equiv). After 30 minutes, HPLC grade acetone (0.25 mL, 0.93 equiv) was added dropwise. The mixture was kept at  $-78\text{ }^{\circ}\text{C}$  for another 30 minutes before warming up to room temperature. The completion of the reaction was followed by TLC. Once complete, the reaction was quenched with sat. NH<sub>4</sub>Cl. The aqueous layers were washed with Et<sub>2</sub>O (3 × 15 mL). The combined organic extracts were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. Column chromatography was used to purify the product, eluting with hexanes and EtOAc to yield the title compounds.



## General procedure for the diboration of propargylic alcohols 4.4a-i and reduced products

### 4.42–4.43 (general procedure Q):

To an argon purged oven dried flask, bis(triphenylphosphine)palladium(II) chloride (17.0 mg, 0.05 equiv), 1,3-bis(2,6-diisopropylphenyl)-1H-imidazol-3-ium-2-ide (21.0 mg, 0.11 equiv), and copper(I) iodide (4.6 mg, 0.05 equiv) were quickly added followed by ACN (1.45 mL of 1.95 mL, 0.25 M total). The catalysts and ligand were premixed under argon at room temperature for 30 minutes. Afterwards, propargylic alcohols **4.4a-k** (37  $\mu$ L, 1.0 equiv, 0.484 mmol) and 2,3,4,6,7,8,9,10-octahydropyrimido[1,2-a]zapeprine (74  $\mu$ L, 1.0 equiv) were added. In a separate flask, (perfluorophenyl)boronic acid (5.1 mg, 0.05 equiv) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (246 mg, 2.0 equiv) were dissolved in ACN (0.5 mL) and added to the original flask via cannulate. The reaction was stirred at ambient temperature for 24 hours. Afterwards, EtOAc was added to the reaction, filtered through a pad of celite, and concentrated *in vacuo*. The residue was purified by column chromatography eluting with hexanes and EtOAc to yield the desired compound. Note: Elution of the product in  $\leq 15$  minutes is important due to the product degrading on silica.



### General procedure for dibromocyclopropyl 4.45 (general procedure R):

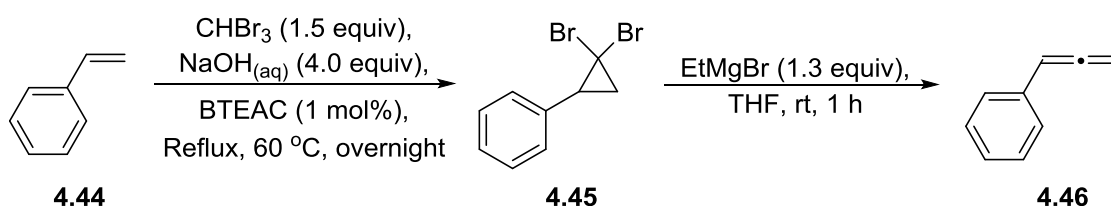
Styrene **4.44** (0.220 mL, 1.0 equiv), bromoform (0.252 mL, 1.5 equiv), and benzyltriethylammonium chloride (4.37 mg, 0.01 equiv) were added to an argon purged oven dried flask equipped with a reflux condenser. After the reaction was heated to 60  $^{\circ}\text{C}$ , aqueous

sodium hydroxide (307 mg, 25 M in DI H<sub>2</sub>O, 4.0 equiv) was added dropwise. The reaction was allowed to stir overnight. The crude reaction mixture was extracted with CDCl<sub>3</sub> (3 × 15 mL). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The resulting product was purified using Kugelrohr distillation to furnish the desired product.

**General procedure for the synthesis of phenyl allene 4.46 (general procedure S):**

(2,2-dibromocyclopropyl)benzene **4.45** (0.4 g, 1.0 equiv) was added to an argon purged flask followed by addition of THF (2.9 mL, 0.5 M). Ethylmagnesium bromide solution (0.63 mL of 3M in Et<sub>2</sub>O, 1.3 equiv) was added dropwise and the reaction was stirred at ambient temperature for 1 hour. The reaction was quenched with DI water. After separating the organic and aqueous layers, the aqueous layer was extracted with PET Et<sub>2</sub>O (3 × 10 mL). The organic layers were combined, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The crude product was purified through a silica plug, eluting with PET Et<sub>2</sub>O to furnish the desired product.

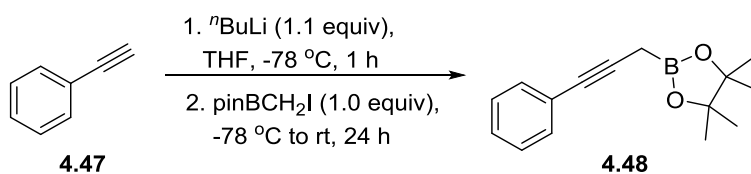
Note: the allene **4.46** is volatile under reduced pressure.



**General procedure for propargylic boronate 4.48 (general procedure T):**

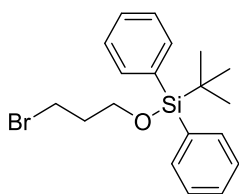
Dry THF (1.9 mL, 0.5 M) and ethynylbenzene **4.47** (108 μL, 1.0 equiv) were added to a N<sub>2</sub> purged round bottom flask. The reaction was cooled to -78 °C before the dropwise addition of *n*-butyllithium (422 μL, 1.1 equiv) over a period of 5 minutes. After stirring for 1 hour, 2-

(iodomethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (257 mg, 1.0 equiv) was added dropwise. The reaction was kept cold for 6 hours before warming up to room temperature overnight. Once complete, the reaction was quenched with DI water and EtOAc. After separating the layers, the aqueous layer was washed with EtOAc (3 × 15 mL) collecting the organic layer each time. The organic layer was then washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The resulting yellow oil was then carried forward crude in the borylation reaction.



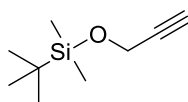
### **Characterization of alcohol protected intermediates 4.35 and 4.38:**

#### **(3-bromopropoxy)-*tert*-butyldiphenylsilane (4.35):**



Compound **4.35** was synthesized according to general procedure L and isolated in a 73% yield as a colorless oil. TLC  $R_f = 0.30$  (99:1 Hex:EtOAc). <sup>1</sup>H and <sup>13</sup>C NMR spectra are consistent with the literature.<sup>16</sup>

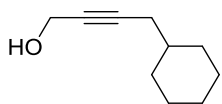
#### ***tert*-butyldimethyl(prop-2-yn-1-yloxy)silane (4.38):**



Compound **4.38** was synthesized according to general procedure L and isolated in a 87% yield as a colorless liquid. TLC  $R_f = 0.35$  (95:5 Hex:EtOAc). <sup>1</sup>H and <sup>13</sup>C NMR spectra are consistent with the literature.<sup>17</sup>

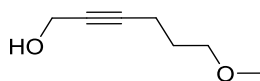
### **Characterization of propargylic alcohols 4.4d-f:**

#### **4-cyclohexylbut-2-yn-1-ol (4.4d):**



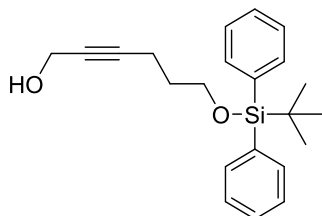
Compound **4.4d** was synthesized according to general procedure M and isolated in a 15% yield as a light yellow oil (bp 245 °C). TLC  $R_f$  = 0.29 (80:20 Hex:EtOAc);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  4.26 (t,  $J$  = 2.2 Hz, 2H), 2.10 (dt,  $J$  = 6.7, 2.2 Hz, 2H), 1.83–1.61 (m, 5H), 1.50 (br s, 1H), 1.50–1.39 (m, 1H), 1.30–1.07 (m, 3H), 0.97 (m, 2H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  85.6, 79.3, 51.6, 37.4, 32.8, 26.7, 26.4, 26.2; GC-MS (+EI): Calcd for  $\text{C}_{10}\text{H}_{16}\text{O}$   $[\text{M}]^+$ : 152.2370, Found: 152.2.

#### 6-methoxyhex-2-yn-1-ol (4.4e):



Compound **4.4e** was synthesized according to general procedure M and isolated in a 21% yield as a light yellow liquid. TLC  $R_f$  = 0.22 (75:25 Hex:EtOAc).  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra are consistent with the literature.<sup>18</sup>

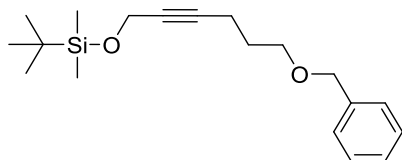
#### 6-((tert-butyl-diphenylsilyloxy)hex-2-yn-1-ol (4.4f):



Compound **4.4f** was synthesized according to general procedure M and isolated in a 32% yield as a yellow oil. TLC  $R_f$  = 0.31 (85:15 Hex:EtOAc).  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra are consistent with the literature.<sup>19</sup>

### Characterization of TBS protected propargylic alcohols 4.40:

#### ((6-(benzyloxy)hex-2-yn-1-yl)oxy)(tert-butyl)dimethylsilane (4.40):

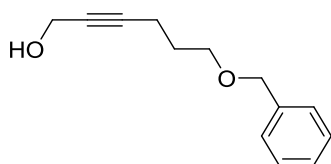


Compound **4.40** was synthesized according to general procedure N and isolated in a 30% yield as a colorless oil (bp >200 °C (decomp)). TLC  $R_f$  = 0.32 (97:3 Hex:Et<sub>2</sub>O);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.37–7.27 (m, 5H), 4.51 (s, 2H), 4.29 (t,  $J$  = 2.2 Hz, 2H), 3.56 (t,  $J$  =

6.2 Hz, 2H), 2.33 (tt,  $J = 7.1, 2.2$  Hz, 2H), 1.85–1.77 (m, 2H), 0.91 (s, 9H), 0.11 (s, 6H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  138.6, 128.5, 127.8, 127.7, 84.8, 79.1, 73.1, 69.0, 52.1, 28.9, 26.0, 18.5, 15.8, -4.9; HRMS (+Mixed EIC): Calcd for  $\text{C}_{19}\text{H}_{31}\text{O}_2\text{Si}$   $[\text{M}+\text{H}]^+$ : 319.2086, Found: 319.2088.

### Characterization of propargylic alcohol 4.4g:

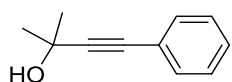
#### 6-(benzyloxy)hex-2-yn-1-ol (4.4g):



Compound **4.4g** was synthesized according to general procedure O and isolated in a 94% yield as a colorless oil. TLC  $R_f = 0.24$  (80:20 Hex:EtOAc).  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra are consistent with the literature.<sup>20</sup>

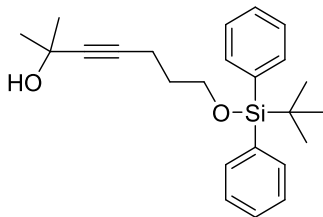
### Characterization of tertiary propargylic alcohols 4.4j-k:

#### 2-methyl-4-phenylbut-3-yn-2-ol (4.4j):



Compound **4.4j** was synthesized according to general procedure P and isolated in a 74% yield as a light yellow solid. TLC  $R_f = 0.32$  (85:15 Hex:EtOAc).  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra are consistent with the literature.<sup>21</sup>

#### 7-((tert-butyldiphenylsilyl)oxy)-2-methylhept-3-yn-2-ol (4.4k):

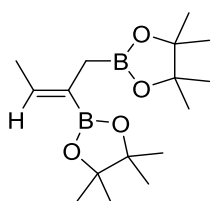


Compound **4.4k** was synthesized according to general procedure O and isolated in a 30% yield as a light yellow oil (bp 290 °C). TLC  $R_f = 0.30$  (90:10 Hex:EtOAc);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.69–7.65 (m, 4H), 7.45–7.36 (m, 6H), 3.73 (t,  $J = 6.0$  Hz, 2H), 2.34 (t,  $J = 7.1$  Hz, 2H), 1.79–1.71 (m, 2H), 1.45 (s, 6H), 1.05 (s, 9H);  $^{13}\text{C}$  NMR (101 MHz,

CDCl<sub>3</sub>) δ 135.7, 134.0, 129.7, 127.7, 85.4, 82.2, 65.4, 62.5, 31.8, 31.7, 27.0, 19.4, 15.3; HRMS (+ESI): Calcd for C<sub>24</sub>H<sub>32</sub>NaO<sub>2</sub>Si [M+Na]<sup>+</sup>: 403.2056, Found: 403.2064.

### **Characterization of diborated products 4.5a-i:**

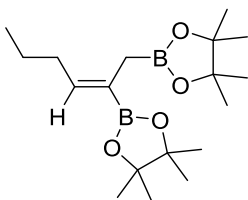
#### **(Z)-2,2'-(but-2-ene-1,3-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane)enoate (4.5a):**



Compound **4.5a** was synthesized according to general procedure Q and isolated in a 36% yield when using but-2-yn-1-ol (**4.4a**) and a 5% yield when using but-2-yne-1,4-diol (**4.4h**) as a yellow oil (bp >235 °C (decomp)). TLC R<sub>f</sub> = 0.40 (90:10 Hex:EtOAc); <sup>1</sup>H NMR (400 MHz,

CDCl<sub>3</sub>) δ 6.38 (qt, *J* = 6.8, 1.4 Hz, 1H), 1.77 (br s, 2H), 1.69 (d, *J* = 6.8 Hz, 3H), 1.24 (s, 12H), 1.22 (s, 12H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 138.7, 83.2, 83.1, 24.9, 14.5; <sup>11</sup>B NMR (128 MHz, CDCl<sub>3</sub>): δ 33.04, 30.32; HRMS (+ESI): Calcd for C<sub>16</sub>H<sub>31</sub>B<sub>2</sub>O<sub>4</sub> [M+H]<sup>+</sup>: 309.2403, Found: 309.2398.

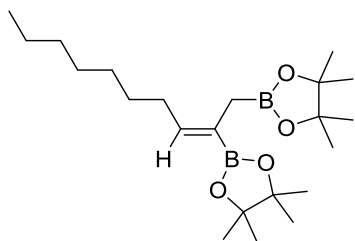
#### **(Z)-2,2'-(hex-2-ene-1,3-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (4.5b):**



Compound **4.5b** was synthesized according to general procedure Q and isolated in a 19% yield as a yellow oil (bp >185 °C (decomp)). R<sub>f</sub> = 0.28 (95:5 Hex:EtOAc); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.26 (tt, *J* = 7.0, 1.4 Hz, 1H), 2.08 (q, *J* = 7.3 Hz, 2H), 1.76 (bs, 2H), 1.47–1.36 (m, 2H),

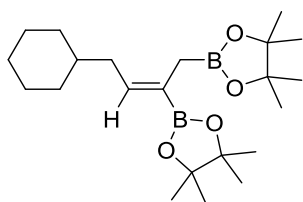
1.25 (s, 12H), 1.21 (s, 12H), 0.90 (t, *J* = 7.3 Hz, 3H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 144.2, 83.2, 83.0, 31.0, 24.91, 24.90, 22.3, 14.3; <sup>11</sup>B NMR (128 MHz, CDCl<sub>3</sub>) δ 33.10, 30.83; HRMS (ESI+): calcd for C<sub>18</sub>H<sub>35</sub>B<sub>2</sub>O<sub>4</sub> [M+H]<sup>+</sup>: 337.2716, Found: 337.2732.

#### **(Z)-2,2'-(dec-2-ene-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (4.5c):**



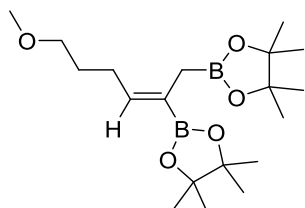
Compound **4.5c** was synthesized according to general procedure Q and isolated in a 35% yield as a yellow oil (bp >145 °C (decomp)). TLC  $R_f$  = 0.26 (95:5 Hex:EtOAc);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.26 (tt,  $J$  = 7.0, 1.3 Hz, 1H), 2.09 (q,  $J$  = 7.2 Hz, 2H), 1.76 (br s, 2H), 1.42–1.34 (m, 2H), 1.33–1.23 (m, 20H), 1.21 (s, 12H), 0.87 (t,  $J$  = 7.0 Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  144.5, 83.1, 83.0, 32.0, 29.7, 29.4, 29.1, 28.9, 24.91, 24.90, 22.8, 14.3;  $^{11}\text{B}$  NMR (128 MHz,  $\text{CDCl}_3$ )  $\delta$  33.08, 30.99; HRMS (ESI+): calcd for  $\text{C}_{22}\text{H}_{43}\text{B}_2\text{O}_4$   $[\text{M}+\text{H}]^+$ : 393.3342, Found: 393.3357.

**(Z)-2,2'-(4-cyclohexylbut-2-ene-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (4.5d):**



Compound **4.5d** was synthesized according to according to general procedure Q and isolated in a 14% yield as a yellow oil (bp >190 °C (decomp)). TLC  $R_f$  = 0.30 (95:5 Hex:EtOAc);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.26 (tt,  $J$  = 7.0, 1.3 Hz, 1H), 1.99 (t,  $J$  = 7.0 Hz, 2H), 1.78–1.52 (m, 10H), 1.42–1.06 (m, 25H), 0.97–0.82 (m, 2H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  142.9, 83.1, 83.0, 38.0, 36.7, 33.5, 26.7, 26.6, 24.93, 24.92;  $^{11}\text{B}$  NMR (128 MHz,  $\text{CDCl}_3$ )  $\delta$  32.99, 31.37; HRMS (+Mixed EIC): calcd for  $\text{C}_{22}\text{H}_{41}\text{B}_2\text{O}_4$   $[\text{M}+\text{H}]^+$ : 391.3185, Found: 391.3157.

**(Z)-2,2'-(6-methoxyhex-2-ene-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (4.5e):**

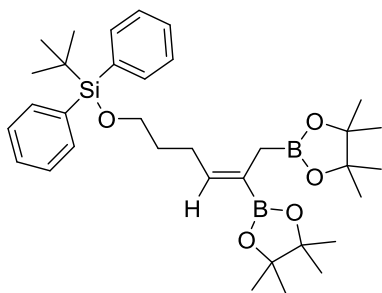


Compound **4.5e** was synthesized according general procedure Q isolated in a 14% yield as an orange oil (bp >200 °C (decomp)). TLC  $R_f$  = 0.29 (85:15 Hex:EtOAc);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.24 (tt,  $J$  = 7.0, 1.4 Hz, 1H), 3.37 (t,  $J$  = 6.7 Hz, 2H), 3.32 (s, 3H), 2.16 (q,  $J$  = 7.5 Hz, 2H), 1.76 (s, 2H), 1.72–1.64 (m, 2H), 1.25 (s, 12H), 1.21 (s, 12H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  143.3, 83.2, 83.1, 72.6, 58.6, 29.0, 25.3, 24.9;  $^{11}\text{B}$  NMR (128 MHz,



CDCl<sub>3</sub>):  $\delta$  33.14, 30.57; HRMS (+ESI): Calcd for C<sub>19</sub>H<sub>37</sub>B<sub>2</sub>O<sub>5</sub> [M+H]<sup>+</sup>: 367.2822, Found: 367.2838.

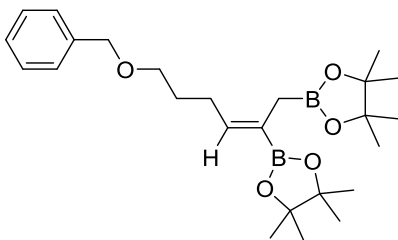
**(Z)-((5,6-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-4-en-1-yl)oxy)(tertbutyl)-diphenylsilane (4.5f):**



Compound **4.5f** was synthesized according to general procedure Q and isolated in a 28% yield as a viscous yellow oil (bp >185 °C). TLC R<sub>f</sub> = 0.34 (90:10 Hex:EtOAc); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.68 -7.64 (m, 4H), 7.43 – 7.34 (m, 6H), 6.26 (tt, *J* = 6.9, 1.4 Hz, 1H), 3.67 (t, *J* = 6.4 Hz, 2H), 2.22–2.14 (m, 2H), 1.77 (br s, 1H), 1.71–1.62 (m, 2H), 1.25 (s, 12H), 1.20 (s, 12H), 1.03 (s, 9H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  143.8, 135.7, 134.3, 129.6, 127.7, 83.2, 83.0, 63.9, 32.2, 27.0, 25.3, 24.92, 24.89, 19.4; <sup>11</sup>B NMR (128 MHz, (CD<sub>3</sub>)<sub>2</sub>CO):  $\delta$  33.79, 31.14; HRMS (+ESI): Calcd for C<sub>34</sub>H<sub>53</sub>B<sub>2</sub>O<sub>5</sub>Si [M+H]<sup>+</sup>: 591.3843, Found: 591.3848.

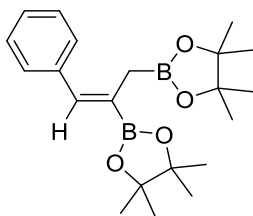
**(Z)-2,2'-(6-(benzyloxy)hex-2-ene-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane)**

**(4.5g):**



Compound **4.5g** was synthesized according to general procedure Q and isolated in a 23% yield as a yellow oil (bp >195 °C). TLC R<sub>f</sub> = 0.28 (80:20 Hex:EtOAc); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.34–7.23 (m, 5H), 6.25 (tt, *J* = 7.0, 1.4 Hz, 1H), 4.49 (s, 2H), 3.48 (t, *J* = 6.7 Hz, 2H), 2.20 (q, *J* = 7.4 Hz, 2H), 1.78–1.69 (m, 4H), 1.25 (s, 12H), 1.21 (s, 12H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  143.4, 138.9, 128.5, 127.7, 127.5, 83.2, 83.1, 72.9, 70.3, 29.1, 25.4, 24.9; <sup>11</sup>B NMR (128 MHz, CDCl<sub>3</sub>)  $\delta$  33.19, 31.59; HRMS (+Mixed EIC): Calcd for C<sub>25</sub>H<sub>41</sub>B<sub>2</sub>O<sub>5</sub> [M+H]<sup>+</sup>: 443.3143, Found: 443.3118.

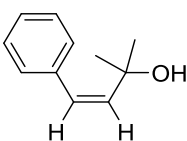
**(Z)-2,2'-(3-phenylprop-2-ene-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (4.5h):**



Compound **4.5h** was synthesized according to general procedure Q and isolated in a 7% yield as a yellow oil. TLC  $R_f = 0.34$  (90:10 Hex:EtOAc).  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra are consistent with the literature.<sup>22</sup>

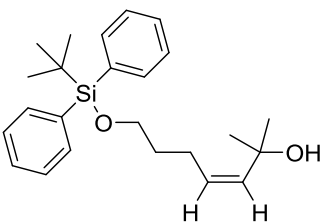
**Characterization of reduced products 4.42–4.43:**

**(Z)-2-methyl-4-phenylbut-3-en-2-ol (4.42):**



Compound **4.42** was synthesized according to general procedure Q and isolated in a 41% yield as a colorless oil. TLC  $R_f = 0.34$  (85:15 Hex:EtOAc).  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra are consistent with the literature.<sup>23</sup>

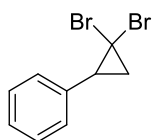
**(Z)-7-((tert-butyldiphenylsilyloxy)-2-methylhept-3-en-2-ol (4.23):**



Compound **4.43** was synthesized according to general procedure Q and isolated in a 20% yield as a light yellow oil (bp 239 °C). TLC  $R_f = 0.27$  (90:10 Hex:EtOAc);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.69–7.65 (m, 4H), 7.45–7.35 (m, 6H), 5.49 (dt,  $J = 11.8, 1.6$  Hz, 1H), 5.31–5.23 (m, 1H), 3.69 (t,  $J = 6.2$  Hz, 2H), 2.47–2.40 (m, 2H), 1.70 (br s, 1H), 1.64–1.55 (m, 2H), 1.36 (s, 6H), 1.05 (s, 9H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  137.5, 135.7, 134.1, 130.2, 129.7, 127.7, 71.8, 63.5, 32.8, 31.3, 27.0, 24.4, 19.3; HRMS (ESI+): calcd for  $\text{C}_{24}\text{H}_{34}\text{NaO}_2\text{Si}$   $[\text{M}+\text{Na}]^+$ : 405.2220, Found: 405.2187.

**Characterization of (2,2-dibromocyclopropyl)benzene 4.45:**

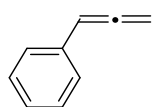
**(2,2-dibromocyclopropyl)benzene (4.45):**



Compound **4.45** was synthesized according to general procedure R and isolated in a 44% yield as a colorless oil. TLC  $R_f = 0.5$  (100% Hex).  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra are consistent with the literature.<sup>24</sup>

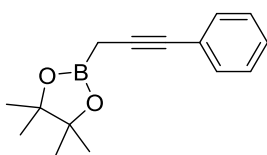
### **Characterization of mechanistic intermediates 4.46 and 4.48:**

#### **propa-1,2-dien-1-ylbenzene (4.46):**



Compound **4.46** was synthesized according to general procedure S and isolated in a 37% yield as a colorless oil. TLC  $R_f = 0.76$  (100% Hex).  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra are consistent with the literature.<sup>24</sup>

#### **4,4,5,5-tetramethyl-2-(3-phenylprop-2-yn-1-yl)-1,3,2-dioxaborolane (4.48):**



Compound **4.48** was synthesized according to general procedure T and obtained in a 40% yield (NMR) as a yellow oil. TLC  $R_f = 0.29$  (80:20 Hexanes:EtOAc);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.46–7.26 (m, 3H), 7.25–7.22 (m, 2H), 2.04 (s, 2H), 1.30 (s, 12H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  131.8, 128.2, 127.3, 124.7, 86.4, 84.2, 79.5, 77.2, 24.9;  $^{11}\text{B}$  NMR (128 MHz,  $\text{CDCl}_3$ ):  $\delta$  22.84; HRMS (+ESI): Calcd for  $\text{C}_{30}\text{H}_{42}\text{B}_2\text{NO}_4$  [ $2\text{M}+\text{NH}_4$ ] $^+$ : 503.3310., Found: 503.3305.

## **5.6 General procedures for stability studies**

### **General procedure to determine the stability of vinyl, allyl diboronate products on column stationary phases:**

Approximately 5.0–7.0 mg of compound **4.5a** was weighed out into a 1 dram vial and dissolved in 1.0 mL of  $\text{CDCl}_3$ . The designated stationary phase was added to the vial that was then purged with argon and wrapped in parafilm. The solution was mixed every few minutes. Afterwards, the solution was filtered and concentrated *in vacuo* before obtaining an NMR yield

using 750  $\mu\text{L}$  of  $\text{CDCl}_3-d_6$  with 0.05% v/v TMSCl as the internal standard. A Bruker Avance III 600 MHz equipped with a BBO probe was used to obtain the NMR spectra. The amount of decomposition was determined by the amount of product lost compared to the pure product. The  $^1\text{H}$  NMR yield from each test are shown below.

Entry	Stationary phase	Time (min)	$^1\text{H}$ NMR yield (%)
1	Silica	15	36
2	Silica	60	12
3	Deactivated silica	15	33
4	Deactivated silica	60	15
5	Florisil	15	77
6	Florisil	60	69
7	Alumnia	15	29
8	Alumnia	60	16

Note: Although the best results were obtained with Florisil, we are unable to use it for purification. The products are not UV active and can only be observed using  $\text{KMnO}_4$  stain. Unfortunately, Florisil TLC plates don't stain effectively which made it difficult to find an ideal solvent system for purification. Therefore, the products were isolated using silica in  $\leq 15$  minutes.

**General procedure to determine the stability of vinyl, allyl diboronate products in solution over time:**

Approximately 6.0 mg of compound **4.5a** was dissolved in 750  $\mu\text{L}$  of  $\text{CDCl}_3-d_6$  with 0.05% v/v TMSCl as the internal standard (sample A). With the same conditions, a separate sample was made but stored under argon and wrapped in parafilm (sample B). Over a period of three days,  $^1\text{H}$  NMR yields were obtained using a Bruker Avance III 600 MHz equipped with a BBO probe to determine the amount of decomposition when the sample was left open-to-air and

under argon. The amount of decomposition was determined by the amount of product lost compared to the initial yield. The  $^1\text{H}$  NMR yields for each sample are shown below. Results showed that the product was stable up to a period of 3 days.

Entry	Time (h)	$^1\text{H}$ NMR yield <b>A</b> (%) <sup>a</sup>	$^1\text{H}$ NMR yield <b>B</b> (%) <sup>b</sup>
1	0	100	100
2	4	97	98
3	8	102	97
4	12	97	98
5	24	102	102
6	36	102	100
7	48	101	103
8	60	97	102
9	72	104	103

<sup>a</sup> Sample stored open-to-air. <sup>b</sup> Sample sealed under argon.

## 5.7 References for Chapter 5

- Guo, X.; Nelson, A. K.; Slebodnick, C.; Santos, W. L., Regio- and Chemoselective Diboration of Allenes with Unsymmetrical Diboron: Formation of Vinyl and Allyl Boronic Acid Derivatives. *ACS Catal.* **2015**, *5*, 2172.
- Calderone, J. A.; Santos, W. L., Copper(II)-Catalyzed Silylation of Activated Alkynes in Water: Diastereodivergent Access to *E*- or *Z*- $\beta$ -Silyl- $\alpha,\beta$ -Unsaturated Carbonyl and Carboxyl Compounds. *Angew. Chem., Int. Ed.* **2014**, *53*, 4154.
- Kwong, C. K.-W.; Fu, M. Y.; Law, H. C.-H.; Toy, P. H., Isomerization of Electron-Poor Alkynes to the Corresponding (*E,E*)-1,3-Dienes Using a Bifunctional Polymeric Catalyst Bearing Triphenylphosphine and Phenol Groups. *Synlett* **2010**, *2010*, 2617.
- Pan, C.; Luo, F.; Wang, W.; Ye, Z.; Cheng, J., Ligand-Free Copper(I)-Catalyzed

- Sonogashira-Type Coupling of Arylboronic Acids with Terminal Alkynes. *Tetrahedron Lett.* **2009**, *50*, 5044.
5. Beveridge, R. E.; Arndtsen, B. A., A Direct, Copper-Catalyzed Functionalization of Pyridines with Alkynes. *Synthesis* **2010**, *2010*, 1000.
  6. Zhang, W.-Z.; Li, W.-J.; Zhang, X.; Zhou, H.; Lu, X.-B., Cu(I)-Catalyzed Carboxylative Coupling of Terminal Alkynes, Allylic Chlorides, and CO<sub>2</sub>. *Org. Lett.* **2010**, *12*, 4748.
  7. Tsujihara, T.; Takenaka, K.; Onitsuka, K.; Hatanaka, M.; Sasai, H., Pd<sup>ii</sup>/Pd<sup>iv</sup> Catalytic Enantioselective Synthesis of Bicyclo[3.1.0]Hexanes via Oxidative Cyclization of Enynes. *J. Am. Chem. Soc.* **2009**, *131*, 3452.
  8. Lee, J.-E.; Kwon, J.; Yun, J., Copper-Catalyzed Addition of Diboron Reagents to  $\alpha,\beta$ -Acetylenic Esters: Efficient Synthesis of  $\beta$ -Boryl- $\alpha,\beta$ -Ethylenic Esters. *Chem. Commun.* **2008**, 733.
  9. Cho, S. H.; Hwang, S. J.; Chang, S., Palladium-Catalyzed C–H Functionalization of Pyridine *N*-Oxides: Highly Selective Alkenylation and Direct Arylation with Unactivated Arenes. *J. Am. Chem. Soc.* **2008**, *130*, 9254.
  10. Barbe, G.; Pelletier, G.; Charette, A. B., Intramolecular Pyridine Activation–Dearomatization Reaction: Highly Stereoselective Synthesis of Polysubstituted Indolizidines and Quinolizidines. *Org. Lett.* **2009**, *11*, 3398.
  11. Ho, M. L.; Flynn, A. B.; Ogilvie, W. W., Single-Isomer Iodochlorination of Alkynes and Chlorination of Alkenes using Tetrabutylammonium Iodide and Dichloroethane. *J. Org. Chem.* **2007**, *72*, 977.
  12. Yadav, J. S.; Bhasker, E. V.; Srihari, P., Synthesis of a Key Intermediate for the Total Synthesis of Pseudopteroxazole. *Tetrahedron* **2010**, *66*, 1997.

13. Linstadt, R. T. H.; Peterson, C. A.; Lippincott, D. J.; Jette, C. I.; Lipshutz, B. H., Stereoselective Silylcupration of Conjugated Alkynes in Water at Room Temperature. *Angew. Chem., Int. Ed.* **2014**, *53*, 4159.
14. Hergenrother, P. J.; Boothman, D. A.; Bair, J. S.; Parkinson, E. I. Compounds and Anti-Tumor NQO1 Substrates. WO2013056073, April 18, 2013.
15. Bair, J. S.; Palchadhuri, R.; Hergenrother, P. J., Chemistry and Biology of Deoxyneboquinone, a Potent Inducer of Cancer Cell Death. *J. Am. Chem. Soc.* **2010**, *132*, 5469.
16. Zurwerra, D.; Glaus, F.; Betschart, L.; Schuster, J.; Gertsch, J.; Ganci, W.; Altmann, K.-H., Total Synthesis of (-)-Zampanolide and Structure–Activity Relationship Studies on (-)-Dactyloide Derivatives. *Chem. - Eur. J.* **2012**, *18*, 16868.
17. Koura, M.; Yamaguchi, Y.; Kurobuchi, S.; Sumida, H.; Watanabe, Y.; Enomoto, T.; Matsuda, T.; Okuda, A.; Koshizawa, T.; Matsumoto, Y.; Shibuya, K., Discovery of a 2-Hydroxyacetophenone Derivative as an Outstanding Linker to Enhance Potency and  $\beta$ -Selectivity of Liver X Receptor Agonist. *Bioorg. Med. Chem.* **2016**, *24*, 3436.
18. Debnar, T.; Dreisigacker, S.; Menche, D., Highly Regioselective Opening of Zirconacyclopentadienes by Remote Coordination: Concise Synthesis of the Furan Core of the Leupyrrins. *Chem. Commun.* **2013**, *49*, 725.
19. Nacro, K.; Baltas, M.; Gorrichon, L., Attempt to Rationalize the Diastereoselectivity in the Addition of Ester Enolate to Optically Active  $\alpha,\beta$ -Epoxyaldehydes. *Tetrahedron* **1999**, *55*, 14013.
20. Schomaker, J. M.; Pulgam, V. R.; Borhan, B., Synthesis of Diastereomerically and

- Enantiomerically Pure 2,3-Disubstituted Tetrahydrofurans Using a Sulfoxonium Ylide. *J. Am. Chem. Soc.* **2004**, *126*, 13600.
21. Gschneidtner, T. A.; Moth-Poulsen, K., A Photolabile Protection Strategy for Terminal Alkynes. *Tetrahedron Lett.* **2013**, *54*, 5426.
  22. Yang, F.-Y.; Cheng, C.-H., Unusual Diboration of Allenes Catalyzed by Palladium Complexes and Organic Iodides: A New Efficient Route to Biboronic Compounds. *J. Am. Chem. Soc.* **2001**, *123*, 761.
  23. Fu, S.; Chen, N.-Y.; Liu, X.; Shao, Z.; Luo, S.-P.; Liu, Q., Ligand-Controlled Cobalt-Catalyzed Transfer Hydrogenation of Alkynes: Stereodivergent Synthesis of Z- and E-Alkenes. *J. Am. Chem. Soc.* **2016**, *138*, 8588.
  24. Matsubara, T.; Takahashi, K.; Ishihara, J.; Hatakeyama, S., Total Synthesis of (-)-Ophiodilactone A and (-)-Ophiodilactone B. *Angew. Chem., Int. Ed.* **2014**, *53*, 757.



# Appendix

