Metal-Catalyzed Formation and Transformations of Carbon–Boron Bonds

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ABSTRACT

Our research seeks new methods for functionalizing organic small molecules using organoboronic derivatives as a versatile handle for late-stage manipulations. Metal-catalyzed formation of new carbon–boron bonds and their subsequent transformations are highlighted.

Among the myriad of unsaturated substrates for conducting borylation reactions, allenes have received minimal attention. These substrates are uniquely advantageous given that diboration results in the formation of both allylic and vinylic boronates. Orthogonal reactivity of the sp\(^2\) and the sp\(^3\) C–B bonds can allow for chemoselective transformations. However, oxidation of the carbon–boron bond is one example in which the conditions are unselective. To address this shortcoming, a platinum catalyst was developed for the diboration of 1,1-diaryl allenes with a differentially protected diboron reagent, pinB—Bdan. The reaction proceeds regioselectively in high yields to furnish olefins bearing a vinylic Bpin and an allylic Bdan moiety. The subsequent chemoselective transformation of each boron center was demonstrated.

Methods for preparing 1,8-diaminonaphthalene protected vinylboronates conjugated to carbonyl groups are severely limited. A simple and efficient protocol was developed for carrying out an environmentally friendly copper(II)-catalyzed β-borylation of alkynoates and alkynamides in water and open-to-air. Following the discriminative activation of the more Lewis acidic pinacol protected boron center in pinB—Bdan, a regio-, stereo- and chemoselective β-borylation of acetylenic substrates delivers (Z)-β-boryl enoates and primary, secondary, and tertiary enamides under very mild conditions.

As an inexpensive and earth abundant metal, catalysts based on copper are highly desirable. An international collaborative project to develop a copper-catalyzed cross-coupling reaction of β-boryl carbonyl compounds was explored. Preliminary results found these substrates to be either unstable towards or unreactive under the reactions conditions screened.
Metal-Catalyzed Formation and Transformations of Carbon–Boron Bonds

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GENERAL AUDIENCE ABSTRACT

The very basis of everything in existence is the atom. The idiosyncratic arrangements and interactions of atoms confer distinctive physical properties which give rise to the biological processes of organic lifeforms or the diverse characteristics of inorganic substances, like salts and minerals. In organic chemistry, the carbon-based backbone of the compound is decorated with so-called functional groups, which govern the physical or biological properties of the molecule. Building the unique structural arrangement of functional groups within a pharmaceutical, for example, requires multi-step reaction sequences and purifications to deliver the desired product. Thus, their assembly must be extremely selective and highly efficient to yield the final compound in useable amounts. The overarching goal of our work is to develop such methods for building complex small molecules from very simple starting materials. The carbon—boron bond is a particularly versatile tool in synthetic chemistry because it offers direct access to a myriad of different functional groups. We utilize the unique properties of boron, a tunable semi-metallic element, in the formation and transformation of carbon—boron bonds with divergent reactivity.

Catalysis offers a modern approach to enhance the selectivity and sustainability of preparative organic chemistry. Energy input is needed to make and break chemical bonds. Conducting the reaction at an elevated temperature, for example, is a conventional way to provide the energy necessary for molecules to come together. Conversely, metal catalysts can be cleverly designed to lower the potential energy barrier, which gives rise to new pathways for carrying out chemical transformations. Moreover, incredibly small amounts of the metal is sufficient because a catalyst propagates the process in a cyclic and repetitive fashion. In this work, metal catalysts were optimized to form carbon—boron bonds from diboron reagents containing two different boron centers. Taking advantage of the orthogonal reactivity of each boron allowed for the selective installation of functional groups in subsequent transformation reactions.
Once upon a time you convinced me that, when I emptied my nasal passages with strong forces of CO₂ (that would be carbon dioxide), I became dumber because I was “blowing my brains out.”

Look who’s laughing now.
Acknowledgements

The notion that a doctoral student could summarize the debts accrued during their program is bizarre. There are indeed far too many important people who have provided inspiration, assistance, and, occasionally, a strong shoulder to share the load or despair upon. Therefore, these words are far more important than the 63,449 words that follow.

Above all others, I would like to recognize the most influential person in my life, Elaine Nelson. Mom has always been the rock that sets me straight when I become overwhelmed, and I owe all of my success to her. Because of her support, I know that I still have the capacity to achieve extraordinary things no matter what obstacles may come. My family can still make me feel special, in spite of graduate school and adulthood affirming that my existence is completely irrelevant.

I spent 2,258 days as a Ph.D. candidate. The most memorable of these were not actually the days, but rather, the late nights I spent pursuing these glowing truths that will only be appreciated by six or seven people, if I am lucky. Since it is highly dangerous to work alone in a laboratory and even more so to declare engaging in such preposterous deeds in a published manuscript, I would like to acknowledge my dear friend and colleague, Dr. Jessica Wynn, who was always by my side from day one. Our nights in the lab constitute the most entertaining nightlife I enjoyed while in graduate school. I would also like to acknowledge the Waffle House because it was always open at the end of the day – usually around 4 or 5 a.m.

“At the end of the day” is a phrase that I heard 27 time before I stopped keeping a tally somewhere in the midst of year two. It almost goes without saying that I should thank my advisor, Dr. Webster Santos, for the support and laboratory space to do my research. Besides the obvious, I would like to acknowledge him for teaching me to be an independent scientist whilst also making time for me if ever I was stuck on a problem. Moreover, I appreciate the encouragement to be bold, even when I am scared to death. “If you are afraid of chemicals, you’re in the wrong business,” Dr. Santos chuckled once. So when others shied away from working with highly toxic retinoid derivatives, these words empowered me to take on the project, but with extreme caution of course.
I would like to recognize my committee members, Drs. Joe Merola, Paul Carlier, and James Tanko, for their endless support throughout my academic career at Virginia Tech. In particular, I would like to thank Dr. Tanko for inspiring me to continue trying to understand physical chemistry. After three rounds of his Chemical Kinetics course, some things have managed to stick. Despite all of the difficulties with the project described in Chapter 3, I never gave up on it because, in this way, the research challenged me to address my weakness. I would like to thank Dr. Carlier, who has given me encouragement and support since the very beginning. At my preliminary exam, he told me that he saw great potential in my future. These words meant a lot to me and gave me confidence to set the bar high so that I may to live up to them. Also, I am especially thankful to my host advisor abroad, Dr. Todd Marder. I really enjoyed his open door policy and pro student approach. The most memorable thing he said to me was, “It’s nice to be paid for your hobby.” I believe this is a measure of absolute satisfaction in one’s career and I will strive to achieve such. Lastly, I would like to recognize Dr. Craig Ogle for getting me excited about organic chemistry and Dr. Felicia Etzkorn, who recruited me at an ACS convention, long past the deadlines to apply to graduate schools. I would have never pursued a career in chemistry if not for these people.

Finally, I would like to acknowledge all of my colleagues at Virginia Tech and the Universität Würzburg. In particular, I am highly grateful to my friends, the editors of this dissertation: Dr. Tom Stennett and Russel Snead, Dr. Molly Congdon, Dr. Marwa Abdel Latif, and Ashley Peralta. I would also like to acknowledge my friend and colleague, Florian Rauch for his satirical encouragement to never give up when beating dead horses... and for the guitar – which kept me sane while beating said horses. While it may go without saying, it certainly should not go without printing, I extend my sincerest appreciation to my research colleagues, Dr. Xi Guo for her mentorship, Sean Rafferty, Cheryl Peck, and Dr. Neeraj Patwardhan. Not only am I most grateful for their assistance in these projects, but also for their patience, reassurance, criticisms, and friendship. In general, I am thankful to all of the people in my life who are now legitimately fed up with the phrase “I am undeniably and completely almost done.”
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<tr>
<th>General Abbreviations</th>
<th>Description</th>
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<tbody>
<tr>
<td>R</td>
<td>generic hydrocarbon or hydrocarbon containing functional groups</td>
</tr>
<tr>
<td>Ar</td>
<td>generic aromatic ring or functionalized aromatic ring</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>Pr</td>
<td>propyl</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>'Pr</td>
<td>iso-propyl</td>
</tr>
<tr>
<td>'Bu</td>
<td>tert-butyl</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>Cy</td>
<td>cyclohexyl, —C$<em>6$H$</em>{11}$</td>
</tr>
<tr>
<td>Tol</td>
<td>para-tolyl, 4-methylphenyl</td>
</tr>
<tr>
<td>OTf</td>
<td>triflate, —OSO$_2$CF$_3$</td>
</tr>
<tr>
<td>Ac</td>
<td>acetate, —C(O)CH$_3$</td>
</tr>
<tr>
<td>LB</td>
<td>Lewis base</td>
</tr>
<tr>
<td>NHC</td>
<td>N-heterocyclic carbene</td>
</tr>
<tr>
<td>M</td>
<td>transition metal</td>
</tr>
<tr>
<td>L</td>
<td>coordinating ligand</td>
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<tr>
<th>Ligands</th>
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<tr>
<td>pin</td>
<td>pinacol glycolato, pinacolato, 2,3-dimethylbutane-2,3-diol</td>
</tr>
<tr>
<td>cat</td>
<td>catechol glycolato, catecholato, benzene-1,2-diol</td>
</tr>
<tr>
<td>neop</td>
<td>neopentyl glycolato, 2,2-dimethylpropane-1,3-diol</td>
</tr>
<tr>
<td>DIPA</td>
<td>diisopropanol amine, 1-(2-hydroxypropylamino)propan-2-ol</td>
</tr>
<tr>
<td>dan</td>
<td>1,8-diaminonaphthalene, naphthalene-1,8-diamine</td>
</tr>
<tr>
<td>dmab</td>
<td>1,2-dimethylaminobenzene, $N,N'$-dimethyl-1,2-benzenediamine</td>
</tr>
<tr>
<td>9-BBN</td>
<td>9-borabicyclo[3.3.1]nonane</td>
</tr>
<tr>
<td>dba</td>
<td>dibenzylideneacetone, (1$E$, 4$E$)-1,5-diphenylpenta-1,4-dien-3-one</td>
</tr>
<tr>
<td>cod</td>
<td>1,5-cyclooctadiene</td>
</tr>
<tr>
<td>acac</td>
<td>pentane-2,4-dione</td>
</tr>
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<td>DMHD</td>
<td>2,6-dimethylheptane-3,5-dione</td>
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<tr>
<td>Cp*</td>
<td>1,2,3,4,5-pentamethylcyclopentadienyl</td>
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<td>dpf</td>
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<tr>
<td>PPh$_3$</td>
<td>triphenylphosphine</td>
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<td>PCy$_3$</td>
<td>tricyclohexylphosphine</td>
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<tr>
<td>[P($3,5$-(CF$_3$)$_2$C$_6$H$_3$)]$_3$</td>
<td>tris($3,5$-bis(trifluoromethyl)phenyl)phosphine</td>
</tr>
<tr>
<td>dppe</td>
<td>ethylenebis(diphenylphosphine), 1,2-bis(diphenylphosphino)ethane</td>
</tr>
<tr>
<td>DPEphos</td>
<td>bis[(2-diphenylphosphino)phenyl] ether, (oxydi-2,1-phenylene)bis(diphenylphosphine) ether</td>
</tr>
<tr>
<td>SPhos</td>
<td>2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl</td>
</tr>
<tr>
<td>Ruphos</td>
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</tr>
<tr>
<td>Xantphos</td>
<td>4,5-bis(diphenylphosphino)-9,9-dimethylxanthene</td>
</tr>
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</table>
Xphos & 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl \\
IPr & \(N,N\)-bis(2,6-diisopropylphenyl)imidazolyl \\
ICy & \(N,N\)-biscyclohexylimidazolyl \\
IMes & 1,3-bis(2,4,6-trimethylphenyl)-imidazolium \\
dtbpy & 4,4'-di-tert-butyl-2,2'-bipyridyl \\
phen & 1,10-phenanthroline \\

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Chapter 1. Introduction to Organoboron Compounds and the Carbon–Boron Bond

In a sense, organic chemists have come to represent the courier between recognizing the rising standards of current technologies and paving innovative pathways towards meeting those demands. The challenges facing society and industry to make processes more selective, more efficient, and more environmentally conscientious are topics in which the evolution of synthetic organic chemistry can address. Catalysis offers a state-of-the-art approach to improving the throughput, atom economy, and sustainability of preparative chemistry. The Noble Prizes in chemistry over the past 100 years can attest to the increasing interest in these areas: Sabatier and Grignard in 1912 (organometallic chemistry), Ziegler and Natta in 1963 (polymerization catalysis), Wilkinson and Fischer in 1973 (organometallic sandwich complexes), Lipscomb in 1976 and Brown in 1979 (organoboron chemistry), Sharpless, Noyori and Knowles in 2001 (chiral catalysis), Grubbs, Schrock and Chauvin in 2005 (olefin metathesis), and, most recently, Heck, Negishi, and Suzuki in 2010 (cross-coupling).

One of the main advantages of catalysis is that the interaction between the catalyst and the substrate can change the reactivity of a functional group and provide new synthetic pathways and selectivities for otherwise inaccessible transformations. For example, a simple alkene is unreactive towards most bases and nucleophiles. Highly reactive intermediates, like radicals or strong reducing agents (e.g. ozone), are needed to modify this carbon–carbon bond. However, the alkene becomes more susceptible to chemical transformations when a transition metal catalyst interacts with its $\pi$ and $\pi^*$ orbitals. In fact, Sabatier’s Nobel Prize winning discovery of metal-catalyzed alkene reduction initiated the development of transition metal catalysis. Sabatier and his post-doctoral researcher, Jean-Baptiste Senderens, passed ethylene over freshly reduced nickel particles in the presence of hydrogen to obtain near quantitative conversion to ethane.\textsuperscript{1}
Around the same time as Sabatier’s discovery, the chemistry between boron and carbon first appeared and was termed the “chemical metallization of carbon” by Ezekiel Weintraub in 1909. Little did Weintraub know, the carbon–boron bond would gain immense popularity by enabling synthetic chemists to install a diverse range of functional groups. Indeed, three of the aforementioned Nobel Laurates were boron chemists. William Lipscomb studied the structure and chemical bonding properties of borylating agents, like boranes, diboranes, and clusters. All the while H.C. Brown had been experimenting with the formation of C—B bonds and their oxidative transformation into C—O bonds. More recently, Suzuki and Miyaura’s development of a palladium-catalyzed reaction presents a versatile route to the formation of C—C bonds from organoboron compounds.

The Suzuki-Miyaura cross-coupling reaction (SMC) has revolutionized the way in which chemists approach small-molecule synthesis. Since a cross-coupling reaction joins two different organic reagents together through a new carbon–carbon bond, these reactions emerged as solutions to otherwise difficult methods for synthesizing elaborate natural products, agrochemicals and pharmaceuticals. The carbon–carbon bond is formed between an organohalide reagent and an organoboron compound using a palladium catalyst. This reaction is a very efficient methodology and, because of its great success, the Suzuki-Miyaura cross-coupling reaction has been extensively studied.

The Lewis acidity of the boron center allows bases and nucleophiles to enhance the polarization of the C—B bond, which is key to its transformative reactivity. In addition to the SMC reaction, organoboronic acids and their derivatives provide direct access to a myriad of different structures. Since the C—B bond can be transformed into C—O, C—N, C—X (X = halogen), C—H, and other C—C bond functional groups (e.g. carbonyls, alkyl groups, etc.), organoboron
Compounds have earned a reputable role as valuable synthetic intermediates. Consequently, methods for preparing them, like those employing bis(pinacolato)diboron ($B_2\text{pin}_2$), have increased exponentially in the last two decades (Figure 1.1). These preparations and synthetic applications are elaborated upon in Sections 1.2 and 1.3, respectively.

The use of organoboron compounds in preparative chemistry is an environmentally conscientious alternative given that most organoboron compounds are generally non-toxic. Consequently, methods for preparing them, like those employing bis(pinacolato)diboron ($B_2\text{pin}_2$), have increased exponentially in the last two decades (Figure 1.1). These preparations and synthetic applications are elaborated upon in Sections 1.2 and 1.3, respectively.

Moreover, this also makes boronic acids viable for incorporation into pharmaceutical compounds. Their unique structural properties qualify organoboronic acids as a new class of isosteres comparable to that of carboxylic acids. Unlike carboxylic acids, however, boronic acids are not naturally occurring functional groups, which makes their analogues interesting structural motifs for new drug candidates. These pharmaceutical applications are discussed in more detail in Section 1.4.

**Figure 1.1.** Number of publications using bis(pinacolato)diboron as a reactant over 20 years span. Data collected from a Scifinder search on September 27, 2016.
Organoboron compounds have idiosyncratic properties, depending on their substitution pattern. For instance, organoboranes, which possess only carbon–boron bonds, are much more reactive and less stable than organoboronic acids, which have only one carbon substituent and two hydroxyl groups. Even less reactive, but more stable, are the corresponding organoboronic ester derivatives. Therefore, it is instructive to briefly review the structure and properties of organoboron compounds, as these features pertain to the transformative reactivity of the C—B bond, and to examine diboron sources, as these reagents are commonly employed to form carbon–boron bonds.

1.1. Organoboronic Acids and their Derivatives

Boron is a semi-metallic element in an electron deficient ground state. With only three valence electrons available for bonding, the trivalent boron center is sp\(^2\) hybridized and adopts a trigonal planar geometry. An empty p orbital confers Lewis acidity, which is the most important determinant of the relative stability and reactivity of an organoboron compound. As will be highlighted in the following discussion, the Lewis acidity of the boron center is subjectively influenced by the orbital overlap of the substituents. For example, the moderate stability of organoboronic acids and esters, as opposed to organoboranes possessing only C—B bonds, is attributed to the electron-rich orbital overlap between the oxygen atoms and the p orbital of the boron center. This also contributes to a partial double bond character, making the B—O bonds shorter and stronger than typical C—B bonds (130 kcal/mol vs 77 kcal/mol).\(^\text{20}\) Such generic properties provide these organometallic compounds with a unique mixture of inorganic and organic characteristics.
1.1.1. Structure and Properties of Organoboronic Acids

Boronic acids are valuable synthetic reagents for distinguished reactions such as the Suzuki-Miyaura,\textsuperscript{12,21} oxidative Heck,\textsuperscript{22} Chan-Evans-Lam,\textsuperscript{23-25} and Liebeskind-Srogl couplings,\textsuperscript{26} as well as addition reactions with enones,\textsuperscript{27,28} carbonyls,\textsuperscript{29,30} and imines.\textsuperscript{31-37} In 1860, Frankland synthesized and isolated the first boronic acid by treating diethylzinc with triethylborate to form the highly reactive and air-sensitive triethylborane. Over time, air oxidizes organoboranes to their corresponding borinic acid, boronic acid and finally boric acid (Scheme 1.1).\textsuperscript{38,39}

![Scheme 1.1. Synthesis and oxidation of organoboron compounds.\textsuperscript{38,39}](image)

Phenylboronic acid is a white crystalline solid and it was characterized by X-ray crystallography in 1977.\textsuperscript{40} Figure 1.2 shows this compound crystallizes as a dimer, linked by a pair of O—H…O hydrogen bonds. The hydrogen bonding network extends even further; each of these units are linked to four other dimers, forming an infinite arrangement of stacked layers. Crystal structures of most other boronic acids also show this pattern, however, intermolecular B—O coordination is also common.\textsuperscript{40,41}

![Figure 1.2. Crystal structure of phenylboronic acid. CCDC # 1232300, reproduced.\textsuperscript{37}](image)

This network of hydrogen bonding diverts the electron density away from the boron center, thereby increasing the susceptibility of organoboronic acids to degradation processes. In general, aromatic boronic acids are more stable towards air and moisture than alkyl and heteroaromatic
boronic acids; however, all boronic acids undergo atmospheric oxidation and autoxidation, dehydration and protodeboronation. While the oxidative cleavage of the C—B bond by adventitious water or air is a thermodynamically favored process, it is kinetically slow for most compounds. Dehydration of the boronic acid forms cyclic and linear oligomeric anhydrides, which are even more susceptible to autoxidation. Protodeboronation, both in the solid state and in situ, is a common problem that lowers the reaction yields of transformative procedures like the SMC reaction. The isolation and purification of organoboronic acids can also be complicated by the amphiphilic boron center, which makes small boronic acids partial solubility in water. For these reasons, ester derivatives of organoboronic acids are quite popular for synthetic purposes.

1.1.2. Structure and Properties of Organoboronic Esters

A wide variety of organoboronic acid derivatives have been studied and some notable examples are provided in Figure 1.3. Diol and diamine protecting groups introduce distinctive dimensions to the stability and reactivity spectrum of the boron center. In general, the inductive donation of alkyl groups and reduced hydrogen bonding gives the organoboronic ester a higher stability towards air and water than their organoboronic acid counterparts. For instance, the pinacol boronic ester 1.2 is less reactive and less amphiphilic than a boronic acid (1.1), which makes these derivatives easier to purify and more stable for long-term storage. Similarly, catechol derivatives (1.3) are also popular due to their stability. These derivatives are more Lewis acidic than pinacolato boronic esters because the electron density of each phenolic oxygen atom has an opposing conjugation to the aromatic ring. While this competing delocalization also gives rise to unique bonding characteristics and reactivities, it lowers the stability of these compounds relative to 1.2. A six-membered ring has more conformational flexibility than a five-membered ring, and the decreased steric bulk makes the neopentyl glycolato boronic ester 1.4 more reactive than 1.2.
Chiral variations, such as (+)-pinanediolato boronic ester 1.5, have also been explored for stereoselective borylation and transformation reactions.\textsuperscript{46} In general, these compounds are expensive to prepare and their ability to confer stereoselection is quite limited.\textsuperscript{47-51}

Azaborolidines represent an interesting class of compounds. Nitrogen is less electronegative than oxygen, and consequently, there is a greater partial double character between the heteroatom and the boron center. This effect can be augmented by the inductive donation of alkyl groups on nitrogen.\textsuperscript{52} However, the steric congestion of substituents may lead a twisted geometry that is not conducive to orbital overlap. This makes the boron center in derivatives like 1.6 more susceptible to nucleophiles, water, and oxidizers. Conversely, the rigidity of 1.7 aligns the orbitals with the boron center, making it inert to non-acidic conditions.\textsuperscript{43,53-62}

Tetrasubstituted organoboronic ester derivatives possess divergent reactivity and stability patterns. For instance, the diethanolamine adduct 1.8 is not overly air stable because it exhibits an intramolecular Lewis acid-base interaction.\textsuperscript{63} This dative bond between nitrogen and boron gives the boron center an sp\textsuperscript{3} hybridization. The bicyclic ring structure forces a distorted tetrahedral
conformation, where the average dihedral angles deviate from 109.47° by 8.21°. This adduct formation and distorted geometry destabilizes the B—O bond by an estimated 12 kcal/mol and makes it prone to degradation and ligand exchange processes. However, in synthetic transformations, a base is not required for activation of the carbon–boron bond because this intramolecular interaction also augments the C—B bond polarization, causing it to be approximately 0.04 Å longer than the C—B bond of 1.1. Conversely, the sp³ hybridized trifluoroborate salt derivatives are exceptionally air stable. One obvious difference between 1.8 and 1.9 is that the trifluoroborate salt is not destabilized by ring strain or a distorted geometry. Moreover, the B—F bonds are much stronger than B—O bonds by about 30 kcal/mol, which gives rise to the increased stability of the boron center relative to the organoboronic acids and esters. However, analogous to the elongated C—B bond of 1.8, the sp³ hybridized boron center of a trifluoroborate salt creates a reactive bond for undergoing synthetic transformations.

While the metathesis illustrated in Scheme 1.2 is a thermodynamically unfavorable process, the formation of boronic esters from boronic acids is a straightforward stoichiometric synthesis. Transesterification of the hydroxyl groups by alcohols or amines is a reversible reaction. Therefore, product precipitation or dehydration techniques (e.g. azeotropic distillation or drying agents) are required to drive the reaction forward. One notable exception to this equilibrium is the formation of trifluoroborate salts, wherein the B—F bond is stronger than the B—O bond. The trifluoroborate salts readily precipitate out of solution when organoboron compounds are treated with potassium hydrogen fluoride.

\[
\text{Scheme 1.2. Synthesis of organoboronic esters from organoboronic acids.}
\]
1.1.3. Structure and Properties of Diboron Compounds

1.1.3.1. B$_2$X$_4$

In 1925, an electrical discharge reduction of boron trichloride was used to prepare diboron tetrachloride (B$_2$Cl$_4$). The general instability of this pyrophoric, colorless liquid hinders its synthetic utility. Highly electronegative halide atoms provide poor orbital overlap with boron. Thus, they do not stabilize the electron deficient boron centers and disproportionation reactions occur rapidly at temperatures above 0 °C. Similarly, the diboron tetrabromide reagent is so reactive it readily attacks stopcock grease and decomposes faster than B$_2$Cl$_4$. Unlike the bromine and chlorine derivatives, however, the diboron tetrafluoride analogue is a thermally stable and significantly less reactive gaseous compound.

1.1.3.2. B$_2$(NMe$_2$)$_4$

In contrast to the diboron tetrahalide compounds, tetrakis(amido)diboron derivatives are thermally stable and have a stronger B—B bond due to resonance contribution and hyperconjugation through orbital overlap. The heteroatoms delocalize the electron density in their occupied p orbitals to the empty π orbitals of the B—B bond. This partial orbital population raises the HOMO and LUMO and decreases the Lewis acidity of the boron centers. However, it is important to note that the boron–boron bond is weaker than tetrakis(alkoxy)diboron compounds because steric congestion imposes a staggered conformation. The N—B—B—N dihedral angle is 90°, which prevents conjugation of the electron density across the B—B bond. These conclusions are supported by a recent study which used solid state NMR to correlate the strength of the B—B bond in a series of...
diboron compounds to their $J^{(11}B, 11B)$ coupling constants. The $J$ coupling of these quadrapolar nuclei was resolved using a $J$-based double quantum filter NMR experiments in the solid state. The experiments determined that a tetrakis(amido)diboron derivative has the weakest B—B bond, relative to the tetrakis(alkoxy)diboron derivatives. Moreover, photoelectron spectroscopy experiments determined that the dimethylamido groups of tetrakis(dimethylamido)diboron are twisted out of the plane, where the lone pair electrons do not have maximum orbital overlap.

Tetrakis(dimethylamido)diboron is prepared in high yields from a two-step, one-pot synthesis, involving the reaction of boron trichloride and tris(dimethylamido)borane followed by the Wurtz coupling of the resulting chlorobis(dimethylamido)borane with highly dispersed sodium particles. Although this compound is extremely moisture sensitive, it is commercially available because provides convenient access to other amido- and alkoxo- diboron derivatives.

1.1.3.3. $\text{B}_2\text{pin}_2$

The pinacol protecting group (Figure 1.6) enhances the stability and strength of the B—B bond through $\pi$-donation and orbital overlap. Due to a planar geometry, this B—B bond is significantly shorter than that in $\text{B}_2(\text{NMe}_2)_4$ by about 0.05 Å (Table 1.1). The correlative $J$-coupling constant for this compound also quantified a significantly stronger B—B bond than $\text{B}_2(\text{NMe}_2)_4$. While the alkoxy ligands provide air, moisture, and thermal resiliency, they also decrease the Lewis acidity of the boron centers and the reactivity of the B—B bond. Consequently, metal catalysts are often needed to engage the B—B bond in addition reactions. The enhanced stability of the pinacol ligand popularized these organoboronic esters and bis(pinacolato)diboron is commonly employed to synthesize organoboron compounds, as demonstrated by Figure 1.1.
1.1.3.4. B$_2$cat$_2$

Bis(catecholato)diboron (Figure 1.7) has a dihedral angle of 0°, producing an eclipsed conformation which is also observed in B$_2$Cl$_4$, B$_2$F$_4$, and B$_2$pin$_2$. Photoelectron spectroscopy examining the orbital overlap of the oxygen and boron atoms found the delocalization of electrons from the oxygen atoms strengthen the B—B bond, resulting in a shorter bond length than other diboron compounds (Table 1.1). This effect is even more pronounced in B$_2$cat$_2$ than in B$_2$pin$_2$ because the aromatic rings become conjugated through the B—B π orbitals. This data is also consistent with the $J$(^11B, ^11B) coupling constant correlation, which established B$_2$cat$_2$ as having the strongest B—B bond. Like bis(pinacolato)diboron, this compound is commercially available and stable to air, moisture, and heat, but usually requires activation by a metal catalyst.

Table 1.1 Comparison of diboron B—B bond lengths.

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<th>Compound</th>
<th>Bond Length (Å)</th>
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<tr>
<td>B$_2$Cl$_4$</td>
<td>1.755</td>
</tr>
<tr>
<td>B$_2$F$_4$ $^a$, $^85,86$</td>
<td>1.675</td>
</tr>
<tr>
<td>B$_2$(NMe$_2$)$_4$ $^a$, $^81$</td>
<td>1.7624</td>
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<tr>
<td>B$_2$pin$_2$ $^87$</td>
<td>1.7116</td>
</tr>
<tr>
<td>B$_2$cat$_2$ $^88$</td>
<td>1.6783</td>
</tr>
<tr>
<td>B$_2$(OH)$_4$ $^b$, $^89$</td>
<td>1.7104, 1.7155</td>
</tr>
<tr>
<td>PDIPA $^64$</td>
<td>1.7212</td>
</tr>
<tr>
<td>PDAN</td>
<td>Unknown</td>
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</tbody>
</table>

$^a$ Gas-phase electron diffraction structure. $^b$ Two crystallographically independent molecules.
1.1.3.5. \( \text{B}_2(\text{OH})_4 \)

Tetrahydroxydiboron first appeared in the literature in the 1950s where it was described as a product from the hydrolysis of various diboron compounds, such as \( \text{B}_2\text{X}_4 \), \( \text{B}_2(\text{OR})_2 \), and \( \text{B}_2(\text{NMe}_2)_4 \). The most widely employed method for its synthesis is from the hydrolysis of \( \text{B}_2(\text{NMe}_2)_4 \) under acidic conditions.\(^{87} \) The \( J \)-coupling solid-state NMR correlation found that this diboron has a very similar \( \text{B—B} \) bond strength to that of \( \text{B}_2\text{pin}_2 \).\(^{82} \) This is also supported by the similar bond lengths in the crystal structures (Table 1.1).\(^{89} \)

1.1.3.6. \( \text{pinB—B(DIPA)} \), PDIPA Diboron

An unsymmetrical diboron is characterized by two boron centers bearing different ligands. Originally proposed in 1968, the efforts to produce such a compound failed on all attempts.\(^{90} \) Santos et al. published the first synthesis and characterization of an unsymmetrical diboron reagent forty-one years later (Figure 1.9).\(^{91,92} \) This unsymmetrical diboron is synthesized by treating bis(pinacolato)diboron with diisopropanol amine (DIPA). The key to the successful isolation of this compound is its precipitation from solution using an 8:1 mixture of diethyl ether and dichloromethane.

Unique to this compound is the dative bond between the nitrogen atom and boron center. This extra electron density pours into the p orbital and creates a novel \( \text{sp}^2-\text{sp}^3 \) mixed diboron.\(^{91} \) The internal rehybridization of the boron atom weakens and elongates the \( \text{B—B} \) bond, much like a Lewis acid-base adduct. Indeed, the crystal structure has a longer \( \text{B—B} \) bond than the tetrakis(alkoxy)diborons. However, \( \text{B}_2(\text{NMe}_2)_4 \) still possesses the longest and weakest \( \text{B—B} \) bond (Table 1.1). The NMR coupling correlation experiments clearly demonstrated that the boron–
boron bond in PDIPA diboron is weakened by the sp$^3$ ligand system, wherein the $J$-coupling constant was found to be between that of a tetrakis(alkylamido)diboron and $\text{B}_2\text{pin}_2$. Furthermore, the B—B bond in this molecule is similar to that of Lewis base coordinated adducts, both in terms of the bond length and the bond strength measured by NMR. While metal catalysts are often used to engage the B—B bond, this intramolecular pre-activation is advantageous because the Bpin moiety is readily transferred in the absence of activators like bases or phosphine additives.

1.1.3.7. **pinB—Bdan, PDAN Diboron**

The pinacolato and 1,8-diaminonaphthalene differentially protected diboron, PDAN, is a relatively new platform in diboron chemistry. The author participated in the optimization of a synthetic route to this diboron from a ligand exchange reaction with preactivated PDIPA diboron. This procedure is described in Section 6.3.1. The 1,8-diaminonaphthalene ligand system locks the nitrogen heteroatoms into a position for optimal orbital overlap with the boron center. Like the catechol ligand, donation of electron density from the heteroatoms into the p orbital of boron is competing with the resonance interaction of lone pairs with the aromatic ring system. However, the empty p orbital confers aromaticity to the ligand system, making it an isostere of the phenalenyl anion. This boron center is much less Lewis acidic than the pinacolato boron center. Activation by a Lewis base chemoselectively forms an adduct with the pinacolato boron center, and polarizes the B—B bond. DFT calculations estimate the difference between a methoxide adduct with Bpin versus Bdan to be on the order of 7.4 kcal/mol. There has been a growing interest over the last decade in applying the unique properties of the 1,3,2-naphthodiazaborole system (Bdan moiety) in functional materials as well as in synthetic applications.
1.2. Conventional Syntheses of Organoboronic Acids and Esters

1.2.1. Trapping Organometallic Reagents with Trialkylborates

The most inexpensive method for synthesis of an organoboronic acid or ester is by reacting an organolithium or an organomagnesium reagent with a borate ester at low temperature (Figure 1.3). These organometallic reagents can easily be formed in situ by a metal-halogen exchange with commercially available organohalides. The major drawback to this approach is a low functional group tolerance because the organometallic intermediate is strongly nucleophilic and the reaction is quenched with an aqueous, acidic workup. For very simple aryl, alkyl, and even alkylboronic acids, however, this is a highly efficient synthesis. The isolation and purification of boronic esters is much preferred due to the partial water solubility of small organoboronic acids. These derivatives are prepared directly by quenching the crude mixture with a diol.

\[
\begin{align*}
R\text{MgX} & \quad \text{or} \quad R\text{Li} & \quad \text{B(OR)}_3 & \quad \text{B(OR)}_2 & \quad \text{H}^+, \text{H}_2\text{O} & \quad R\text{B(OH)}_2 \\
& \quad -60^\circ\text{C} & & & & \\
\end{align*}
\]

Scheme 1.3. Synthesis of organoboronic esters and acids with organometallic reagents (X = halogen). Esters are quenched with the diols.

1.2.2. Coupling of Aryl Halides with Diboron Compounds

A metal-catalyzed coupling reaction is a viable alternative to bypass the harsh reaction conditions and low yields associated with trapping organometallic reagents. Palladium effectively couples an aryl halide with a diboron compound (e.g. B\textsubscript{2}pin\textsubscript{2}, Scheme 1.4). These reaction conditions are extremely mild, employing a weak base to polarize the B—B bond and assist the transmetallation process. In contrast to the organometallic methods, this reaction is tolerant towards a wide array of functional groups such as ketones, esters, and nitriles. A Pd(0) catalytic system with sophisticated ligands, such as XPhos (2-Dicyclohexylphosphino-2’,4’,6’-
triisopropylbiphenyl$^{108}$ or an NHC (N-heterocyclic carbene),$^{109}$ is able to borylate the less reactive aryl chloride substrates.$^{110,111}$ Just as B$_2$pin$_2$ delivers the boronic ester product, B$_2$(OH)$_2$ may be used instead to furnish the boronic acid directly.$^{112}$ Similarly, PDAN diboron can be used in this reaction to access the Ar—Bdan variant.$^{113}$ These coupling reactions can also be performed with boranes (e.g. HBpin) using a Pd(II),$^{114-116}$ or Ni(II)$^{117,118}$ catalyst. More recently, borylations with B$_2$pin$_2$ using a Co(I)$^{119}$ and Cu(I)$^{120}$ catalysts were also reported, but have been under explored.

### 1.2.3. C—H Activation

One of the most intriguing modes of synthetic functionalization is through the activation of a C—H bond by a metal catalyst. While these methods have been known for over 50 years, only recently has C—H activation developed a niche in organic synthesis.$^{121,122}$ In 1995, Hartwig’s group serendipitously discovered that metal–boryl complexes, such as those based on rhodium, react with hydrocarbons to borylate the C—H bond (Scheme 1.5).$^{123-126}$ The reaction of aliphatics occurs exclusively on primary carbons and is selective for the least sterically hindered and the most electron-deficient C—H bond. These reaction conditions can be applied to benzene, which generates high yields of PhBpin under neat conditions. However, many functional groups cannot endure such high temperatures. As such, a fruitful collaboration between Hartwig, Ishiyama, and Miyaura et al.$^{127}$ led to the optimization of an iridium catalyst with a bipyridine ligand for the borylation of arenes at room temperature (Scheme 1.5). These conditions are applicable towards a diverse scope of aromatic substrates. In general, electron-poor aromatic rings are better substrates and the regioselectivity of the addition is governed solely by steric interactions.$^{127-129}$
The iridium-catalyzed C—H borylation was expanded to include heterocyclic substrates by the Marder group. A collaborative project with Steel et al. led to the development of microwave-assisted conditions which shortened the reaction times and allowed for tandem borylation-SMC reactions.

1.2.4. Monoboration of Unsaturated Organic Compounds

Nobel laureate, H.C. Brown, is arguably the father of organoborane chemistry for his innovative contributions to the development of their synthetic applications. Brown discovered that hydroborane (BH₃) reduces unsaturated carbon–carbon bonds, forming new C—H and C—B bonds. Hydroboration with alkoxy- or alkylboranes (HB(OR)₂ and HBR₂) provides convenient access to organoboron compounds bearing one carbon–boron bond (Scheme 1.6). When a terminal alkyne is reacted with a borane, a regioselective syn-addition places the boron moiety on the terminal carbon atom and stereoselectively affords the trans-alkenylboronic ester. Hydrolysis of the ester delivers the boronic acid. Catecholborane and pinacolborane furnish the desired alkenylboronic esters. However, diboration of the substrate is frequently observed with small
Boranes, like BH$_3$. This is also encountered with alkylboranes, necessitating bulky substituent (e.g. cyclohexyl or 9-BBN = 9-borabicyclo[3.3.1]nonane) to prevent a second reaction from giving the 1,1-diborated product.\(^8\)

Boranes are sufficiently reactive to reduce unsaturated compounds; however, the use of a metal catalyst provides a new mode access to organoboronic acids and esters.\(^{137-139}\) For example, uncatalyzed hydroboration reactions with dioxaboranes require heating and long reaction times.\(^9,140-142\) The efficiency of these reactions can be improved with Rh(I),\(^{143-145}\) Pd(II),\(^{138,146}\) Zr(II),\(^{139,147}\) and Ti(II)\(^{148}\) catalysts. Furthermore, since hydroboration also reduces carbonyls, a double bond can be chemoselectivity hydroborated in the presence of a ketone using Wilkinson’s complex, [Rh(PPh$_3$)$_3$Cl].\(^{144}\) Of particular note, a metal catalyst can also provide access to the (Z)-alkenylboron product through an anti-addition process (Scheme 1.7).\(^{149}\) This methodology was used to access a key intermediate in the synthesis of fostriecin.\(^{150}\)

**Scheme 1.6.** Hydroboration of terminal alkynes with dioxaboranes (top) and alkylboranes (bottom). Syn-addition gives the cis-alkenylboron compound.\(^7,8,134-136\)

**Scheme 1.7.** The catalyzed and uncatalyzed hydroboration of a terminal alkynes provide complementary access to the $E$ and $Z$ alkenes.\(^{149}\)
Using a cheap and earth abundant copper catalyst, formal hydroboration takes place with diboron compounds (Figure 1.11). Miyaura and co-workers pioneered the addition of a borylcopper species to terminal alkynes using stoichiometric amounts of CuCl and B₂pin₂. They discovered that complex 1.10 undergoes syn-addition with an alkyne to generate the vinylic copper species, 1.11. However, under these conditions, the regioselectivity is poor and could not be controlled sterically with ancillary ligands. Yun et al. discovered that methanol carries out protonolysis of 1.11 and turns over the active catalyst, 1.12. Under these conditions, regioselective formal hydroboration could be optimized for terminal and internal alkynes, including aryl substituted and propargyl substrates, as well as 1,3-enynes, allenies, and 1,3-dienes. The particular phosphine or NHC ancillary ligand is elemental in the success of these reactions because the electronic nature of the substrate determines the selectivity when there are no significant steric interactions. Copper(II) oxide nanoparticles also show catalytic activity for carrying out formal hydroboration.

1.2.5. Diboration of Unsaturated Hydrocarbons

The formation of two carbon–boron bonds using a diboron reagent was first reported in 1954 by Schlesinger and co-workers when they noted that a reaction between diboron tetrachloride, B₂Cl₄, and ethylene formed products which decomposed rapidly. The highly unstable nature of B₂X₄ (X = Cl or Br) limited their use for practical synthetic purposes and
attention was turned to the tetrakis(amino)- and tetrakis(alkoxy)diboron derivatives.\textsuperscript{73,76-79,166} While the tetrakis(alkoxy)diboron derivatives are more practical for laboratory settings, the heteroatom conjugation also strengthens the B—B bond (104 kcal/mol), requiring low-valent transition metals to assist bond cleavage.\textsuperscript{20,75,79,167,168} Platinum, iridium, rhodium, and palladium have all been implemented for the diboration of alkynes, alkenes, 1,4- and 1,2-dienes (allenes).\textsuperscript{169,170}

1.2.5.1. Alkyne Diboration

In 1993, Ishiyama, Matsuda, Miyaura, and Suzuki demonstrated the syn-addition of bis(pinacolato)diboron to an unsaturated substrate. Alkyne diboration, catalyzed by tetrakis(triphenylphosphine) platinum(0), Pt(PPh\textsubscript{3})\textsubscript{4}, produces cis-bis(boryl)alkenes (Scheme 1.8).\textsuperscript{171} High yields are obtained with terminal and internal alkynes bearing diverse functional groups (79-89%).\textsuperscript{171,172}

\[ \text{R} \equiv \equiv \text{R} + \begin{array}{c}
\text{O} \\
\text{B} \equiv \equiv \\
\text{B} \\
\text{O}
\end{array} \xrightarrow{\text{Pt(PPh\textsubscript{3})\textsubscript{4}}} \begin{array}{c}
\text{pinB} \\
\text{R} \\
\text{Bpin}
\end{array} \quad \text{DMF} \quad 80 \degree C \quad \text{79-89\%}
\]

Scheme 1.8. Platinum-catalyzed diboryl addition of bis(pinacolato)diboron to alkynes.\textsuperscript{171}

Ligand selection drastically affects the catalytic activity in diboration reactions. For example, no reaction is observed with chelating phosphine ligands or with phosphine-free Pt(dba)\textsubscript{2} and Pt(cod)\textsubscript{2} catalysts.\textsuperscript{173} Strong σ-donor ligands facilitate the oxidative addition of the diboron reagent to the catalyst. As such, there is a positive correlation between the basicity of the phosphine and the catalytic activity of the complex, wherein PPh\textsubscript{2}(o-Tol) > PC\textsubscript{3}y > P\textsuperscript{a}Bu\textsubscript{3} ≈ PMe\textsubscript{2}Ph > PMePh\textsubscript{2} > PPh\textsubscript{3} > no phosphine ≈ P(C\textsubscript{6}F\textsubscript{5})\textsubscript{3} ≈ P(o-Tol)\textsubscript{3} > P\textsuperscript{b}Bu\textsubscript{3}.\textsuperscript{173} The two notable exceptions in this trend, P\textsuperscript{b}Bu\textsubscript{3} and PPh\textsubscript{2}(o-Tol), indicate the catalyst is sensitive to steric interactions. Tris(tert-butyl)phosphine is a strong σ-donor, however, the bulkiness of this ligand may prevent the catalyst
from interacting with the diboron reagent.\textsuperscript{173} Since the \(\sigma\)-donor strength of PPh\(_2\)(o-Tol) is expected to be comparable to PPh\(_3\), the superior activity of this catalytic complex must be a result of the increased cone angle.\textsuperscript{173} It is possible that the additional methyl substituent leads to an under-ligated [L\(_3\)Pt] complex with an open coordination site.

A few other transition metal catalyst have also been explored in the past decade. In 2006, an \textit{anti}-addition side product was observed in the presence of a cobalt(I) catalyst.\textsuperscript{119} While this was a surprising finding, no follow-up has been reported to date. A copper(II) catalyst was optimized for the diboration of alkynes and arynes. The conditions are mild, but high temperatures are required and only a hydrocarbon substrate scope was explored.\textsuperscript{120} Most recently, diboration was achieved with catalytic FeBr\(_2\) and LiOMe in THF at 80 °C. An interesting feature about this catalytic system is that carboboration can be performed in the presence of an organohalide.\textsuperscript{174} Finally, a purely organocatalytic borylation reaction is noteworthy. Unique to this approach is that an organosulfide uses light to catalyze the diboration reaction of terminal alkynes by way of a boryl-centered radical.\textsuperscript{175}

\subsection*{1.2.5.2. Alkene Diboration}

While investigating the mechanism for rhodium-catalyzed hydroboration, Marder and co-workers found that [Rh(PPh\(_3\))\(_2\)Bcat\(_2\)Cl] achieved a 1,2-diboryl addition to vinylanisole. However, this reaction was compromised by competing \(\beta\)-hydride eliminations yielding a mixture of products.\textsuperscript{176} Reasoning that a less electron-rich gold(I) complex would inhibit the competing \(\beta\)-

![Scheme 1.9](image)

\textbf{Scheme 1.9.} Diboration of 4-vinyl-anisole with a gold(I) complex.\textsuperscript{177}
hydride elimination process, they established the first successful method for diborating alkenes in 1995 (Scheme 1.9).\textsuperscript{177,178}

Phosphine-ligated platinum complexes are ineffective catalysts because phosphorus has d orbitals which overlap with metals better than carbon sp\textsuperscript{2} orbitals. As such, phosphine-free platinum(0) complexes are suitable since they eliminate the competition between phosphine and olefin coordination, as was discovered by two independent researchers in 1997.\textsuperscript{179,180}

Based on their report that Pt(dba)\textsubscript{2} catalyzes the addition of B\textsubscript{2}pin\textsubscript{2} to 1,3-dienes,\textsuperscript{181} Miyaura et al. extended these conditions to diborate terminal and strained cyclic alkenes with good yields (76-86\%). However, diboration of internal alkenes is too slow to be synthetically useful.\textsuperscript{179}

Similarly, Smith et al. used bis(catecholato) diboron reagent to diborate terminal alkenes and strained cyclic alkenes with the Pt(cod)\textsubscript{2} in higher yields (82-95\%).\textsuperscript{180} In contrast to Miyaura’s reaction, internal olefin substrates produces a complex mixture of products, a result noted previously by Marder and co-workers with the rhodium catalyst. Since the metal–hydride bond has better orbital overlap than an sp\textsuperscript{3} carbon–metal intermediate, β-hydride elimination occurs readily, producing HBcat and an alkenylboron compound. Diboration and hydroboration reactions ensue to produce the observed mixture of products.\textsuperscript{180} Later, Marder and co-workers found a zwitterionic rhodium complex could obtained a clean diboration of internal alkynes with B\textsubscript{2}cat\textsubscript{2}.\textsuperscript{182}

\subsection*{1.2.5.3. Allene Diboration}

The first example of diboron addition to an allene was established in 1998.\textsuperscript{183} Using a Pt(PPh\textsubscript{3})\textsubscript{4} catalyst in toluene at 80 °C, Miyaura and co-workers found that bis(pinacolato)diboron adds to a variety of allenic substrates to yield a mixture of regioisomers (Scheme 1.10). Parallel to the alkyne diboration, the phosphine has considerable influence on the reactivity of the platinum(0) catalyst, as well as the regioselectivity of the addition. For instance, PCy\textsubscript{3} provided the highest
reactivity, followed by P(4-MeOC₆H₄)₃ > P(4-ClC₆H₄)₃ > PPh₃. The distribution of products is controlled solely by the steric interactions. Diboration of monosubstituted 1,2-dienes with Pt(PPh₃)₄ preferentially on the internal double bond (1.13, R' = H). Generation of 1.14 is only favored when bulkier ligands, such as PCy₃, are used to diborate 1,1-disubstituted allenes.¹⁸³

In the following years, alternative transition metal catalysts were developed based on palladium¹⁸⁴,¹⁸⁵ and copper.¹⁸⁶,¹⁸⁷ Stereoselective¹⁸⁸ and metal-free¹⁸⁹ approaches have also been realized. The metal-free reaction is performed simply by treating a mixture of B₂pin₂ and methanol and with a catalytic amount of sodium tert-butoxide at 45 °C in THF (Scheme 1.11). Interestingly, the base is sufficient for activating the diboron reagent through a Lewis acid-base adduct. It is important to note that this reaction is complementary to the metal-catalyzed reactions because the addition takes place regioselectively on the terminal double bond. However, only one example has been explored and the stereochemistry was not provided.

Scheme 1.11. Transition metal-free diboration of 1-cyclohexyl-1,2-propadiene.¹⁸⁹
1.2.6. Borylation of Carbonyl Compounds with Diboron Reagents

1.2.6.1. 1,2-Diboration of Aldehydes and Ketones

In 2005, Sadighi et al. described a highly reactive copper(I) complex, [(IPr)Cu(O'Bu)] (IPr = N,N-bis(2,6-diisopropylphenyl)imidazolyl), that reacts with B₂pin₂ to generate a borylcopper(I) species in situ.¹⁹⁰ Exchanging the IPr ligand for the less sterically demanding ICy ligand (N,N-biscyclohexylimidazolyl) enables the borylcopper intermediate to undergo a 1,2-addition to aldehydes (Scheme 1.12). A wide scope of aldehydes may be employed to give the corresponding α-hydroxyboronate esters following the hydrolysis of the B—O bond upon workup.¹⁹¹

\[
[(ICy)CuBpin] \xrightarrow{\text{H}} (ICy)Cu-O \xrightarrow{\text{R}} \frac{\text{Bpin}}{\text{H}} \xrightarrow{\text{R}} \frac{\text{Bpin}}{\text{Bpin}} + [(ICy)CuBpin]
\]

Scheme 1.12. A copper-catalyzed 1,2-diboration of aldehydes to access α-boryl alcohols.¹⁹¹

Shortly thereafter, Molander noted that the addition of 2 equivalents of methanol provides a proton source for proteolytic cleavage, which greatly reduces the reaction time from 22 hours to 1.5 hours.¹⁹² That same year, Clark expanded the reaction conditions to include ketones. Of note, a modest diastereoselectivity was found when an α-chiral ketone was used. In the transition state, the orientation of the η-2 complex prior to insertion imparts this selectivity (Figure 1.12).¹⁹³⁻¹⁹⁵

![Figure 1.12. Felkin-Anh model of the 1,2-diboration reaction. The geometry of the η-2 intermediate governs stereoselectivity of the insertion process.⁰³]

1.2.6.2. β-Borylation of α,β-Unsaturated Carbonyls in Organic Solvents

Enthusiasm for conjugate additions to α,β-unsaturated carbonyl compounds incited almost two decades of research to refining this method of accessing β-boryl carbonyl compounds.³⁷,⁴⁶,¹⁹⁶-
The β–borylation with diboron compounds (e.g. B\textsubscript{2}pin\textsubscript{2}) was discovered by Marder and Norman et al. in 1997 (Scheme 1.13).\textsuperscript{202-204} The 1,4-conjugate addition occurs readily in the presence of [Pt(C\textsubscript{2}H\textsubscript{3})(PPh\textsubscript{3})\textsubscript{2}] at 80 °C to afford the (Z)-enolate quantitatively. This was the first example of a β-boryl ketone, which quickly became a synthetically useful structural motif and propelled interest in this area. In the following years, palladium,\textsuperscript{205,206} rhodium,\textsuperscript{207-210} nickel,\textsuperscript{206,211} and zinc\textsuperscript{212} catalysts were developed for the β-borylation of α,β-unsaturated carbonyls. At the turn of the twenty-first century, the Hosomi\textsuperscript{213} and Miyaura\textsuperscript{151,152} research groups concomitantly demonstrated that copper(I), a more economical catalyst, can also carry out these reactions. Since copper salts are abundant in the earth’s crust, they constitute an inexpensive, environmentally benign, and sustainable alternative to rare earth metal catalysts.

Hosomi and Miyaura both established that pre-activation of the diboron species is crucial for the transmetallation of boron to copper.\textsuperscript{151,152,213} Given that boron is highly electrophilic and only weakly nucleophilic, coordination of a Lewis base (LB) is necessary to cause the boron–boron bond to become longer and more electron-rich. This increases the nucleophilicity of boron and transfers a moiety from the adduct to the electrophilic copper(I) precatalyst (Figure 1.13).\textsuperscript{214} These adducts have also been proposed in the metal-free β-borylation reactions developed by both Hoveyda and Fernández.\textsuperscript{215-217} In several cases, they have been isolated and characterized.\textsuperscript{218,219} The resulting borylcopper(I) intermediate 1.17 (L = NHC) has also been isolated and validated as

\[ \begin{align*}
\text{Ph} & \quad \text{O} \quad \text{R} \quad \xrightarrow{\text{B}_2\text{pin}_2, [\text{Pt}]} \quad \text{toluene, 80 °C, 12 h} \quad \xrightarrow{\text{H}_2\text{O}} \quad \text{Ph} & \quad \text{O} \quad \text{Bpin} \quad \text{R} \\
\text{1.15} & \quad \xrightarrow{\text{1.16}} & \quad \text{pinB} & \quad \text{O} \quad \text{Bpin} & \quad \text{R} \\
\text{R} = \text{Me, Ph} 
\end{align*} \]
the active catalytic species.\cite{164,190,214} Quantum-chemical calculations by Lin, Marder and co-workers elucidated that 1.17 coordinates to the C—C double bond of 1.15. Insertion into the Cu—B bond is a 3,4-addition process that gives the carbon-bound C-enolate 1.18, which can easily tautomerize to 1.19 (Figure 1.13). These studies also determined that direct metathesis with B$_2$pin$_2$ occurs only with the copper-bound O-enolate 1.19.\cite{220} For this reason, the equilibrium of 1.18 and 1.19 directly affects the catalytic turnover. This insight was later corroborated by deuterium-labeled NMR experiments.\cite{221} In view of this, it is not surprising that the aprotic conditions initially

\textbf{Figure 1.13.} Proposed mechanism of the copper(I)-catalyzed conjugate addition with bis(pinacolato)diboron.\cite{214,220}
optimized by Hosomi and Miyaura generally required long reaction times (>20 h) to obtain good yields.

Based on the copper-catalyzed conjugate reduction of lactones and lactams, in which an alcohol additive encourages σ-bond metathesis by protonating organocopper enolates, Yun et al. reasoned that supplementing methanol in the reaction mixture would rapidly quench the postulated organocopper intermediates and accelerate the rate of β-borylation. Alcoholysis of either tautomer delivers the final product, 1.16, and compound 1.20, which readily executes σ-bond metathesis with B₂pin₂ to regenerate the active catalyst, 1.17. DFT calculations supported these results, demonstrating that the protic species reacts with both the C- and O-enolates, 1.18 and 1.19, but does not affect the active borylcopper(I) species 1.17.

According to the proposed mechanism, it is necessary for a Lewis base to activate the diboron reagent for σ-bond metathesis. Inspired by the structure of the Lewis acid-base adduct, the Santos group designed a novel sp²-sp³ hybridized diboron compound, pinacolato diisopropanolaminato diboron, PDIPA diboron. Internal chelation eliminates the need for basic conditions. In the presence of copper(I) salts, the pinacolato boronate is chemoselectively transferred to α,β-unsaturated compounds at room temperature (Scheme 1.14).

\[
\text{PDIPA diboron} \quad 1.17
\]

**Scheme 1.14.** Copper(I)-catalyzed β-borylation of α,β-unsaturated carbonyl compounds with PDIPA diboron. 64,91
1.3. Transformations of the Carbon–Boron Bond

Organoboronic acids and their derivatives became an increasingly popular class of compounds due to their ease of synthesis, availability, functional group tolerance, and versatility in synthetic applications. The electron-deficient and Lewis acidity of the boron center facilitates the transformation of C—B bonds into a comprehensive scope of functional groups (Figure 1.14).

![Figure 1.14. Synthetic transformations of the carbon–boron bond.](image)

1.3.1. Oxidation

The oldest transformation to find synthetic application is the formation of an alcohol by oxidizing the carbon–boron bond in an alkaline peroxide solution.\(^7,225,226\) The oxidation of an alkyl or alkenylboronate generates the corresponding alcohol or carbonyl.\(^227-229\) This reaction is not generally used in the preparation of phenols since there are cheaper, more efficient syntheses.\(^19\) A
notable application of this chemistry is for late-stage transformations in a multi-step synthesis. Many natural products feature alcohols and carbonyls. However, the electrophilic carbonyl or protic functional group is not always amenable to other reaction conditions. As such, the C—B bond can serve as a place holder until later in the synthetic pathway. This methodology also serves to avoid the use of protecting groups, which can sometimes be problematic to remove. Milder conditions for this transformation have been developed which employ sodium perborate, oxone, or hydroxylamine as the oxidant.

### 1.3.2. Halogenation

Organoboronic acids and esters can also provide organohalides through a halodeboronation process. An aqueous solution of iodine with excess potassium iodide provides the C—I bond. The carbon–boron bond is converted to the corresponding organohalide using cuprous chloride or cuprous bromide. Alternatively, an aqueous solution of chlorine or bromine may be employed. No reaction occurs under anhydrous conditions, even when irradiated with light, which means that the C—B bond is ignored by radicals. Furthermore, unlike arylboronic acids, alkylboronic acids are unreactive at a pH below 7. Thus, it is proposed that the boron center is activated by a Lewis acid-base interaction and an electrophilic substitution process takes place. The C—F bond is obtained when an arylboronic acid is reacted with cesium fluoroxy sulfate in methanol.

### 1.3.3. Amination

It is possible to form carbon–nitrogen bonds from organoboronic acids and esters. However, these reactions are difficult due to an ineffective association between weak amine bases.
and the boron center. For example, to form an azide, stoichiometric amounts of lead(IV) acetate with catalytic amounts of mercury acetate must be used to form a more reactive organolead intermediate from the organoboronic acid.\textsuperscript{239} Nitration is performed under milder conditions using either silver nitrate or ammonium nitrate, but only when trimethylsilylchloride is added to make a more reactive nitrating agent.\textsuperscript{240,241} Until recently, standard electrophilic amination reaction conditions required conversion of an organoboronic derivative to the more Lewis acidic trialkylborane.\textsuperscript{242} However, rather than altering the reactivity of the substrate, increasing the nucleophilicity of the amination reagent is a more direct solution and lithiation of alkoxyamines readily provides an adequate intermediate for carrying out this process (Scheme 1.16).\textsuperscript{243}

**1.3.4. Homologation**

Analogous to the amination reaction, the homologation reaction uses a strong organometallic nucleophile to attack the boron center and induce a boron-promoted 1,2-rearrangement on (α-haloalkyl)boronic esters (Scheme 1.17). The homologation reaction can be

**Scheme 1.16.** Mechanism for the amination of organoboronic esters,\textsuperscript{243}
performed on alkyl or alkenylboronic esters. This powerful approach to modifying the organic backbone of the boronic ester retains the carbon–boron bond for subsequent transformations. When α-haloalkyl organometallics are employed, the reaction can be repeated. The development of an asymmetric variation to this chemistry was revolutionary in the field of C–C bond formation in the 1980s. Matteson and co-workers studied the formation of chiral α-boronates from a ZnCl$_2$-catalyzed addition of dichloromethylthium to boronic esters bearing a C$_2$ symmetrical 1,2-diol ligand (Scheme 1.17).$^{47-51}$ These chiral α-chloroboronates undergo reactions with carbanions, but heteroatom nucleophiles can be substituted to provide chiral amines, ethers, or thioethers.$^{49,244}$

This methodology has been extensively employed in the synthesis of complex natural products.$^{50,245-247}$ A simple example is the preparation of 4-methyl-3-heptanol diastereomers (Scheme 1.18).$^{248}$ These reactions take place with stereoselection of ≥99.9%. Homologation and methylation was performed on (4R,5R)-dioxaborolane, 1.21. Intermediate 1.22 was then homologated again and ethylated to give 1.23. Oxidation of the carbon–boron bond provides 1.24, a compound found in the aggregation pheromone of an elm bark beetle, Scolytus multistriatus (Scheme 1.18, Top). Using the (S)-enantiomer of a methyl boronic ester, 1.25, the diastereomer is obtained in an analogous fashion. Compound 1.28 is the trail pheromone of a Southeast Asian ponerine ant, Leptogenys diminuta (Scheme 1.18, bottom).$^{248}$
1.3.5. Crotyl Borane Allylation

Elegant methodologies for forming new carbon–carbon bonds via the crotyl borane allylation of carbonyls are widely employed. Chain elongation of the carbon backbone is achieved through the coupling of an allylic boronate with an aldehyde. A formal reduction of the carbonyl occurs to provide the homoallylic alcohol. Unique to this transformation is that diastereoselectivity is controlled solely by 1,3-diaxial interactions in the transition state (Scheme 1.19).\textsuperscript{249,250} Due to the many chiral centers bearing alcohols in natural products, this reaction is commonly used in their synthesis. For example, preparation of stereochemically defined β-methyl alcohol or \textit{vic}-diol functionalities in pheromones, as well as macrolide and polyether antibiotics, is aided by this method.\textsuperscript{250} Generation of an imine \textit{in situ}, using NH\textsubscript{3} and ethanol, is a notable variation for producing the homoallylic amine.\textsuperscript{36,251-254}

Excellent enantioselectivities are obtained when these reactions are metal-catalyzed. Serving as a Lewis acids, scandium triflate promotes the allylation by coordinating to the exocyclic oxygen atoms of the boronic ester. This increases the electrophilicity of the boron center and allows the reaction to be conducted at low temperatures which improves stereoselectivity.\textsuperscript{255,256} The allylation reaction with ketones suffers from unavoidable 1,3-diaxial interactions in the transition state. The insertion of a transition metal into the C—B bond overcomes this drawback by forming a more reactive metal–allyl intermediate.\textsuperscript{257,258}

\begin{equation}
\text{Scheme 1.19. Diastereoselective allylation of an aldehyde.}
\end{equation}

\textit{Syn : Anti} = 97 : 3\textsuperscript{250}
1.3.6. The Suzuki-Miyaura Cross-Coupling Reaction

In the modern era of organic chemistry, a palladium-catalyzed cross-coupling reaction is one of the most important and useful approach for the construction of new carbon–carbon bonds. The extensive applications of these reactions emerged as solutions to otherwise difficult synthetic protocols and earned them recognition by the 2010 Nobel Prize in chemistry.\textsuperscript{251} In 1979, under the direction of Prof. Suzuki, Miyaura discovered that an organoboronic acid or ester reacts with an organohalide in the presence of a palladium(0) catalyst (Scheme 1.20).\textsuperscript{11} The Suzuki-Miyaura cross-coupling reaction (SMC) is a well-known transformation of the C–B bond, and the mildly basic conditions it entails are extremely tolerant to a wide scope of substrates. Organoboronic acids, esters, and organoboranes are all suitable cross-coupling partners. In view of the commercial availability of organoboronic acids and organohalides, the high functional group tolerance, and the stereoselective protocols, the SMC is a powerful tool for preparing complex small molecules, natural products, agrochemicals and pharmaceuticals.

Scheme 1.20. Typical conditions for the Suzuki-Miyaura cross-coupling reaction.\textsuperscript{11}

In the catalytic cycle, oxidative addition of the organohalide to the zerovalent palladium catalyst generates the organopalladium(II) complex, 1.30 (Figure 1.15). Mechanistic investigations indicated this to be the rate-limiting step. In general, electron-deficient arylhalides are better cross-coupling partners and the choice of halide shows a reactivity trend of I > OTf > Br > Cl. With less reactive organohalides, the reaction rate becomes first-order with respect to the
Stoichiometric experiments revealed that an equilibrium takes place between the organopalladium(II) halide \( \text{1.30} \) and the organopalladium(II) hydroxide species \( \text{1.32} \) \((R^3 = H)\). In order for transmetallation of the organoboronic acid to occur, the C—B bond must first be activated by a Lewis base. Arguably, it is kinetically indistinguishable whether the boronic acid is activated by the excess base in the reaction mixture or by the base coordinated to palladium in \( \text{1.32} \). In the latter case, transmetallation is proposed to proceed via a four-membered transition state, as illustrated in Figure 1.16. Nevertheless, in either transmetallation process, a Lewis acid-base activation of the boron center is necessary to give \( \text{1.34} \). Reductive elimination of the two organic structures forms the new carbon–carbon bond and regenerate \( \text{1.29} \).

**Figure 1.15.** Proposed mechanism for the Suzuki-Miyaura cross-coupling reaction.

**Figure 1.16.** Proposed transmetallation transition state.
The steric bulk of biaryl Buchwald ligands, like SPhos (2-Dicyclohexylphosphino-2’,6’-dimethoxybiphenyl), promotes ligand dissociation, and the unique coordination of the *ipso*-carbon to the metal center can stabilize an underligated complex. The reactivity of these catalysts is so effective that the cross-coupling of aryl chlorides occurs readily at room temperature with catalyst loadings as little as 1.0-1.5 mol%. Stereoselection of alkenyl substrates is observed in sp²–sp² cross-coupling reactions since the oxidative addition, transmetallation, and reductive elimination processes all occur with stereochemical retention. However, allylic or benzylic halide substrates typically undergo inversion. In this case, the stereoselection of these sp²–sp³ cross-coupling reactions is determined by the oxidative addition of the organohalide.

While there are hundreds of thousands of examples of sp²–sp² cross-coupling reactions, there are very few extensions to cross-coupling sp³ hybridized substrates. The sp³-sp³ cross-coupling is an extremely challenging transformation for several reasons. Firstly, every step is kinetically slow and, at every stage, competing β-hydride elimination pathways deter the reaction from yielding the desired product. The first example of a successful alkyl-alkyl SMC appeared in 1997, wherein a Suzuki-type reaction of a cyclopropyl boronic esters was optimized for preparing bicyclopropane derivatives with up to 71% yield. Similar yields were obtained when cyclopropyl boronic acids and esters were coupled with allylic and benzylic halides. Linear alkyl chains between 9-BBN organoborane and alkyl bromides were successfully cross-coupled under standard conditions in the presence of a Pd/NHC catalyst, albeit in low yields (28-56%). Fu and co-workers optimized the reaction conditions to cross-coupling 9-BBN alkylboranes and alkylboronic acids with alkyl bromides, chlorides, and tosylates (Scheme 1.21). Food sigma-donating and sterically bulky alkyl phosphines, such as PCy₃ or P'Bu₂Me, are key to the success of these reactions. The best results with alkyl bromides were obtained with...
tricyclohexylphosphine, whereas bis(tert-butyl)methylphosphine was more suitable for alkyl tosylates. Trifluoroborate salts have also gained momentum as convenient reagents for difficult cross-coupling alkylations. A few more examples throughout the last decade have appeared, but they are sparse.

### 1.3.7. Copper-Catalyzed Coupling Reactions

The original Ullmann condensation formed biaryl C—C linkages with copper powder and the coupling reactions described here are essentially modifications of the Ullmann and Goldberg condensation reactions. As such, the cross-coupling reaction can be viewed as essentially a σ-bond metathesis between an organic nucleophile and an electrophilic species (Scheme 1.22).

**Scheme 1.22.** Basic representation of a transition metal-mediated cross-coupling reaction.

In palladium-catalyzed cross-coupling reactions, like the SMC, palladium(0) activates the organic electrophile and a base makes the organoboron compound nucleophilic. Palladium(II)
intermediates are key to this chemistry, wherein the metal can accommodate both of the reactants and facilitate their coupling. Conversely, a copper catalyst activates the organoboronic nucleophile, forming a reactive organocopper species (usually in the +1 or +3 oxidation state). While copper(III) species are isoelectronic to the d^8 palladium(II) complex, this high oxidation state of copper is extremely unstable and the coordination sphere is too small to accommodate both substrates. Therefore, copper(III) complexes cannot perform ligand exchanges and are prone to the reverse reductive elimination. The following discussion will highlight the key mechanistic details that make this chemistry possible and the complementary applications of both catalysts.

1.3.7.1. The Chan-Evans-Lam Reaction

As previously discussed, the transformation of a carbon–boron bond into an amine linkage is carried out by an amination reaction or with the crotyl borane allylation using an in situ generated imine. However, the amination reaction has a narrow functional group tolerance since harshly basic conditions are required, and the allylation method is hampered by steric interactions with larger substrates. So, like many examples presented herein, metal-catalyzed synthetic transformations were developed to provide solutions to these limitations. The Buchwald-Hartwig coupling was the first metal-catalyzed reaction to form ether and secondary amine linkages from C—B bonds using noble metal catalysts based on palladium. Then, in 1998, a consecutive series of papers appeared in Tetrahedron Letters from three independent researchers describing the copper-catalyzed C—O and C—N coupling variants now known as the Chan-Evans-Lam coupling.

Using a copper(II) catalyst, this reaction couples organoboronic acids and esters with alcohols or amines to form the corresponding ethers or secondary/tertiary amines (Figure 1.17). This reaction is a convenient, non-toxic, and economical approach that is carried out under
extremely mild conditions at room temperature. In the analogous palladium-catalyzed Buchwald-Hartwig coupling, oxidative addition of the organic electrophile generates a stable palladium(II) intermediate. Conversely, copper catalysts generally do not undergo oxidative additions and instead, the organoboron reagent is exchanged for an acetate ligand to generate $1.38$ (Figure 1.17). This is the rate-limiting step, and less Lewis acidic organoboron compounds are more difficult to couple. Kinetic studies measuring this process found additives, like acetic acid and sodium acetate, would inhibit the reaction. $^{278}$ This evidence strongly suggests that the boron center is likely activated by the copper-ligated acetate through a six-membered transition state, $1.37$. The exact mechanism for generating the desired product from the subsequent reductive elimination was teased out in 2012 by anaerobic, stoichiometric single-turnover experiments. $^{278}$ These anaerobic experiments provided evidence that $1.38$ is likely oxidized by a Cu$^{II}$/Cu$^I$ reduction, generating a
highly reactive and transient copper(III) species (1.39). Reductive elimination, probably through nucleophilic attack by the heteroatom, extrudes another copper(I) complex which is easily oxidized back to the active copper(II) catalyst by air. In a related study, a stabilized copper(III) intermediate paralleling 1.39 was characterized and this species showed facile carbon-heteroatom bond formations with oxygen and nitrogen.

While the original reports of these coupling reactions used stoichiometric amounts of copper, Collman and co-workers examined the C—N coupling and reduced the copper loading to catalytic amounts using [Cu(OH)TMEDA]₂Cl₂. They even optimized the reaction to be carried out in water at room temperature. However, substoichiometric amounts of copper in the Evans C—O bond cross-coupling reaction delivered low yields. Furthermore, these cross-coupling reactions were limited to phenols, as alkyl alcohols did not react. To address these issues, Batey and Quach employed trifluoroborate salts, which allowed for copper loadings to be reduced to catalytic amounts. Gratifyingly, these conditions are generalizable for coupling a wide range of functionalized aryl and alkenyl trifluoroborate salts with primary, secondary, and aryl alcohols.

Due to the extensive applications in natural product and biologically active compound syntheses, the benefits and limitations of C—N bond formation couplings have been extensively reviewed. In general, while the copper-catalyzed reactions, including C—O bond couplings, provide sustainable alternatives to palladium-catalyzed reactions, their applications are often limited by a narrow substrate scope, long reaction times (18 h – 13 days), moderate yields, and the requirement of excess the organoboron reagent due to autoxidation. However, palladium catalysts do not always offer solutions to these problems, and both approaches must be optimized to suit the specific coupling. A nice example of how these catalytic systems complement each other is the synthesis of tariquidar derivatives, in which the Chan-Lam N-arylation reaction
succeeded where the Buchwald-Hartwig method failed due to solubility.\textsuperscript{291} Presently, there lacks efficient and generalizable methods for the carbon-heteroatom transformation of organoboron compounds.

1.3.7.2. Homo- and Cross-Coupling Reactions

Following the disclosure and catalytic optimization of the Chan-Evans-Lam reaction, cross-coupling chemistry entered a renaissance, wherein copper quickly became a hot topic for researchers interested in developing sustainable alternatives to palladium catalysis. An initial report by Rothenberg and co-workers in 2002 disclosed that colloidal copper-nanoclusters catalyze an SMC-like cross-coupling, demonstrating that this noble metal chemistry could be supplanted by copper.\textsuperscript{292,293} These copper-based nanoclusters were colloidal mixtures with palladium and other metals, but they inspired the exploration of copper-based catalytic systems nonetheless.

Symmetrical biaryls are easily synthesized via the homo-coupling of aryl boronic acids in the presence of Cu(OAc)$_2$. Like the Chan-Evans-Lam reactions, these reactions are stirred vigorously and conducted open-to-air where dissolved oxygen regenerates the copper species. As such, homo-coupling is often problematic in Chan-Evans-Lam reactions. Electron-poor arylboronic acids give the best results and sterically hindered 2,6-disubstituted substrates are unreactive. Improvements to this reaction were realized six years later, when Kirai and Yamamoto discovered that the 1,10-phenanthroline dimer of ($\mu$-hydroxido)cupper(II), [(phen)Cu($\mu$-OH)]$_2$Cl$_2$, facilitates the rate-determining transmetallation step.\textsuperscript{294} They attribute the success of this complex to the concomitant one-electron reduction of each copper center from a bimetallic organocopper(II) intermediate. Indeed, a wide variety of electron-rich and poor substrates undergo homo-coupling in good to excellent yields. However, this reaction is also sensitive to steric effects and low yields were obtained with ortho-substituted and 2,6-disubstituted substrates.
Chemoselectivity for the homo-coupled product, rather than a cross-coupled product, was observed when 4-iodophenylboronic acid was homocoupled in a 74% yield. It is important to note that this selectivity would not be possible in the presence of a palladium catalyst.

A myriad of cross-coupling protocols have emerged within the last decade, beginning with the seminal report by Wang and Li in 2006. Their catalytic system consists of copper(I) iodide and DABCO (DABCO = 1,4-diazabicyclo[2.2.2]octane) with Cs$_2$CO$_3$ base (Scheme 1.23). While this protocol utilized a mild base, the reaction conditions are harsh in that they are conducted at high temperatures between 125-135 °C. Mechanistically, it is proposed that an organocopper intermediate engages in a nucleophilic aromatic substitution reaction with the organohalide. Thus it follows that electron-withdrawing substituents on the organohalide and good leaving groups facilitated the reaction. Under these conditions, aryl iodides are good coupling partners, whereas aryl bromides necessitate stoichiometric amounts of CuI at 150 °C and aryl chlorides are unreactive.

The extension of copper catalysis for sp$^2$-sp$^3$ cross-coupling reactions was realized more recently, beginning with a copper-catalyzed S$_N$2$'$ addition. Sawamura et al. used a copper(I) acac catalyst (acac = pentane-2,4-dione) to facilitate an allyl-aryl coupling of neopentyl glycolato arylboronic esters with (Z)-cyclic and acyclic allylic phosphonates (Scheme 1.24). This reaction stereoselectivity delivers excellent yields of the γ-aryl substituted (E)-products. Interestingly, the addition of 0.9 equivalents of water is required, although its purpose is still ambiguous. This is
Scheme 1.24. Summary of $S_N2'$ cross-coupling reactions.$^{296-299}$

Another notable example where the copper catalyst complements the palladium variant, which only reacts with (Z)-isomers.$^{297,298}$

Lalic and co-workers improved the catalytic system to engage the less reactive allyl chlorides and pinacolato arylboronic esters in the $S_N2'$ cross-coupling (Scheme 1.24).$^{299}$ The copper(I) catalyst is supported by IMes (IMes = 1,3-bis(2,4,6-trimethylphenyl)-imidazolium) and is suitable for cross-coupling both ($E$)- and (Z)-allylic chlorides in an $S_N2'$ fashion. The regioselectivity (for $S_N2'$ addition versus $S_N2$ addition) is sensitive to the electronic nature of the arylboronic ester and the cation. Electron-rich boronic esters were highly selective with potassium tert-butoxide, whereas electron-poor boronic esters preferred bases with a sodium cation.$^{299}$

Recently, this addition was extended to the cross-coupling of 1,1-diborylalkanes with allylic chlorides.$^{300}$ The same catalytic system is used, but the reaction is carried out with 3 equivalents of LiO'Bu in toluene. Lalic’s NHC-copper(I)-catalyzed addition did not proceed in the presence of this base, which further demonstrates the electronic sensitivity of these reactions.

<table>
<thead>
<tr>
<th>Leaving Group</th>
<th>Boronic Ester</th>
<th>Ligand</th>
<th>Additive(s)</th>
<th>Solvent</th>
<th>Yields</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{O}_2\text{POEt}$</td>
<td>$\text{B(OEt)}_2$</td>
<td>$\text{CO}_2\text{H}$</td>
<td>KO'Bu (3 equiv.) H$_2$O (0.9 equiv.)</td>
<td>CH$_3$CN</td>
<td>42-88%</td>
</tr>
<tr>
<td>$\text{O}=\text{O}$</td>
<td>$\text{B(OEt)}_2$</td>
<td>$\text{Mes}=\text{N}=\text{Mes}$</td>
<td>KO'Bu or NaO'Pent (1 equiv.)</td>
<td>1,4-dioxane</td>
<td>66-99%</td>
</tr>
</tbody>
</table>

41
The pioneering work in direct copper-catalyzed sp²-sp³ cross-coupling reactions began in 2011. After an extensive screening of copper sources and bases, optimal conditions using copper(I) iodide and lithium tert-butoxide in DMF at 60 °C effectively cross-coupled neopentyl glycolato arylboronic esters with alkyl tosylates and halides (Scheme 1.25). Modest to good yields were obtained, with the increasing reactivity trend of chloride < mesylate < tosylate < bromide < iodide. Neopentyl glycolato arylboronic esters are the most effective derivatives. The cross-coupling reaction of the neopentyl glycolato phenylboronic ester with decyl tosylate gave an 87% yield, whereas a 76% yield was obtained with phenyl boronic acid and a 65% yield was achieved with the pinacolato boronic ester. Notably, the cross-coupling of alkyl bromide and tosylate electrophiles under these conditions is peculiar given that these substrates are notoriously difficult to cross-couple with palladium catalysts; the aforementioned cross-couplings using the PCy₃ or P'Bu₂Me ligated palladium catalysts are distinguished exceptions.

Scheme 1.25. Summary of sp²-sp³ copper-catalyzed cross-coupling reactions.
Primary and secondary benzyl halides have also proven to be suitable cross-coupling partners with neopentyl glycolato arylboronic esters (Scheme 1.25). The optimized conditions for primary benzyl substrates employs a CuI/DMHD (DMHD = 2,6-dimethylheptane-3,5-dione) in NMCPL (N-methylcaprolactam, solvent). Even sterically hindered and β-hydrogen-containing alkyl halides or pseudohalides are cross-coupled in good yields when the catalyst is ligated with quinolin-8-ol.\textsuperscript{301} This is a notable reaction because standard SMC conditions form organopalladium(II) intermediates from the alkyl halides and β-hydride elimination are commonly encountered. The circumvention of this problem is made possible by copper because the catalyst interacts with the arylboronic ester.

The most remarkable area that copper catalysis serves to complement a palladium cross-coupling is in the development of the elusive sp\textsuperscript{3}-sp\textsuperscript{3} cross-coupling reaction. As previously mentioned, these reactions are extremely difficult due to kinetically slow processes and competing β-hydride eliminations. Very few examples of palladium-catalyzed couplings are known. However, in copper-catalyzed reactions, the highly nucleophilic organocopper species does not suffer from β-hydride eliminations and readily undergoes cross-coupling reactions with sp\textsuperscript{3} hybridized electrophiles. In recent years, two methods emerged that use either a 9-BBN substrate or a gem-diboronate ester in the presence of copper(I) iodide and LiO'Bu.\textsuperscript{302,303} While generalizable catalytic methods are still being sought, currently these conditions are state-of-the-art, tolerating a broad scope of functional groups, including acetics, esters, nitriles, olefins and heterocycles. Most recently, these conditions have been effectively applied towards the cross-coupling of allylboronic esters with primary, secondary, and tertiary alkyl halides.\textsuperscript{304} This reaction is remarkable because these unactivated halides are particularly susceptible to β-hydride eliminations in palladium-catalyzed SMC reactions.
1.4. Pharmaceutical Applications

The oral LD\textsubscript{50} of boric acid is 3450 mg/kg in a mouse, and it is widely accepted to be nontoxic to humans.\textsuperscript{17,19} Thus, incorporation of boronic acids into drug scaffolds has increased over the years. The first pharmaceutical to employ a non-natural heteroatom was the peptidyl boronic acid, Bortezomib (Velcade®, Figure 1.18).\textsuperscript{305} It was FDA approved in 2003 and is used to treat multiple myeloma and mantel cell lymphoma. This antineoplastic drug inhibits the 20S proteasome, which carries out protein degradation.\textsuperscript{306-308} More recently, Tavaborole gained FDA approval in 2014 as an antifungal, topical medication for treating onychomycosis.\textsuperscript{309} Tavaborole forms a reversible covalent bond with the 2’- and 3’-hydroxyl groups in the cytoplasmic leucyl-tRNA synthase of yeast. Both of these biologically active small molecules bind hydroxyl groups to form reversible boronate adducts. The Santos research group was inspired by these examples and, recently, they have begun to incorporate a phenylalanine boronic acid (L-BPA, Figure 1.18) into libraries of branched peptides targeting HIV RNA.\textsuperscript{310-312} The hypothesis is that the affinity for an RNA target and the selectivity for RNA over DNA would be enhanced by a

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure18}
\caption{Boron-containing pharmaceutical compounds, candidates, and biologically active structures. (AA = naturally occurring amino acids; AA* = lysine branching unit).}
\end{figure}
reversible covalent adduct formation with the 2’-hydroxyl of RNA, as illustrated in Figure 1.18. This theory was supported when removing the boronic acid from a peptide possessing a low micromolar dissociation constant towards the RRE IIB target resulted in a six-fold decrease of the binding affinity. Furthermore, it was demonstrated that the binding affinity could be tuned by increasing the Lewis acidity of the boron center; an improved binding affinity was observed when an electron-withdrawing fluorine atom ortho to the boronic acid substituent was installed.

The two naturally occurring stable isotopes of boron, $^{10}$B (19.9%) and $^{11}$B (80.1%), have been analyzed for use in a relatively new approach to chemotherapy. The conundrum facing cancer treatment research is selectively targeting cancerous tumor cells over healthy normal cells. This is a difficult problem because cancer cells are, in most ways, biologically similar to healthy cells, save for a defect in the regulation of cell growth and differentiation. Neutron capture therapy (NCT) addresses this issue by necessitating a direct and specific area of harmful irradiation. It uses the intrinsic ability of a $^{10}$B atom to absorb thermal, or slow neutrons, whose energy is well below that capable of ionizing tissue. The absorption of the neutron triggers a nuclear fission process within the atom which emits lethally energetic, but very short ranged, $\alpha$-particles capable of destroying nearby malignant tumor cells. While this approach to cancer treatment is still in clinical trials for approval in the US, the first trial treated the diffuse metastases of colon carcinoma in the liver of a 42 year old man in Pavia, Italy on December 19, 2001. The man lived 44 months of high quality life, which is a praised success in light of a mean survival time of 4-10 months for this condition. Moreover, this clinical trial demonstrated the selectivity for cancerous cell over normal tissue and its high efficacy. Today, BNCT is a rapidly developing field of research and successful clinical trials for treating melanoma skin cancer, parotid cancer, head and neck cancers, and brain tumors are paving the way for future therapies.
1.5. Dissertation Overview

The overarching goal of this research is to develop sustainable and efficient modes of functionalizing small molecules in preparative organic chemistry. Specifically, the aims were to:

1. Diborate allenic substrates with a differentially protected diboron reagent and demonstrate the orthogonal reactive of the different C—B bonds in transformation reactions.

2. Provide direct access to 1,8-diaminonaphthalene protected β-boryl carbonyl compounds using an economical copper catalyst in an aqueous solvent.

3. Explore the cross-coupling β-boryl carbonyl compounds with copper catalysts.

Chapter 1 introduced an overview of the basic classes, physical properties, relative stability and synthesis of organoboron compounds. Their preparations were examined with a detailed focus on diboration and β-borylations reactions. Special attention was given to the current interest in developing sustainable methods using copper catalysts. A follow-up discussion of organoboronic acids and esters as synthetic intermediates highlighted their importance as valuable synthons to preparative chemistry. Recent developments regarding metal-catalyzed transformations were accented. Lastly, examples of organoboronic acids and derivatives as pharmaceutical agents were briefly described.

Chapter 2 discloses the development of a platinum-catalyzed diboration of 1,1-disubstituted allenes with a differentially protected diboron reagent. A more detailed discussion of allene diboration is presented. The catalytic system and reaction conditions were optimized to provide the desired products with high yields and regioselectivity. A small substrate scope was explored and the synthetic utility of these products was demonstrated in chemoselective transformations.
The topic of Chapter 3 is the synthesis of the allenic substrates presented in Chapter 2. Several of these compounds and their intermediates are uncharacterized or unknown in the literature; a facile synthetic route to diaryl alkenes from ketones is described. 1,1-Dibromocyclopropane intermediates, like those synthesized in this chapter, show promising potential for applications in material and preparative chemistry. During the synthesis of these allenes, the identification of a gem-dibromocyclopropane as a near-atropisomer was most intriguing. This chapter details an extensive investigation regarding the characterization, origins of rotational restriction, conformational analyses, and the kinetic rate of isomerization.

In Chapter 4, specific consideration is given to the current interest in developing sustainable methods using aqueous solvents and copper catalysts. The development of a copper(II)-catalyzed borylation with a differentially protected diboron reagent in an aqueous solvent is reported. The reaction conditions were optimized to borylated a wide scope of α,β-unsaturated acetylenic esters and amides with exclusive stereoselectivity.

Chapter 5 examines the current state of transformative research within the context of underdeveloped and ongoing projects. The future outlook of these endeavors and strategies to address related limitations are presented. In particular, the results of a collaborative project with the Marder group exploring copper-catalyzed cross-coupling reactions of β-boryl carbonyl compounds are reviewed.

General methods, instrumentation, experimental procedures, and product characterization data for chapters 2-5 are provided in Chapter 6. References for known compounds are also documented.
1.6. References


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Chapter 2. Regio- and Stereoselective Diboration of Allenes with a Differentially Protected Diboron: Formation of Vinyl and Allyl Boronic Acid Derivatives

2.1. Contributions

The work described in this chapter was inspired by the Highland’s seminar of Dr. William Roush, which propagated a discussion of borylating allenes with unsymmetrical diboron compounds - the details of which were conceived and guided by the principal investigator, Dr. Webster Santos. This work was conducted in collaboration with a senior member colleague, Dr. Xi Guo. The author of this chapter is singly responsible for the development of GC-MS analytical methods, the synthesis of the substrates, the initial syntheses of inorganic catalysts including Pt(PPh₃)₄ and Pt₂(dba)₃, optimization experiments involving PCy₃ and PPh₃, the investigation of stereoselectivity, assisting with the exploration of the substrate scope, and results verification. The screening of phosphine and other metal catalysts, the optimization experiments in different solvents and at different temperatures, as well as the subsequent reactions of the bis-borylated products were all performed solely by Dr. Xi Guo (a more detailed description of these experiments can be found in her dissertation). The author of this chapter performed and developed the technique for the recrystallization of the bis-borylated compounds provided herein. Dr. Xi Guo submitted and analyzed X-ray structural data for compounds 3.14 and 3.26a. The author submitted and analyzed X-ray structural data for compounds 3.21a, 3.23a and 3.23b, 3.25a, 3.27a, 3.28a, and 3.29a. The crystallographic data collection and processing for all compounds was performed by Dr. Carla Slebodnick. The published manuscript was prepared by Xi Guo and has not been quoted herein. We acknowledge the National Science Foundation (CHE-1414458) and ACS Petroleum Research Fund for their financial contributions to this research. Finally, great appreciation is extended to Dr. Molly Congdon for careful review of this chapter.
2.2. Abstract

A transition metal-catalyzed diboration is a method for the reduction of an unsaturated organic molecule by the 1,2-addition process of two boron moieties. Subsequent transformations of these newly formed C—B bonds allows for the functionalization of the molecule. Herein, a catalytic system based on platinum was developed for carrying out a regio- and chemoselective diboration of 1,1-disubstituted allenes using a differentially protected diboron. The regioselective addition of both boron moieties to the terminal double bond of the substrate occurs exclusively; and, when appropriately substituted, a modest stereoselective preference for (E)-isomeric compounds was observed. The reaction conditions demonstrate high chemoselective boron transfer to furnish the vinyl and allylic boronates in good to excellent yield. Subsequent transformations of the bis-borylated products to other functional groups is demonstrated. In particular, conditions for the chemoselective cross-coupling were determined.

2.3. Introduction

A quick and efficient approach to build highly functionalized small molecules is operative using synthetic intermediates featuring multiple carbon–boron bonds. Efficacious access to such substrates can be achieved through metal-catalyzed diboration across unsaturated carbon–carbon bonds, such as alkenes, alkynes, and dienes. These C—B bonds provide versatile synthetic intermediates for cross-coupling reactions and transformations to other valuable functional groups. However, instances when two identical boron centers are present within the substrate and/or reactants, it becomes difficult to control which boronate undergoes transformation (Scheme 2.1a). Since the ligand system on the boron atom largely governs its reactivity,

\[
\begin{align*}
\text{a) } & \quad (\text{RO})_2\text{BB(OR)}_2 \xrightarrow{\text{[Pd], base}} \text{Ar} \xrightarrow{\text{Ar-X}} \text{Ar} \\
\text{b) } & \quad (\text{RO})_2\text{BBdan} \xrightarrow{\text{[Pd], base}} \text{Ar} \xrightarrow{\text{Ar-X}} \text{Bdan} \xrightarrow{\text{H}^+_{\text{aq}}} \text{Ar} \xrightarrow{\text{B(OH)}_2} \text{Ar} \\
\text{c) } & \quad \text{Irr} \xrightarrow{\text{Pd(PBu}_3)_2, \text{CsF, THF, 60 °C}} \text{R}^2 \xrightarrow{\text{HCl}_{\text{aq}}, \text{THF}} \text{R}^3 \xrightarrow{\text{Pd(PBu}_3)_2, \text{CsF, THF, 60 °C}} \text{R}^4
\end{align*}
\]

Scheme 2.1. Illustration of the masking strategy towards chemoselective transformations.
chemoselective differentiation can be achieved by masking one boron center with a protecting group, such as 1,8-diaminonaphthalene (dan), and unmasking it for subsequent transformations (Scheme 2.1, b<sup>45</sup> and c<sup>32</sup>). Such manipulation of the boronic acid reactivity in cross-coupling reactions with, otherwise equivalent, C—B bonds was conceptualized in 2007 by Noguchi, Hojo, and Suginome.<sup>29</sup> Highly efficient synthetic schemes for producing a wide range of functionalized oligoarenes,<sup>29,30</sup> dendrimers,<sup>31</sup> and oligo(phenylene vinylene) compounds<sup>32</sup> through iterative SMC reactions demonstrates the practicality of developing such approaches (Scheme 2.1c<sup>32</sup>).

Prior to the strategy of masking the boron center, the orthogonal reactivity between sp<sup>2</sup> and sp<sup>3</sup> hybridized carbon–boron bonds offered chemoselective differentiation. Allenes (e.g. 2.1) are an attractive choice because they can be uniquely diborated to provide an sp<sup>2</sup> vinyl and sp<sup>3</sup> allylic boronate (2.2a). These synthetic intermediates can be engaged in chemoselective tandem reactions, as demonstrated by Morken and co-workers (Scheme 2.2).<sup>27,28,33-35</sup>

**Scheme 2.2.** A variety of transformations can be conducted to produce a diverse array of organic compounds from the enantioselective diboration of a prochiral allene.<sup>27, 28, 33-35</sup>
Despite the potential synthetic utility these compounds offer, there are still very few methods for allene diboration. The seminal work by Miyaura and co-workers did not emerge until 1998. A platinum(0) catalyst complexed with phosphine ligands facilitates the addition of $\text{B}_2\text{pin}_2$ to the allenic substrate, with a high predisposition to diborate the internal double bond (Table 2.1). However, selectivity for the terminal double bond was sterically favored with 1,1-disubstituted allenes and bulky ligands such as tricyclohexyl phosphine.

Table 2.1. Platinum(0)-catalyzed diboration of allenes with bis(pinacolato)diboron.$^{36}$

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Triphenylphosphine (PPh₃)</th>
<th>Tricyclohexylphosphine (PCy₃)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% Yield</td>
<td>Selectivity (a:b)</td>
</tr>
<tr>
<td>Ph</td>
<td>94</td>
<td>71:29</td>
</tr>
<tr>
<td></td>
<td>98</td>
<td>24:76</td>
</tr>
<tr>
<td></td>
<td>96</td>
<td>50:50</td>
</tr>
</tbody>
</table>

This type of reaction is proposed to proceed via oxidative addition of the diboron to the metal catalyst to generate a bis(boryl)platinum(II) intermediate 2.3 (Figure 2.1). Insertion of the allene into metal–boron bond of 2.3 places a Bpin group on the sp hybridized carbon of the allene and affords the $\pi$-allyl complex 2.4. Reductive elimination preferentially occurs at the substituted
carbon with monosubstituted allenes and at terminal carbon with disubstituted allenes to provide 2.2a and 2.2b, respectively.\(^{36}\)

Although platinum complexes were efficacious for the diboration of unsaturated substrates, it soon became highly desirable to develop a palladium catalyst for this process. In theory, the palladium catalyst, with the same valence electron configuration as platinum, would be able to diborate the substrate and then be recycled in a one-pot tandem SMC reaction. Initially, palladium analogues were inactive, but computational analysis provided insights that ultimately led to the development of these catalytic systems (Figure 2.2). The proposed oxidative addition of the diboron (e.g. B\(_2\)pin\(_2\)) to a palladium(0) catalyst was theoretically determined to have a lower activation barrier (8.6 kcal/mol) than the respective platinum(0) catalyst (14.0 kcal/mol).\(^{37-39}\) In spite of it being easier to form, the bis(boryl)palladium(II) complex was calculated to be 15.9
kcal/mol higher in energy than the analogous platinum complex.\textsuperscript{37} Moreover, this is an endothermic process for palladium, whereas the formation of the platinum(II) intermediate is exothermic, which makes the reversible process of reductively eliminating the diboron reagent from the palladium catalyst more favorable. This evidence led researchers to develop innovative solutions to address the unfavorable equilibrium.

Employing a co-catalyst to bypass the metastable diboryl palladium intermediate became one such solution developed by Yang and Cheng.\textsuperscript{40} In addition to catalyzing the diboration with palladium, their reaction provided a complementary diboration to the platinum-catalyzed reaction, in which both monosubstituted and 1,1-dimethyl allenes are exclusively borylated on the terminal bond with high stereoselectivity for the (Z)-product (>93\%).\textsuperscript{40} The alkenyl iodide co-catalyst assists the oxidative addition process by generating an iodo(pinacolato)boron species \textsuperscript{2.8 in situ}

\textbf{Figure 2.2.} Comparison of the potential energy profiles for the reaction of a diboron with platinum(0), shown in blue, and palladium(0), shown in red.\textsuperscript{37-39}
When this reagent undergoes oxidative addition with the palladium catalyst, a more stable intermediate (2.9) than the bis(boryl)palladium(II) complex is formed. Insertion of the substrate into the metal–boron bond of 2.9 provides 2.10. Transmetallation with B$_2$pin$_2$ regenerates the iodoaryl species, 2.8. Reductive elimination from the π-allyl 2.11 provides the product and restarts the catalytic cycle. The stereoselectivity for the (Z)-isomer presumably results from steric interactions during the insertion step (Figure 2.4). It is unknown why the reaction favors addition to the terminal double bond.
An alternative approach to palladium-catalyzed diboration involved stabilizing the bis(boryl)palladium(II) intermediate. Morken and co-workers reasoned that phosphoramidites, which are strong σ-donor ligands, would have less back bonding interactions with the metal due to the high energy of the metal–phosphorous σ* orbital, thereby allowing the metal to back-bond with the empty p orbital of the coordinated borons. This interaction stabilizes the bis(boryl)palladium(II) intermediates and allows for the insertion process to take place. Analogous to the platinum-catalyzed diboration, addition occurs exclusively on the internal double bond (Scheme 2.3). Moreover, the tunable nature of phosphoramidite ligands allowed for a stereoselective reaction to be achieved with these prochiral allenic substrates. A TADDOL (α,α,α',α'-tetraaryl-2,2-disubstituted 1,3-dioxolane-4,5-dimethanol) derived phosphoramidite ligand, 2.12, procures high levels of asymmetric induction (90-98% ee) for the diboration of a variety of monosubstituted allenes and in good yields (52-92%).

![Scheme 2.3. The stereoselective palladium(0)-catalyzed diboration of monosubstituted allenes developed by Morken et al.](image)

Until recently, transition metal-catalyzed diboration of unsaturated substrates has been limited to symmetrical diboron reagents bearing protecting groups such as pinacol, catechol, and neopentylglycol. There are very few examples which employ unsymmetrical diboron reagents for borylation reactions. The Santos group synthesized and characterized the first known
unsymmetrical diboron reagent, PDIPA diboron (Scheme 2.4).\textsuperscript{41,42} This internally activated, \(sp^2\)-\(sp^3\) hybridized diboron compound was shown to be a particularly effective reagent for the regioselective conjugate addition of Bpin to the \(\beta\)-carbon of \(\alpha,\beta,\gamma\)-unsaturated ketones, esters and allenoates under mild, copper-catalyzed conditions.\textsuperscript{41-43}

In 2010, Iwadate and Suginome synthesized and characterized the differentially protected diboron reagent, pinB—Bdan 2.13 (PDAN diboron, dan = 1,8-diaminonaphthalene).\textsuperscript{45} In this report, conditions were optimized for the regioselective diboration of alkynes (Scheme 2.5a). Since the dan moiety is a particularly effective masking group for the boron center,\textsuperscript{29-32,47-51} the diboration

\textbf{Scheme 2.4.} Copper-catalyzed borylation of \(\alpha,\beta,\gamma\)-unsaturated allenoates with unsymmetrical PDIPA diboron.\textsuperscript{43

\textbf{Scheme 2.5.} (a) Regioselective diboration of alkynes with PDAN diboron. (b) Chemoselective transformations of the boron centers.\textsuperscript{45}
of alkynes with this reagent provides a versatile handle for chemoselectively engaging each boron center in subsequent transformations (Scheme 2.5b).

Notwithstanding the orthogonal reactivity presented by the installation of the pinacol and 1,8-diaminonaphthalene boron centers, the formation of the vinylic and allylic C—B bonds which arise from diboration of allenes presented an interesting area of research. Herein, the regio- and stereoselectivity challenges are addressed by optimizing conditions for the diboration of 1,1-disubstituted allenes using PDAN diboron 2.13. The terminal double bond undergoes the addition process regioselectively, installing the Bpin moiety on the central sp carbon of the allene and the Bdan moiety on the terminal sp² carbon and affording the vinylic and allylic boronyl groups, respectively. Chemoselective cross-coupling and oxidation reactions were demonstrated to highlight the utility of this methodology.

2.4. Results and Discussion

2.4.1. Optimization and Characterization of the Diboration Reaction

Preliminary studies were performed with phenylallene as the model substrate. The diboration reaction of this substrate with a differentially protected diboron reagent poses a significant regio- and stereoselectivity challenge; namely, up to six different bis-borylated constitutional and stereoisomers could be obtained (Scheme 2.6). Separation and characterization of the isomers would also be a difficult undertaking.

As such, an appropriate choice of the catalytic system was sought to provide control of the product distribution. A variety of reaction conditions were screened, as summarized in Table 2.2. Treatment of phenylallene with “ligandless” Pt₂(dba)₃ and diboron 2.13 in toluene at 80 °C
afforded only two isomers and in good yield (entry 1). The isomeric distribution was identified by GC-MS, wherein 2 peaks with identical molecular mass and near identical ionization patterns were observed. Column chromatography over silica co-eluted the isomers. The $^1$H NMR of the mixture identified that the major isomer resulted from diboration of the internal double bond, wherein it could be either 2.14 or 2.15, and that the minor isomer resulted from the diboration of the terminal double bond, wherein it could be either stereoisomer of 2.16 or 2.17. Gratifyingly, the major product could be selectively recrystallized from the mixture with hexane; this was confirmed by NMR characterization of the collected crystals. Given that the Nuclear Overhauser Effect (nOe) signals provided inconclusive structural data, X-ray crystallography of the major isomer was employed to differentiate between the two possibilities. The major product was identified as 2.14 (Figure 2.5).

The minor isomer was later identified as (Z)-2.16 via NMR experiments. From this initial result, it was concluded that the platinum(0) catalyst diborates the internal double bond with a predisposition for installing the Bdan moiety on the

**Scheme 2.6.** Broad overview of the synthetic challenge of the proposed diboration.
sp² hybridized carbon of the substrate. Regioselectivity was unaffected by increasing or decreasing the catalyst loading (entries 2-3).

Table 2.2. Optimization of reaction conditions.a,*

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol %)</th>
<th>Ligand (mol %)</th>
<th>Yieldb</th>
<th>Ratio 2.14 : Z-2.16 : Z-2.17 : Xc</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pt(dba)₃ (4)</td>
<td>—</td>
<td>56</td>
<td>78:22:0:0</td>
</tr>
<tr>
<td>2</td>
<td>Pt(dba)₃ (2)</td>
<td>—</td>
<td>16</td>
<td>73:27:0:0</td>
</tr>
<tr>
<td>3</td>
<td>Pt(dba)₃ (8)</td>
<td>—</td>
<td>45</td>
<td>76:24:0:0</td>
</tr>
<tr>
<td>4</td>
<td>Pt(dba)₃ (4)</td>
<td>PPh₃ (6)</td>
<td>63</td>
<td>67:16:5:12</td>
</tr>
<tr>
<td>5</td>
<td>Pt(dba)₃ (4)</td>
<td>PCy₃ (6)</td>
<td>34</td>
<td>80:20:0:0</td>
</tr>
<tr>
<td>6</td>
<td>Pt(dba)₃ (4)</td>
<td>P[3,5-(CF₃)₂C₆H₃] (6)</td>
<td>72</td>
<td>45:5:28:22</td>
</tr>
<tr>
<td>7</td>
<td>Pt(dba)₃ (4)</td>
<td>SPhos (6)</td>
<td>36</td>
<td>90:10:0:0d</td>
</tr>
<tr>
<td>8</td>
<td>Pt(dba)₃ (4)</td>
<td>Ruphos (6)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>9</td>
<td>Pt(dba)₃ (4)</td>
<td>dppe (6)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>10</td>
<td>Pt(dba)₃ (4)</td>
<td>DPEphos (6)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>11</td>
<td>Pt(dba)₃ (4)</td>
<td>Xantphos (6)</td>
<td>66</td>
<td>3:62:35:0</td>
</tr>
<tr>
<td>12</td>
<td>Pt(dba)₃ (4)</td>
<td>P(OEt)₃ (6)</td>
<td>68</td>
<td>68:19:9:4</td>
</tr>
<tr>
<td>13</td>
<td>Pt(dba)₃ (4)</td>
<td>P(OPh)₃ (6)</td>
<td>trace</td>
<td>—</td>
</tr>
<tr>
<td>14</td>
<td>[IrCl(cod)]₂ (2.5)</td>
<td>—</td>
<td>12</td>
<td>0:100:0:0d</td>
</tr>
<tr>
<td>15</td>
<td>[IrCl(cod)]₂ (2.5)</td>
<td>PPh₃ (6)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>16</td>
<td>[RhCl(cod)]₂ (2.5)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>17</td>
<td>Pd₂(dba)₃ (2.5)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

a Reaction conditions: pinB—Bdan (0.136 mmol), phenylallene (0.163 mmol), toluene (1 mL) at 80 °C for 24 h. b Isolated yields. c Determined by GC analysis of the crude reaction mixture. d The same isomeric ratio and yield were obtained at 100 °C.

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Abbreviations: SPhos = 2-dicyclohexylphosphino-2’,6’-dimethoxybiphenyl; Ruphos = 2-dicyclohexylphosphino-2’,6’-diisopropoxybiphenyl; Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthened; dppe = ethylenebis(diphenylphosphine); DPEphos = (Oxydi-2,1-phenylene)bis(diphenylphosphine).
To improve the regioselectivity of the reaction, a variety catalytic systems with phosphine ligands were explored. Although yield of the reaction was improved from 56% to 63% with triphenylphosphine as the ligand (entry 4), a complex mixture of all six potential products was observed. Unexpectedly, a comparable selectivity for the internal double bond diboration was obtained with and without tricyclohexylphosphine (entries 5 and 1), a sterically bulky ligand, and lower yields were obtained with this ligand (34% and 56%, respectively). It is interesting to compare these results with the original B$_2$pin$_2$ diboration. In 1998, it was found that under the same conditions, borylation with Pt$_2$(dba)$_3$ provided low yields (50%) due to catalyst decomposition.$^{36}$ As evidenced by entries 1-3, catalytic decomposition of Pt$_2$(dba)$_3$ does not lead to low yields in this reaction. It is, therefore, reasonable to infer that the bis(boryl) platinum(II) intermediate is stabilized when ligated with a Bdan moiety. Also unlike the diboration reaction with PDAN, a 68:32 ratio favoring diboration of the terminal double (2.2b, Table 2.1) bond was obtained in an 84% yield when the PCy$_3$ ligand was employed in the B$_2$pin$_2$ diboration reaction.$^{36}$ The observation that diboration with PDAN affords 2.14 as the major product suggests that the Bdan moiety decreases the steric influence of the tricyclohexylphosphine ligand on regioselectivity.

Inspired by the high regioselectivity and yields obtained when Suginome et al. ligated platinum(0) with P[3,5-(CF$_3$)$_2$C$_6$H$_3$)$_3$ for the unsymmetrical diboration of alkynes with PDAN diboron, this catalytic system was explored for the diboration of phenyl allene.$^{45}$ While a high yield of allene diboration occurred, there was very little selectivity in the product distribution (entry 6). Employing Buchwald’s ligand, SPhos (2-dicyclohexylphosphino-2’,6’-dimethoxybiphenyl, 2.18, Figure 2.6), resulted in an excellent regioselectivity for 2.14. This reaction gave a 90:10 ratio of just two isomers, 2.14 and (Z)-2.16, albeit in a low yield (36%, entry 7). Interestingly, no reaction occurred when a similar but more sterically demanding ligand,
Ruphos (2-dicyclohexylphosphino-2’,6’-diisopropoxybiphenyl, 2.19), was used. This would suggest that the 2’ and 6’ substituent are in close proximity to the reaction center, perhaps sterically encumbering an open coordination site wherein the allene undergoes insertion (see also Figure 2.12).

Bidentate phosphine ligands, dppe (1,2-bis(diphenylphosphino)ethane) and DPEphos (bis[(2-diphenylphosphino)phenyl] ether), also gave no reaction (entries 8-10). In contrast, the bidentate ligand, Xantphos (4,5-bis(diphenylphosphino)-9,9-dimethylxanthene), reversed the regioselectivity to favor addition to the terminal double bond and stereoselectively afforded the (Z)-isomers (entry 11). In the $^1$H NMR of this mixture of isomers, two methylene signals were observed, wherein, the signal for (Z)-2.16 was identified. Compound (Z)-2.17 was differentiated from the (E)-2.17 by performing a 1D nOe study on the mixture. A promising distribution of isomers was obtained when triethylphosphinite was used; however, increasing the steric bulk of this ligand with triphenylphosphite resulted in no reaction (entries 12-13).

When other transition metal catalysts were tested, an iridium catalyst gave a regio- and stereoselective diboration to generated (Z)-2.16 exclusively, which enabled a full characterization of this isomer. Unfortunately, the formation of polymeric by-products negatively impacted the yield and attempts to improve the yield with different reaction conditions (i.e. solvent, temp, and ligand) were unsuccessful (entries 14-15). Other metals, such as rhodium and palladium, were found to be ineffective catalysts (entries 16-17).
These results found that the P[3,5-(CF₃)₂C₆H₃]₃ ligand provided the highest reaction yield, but the best selectivity was obtained using the SPhos ligand. With both of these catalytic systems, the reaction conditions were optimized (Table 2.3). However, increasing the temperature by 20 degrees did not affect the selectivity, nor did the reaction proceed at a lower temperature or in polar solvents.

Table 2.3. Optimization of reaction conditions.¹

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>Yieldb</th>
<th>Product Ratio ².14:(Z)-2.15:XC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Toluene</td>
<td>55</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>Toluene</td>
<td>80</td>
<td>72%</td>
<td>45 : 5 : 50</td>
</tr>
<tr>
<td>3</td>
<td>Toluene</td>
<td>100</td>
<td>70%</td>
<td>47 : 9 : 44</td>
</tr>
<tr>
<td>4</td>
<td>Dioxane</td>
<td>80</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>DMF</td>
<td>80</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

¹ Reaction conditions: pinB—Bdan (0.136 mmol), disubstituted allene (0.163 mmol), Pt(dba)₃ (5.35 μmol), ligand (8.16 μmol) and toluene (1 mL) at 80 °C for 24 h. ² Isolated yield of product mixture. ³ Determined by GC analysis the crude reaction mixture.

Being unable to obtain satisfactory results with a monosubstituted allene, attention was turned to 1,1-disubstituted allenes (Table 2.4), suspecting that a large steric contribution would enhance regioselectivity. Indeed, both 1,1-methylphenyl allene 2.20 and 1,1-diphenyl allene 2.22 reacted with these platinum-phosphine complexes to provide exclusive addition to the terminal double bond of these substrates. High stereoselectivity for the (E)-isomer was observed in the borylation of allene 2.20. While the P[3,5-(CF₃)₂C₆H₃]₃ ligand continued to provide inconsistent regioselective installation of the boron moieties, the SPhos platinum complex maintained high selectivity and improved reaction yields were achieved with these substrates. As such, the SPhos
catalytic system under these conditions was determined to be optimal for the diboration of 1,1-disubstituted allenes.

Table 2.4. Ligand screening with 1,1-disubstituted allenes.

![Ligand screening with 1,1-disubstituted allenes](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Substrate</th>
<th>Yield</th>
<th>Ratio a:b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SPhos</td>
<td><img src="image" alt="Substrate 2.20" /></td>
<td>75</td>
<td>94:6</td>
</tr>
<tr>
<td>2</td>
<td>SPhos</td>
<td><img src="image" alt="Substrate 2.22" /></td>
<td>85</td>
<td>94:6</td>
</tr>
<tr>
<td>3</td>
<td>P[3,5-(CF₃)₂C₆H₃]₃</td>
<td><img src="image" alt="Substrate 2.20" /></td>
<td>76</td>
<td>76:24</td>
</tr>
<tr>
<td>4</td>
<td>P[3,5-(CF₃)₂C₆H₃]₃</td>
<td><img src="image" alt="Substrate 2.22" /></td>
<td>91</td>
<td>33:67</td>
</tr>
</tbody>
</table>

*a* Reaction conditions: pinB—Bdan (0.136 mmol), disubstituted allene (0.163 mmol), Pt(dba)₃ (5.35 µmol), ligand (8.16 µmol) and toluene (1 mL) at 80 °C for 24 h. *b* Isolated yield of product mixture. *c* Determined by GC analysis of the crude reaction mixture. *d* These values represent a mixture of *(E)-2.21b* and the two *(Z)-isomers.* Reproduced with permission.

2.4.2. Structural Determination of the 1,1-Disubstituted Products

As noted in Table 2.4, the borylation of 1-methyl-1-phenyl allene, 2.20, produced 4 products in total. These were all identified as terminal borylation constitutional and stereoisomers, wherein the ¹H NMR of the crude reaction mixture exhibited four methylene proton signals. The
major product, (E)-2.31a, was selectively recrystallized from the mixture of isomers. This compound was then fully characterized by single crystal X-ray diffraction (Figure 2.7).

The 1,1-diphenyl allene borylation products were also identified as 2 terminal addition products from the $^1$H NMR of the crude material (2.23a and 2.23b). It was observed that the chemical shift for the methylene group attached to the major product unit appeared downfield relative to the methylene in the minor product. Single-crystal X-ray diffraction had to be employed because nOe studies could not unambiguously identify where the Bpin and Bdan moieties were installed. The major isomer, 2.23a, was isolated from the mixture of by recrystallization in hexane and the X-ray structure analysis provided unambiguous structural determination. From entry 4 (Table 2.4), which provided a slight excess of 2.23b as the major product, a sufficient amount of this product was isolated using column chromatography and recrystallized for X-ray structure analysis. The crystal structures of both isomers are presented in Figure 2.8.

Figure 2.8. Anisotropic displacement ellipsoid drawings (50%) of 3.23a (left) and 3.23b (right). CCDC # 1039452 and 1039451, respectively.

2.4.3. Substrate Scope

The optimized reaction conditions using Pt(dba)$_3$ (4 mol %) with SPhos (6 mol%) in toluene at 80 °C were applied to the diboration of a variety of disubstituted allenes. As presented
in Table 2.5, the 1,1-diaryl allenes readily undergo reaction with pinB–Bdan to afford the products in high yields and with good to excellent regio- and stereoselectivity. Analogous to the borylation of 2.20, 1-isobutyl-1-phenyl allene produced 4 terminal addition products in a high yield (entry 1). The diboration of this allene was less stereoselective for (E)-2.25a. In fact, the side product ratio (32%) was predominately (Z)-2.25a (determined by 1D-selective nOe analysis of the mixture). This finding indicates that the observed selectivity arises purely from steric interactions.

Next, a panel of symmetrical 1,1-diaryl allenes were explored. Para-substituted aryl rings bearing a methyl group or an electron-withdrawing halogen, such as chlorine or fluorine, underwent diboration with excellent selectivities and yields (entries 2-4). The major product could

Table 2.5. Diboration of disubstituted allenes with pinB—Bdan.\(^a,^*\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Major Product</th>
<th>Yield(^b)</th>
<th>Ratio (a:b)(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Substrate Image" /></td>
<td><img src="image2" alt="Product Image" /></td>
<td>95</td>
<td>68:32(^d)</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Substrate Image" /></td>
<td><img src="image4" alt="Product Image" /></td>
<td>82</td>
<td>92:8</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Substrate Image" /></td>
<td><img src="image6" alt="Product Image" /></td>
<td>86</td>
<td>94:6</td>
</tr>
</tbody>
</table>
Reaction conditions: pinB–Bdan (0.136 mmol), disubstituted allene (0.163 mmol), Pt(dba)$_3$ (5.35 µmol), ligand (8.16 µmol) and toluene (1 mL) at 80 °C for 24 h. Isolated yield of product mixture. Determined by GC analysis of the crude reaction mixture, unless otherwise noted. Value represents a mixture of (E)-2.25b and the other regioisomers. Determined by $^1$HNMR analysis of the crude reaction mixture.

* Reproduced with permission.
be recrystallized from the isomeric mixture in hexane. Analysis of the crystal structures was used to confirm the previous observation that chemical shift of the methylene protons geminal to the Bdan group is found downfield relative to the methylene protons germinal to Bpin (Figure 2.9). This trend was established to be independent of aryl substitution, and the product identification of other 1,1-diaryl borylation reactions was analyzed by analysis of the crude $^1\text{H}$ NMR.

Electron-donating substituents in the 4-position of the aryl rings, such as methyl and ethyl ethers, also generated the desired products in high selectivities and yields (entries 5-6); however, a diminished selectivity was obtained with larger hydrocarbon substituents in the 4-position, such as the propyl ether and the phenyl ring (entries 7-8). Comparing the selectivity of borylating unsubstituted 1,1-diaryl allene (94:6, entry 2) to those bearing electron donating substituents (Me = 92:8, entry 2 and OR = 90:10, entries 5-7) in Table 2.5, a mild decrease in selectivity is noted.

**Figure 2.9.** Anisotropic displacement ellipsoid drawings (50%) of entries 1-5 (Table 3.5). Hydrogens have been excluded for clarity. Entries 1-5 CCDC # 1039457, not published, 1039453, 1039456, and 1427814.
Likewise, the borylation of electron deficient diaryl substrates consistently gave the highest selectivities (>94%), and a trend with increasing withdrawing strength of the substituent is noted (Cl < F < CF₃, entries 3, 4, and 10, Table 2.4). In fact, a near quantitative isolation of the major product was generated from the diboration of 3,3'-trifluoromethyl diaryl allene (entry 10). A possible limitation of this diboration reaction is steric bulk in the 2-position, which drastically decreases selectivity of the reaction, as seen in entry 9. In this case, it is likely that steric interactions from the ortho-methyl substituents hinder the insertion process.

2.4.4. Proposed Mechanism

A proposed mechanism is depicted in Figure 2.10, which is based largely on the detailed mechanistic studies of palladium-catalyzed diboration of allenes by Morken et al.³⁴ The bis(boryl)platinum(II) intermediate, 2.35, is generated following the oxidative addition of the differentially protected diboron onto the Pt(0) complex. Following the dissociation of a ligand to

![Figure 2.10](image)

*Reproduced with permission.
provide an open coordination site, the less substituted terminal double bond of the allene coordinates to the complex. Based on the observed selectivity, it is inferred that insertion of the substrate prefers the Pt—Bpin bond. Analogous palladium-catalyzed allenic diboration investigation, which showed that this insertion process occurs at the central sp hybridized carbon of the substrate, the more stable π-allyl PtII intermediate (2.37) is formed. This allylic intermediate can isomerize to provide 2.39 with mono-substituted substrates, such as phenyl allene. Reductive elimination occurs more readily from this sterically encumbered intermediate to furnish the major product 2.14. The steric bulk of 1,1-disubstituted allenes prevents this isomerization. As a result, reductive elimination can only occur from 2.38 to provide the terminal diboration products 2.21a and 2.23a-2.34a.

Ishiyama et al. reported NMR evidence for the oxidative addition of a bis(pinacolato)diboron to platinum(0) in 1993 and the same authors later published the crystal structure (left, Figure 2.11). Recently, the use of pinB—Bdan has increased and the crystal structure of a similar platinum complex resulting from the oxidative addition of a differentially protected diboron reagent was published by Borner and Kleeberg (right, Figure 2.11, dmab = 1,2-di(methylamino)benzene). A comparison of relative bond lengths and angles is given in Table 2.6. The B—Pt—B bond angle is slightly smaller in the unsymmetrical diboron platinum complex.

**Figure 2.11.** Anisotropic displacement ellipsoid drawings (50%) of bis(boryl) platinum(II) complexes. Left: Symmetrical [(PPh3)2Pt(Bpin)2], CCDC # 1316274. Right: Unsymmetrical [(PPh3)2Pt(Bpin)(Bdmab)], CCDC # 992148. Hydrogens have been excluded for clarity.
Interestingly, the platinum–boron bond lengths are comparable in both complexes, regardless of the protecting group on the boron center. This is due to the trans-effect of the phosphine ligand and, mechanistically, this would account for the lack of selectivity in the allene diboration when PPh₃ was used. A noteworthy effect that the different boron ligands seems to have is the large difference in the P–Pt–B bond angles for the two ligands. The larger bond angle for the P–Pt–Bpin would indicate that Bpin is more sterically demanding ligand than the diamino boronate. This steric effect may promote the dissociation of the phosphine ligand cis to the Bpin, thereby creating an open coordination site for the substrate to undergo insertion into the Pt–Bpin bond. Indeed, a modest selectivity (67%) was observed for the major isomer which places the Bpin on the sp² carbon when using the PPh₃ ligand system.

<table>
<thead>
<tr>
<th>Bond</th>
<th>Length (Å)</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
<tr>
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<td>2.077</td>
</tr>
<tr>
<td>P—Bpin</td>
<td>2.078</td>
</tr>
<tr>
<td>P1—Pt—P2</td>
<td>102.6°</td>
</tr>
<tr>
<td>P—P1—Bpin</td>
<td>89.0–93.0°</td>
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<tr>
<td>Bpin-Pt-Bpin</td>
<td>75.3°</td>
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<table>
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<th>Angle</th>
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<tr>
<td>P—Bpin</td>
<td>93.3°</td>
</tr>
<tr>
<td>Bpin-Pt-Bpin</td>
<td>72.4°</td>
</tr>
</tbody>
</table>

Table 2.6. Comparison of the bond lengths and bond angles of bis(boryl) platinum(II) complexes.¹³,₅²

Several crystal structures have documented unique coordination chemistry taking place between the metal and the biphenyl ring of SPhos. In these complexes, the second aryl ring sits at a twisted angle relative to the first which enables the ring to interact with the metal center directly.
through the ipso-carbon (Figure 2.12). This interaction is suspected to improve the catalytic activity in reactions like the Suzuki-Miyaura cross-coupling by stabilizing a more reactive metal complex with an open coordination site.\textsuperscript{56}

Considering that steric interactions would give rise to a monophosphine complex, the coordinated ipso-carbon is expected to have a reduced \textit{Trans} Effect on the Pt—B bond as compared to a phosphine. As such, it would be expected that the Pt—B bond lengths would differ within the Pt/SPhos complex. The product distribution suggests that the Bdan moiety would be \textit{trans} to the ipso-carbon and the Bpin moiety would be \textit{trans} to the phosphine. This places the Bpin next to the site where the allene coordinates prior to insertion. This arrangement may be favorable because the Bpin is expected to have a greater steric clash with the cyclohexyl substituents.

\textbf{Figure 2.12.} Equilibrium for ligand dissociation between [Pd(SPhos)\textsubscript{2}] and [Pd(SPhos)(dba)] (top). Associated ORTEP diagrams for 2.40 and 2.41 with hydrogens omitted for clarity. Thermal ellipsoids are at 50\% probability (bottom). CCDC # 268750 and 227390, respectively.\textsuperscript{56}
2.5. Synthetic Application of Diborated Products via Chemoselective Transformations

It was demonstrated that this protocol is scalable by subjecting 1.6 mmol of 1,1-diphenylallene to the reaction conditions. Product 2.23a was obtained in a 78% yield and with equivalent selectivity. It was envisioned that, in addition to the reactivity differences between vinylic and allylic boron moieties, the orthogonal protecting groups on the boron centers would provide access to a wide scope of compounds through the chemoselective functionalization of a common intermediate. To demonstrate the utility of this diboration reaction, such transformations were performed (Scheme 2.7).

**Scheme 2.7.** Chemoselective transformations of differentially protected diboration product.
* Reproduced with permission.
A tetrasubstituted alkene was prepared from 2.23a and 4-methylboromobenzene under standard Suzuki-Miyaura cross-coupling conditions. In this reaction, the pinacol protected vinylboronic ester chemoselectively cross-couples in the presence of the allylic diaminoboryl group. The diaminonaphthalene protecting group is then hydrolyzed under acidic conditions to furnish the boronic acid, which can be oxidized to provide an allylic alcohol (2.43) or trapped as a pinacol ester, 2.44. Treatment of 2.44 with standard cross-coupling reaction conditions failed to provide the desired product. In follow-up experiments, it was determined that in the presence of a mild base, such as cesium carbonate at 80 °C, a terminal alkene (2.46) is produced quantitatively. This could be the result of a 1,3-borotropic shift followed by protodeboronation. Further exploration of this chemistry determined that under strongly basic conditions, such as those required for an amination reaction, quantitative protodeboronation occurs to give the tetrasubstituted alkene 2.45. As such, the allylboronic ester 2.44 was determined to be too unstable for these conditions and was converted into the corresponding trifluoroborate salt 2.47. Indeed, under the cross-coupling conditions developed by Morken et al. this compound is suitable for achieving the desired sp²-sp³ cross-coupling reaction to generate product 2.48. Under these unoptimized conditions, low yields of this product were obtained (23%, NMR yield) and separation from the aforementioned alkenyl byproducts was difficult.

### 2.6. Conclusions

In summary, a platinum-catalyzed diboration of 1,1-disubstituted allenes using SPhos as the ligand was developed for the regioselective addition of two differentially protected boron moieties to the terminal double bond. These studies demonstrated the chemoselective transfer of Bpin to the substrate’s internal sp hybridized carbon atom and Bdan to the sp² hybridized carbon
with good to excellent stereoselectivity. Furthermore, the utility of these bis-borylated products as synthetic intermediates was demonstrated, wherein each boron center undergoes chemoselective reactions to afford highly substituted alkenes. Detailed mechanistic studies, including the characterization of the differentially protected bis(boryl) platinum(II) intermediate, are subjects for future work on this project.

2.7. References


(14) Ely, R. J.; Morken, J. P. Ni(0)-Catalyzed 1,4-Selective Diboration of Conjugated Dienes. *Org. Lett.* **2010**, 12, 4348-4351.


Chapter 3. Conformational Analysis of ortho-Substituted 1,1-Dibromo-2,2-diphenylcyclopropanes: An NMR and DFT Study

3.1. Contributions

The advisor, Prof. Webster Santos, encouraged the author to pursue the analysis of an unexpected NMR result. The author sought the expertise of the following collaborators: Dr. Neeraj Patwardhan, Prof. Paul Carlier, Dr. Narasimha Murthy, and Dr. Carla Slebodnick.

Dr. Neeraj Patwardhan collaborated in the beginning stages. The DFT calculations were his major contribution. Neeraj performed these analyses, organized the data, and jointly interpreted the results based on the author’s proposed mechanism. He provided a synopsis of these findings. An expansion of Neeraj’s shared ideas regarding the future directions are outlined in Section 3.6.

Prof. Carlier was an indispensable mentor and consultant on the physical chemistry aspects of this research. He strongly supported these investigations and guided the direction of the project with experimental suggestions. The proposal to extrapolate thermodynamic parameters from variable temperature NMR and EXSY experiments were his major contributions. He also assisted in the verification of the author’s analyses and provided feedback on these results.

Dr. Murthy was a key collaborator in this work. His NMR expertise enabled the author to collect the experimental data. Method development, pulse sequence optimization, and experimentally determining range of mixing times were his major contributions to this work. He also examined the data and provided feedback based on his extensive expertise in the field.

The crystallographic data was collected and processed by Dr. Carla Slebodnick.

The author synthesized the compounds reported here, performed all NMR experiments (excluding the mixing time optimization), analyzed and interpreted the data, and wrote the chapter. Special thanks to Marwa Abdel Latif for reviewing this chapter.
3.2. Abstract

The synthesis and characterization of new allenes is described. An addition-elimination method was developed for the synthesis of alkenes from ketones. The synthetic scheme for the allenes uses the Doering-Moore-Skattebøl reaction, which proceeds through a 1,1-dibromocyclopropane intermediate. During the synthesis of these allenes, a gem-dibromocyclopropane intermediate was identified as a near-atropisomer. Chiral rotamers have not been characterized in this structural motif before. Therefore, detailed investigations of the origins of rotational restriction, conformational analyses, and the kinetic rate constants for isomerization were examined. DFT calculations with a B3LYP/6-31G* model revealed that the isomerization proceeds through a meso-intermediate and the free energy of activation was found to be 12.9 kcal/mol with a transition state energy of 13.5 kcal. On a 600 MHz instrument, a rate constant was estimated at the coalescence temperature which provided a $\Delta G^\ddagger_{Tc}$ of 12.0 ± 0.2 kcal/mol at 268.0 K. Line shape analysis of variable temperature $^1$H NMR spectra was used to determine the rate constants for the interconversion at temperatures between 239.9 and 315.2 K. Extrapolation of thermodynamic components from an Eyring plot evaluated the enthalpic and entropic contributions to the free energy of activation to be 14.0 ± 0.7 kcal/mol and 7 ± 2 e.u., respectively. This data gives a free energy barrier of 12.1 ± 0.3 kcal/mol in this temperature range, which is in excellent agreement with the values assessed by the other methods. Finally, the Arrhenius relationship revealed the activation energy for the isomerization is 14.6 ± 0.7 kcal/mol.
3.3. Introduction

3.3.1. Allenes from \textit{gem}-Dibromocyclopropanes

Allenes comprise a class of compounds characterized by a 1,2-propadiene functional group. Since 1954, when the cumulative double bond structure of an allene was characterized by IR and UV spectroscopy, interest in these compounds has grown from academic intrigue to extravagant synthetic applications.\textsuperscript{1} These reactive compounds have been identified in well over a hundred natural products and undergo a broad range of reactions such as sigmatropic rearrangements, cycloaddition reactions, radical reactions, and ionic additions.\textsuperscript{2} As seen in Chapter 2, the products of these reactions often retain a double bond, rendering allenes as unique synthetic substrates. Thus it follows that there are a wide variety of methods to synthesize allenes.\textsuperscript{3-5}

Several methods for their synthesis have stood the test of time as generic and versatile protocols. Most notably, the Doering-Moore-Skattebøl reaction was the first synthetic method developed and is still commonly employed (Scheme 3.1).\textsuperscript{6} Rearrangements including \textit{[3,3]}- and \textit{[2,3]}-sigmatropic shifts and Claisen reactions are alternative synthetic routes.\textsuperscript{3-5} Using propargyl electrophiles, elimination reactions, homologation and modified Wittig, Wittig-Horner, and Horner-Wadsworth-Emmons are other ways to access functionalized allenes.\textsuperscript{5} More recently, the exploitation of transition metals to form the allene has emerged as a common approach, especially for stereocontrolled synthesis of chiral allenes.\textsuperscript{4,7-10}

The procedures used to prepare the compounds presented here employed the conventional methods inspired by the original work of Doering and LaFlamme (Scheme 3.1). Doering prepared

\[
\begin{align*}
\text{Br} & \quad \text{Br} \\
\text{R} & \\
+ \quad \text{R-Li} \\
\rightarrow \\
\text{R} &
\end{align*}
\]

\textbf{Scheme 3.1.} The Doering-Moore-Skattebøl synthesis of allenes.\textsuperscript{6}
a gem-dichlorocarbene in situ from chloroform using potassium tert-butoxide. Today, the most common method for generating the dihalocarbene employs triethylbenzylammonium chloride (TEBA), a phase transfer catalyst. This reaction occurs under remarkably mild conditions, despite the use of highly concentrated (25 M) sodium hydroxide.\textsuperscript{11,12} The phase transfer catalyst ensures that there is such a low concentration of hydroxide in the organic phase that even allylic esters can be cyclopropanated without significant hydrolysis of the ester.\textsuperscript{13} At the interface between the organic and aqueous layer, TEBA assists the deprotonation of the haloform by the base. The highly electronegative halogen then leaves to generate the carbene which undergo a [2+1]-cycloaddition with alkenes (Figure 3.1). The dichloro- and dibromocyclopropanes constitute classic examples. Difluorocarbenes are gaining popularity, however, they require extreme conditions to form.\textsuperscript{14-18} Conversely, diiodocarbenes are unstable.\textsuperscript{19,20} Methods for preparing mixed dihalocarbenes are also known, however, their addition to alkenes is typically non-selective and low yielding.\textsuperscript{21-24}

Carbenes have an interesting structure. They can exist in either the singlet or the triplet state (3.3a and 3.3b, Figure 3.1).\textsuperscript{25,26} Each of these unique structures also gives way to divergent

\textbf{Figure 3.1.} Mechanism for the formation of gem-dihalocarbene (X = F, Cl, Br).
reactivity. Singlet carbenes are electrophilic and typically engage in concerted reactions, whereas a diradical, triplet carbene undergoes stepwise, single electron additions. In the ground state, singlet gem-dihalocarbenes are around 10-35 kcal/mol lower in energy than that of the triplet carbene, depending on the particular halogens. As such, in the Doering-LaFlamme cyclopropanation, the singlet carbene reacts with an olefin to afford a gem-dichlorocyclopropane in a concerted manner. For substituted alkenes, these reactions are stereospecific, retaining the cis or trans stereochemistry of the alkene. However, when the R groups are inequivalent, these reactions are rarely enatioselective.

By treating gem-dibromocyclopropanes at elevated temperatures with pieces of sodium or magnesium, Doering and LaFlamme obtained the corresponding allenes in fair yields. Building upon this, Moore et al. and Skattebøl independently discovered that alkyllithium reagents delivered the allenes in high yields at temperatures between –100 and –78 °C. If the reaction mixture is too warm, however, it yields a complex mixture of allene and other hydrocarbon side products which are difficult to separate. These reactions proceed via metal-halogen exchange, which is suspected to be in equilibrium with the dibromocyclopropane (3.6, Scheme 3.2). Elimination of lithium bromide provides the cyclopropylidene intermediate 3.7. This singlet carbene then rearranges to give the allene.

Scheme 3.2. Metal-halogen exchange and formation of phenyl allene.

Doeing and LaFlamme’s initial observation that magnesium metal reacts with the gem-dichlorocyclopropanes to generate allenes led others to explore organometallic conversions based on Grignard reagents. In the 1960s and 70s, Seyferth and co-workers found these
reactions yielded mono-hydrodebromination when gem-dibromocyclopropanes were treated with methylmagnesium bromide.\textsuperscript{36,42} Moreover, the products from their reactions were not indicative of a cyclopropylidene intermediate (3.7).\textsuperscript{36} For nearly 30 years, this chemistry was abandoned until a report briefly mentioned that 1,1-dibromo-2-hexylcyclopropane furnished 1,2-nonadiene in a 95\% yield in the presence of butylmagnesium bromide in THF.\textsuperscript{45} This interesting side note led Baird, Nizovtsev, and Bolesov to do an extensive investigation on this chemistry.\textsuperscript{41}

Three more commercially available Grignard reagents are effective: EtMgBr, EtMgCl and iPrMgBr. At room temperature and within 30 mins, unstrained, allenic hydrocarbon are obtained in 91-96\% yields after purification. Benzylmagnesium bromide, tBuMgBr, and MeMgBr gave a mixture of the allene with dehalogenated cyclopropanes and PhMgBr was unreactive. Mechanistic studies verified that this reaction also proceeds through the carbene intermediate, 3.7.\textsuperscript{41}

During the synthesis of a library of allenes, it was discovered that several of these allenes and gem-dibromocyclopropanes were uncharacterized in the literature. Moreover, an interesting gem-dibromocyclopropane intermediate was identified which gave rise to further investigation of these intermediates.

\textbf{3.3.2. Significance of gem-Dihalocyclopropane Intermediates}

\textit{gem}-Dihalocyclopropanes are valuable starting materials for other compounds as well. For example, monohalocyclopropanes, cyclopropanes, cyclopropenes, acetics, ketals, alkenes, dienes, expanded cyclic, bicyclic, and spirocyclic compounds, and many more functional groups can be generated from them; the extensive synthetic applications warranted their review.\textsuperscript{6,15,19,46} As a substrate, the \textit{gem}-dihalocyclopropane structural motif is incredibly stable towards most reaction conditions and, only when the appropriate reaction conditions are applied, does an electrocyclic ring-opening process occur to furnish the allylic carbocation (3.10, Scheme 3.3a). This reactive
intermediate is usually trapped by an inter- or intra-molecular nucleophile to form a highly substituted alkenyl halide. These alkenyl halides provide versatile substrates for subsequent Suzuki-Miyaura cross-coupling reactions, yielding highly tetrasubstituted alkenes in a stereocontrolled manner. This chemistry was used to synthesize the racemic and the enantiopure variants of γ-Lacorane (Scheme 3.3b). The diastereoselective electrocyclic ring-opening from 3.13 to 3.14 proceeds in a predictable disrotatory manner, as expected based on Woodward-Hoffman rules for two-electron systems (Figure 3.2). A single diastereomer can be obtained when the nucleophile enters while the halide is leaving in a concerted fashion. This process is most selective for ring-expansions, however, anchimeric assistance from other functional groups has also been demonstrated. The most notable application of this reaction is in alkaloid and natural product syntheses.

**Scheme 3.3.** (a) 1,1-Dibromocyclopropanes subject to a silver-catalyzed electrocyclic ring-opening and nucleophilic attack followed by a Suzuki-Miyaura cross-coupling reaction. (b) Application for the synthesis of a natural product.
Despite their exceptional ease of access and unique chemistry, these compounds are widely underutilized. Efficient methods for the generating enantiopure chiral gem-dihalocyclopropane structures continues to be a synthetic challenge. This is particularly surprising, given that gem-dihalocyclopropane enantiomers show remarkably different bioactivity as mGluRs agonists (3.17, Figure 3.3).\textsuperscript{58} Currently, these difluorocyclopropanes are a popular isostere in biologically active compounds.\textsuperscript{59,60} Chiral difluorocyclopropanes have also been examined in recent years, showing great potential in liquid-crystalline materials (3.20).\textsuperscript{61,62} Optically active gem-dihalospirocyclic derivatives of cycloheptane, like 3.21, are interesting ferroelectric liquid-crystalline compounds possessing unique phenomenon regarding their helical twisting power.\textsuperscript{62} The difluoro variant gave the most unusual results. Recently, progress has been made to improve the ease of generating the gem-difluorocarbenes under milder and less dangerous conditions.\textsuperscript{18} However, these methods do not yet deliver enantiopure compounds.

**Figure 3.3.** Biologically active compounds and materials of interest featuring a chiral 1,1-dihalocyclopropane.
The most common method for obtaining the enantiopure \textit{gem}-dihalocyclopropene derivatives in Figure 3.3 is through biotransformations using enzymes and microorganisms for the resolution of racemic mixtures and desymmetrizing \textit{meso} compounds.\textsuperscript{61,63} However, this technique comes at the cost of the undesired enantiomer and the success of these methods is strongly influenced by the halogen substituent. There are only a handful of examples of direct enantioselective syntheses. Daran and co-workers obtained enantiopure 1,1-dihalocyclopropyl derivatives of limone.\textsuperscript{64} Chiral auxiliaries have been examined with minimal success.\textsuperscript{65} In fact, there are only three enantioselective methods for delivering these compounds. One of which uses rhodium to form bicyclic lactone and achieves 47-52\% ee for the 1,1-dibromocyclopropane.\textsuperscript{66} The other two examples form a spirocyclic compound as a single diastereomer through an addition-elimination reaction with α,β-unsaturated ketones.\textsuperscript{67,68} As such, a direct and convenient method for accessing enantiopure derivatives would be of great interest to the scientific community.

\textbf{3.3.3. Project Overview}

The initial goal of this project was to prepare a library of 1,1-substituted allenes for the borylation reactions described in Chapter 2. While preparing these compounds, it was noticed that several derivatives had not yet been reported in the literature. The most interesting aspect of this project came when a \textit{gem}-dibromocyclopropane derivative was found to exhibit conformational isomerism. This compound is a rare example of conformational restriction about an (aryl)sp\textsuperscript{2}–Csp\textsuperscript{3} bond because it features a cyclopropane.\textsuperscript{69-75} Indeed, this is the first example of a cyclopropyl rotamer. It is envisioned that future direction of will work towards developing true \textit{gem}-dihalocyclopropyl atropisomers, whose interconversion at a given temperature possess a half-life in excess of 1000 s (about 16.7 min).\textsuperscript{76} The conformational rigidity of an atropisomer reduces rotational mobility, which is an important aspect of ferroelectric liquid crystals because the rigidity
of a chiral system is inversely correlated to the effective dipole moment and encourages spontaneous polarization. While atropisomers have been extensively employed in liquid crystals, derivatives of the compound reported here would represent a new class of chiral structural motifs in the field. Thus, characterizing the rotational barrier that this compound possesses provides a basis for future exploration in this area and its applications.

3.4. Results and Discussion

3.4.1. Development of the Allene Synthesis

The *gem*-dibromocyclopropanes and allenes presented in this account were prepared from commercially available ketones and alkenes. While the Wittig reaction provides moderate yields of alkenes 3.27-3.31 (Table 3.1), in many cases, this method was riddled with undesired side products. For instance, 3.23 gave only a 55% yield of the desired product under standard Wittig reaction conditions. Similarly, electron deficient aryl rings were also low yielding, wherein the conversion of 3.25 to the alkene was obtained in a 33% yield, and the Wittig reaction fails to produce even trace amounts of the product from 3,3'-bis(trifluoromethyl)benzophenone 3.26. An alternative olefination using methanesulfonyl chloride to produce this alkene is known, but only a 39% yield was reported.77 Taking advantage of the electrophilic benzophenone carbonyl, a facile addition-elimination method was developed to obtain the desired alkenes 3.27-3.31 in exceptionally high yields. Conventionally, this addition-elimination approach would use a Grignard reagent for the addition of a methyl group;78 however, the use of methyllithium at −78 °C is also reported.79 Complete conversion of benzophenones to their corresponding alcohols with methyllithium takes place immediately at room temperature. On small scales, these reactions were not exothermic and did not require cooling. A short reflux of the crude material with catalytic *p*—
toluenesulfonic acid delivers the desired 1,1-diphenylethylene products in 83-97% yields over two steps. Both electron-rich and electron-poor benzophenones are suitable substrates (entries 1-5).

**Table 3.1.** Synthesis of 1,1-disubstituted alkenes.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)$^a$</th>
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<td><img src="image" alt="3.27" /></td>
<td>92</td>
</tr>
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<tr>
<td>5</td>
<td><img src="image" alt="3.26" /></td>
<td><img src="image" alt="3.31" /></td>
<td>85</td>
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</tbody>
</table>

$^a$ Isolated yield averaged from two or more experiments over two steps.
With the alkenes in hand, the Doering-LaFlamme cyclopropanation was carried out with bromoform and TEBA at an elevated temperature. Subsequently, these compounds were treated with ethyl magnesium bromide to generate the corresponding 1,1-disubstituted allenes. Table 3.2 presents a subset of the allenes prepared in this manner (full characterizations of all allenes are found in Sections 6.4.6 and 6.4.7). Moderate yields of the gem-dibromocyclopropanes 3.32-3.38 were obtained. Independent of the substituents, the metal-halogen exchange using ethyl magnesium bromide readily provided the allenes (3.39-3.45) in high yields, as expected.

Table 3.2. Synthesis of 1,1-disubstituted gem-dibromocyclopropanes and allenes.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Products 3.32-3.38</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Products 3.39-3.45</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
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<td>70</td>
<td><img src="image" alt="3.39" /></td>
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<td>70</td>
<td><img src="image" alt="3.40" /></td>
<td>91</td>
</tr>
</tbody>
</table>
Isolated yields averaged from three or more reactions.

Prepared from commercially available alkene.

Alkene prepared from α-bromo styrene, see Section 6.4.1 for details.
Characterization of these new compounds led to an interesting finding. Anisochronous $^1$H NMR signals were observed in the room temperature spectrum of compound **3.37** (Figure 3.4). The hydrogens on C$_{10}$ and C$_{10}'$ appear as one broad singlet at 7.80 ppm, indicating that these protons are undergoing an exchange process. The methylene protons on C$_3$ exhibit a similar line broadening effect at 2.49 ppm. An exchange process (in this case, rotation) that is “slow” on the $^1$H NMR timescale gives a broadened peak for otherwise chemically equivalent protons. Since rotamers and atropisomers in a *gem*-dihalocyclopropane derivative have never been reported, to our knowledge, this compound provided an interesting platform for research. To assess the mechanism of interconversion, spectroscopic techniques as well as single crystal X-ray diffraction and DFT analyses were applied.

![Figure 3.4. $^1$H NMR of 2,2'-(2,2-dibromocyclopropane-1,1-diyl)bis(methylbenzene), 3.37, in CDCl$_3$ at 28 °C. Spectrum recorded on a 600 MHz spectrometer. Anisochronous signals observed for the protons on C$_9$ and C$_{9'}$ as well as the methylene protons on C$_2$.](image-url)
3.4.2. Characterization of Compound 3.37

3.4.2.1. Variable Temperature NMR Studies

*High Temperature Analysis:*

Compound 3.37 was studied at a broad range of temperatures. Firstly, by raising the temperature of the sample, thermal energy overcomes the barrier to rotation. Heating the sample from 30 to 85 °C in $d_6$-DMSO (Figure 3.5) resolves the *ortho*-hydrogen into the expected doublet at 7.80 ppm ($J = 7.8$ Hz). The overlapping signals for the methyl substituents and the cyclopropyl methylene are fully resolved into singlet peaks at 2.48 and 2.58 ppm, respectively.

![Variable temperature 1H NMR of 3.37 between 30 and 80 °C in $d_6$-DMSO. Spectra recorded on a 600 MHz spectrometer. Calibrated temperatures in Kelvin are given (see Section 6.4.5 for details). X marks the resonance of a $d_5$-DMSO impurity.](image)

**Figure 3.5.** Variable temperature $^1$H NMR of 3.37 between 30 and 80 °C in $d_6$-DMSO. Spectra recorded on a 600 MHz spectrometer. Calibrated temperatures in Kelvin are given (see Section 6.4.5 for details). X marks the resonance of a $d_5$-DMSO impurity.
Low Temperature Analysis:

Compound 3.37 was then studied at low temperatures between 30 and –33 °C in CDCl₃. Upon cooling the sample, the line shape for the aromatic C₁₀ protons broadened significantly (Figure 3.6). Similarly, the methyl substituents at 2.52 ppm and the methylene protons at 2.49 ppm also exhibit line broadening at lower temperatures. The ortho-protons reach a coalescence point between 270.8 and 259.6 K, and are fully resolved into their diastereotopic signals by 248.3 K. The coalescence point for the methyl substituents at 2.52 ppm is between 270.8 and 259.6 K. It is noted that the cyclopropyl methylene hydrogens overlap the methyl substituent signals, and it is therefore not possible to determine the exact coalescence temperature for these signals in CDCl₃.

![Figure 3.6. Variable temperature ¹H NMR of 3.37 between 30 and –33 °C in CDCl₃. Calibrated temperatures in Kelvin are given. Spectra recorded on a 600 MHz spectrometer](image-url)
Coalescence Point Analysis:

To analyze the rate at which isomerization occurs through rotations about the (aryl)C—C(sp³) bonds, the exact coalescence temperature \( T_c \) for the exchanging signals was found by examining several spectra recorded at 0.5 °C increments between 270.8 and 259.6 K, and between 253.9 and 259.6 K (Figure 3.7). Inspection of this data finds a coalescence temperature at 268.0 ± 3 K (−5.15 °C) was found for the ortho-protons on the aromatic ring; similarly, the methyl substituents coalesce at 255.2 ± 3 K (−18.0 °C).

3.4.2.2. Kinetic Parameters Derived from VT NMR Studies

Calculation of Gibbs Free Energy of Activation:

From this data, Gibb’s free energy of activation for the barrier to rotation about the (aryl)C—C(sp³) bond can be calculated. At the coalescence temperature, the exchange rate constant is determined using the Gutowsky-Holm equation\(^{80}\) as follows:

\[
k_{T_c} = \frac{\pi \Delta v}{\sqrt{2}} = 2.22 \Delta v
\]

\[(\text{Eq. 3-1})\]
where, ∆v is the separation difference in Hertz between the two signals in the absence of exchange. At –33 °C, a difference of 411.62 Hz was measured for the ortho-protons and 146.87 Hz was measured for the methyl substituents in the 1H NMR spectra (solvent = CDCl3). Thus, the rate constants were determined to be:

\[ k_{268.0} = 914 \pm 2 \text{ sec}^{-1} \] (ortho-protons)

\[ k_{255.2} = 326 \pm 2 \text{ sec}^{-1} \] (methyl protons)

The rotational barrier \( \Delta G^\neq_{T_c} \) is related to the rate constant through the Eyring equation, as follows:

\[ k_{T_c} = \chi \frac{k_B T_c}{h} e^{-\Delta G^\neq_{T_c}/R T_c} \] (Eq. 3-2)

where, \( \chi = \) the transmission coefficient (assumed to be unity), \( k_B = \) Boltzmann’s distribution constant, \( h = \) Planck’s constant, and \( R = \) ideal gas constant. Thus, using the coalescence temperatures and the calculated rate constants, the free energy of the transition state was determined by Equation 3-3.

\[ \Delta G^\neq_{T_c} = 4.58 T_c (10.32 + \log \frac{T_c}{k_{T_c}}) \text{ cal mol}^{-1} \] (Eq. 3-3)

Therefore, the \( \Delta G^\neq_{T_c} \) for the rotation is:

\[ \Delta G^\neq_{268.0} = 12.0 \pm 0.2 \text{ kcal/mol} \] (ortho-protons)

\[ \Delta G^\neq_{255.2} = 11.9 \pm 0.2 \text{ kcal/mol} \] (methyl protons)

3.4.3. Determining the Origins of Rotational Restriction

It was hypothesized that steric interactions between the ortho methyl substituents and the bromine atoms resulted in the rotameric equilibrium. To validate this hypothesis, a mono-hydrodebrromination analogue was prepared by adding EtMgBr to a solution of 3.37 in THF at –78 °C and quenching the organometallic intermediate with methanol. The resulting compound, 3.37b, is racemic at the C1 position and a doublet of doublets is observed for this hydrogen at 3.97
ppm ($J = 8.0, 4.4$ Hz) in the $^1$H NMR at room temperature (Figure 3.8). This proton signal is split by the diastereotopic methylene hydrogens, which appear as individual doublet of doublets at 1.59 and 1.96 ppm ($J = 6.3, 4.4$ Hz). Unique singlets for the methyl substituents appear at 2.28 and 2.33 ppm. The aromatic hydrogens *ortho* to the cyclopropyl ring are found to be a doublet of doublet of doublets at 7.52 ppm ($J = 7.1, 5.1, 1.6$ Hz). This splitting pattern indicates that the aromatic rings are also diastereotopic. No line broadening is observed in this NMR, indicating that the loss of one bromine atom results in the free rotation of at least one aromatic ring.

**Figure 3.8.** $^1$H NMR of 3.37b in CDCl$_3$ at room temperature on a 500 MHz spectrometer.
Finally, the cyclopropane derivative, \textbf{3.37c}, was prepared by adding \textit{n}-butyllithium to a solution of \textbf{3.37b} in THF at \(-78\) °C and quenching with methanol. This compound showed no resolution of the methyl substituents, methylene hydrogens or aromatic hydrogens in the \textsuperscript{1}H NMR (Figure 3.9).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure3.9.png}
\caption{\textsuperscript{1}H NMR of \textbf{3.37c} in CDCl\textsubscript{3} at room temperature on a 600 MHz spectrometer.}
\end{figure}

\textbf{3.4.4. Mechanistic Analysis using DFT Calculations}

To model the hindered rotation and identify the resulting conformational isomers of \textbf{3.37}, an MMFF analysis was performed (Figure. 3.10). Four possible conformers were identified: conformer \textit{A} features an \textit{anti} disposition of the two \textit{ortho}-methyl substituents on the aryl rings. This conformer is isoenergetic to its enantiomer, conformer \textit{ent-A}. The two proposed intermediate
conformers that are *meso*-conformers possessing either steric clashes between the *ortho*-methyl substituents on the phenyl rings (conformer B), or steric clashes between the *ortho*-methyl substituents and the bromine atoms on the cyclopropane (conformer C).

These conformers were then subjected to geometry optimization by a B3LYP/6-31G* model, which established that lowest energy conformers (A and *ent*-A) were 2.3 kcal/mol lower in energy as compared to conformer B, and 5.0 kcal/mol lower than conformer C (Figure 3.10). The rotational isomerization process from A to *ent*-A proceeds through conformer B, which possess the lowest potential energy of these two high-energy intermediates.

The corresponding transition states for this rotation process were also modeled. As depicted in the conformation analysis diagram, Figure 3.11, one possibility to arrive at conformer B rotates the *ortho*-methyl substituent towards the bromine substituent on the cyclopropyl ring. However, when these groups come within a 2.1 Å distance of each other, a very high energy transition state is observed. This finding supports the hypothesis that conformational restriction arises from the steric interaction between the *ortho*-substituent and the bromine atom, and that this is not a favorable pathway for isomerization. Alternatively, the energy profile for this transition predicts that the rotation along the \( C_{\text{cyclopropyl}} - C_{\text{phenyl}} \) bond pushes the methyl substituent between the aryl
rings to arrive at conformer B. A similar rotation leads to ent-A or back to A, depending on which C\textsubscript{cyclopropyl}—C\textsubscript{phenyl} bond of conformer B is rotated. The free energy for this rotational process near the observed coalescence temperature (271.3 K) was calculated from the vibrational frequencies and scaled by a factor of 0.9804 using the freqchk utility of Gaussian 09. The free energy of activation $\Delta G_{271.3}^{\circ}$ was found to be 12.9 kcal/mol, which is in excellent agreement with free energy extrapolated from the corrected coalescence temperature of 268.0 ($\Delta G_{268.0}^{\circ} = 12.0$ kcal/mol).

3.4.5. Solid State Analysis by Single Crystal X-ray Diffraction

Recrystallization from methanol allowed for the single-crystal X-ray diffraction to be obtained (Figure 3.12). The crystal structure confirms that the most stable solid state conformation is conformer A and ent-A. Not unexpectedly, intermediate meso-conformers, B or C, were not
present. In the unit cell of this heterochiral crystal, two pairs of molecules \( Z = 4 \) having opposite chirality were observed.

### 3.4.6. Analysis of the Rate Constant using NMR Spectroscopy

An Exchange Spectroscopy (EXSY) experiment that detects chemical and conformational exchanges between nuclei by NMR. The quantitative analysis of this spectrum can be used to measure the rate constant. The EXSY experiment has the same pulse sequence as a Nuclear Overhauser Effect Spectroscopy (NOESY) experiment (Figure 3.13). The first pulse (of phase ±π) places magnetization the spin of proton nuclei on the y-axis. After some time, \( t_1 \), the second pulse places \( z \)-magnetization on the spin. During the mixing time, \( \tau_{\text{mix}} \), the spin of one nuclei may undergo chemical exchange with another nuclei resulting in a transfer of the magnetized frequency label. The final pulse returns all nuclei to the y-axis for detection. Effectively, through the magnetization transfer, both nuclei possess both frequency labels and are aligned in the same phase. Chemical kinetics of the interconversion governs the extent of this transfer, meaning that the rate constant, \( k_{\text{obs}} \), for the exchange process can be derived from a measurement of the signal intensity. The spectrum of the exchanging nuclei shows cross-peaks that are in the same phase as the diagonal peaks. These are differentiated from the nOe cross-peaks of nuclei in close proximity (5-6 Å), which are in the opposite phase of the diagonal.

![Figure 3.12. ORTEP plot of compound 3.37. Ellipsoids shown based on a 50% probability. Hydrogens have been removed for clarity.](image)

![Figure 3.13. The pulse sequence for EXSY (and NOESY).](image)
peaks. An nOe magnetization transfer happens during the mixing time because these nuclei are experiencing mutual cross-relaxation, which does not align their phases with the diagonal peaks. The difference is seen by the contrasting colors in the 2D NMR spectrum of 3.37 shown in Figure 3.14. The red peaks along the diagonal are in the positive phase, as are the exchange signals. Conversely, the nOe signals are blue, indicating that they are in the negative phase. The pictorial diagram on the right illustrates the different processes that give these results. The exchange signals represent the protons as they change their relative position. Near the bromine atoms, these signals are deshielded and appear downfield. The labeled nOe signals correspond to the each ortho-

![Figure 3.14. Left: A 2D EXSY Experiment at –33 °C. Spectra taken in CDCl$_3$ with a mixing time of 650 ms. Right: Diagram illustrating the exchange and nOe signals in 3.37.](image)

hydrogen being in close proximity to both of the methyl substituents. All four combinations of diastereotopic proton correlations are observable.

The mixing time, $\tau_{\text{mix}}$, is critically important to this experiment because this is when the magnetization transfer happens. The rate constant of the exchange process is quantified by the relative intensity of the peaks which are a direct measure of the magnetization transfer (Equation
Therefore, if the mixing time is too short, then small cross-peaks will be observed; if the mixing time is too long, then the linear assumption implicit to the calculations will be violated. The optimal mixing time window was experimentally determined by measuring the peak intensity of the ortho-hydrogens at different mixing times. In Figure 3.15, the plot of this data clearly shows that the most dramatic changes occur with mixing times below 1.00 s and that the linear range is between 0.05 and approximately 0.75 s. Therefore, mixing times of 0.35, 0.5, and 0.65 s were selected.

![Optimization of the Mixing Time](image)

**Figure 3.15.** Graphical analysis of the ortho-proton signal (7.42 ppm) as a function of mixing time for compound 3.37 at room temperature.

The 2D NOESY pulse sequences were performed at 5° increments between 0 and –25 °C. For each temperature, three spectra were acquired at the 3 different mixing times. The peak volumes of the ortho-hydrogens along the diagonal (A_{aa} and A_{bb}) and their corresponding cross-peaks (A_{ab} and A_{ba}) were integrated. The relative ratio of these volumes, r, was used to derive a rate constant for each temperature, as described in Equations 3-4 and 3-5.

\[
r = \frac{[A_{aa} + A_{bb}]}{[A_{ab} + A_{ba}]} \quad \text{(Eq. 3-4)}
\]

\[
k_{obs} = \frac{1}{\tau_{mix}} \ln \left( \frac{r+1}{r-1} \right) \quad \text{(Eq. 3-5)}
\]
From this, the thermodynamic parameters of activation for the isomerization of 3.37 could be extrapolated using the Eyring Equation:

\[ k_{\text{obs}} = \frac{K_B T}{h} e^{\Delta S^\neq / R} e^{\Delta H^\neq / RT} \]  
(Eq. 3-6)

Unfortunately, integrating the area under the peaks in the EXSY spectra did not provide quantitative data for this analysis. It is suspected that the temperature range in which this data was collected is too close to the coalescence temperature for adequate resolution of the signals. As a result, the overlap precluded an accurate measurement of the peak intensities. An example of this interference is clearly seen in Figure 3.14 where, in the 2-3 ppm cross-section, poor resolution of the signals is observed.

Given that the interconversion of 3.37 is a first-order reversible process, the simplicity of the uncoupled nuclei allows for a complete line shape analysis of the 1D NMR spectra to derive rate constants for the interconversion. This is done by using the modified Bloch equations.81,82 From the spectra recorded above and around the coalescence temperature, between 265.5 and 315.2 K, Equation 3-7 was used to determine a rate constant in this fast exchange regime.

\[ k_{\text{obs}} = \frac{\pi (\Delta v)^2}{2(\text{LW}_{1/2} - \text{NLW}_{1/2})} \]  
(Eq. 3-7)

The linewidth at half-height (LW$_{1/2}$) was measured for the broadened signals corresponding to the ortho-hydrogens and this was referenced to the natural linewidth at half-height (NLW$_{1/2}$) of either an internal standard (TMS) or the non-coalescing signals at 234.4 K; both references delivered the same rate constant within error.

![Figure 3.16](image)

**Figure 3.16.** Proton spectrum of 3.37 at 292.9 K illustrating the linewidth at half-height (LW$_{1/2}$).
At temperatures well below the coalescence point, where the two peaks are resolved due to slow exchange, the linewidth at half-height was measured for each signal and referenced to the natural linewidth. Equation 3-8 was applied for analyzing the rate constant in this region.

\[ k_{\text{obs}} = \pi (L W_{1/2} - N L W_{1/2}) \]  

(Eq. 3-8)

When the rate constants determined in this manner were fitted to the Eyring equation, a linear relationship was obtained (Figure 3.17). The enthalpy barrier (\(\Delta H^\ne\)) for the dynamic process was calculated to be 14.0 ± 0.7 kcal/mol from the slope of this line. From the intercept, a small entropy change in the transition state (\(\Delta S^\ne\)) of 7 ± 2 e.u. was observed. A free energy barrier of 12.1 ± 0.3 kcal/mol at 268 K was obtained from these results (Table 3.3).

The Arrhenius equation relates the activation of energy (\(E_a\)) for interconversion to the observed rate constants:

\[ k_{\text{obs}} = A e^{-E_a/(RT)} \]  

(Eq. 3-9)

The activation energy (\(E_a\)) was found to be 14.6 ± 0.7 kcal/mol.
3.5. Conclusions

Based on the calculated ΔH≠ and ΔS≠ values provided by the line shape analysis, a ΔG268.0 of 12.1 kcal/mol was obtained, which matches the value determined from Tc analysis. Thus, the barrier for rotation around the Caryl—Ccyclopropyl bond is principally enthalpic in origin. These results also agree with ΔG≠ and ΔE≠ from B3LYP/6-31G* calculations (12.9 kcal/mol and 13.5 kcal, respectively). As expected, this data indicates that the rotation barrier for isomerization falls near the boundary of atropisomerism.

In the absence of a stereogenic center, configurational atropisomerism arises when the rotational restriction has a barrier exceeding 22 kcal/mol. With a Gibbs free energy barrier around 12.0 kcal/mol, compound 3.37 would be classified as a “near-atropisomer,” which are on the order of 9-22 kcal/mol. These experiments provide conclusive evidence that the restricted rotation is a consequence of steric interactions between the bromine atoms and the aryl ring substituents. Increasing the size of these substituent will lead to isolatable conformers exceeding the standard of 22 kcal/mol. These compounds have yet to be attained, but their applications may have promising potential in the exploration of new materials or the stereoselective synthesis of

### Table 3.3. Summary of thermodynamic results.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>VT NMR Experiment</th>
<th>DFT Calculation</th>
<th>Line Shape Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔH≠</td>
<td>(ΔE) 13.5 kcal</td>
<td>14.0 ± 0.7 kcal/mol</td>
<td></td>
</tr>
<tr>
<td>ΔS≠</td>
<td></td>
<td>7 ± 2 e.u.</td>
<td></td>
</tr>
<tr>
<td>ΔG≠</td>
<td>12.0 ± 0.2 kcal/mol (268.0 K)</td>
<td>12.9 kcal/mol (271.3 K)</td>
<td>12.1 ± 0.3 kcal/mol</td>
</tr>
<tr>
<td>Ea</td>
<td>14.6 ± 0.7 kcal/mol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>6×10¹⁴ sec⁻¹</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
enantiopure \textit{gem}-dihalocyclopropanes. The incorporation of the dihalocyclopropane motif in liquid crystals has been forgotten about since the aforementioned examples in 2000 and 2007. Moreover, the axial chirality may provide a new pathway to accessing enantiopure cyclopropanes in the carbene reaction or in subsequent transformation.

\section*{3.6. Future Directions}

The future work of this project is to find optimal substituents by establishing a trend for the restricted rotation. Variations of \( R \) and \( R_1 \) will lead to some interesting insight (Figure 3.18). Recently, Clayden and co-workers studied the electronic and steric influence of conformational atropisomerism about the \((\text{aryl})\text{sp}^2-\text{Csp}^3\) bonds in \textit{ortho}-substituted cannabidiol and linderatin derivatives. A similar study is envisioned. It has been noted that the starting material substrates can be quickly synthesized from readily available ketones using a microwave reactor and cobalt catalyst.

A 2,2',6,6'-substitution pattern would be exceedingly interesting. Dimesityl compounds were found to have a propeller-like, coupled rotation; the addition of the dihalocyclopropyl will certainly increase this effect. Moreover, it would be extraordinarily worthwhile to use this type of interaction to develop a stereoselective cyclopropanation.

The subsequent reactions of 3.37 and other derivatives, regardless of their rotational barrier, should be explored. While control of the conformational equilibria is difficult for “near-atropisomers”, dynamic kinetic resolution can be employed selectively engage one isomer over the other. Taking advantage of the Curtin-Hammett principle, this approach was employed by
Bringmann et al.\textsuperscript{86,87} for the synthesis of a myriad of biaryl compounds. Substituents like ethers or amines may provide a chelating arm for selective lithiation of the halides (Figure 3.19). Similarly, amines and phosphines would provide chelation sites for metal insertion into C—X bond, which could give rise to a new ligand class.

3.7. References


Ziyat, H.; Ait Itto, M. Y.; Ali, M. A.; Karim, A.; Riahi, A.; Daran, J.-C. Absolute Configuration Determination of Two Optically Active Cyclopropyl-Ketoacids: (1’S, 3S) 3-(2’,2’-


Chapter 4. Chemo-, Regio-, and Stereoselective Copper(II)-Catalyzed Borylation of Acetylenic Esters and Amides in an Aqueous Medium

4.1. Contributions

The idea for this project had been passed around in our group for some time. I approached the problem with a singular focus: to keep this chemistry green. Shortly after stumbling upon the key to this chemistry, my very talented undergraduate student, Sean Rafferty, performed preliminary experiments on the effects of different solvents systems and ratios. He was in charge of synthesizing alkynoates and prepared the substrates for compounds 4.10-4.19. Sean also provided a triplicate experiment for the borylation of most alkynoate substrates. The author of this chapter synthesized the substrates for compounds 4.20-4.23 as well as some of the alkynoate and alkyramidie substrates when needed.

The optimization of reaction conditions, the development of analytical and purification techniques, and duplicate borylations of all compounds were the major contributions of the author. Cheryl Peck and the present author outlined the alkyramidie substrates and synthetic approach. Her major contributions included synthesizing these, assisting in the optimization, and providing a triplicate borylation of the alkyramidie substrates. She was solely responsible for the borylation and characterization of 4.34. Furthermore, she provided substantial contributions to the collection of this characterization data. The author of this chapter wrote the publication and obtained external funding courtesy of the Graduate Research Development Program in the amount of $600. Financial support was also provided by the NSF (CHE-1414458). Dr. Santos oversaw the progress of the project, revised the manuscript and encourage the exploration of alkyramidies. A great appreciation is extended to the editors of the manuscript (Emily Neeve) and this chapter (Ashley Peralta).
4.2. 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 β-borylation protocol proceeds in a remarkably chemo-, regio-, and stereoselective fashion to afford 1,8-diaminonaphthalene protected (Z)-β-boryl enoates and primary, secondary and tertiary enamides in good to excellent yields. These reactions demonstrate a high tolerance toward a variety of alkyl, aryl, and heteroatom functional groups and provide convenient access to a diverse range of vinylboronic acid derivatives.

\[ \text{CuSO}_4, \text{4-picoline} \]
\[ 9:1 \text{H}_2\text{O}:\text{EtOH}, 50^\circ\text{C} \]
\[ X = \text{OR} \]

\[ \text{CuSO}_4, \text{4-picoline} \]
\[ 2\% \text{TPGS-750-M} \]
\[ 9:1 \text{H}_2\text{O}:\text{EtOH}, 50^\circ\text{C} \]
\[ X = \text{NH}_2, \text{NHR}, \text{NR}_2 \]

- aqueous solvent
- atmospheric conditions
- (Z)-exclusive products
- wide substrate scope
- up to 95% yield, 29 examples

4.3. Introduction

The copper(I)-catalyzed β-borylations that were introduced in Chapter 1 are all performed in organic solvents. However, water is the cheapest and most environmentally friendly solvent available for conducting organic reactions.\(^1\text{-}^4\) This renewable resource also provides the potential ability to develop highly efficient catalyst recycling processes when the reaction substrate and products are sparingly soluble.\(^5\) Naturally, the development of aqueous borylation reactions has been a topic of great interest, but widespread implementations are still scarce.\(^6\text{-}^{14}\)

4.3.1. Water as a Solvent

Organic solvents constitute the majority of waste generated from synthetic chemistry and approaches to sustainable chemical processes are now considering non-traditional solvents.\(^1,^2,^5,^15\) Among them, neat methods,\(^16\) supercritical \(\text{CO}_2,\(^17\) ionic liquids,\(^18\) and especially water\(^3,^4,^19\text{-}^{23}\) have become increasingly popular. Water is a notably enticing solvent choice partly due to its cost-effectiveness, but moreover because it is not flammable or toxic. However, solubility issues have generally hindered the laboratory development of many organic reactions in an aqueous medium.

The ancient alchimia that all reactants must be in solution was debunked in 1980, when Breslow found that a Diel-Alder reaction rate was enhanced in water by a hydrophobic effect.\(^24\) In regards to this publication, Breslow stated, “After that paper, everybody got very excited about using water.”\(^25\) Aqueous-based chemistry further bourgeoned when Sharpless et al. described an “on-water” process, wherein all of the components are insoluble.\(^26\) One recent development to facilitate the transition of organic reactions to water-based systems has been the design of amphiphilic surfactant species. These additives bear a lipophilic segment that serves as the organic solvent when they self-assemble into micelles.\(^5\) At concentrations on the order of \(10^{-3}\) to \(10^{-7}\), these “nanoreactors” contain the substrates and/or catalyst for carrying out the desired transformation
that may otherwise be unreactive in an aqueous medium. Since the micellar nanoparticles function as the solvent, many “designer” surfactants have appeared which pose new dimensions to solvent parameter optimization: namely, particle size and, occasionally, shape.\(^5\)

Several metrics to gauge the environmental and economic benefits associated with a given reaction have been implemented over the last few decades. The Environmental Factor, or E Factor, is one such measurement that has become ubiquitous to green chemistry since its introduction by Sheldon in 1992.\(^27\) This numerical evaluation defines the overall “greenness” of the reaction by correlating the weight of generated waste relative to the weight of isolated product (Equation 4-1).

\[
E \text{Factor} = \frac{\text{kg of waste}}{\text{kg of desired product}} \quad \text{(Eq. 4-1)}
\]

While Sheldon’s original E Factor does not account for aqueous waste, recent adaptions now include both the organic solvents as well as the waste water to provide a true reflection of the overall process. Typical E Factors range from 25-100, while the inclusion of waste water would substantially increase these numbers.\(^28\) To exemplify the advantages of using micellar technology, the E Factors were determined for several palladium-catalyzed procedures published by pharmaceutical companies (e.g. Heck,\(^29\) Suzuki-Miyaura,\(^30\) and Sonogashira\(^31\) couplings) and compared to the analogous aqueous-based micellar reactions. These results are summarized in Table 4.1.\(^28\) Compared to the traditional protocols in organic solvents, the E Factors of the aqueous reactions are considerably minimalized in these examples. Moreover, the hydrophobic effect of the aqueous solvent enables the reaction to proceed at room temperature, which is advantageous in terms of energy conservation. When heat is required to initiate or drive the reaction forward in an organic solvent, it can often lead to varying amounts of unavoidable side products. Thus, it follows that under the aqueous micellar catalysis conditions, the isolated yields were also higher.
### Table 4.1. Comparison of the E Factors for micellar catalysis in water versus catalysis in organic solvents.\textsuperscript{28}

(\textit{DMF} = \textit{N,N}-dimethylformamide, \textit{dtbpf} = 1,1’-bis(di-tert-butylphosphino)ferrocene, \textit{XPhos} = 2-dicyclohexylphosphanyl-2’,4’,6’-triisopropylbiphenyl)

#### Heck Coupling

\[
\begin{align*}
\text{E Factor based on organic solvent} & \quad \text{E Factor including aqueous workup} & \quad \text{Yield (\%)} \\
\text{Traditional Catalysis}^{29} & 40.3 & 137 & 65 \\
\text{Micellar Catalysis}^{28} & 2.2 & 7.6 & 92
\end{align*}
\]

#### Suzuki-Miyaura Coupling

\[
\begin{align*}
\text{E Factor based on organic solvent} & \quad \text{E Factor including aqueous workup} & \quad \text{Yield (\%)} \\
\text{Traditional Catalysis}^{30} & 42 & 83 & 80 \\
\text{Micellar Catalysis}^{28} & 3.9 & 8.3 & 93
\end{align*}
\]
An aqueous reaction mixture never has to leave the reaction vessel. Extraction of the organic products can be performed directly by the addition of minimal amounts of organic solvent. As such, when the catalyst is water soluble or when micellar catalysis is used, the aqueous solution can be recycled in subsequent reactions. This provides not only lower E Factors, but also increases the efficacy of the catalytic system. Such reusability is analogous to heterogeneous catalysis, wherein it is oftentimes considerably advantageous to recover an expensive catalyst.

4.3.2. The Copper-Catalyzed β-Borylation

Vinylboronic acids and their derivatives serve as valuable intermediates in organic synthesis, particularly as substrates in Suzuki-Miyaura cross-coupling reactions.\textsuperscript{32-35} As a consequence, efficient and economical methods for their preparation are essential. Access to these derivatives \textit{via} borylations of alkynes with boron sources such as HBpin and B\textsubscript{2}pin\textsubscript{2} are well established. This includes uncatalyzed,\textsuperscript{36} transition metal-catalyzed,\textsuperscript{37,38} and acid/base-catalyzed\textsuperscript{39,40} processes.\textsuperscript{41} Some disadvantages of these approaches include the use of organic

<table>
<thead>
<tr>
<th></th>
<th>E Factor based on organic solvent</th>
<th>E Factor including aqueous workup</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditional Catalysis\textsuperscript{31} (R = Me)</td>
<td>31.1</td>
<td>37.9</td>
<td>83</td>
</tr>
<tr>
<td>Micellar Catalysis\textsuperscript{28} (R = Et)</td>
<td>3.7</td>
<td>7</td>
<td>94</td>
</tr>
</tbody>
</table>

\textbf{Sonogashira Coupling}

- PdCl\textsubscript{2} (0.6 mol\%), PPh\textsubscript{3} (1.2 mol \%)
- CuI, Et\textsubscript{3}N, EtOAc, 50 °C, 4h
- [Pd(CH\textsubscript{2}CN)\textsubscript{2}Cl\textsubscript{2}] (2.6 mol\%)
- XPhos (5.2 mol\%), Et\textsubscript{3}N  
  2 wt\% TPGS-750-M/H\textsubscript{2}O (1.5 M)  
  rt, 18 h
solvents and precious metals such as platinum or palladium, and the production of toxic waste. Additionally, among the myriad of vinylboronic acid derivatives, routes to conjugated vinylboronates bearing carbonyl groups are severely limited, and borylation methods of primary and secondary amides are non-existent.\textsuperscript{42,43} Because of the utility of vinylboronic acids, simple, efficient, and sustainable methods for their synthesis are essential.

The enthusiasm for sustainable chemistry in recent years has encouraged the development of non-toxic, earth abundant catalysts such as those based on copper.\textsuperscript{44,45} As discussed in Chapter 1, the copper-catalyzed conjugate addition of B\textsubscript{2}pin\textsubscript{2} to \(\alpha,\beta\)-unsaturated carbonyl compounds has been extensively explored under an inert atmosphere using a copper(I) catalyst and a strong base in an organic solvent.\textsuperscript{12,46-50} Transitioning this chemistry to a water-based reaction medium began with DFT studies by Dang, Lin, and Marder who confirmed that the active borylcopper intermediates are unaffected by the presence of protic species, including water.\textsuperscript{51} Shortly thereafter, a copper(I)-catalyzed reaction that employed water as a co-solvent in THF was published by Yun \textit{et al.} However, substituents on the \(\beta\)-carbon slowed this reaction, which also decreased product yields owing to the known decomposition of copper(I) hydroxide to the less reactive, corresponding oxides.\textsuperscript{52}

To address this limitation, the Santos Lab tested the viability of a copper(I) catalyst under aqueous, ambient conditions and modest conversions (up to 77\%) were obtained.\textsuperscript{53} It was suspected that the known disproportionation of copper(I) into copper(II) and copper(0) under aqueous conditions skewed the interpretation of the active catalytic species.\textsuperscript{6-13} In light of this, and given that copper(I) species are insoluble in water, they further explored copper(II) alternatives for the conjugate addition of B\textsubscript{2}pin\textsubscript{2} to \(\alpha,\beta\)-unsaturated ketones and esters. Scheme 4.2 illustrates the successful diboration of chalcone under aqueous conditions. This \(\beta\)-boryl ketone is obtained in
96% yield, even on the preparative scale. Whereas all other examples given were liquid substrates, chalcone is a solid, and dissolving it in a minimal amount of THF is necessary.

Consistent with previous research, the diboron compound must be activated by a Lewis base. As depicted in Scheme 4.2, water coordinates to B_{2}pin_{2} to form the tetrahedral sp^{2}-sp^{3} hybridized diboron intermediate 4.3. This process is assisted by 4-picoline and allows for the sp^{2} hybridized Bpin moiety to be transferred to the copper catalyst. In view of the fact that the copper catalyst is water soluble and given that the reaction with chalcone necessitated THF, it is plausible to conclude that this reaction takes place in water, rather than on water. Trace amounts of the liquid hydrophobic substrates (e.g. cyclohexanone) in the aqueous phase would be sufficient to drive the reaction forward.

Building off this chemistry, these aqueous conjugate additions were extended to a wide variety of electron deficient unsaturated C—C bonds, including esters, nitriles, and sulfones.
Moreover, alkynoate substrates could be borylated in a stereo-, regio-, and chemoselective fashion to afford \((Z)\)-\(\beta\)-borylated-\(\alpha,\beta\)-unsaturated esters (Scheme 4.3).\(^{59}\) These reaction conditions are extremely mild, employing a commercially available amine base. Furthermore, the inexpensive copper(II) catalytic system is resistant to oxidation, which allows these reactions to be performed under atmospheric conditions. Intrinsically, this protocol presents an environmentally friendly alternative to the aforementioned air-sensitive copper(I) and platinum-catalyzed conjugate addition protocols.

### 4.3.3. 1,8-Diaminonaphthalene Protected \(\beta\)-Boryl Carbonyl Compounds

Among the various protecting groups for boron, the pinacol moiety (pin) is a standout, popular choice because of its general stability and compatibility with numerous reaction conditions.\(^{46}\) Recently, the 1,8-diaminonaphthyl organoboronic reagents \((R—\text{Bdan})\) are drawing increased attention as synthetic intermediates with an orthogonal protecting group.\(^{60-66}\) This moiety is attractive because of its robustness and compatibility, but moreover because it masks the reactivity of the boron center. As seen in Chapter 2, chemoselective transformations of Bpin derivatives occur in the presence of the Bdan group.\(^{60,61,63,64,67-70}\) The many advantages of having the boron center protected by the 1,8-diaminonaphthalene ligand poses these compounds as attractive substrates for reactions that are common to vinylic \(\beta\)-boryl carbonyl compounds. These include, for example, inter- and intramolecular Diels-Alder reactions,\(^{71}\) radical additions,\(^{72}\)
cyclopropanation, as well as asymmetric dipolar cycloaddition and 1,4-additions. Therefore, efficient methods for conjugate additions of Bdan are valuable.

In 2004, Hall and co-workers pioneered a multistep methodology to incorporate Bdan on the vinylic β-carbon of esters (Scheme 4.4). Due to regioselectivity issues, access to these compounds is limited to esters containing no substituents on the β-carbon. Regardless, the copper-catalyzed enantioselective conjugate borylation, alkylation, and reduction reactions that were also developed by Hall and co-workers demonstrate the potential utility of these compounds as synthetic intermediates. A differentially protected diboron reagent, pinB—Bdan (4.7) has been particularly useful for the incorporation of the Bdan substituent. Using this reagent, a metal-free conjugate addition procedure from Fernández et al. established an efficient and stereoselective β-borylation of Bdan with α,β-unsaturated ketones and esters via the

Scheme 4.4. Synthesis and applications of Bdan vinylic β-boryl esters.
chemoselective activation of pinB—Bdan by a strong base or phosphine. Unfortunately, this approach does not provide access to the vinylic β-boryl carbonyl compounds, which are still a synthetic challenge.

4.3.4. Project Overview

The exploration of these compounds as synthetic intermediates has been stalled by the limited access to structurally diverse 1,8-diaminonaphthalene protected β-boryl-α,β-unsaturated carbonyl compounds. Interest in developing sustainable methods for the borylation of activated carbon–carbon bonds and the paucity of borylation reactions in water, prompted the speculation that the differentially protected diboron, pinB—Bdan, could be substituted for B₂pin₂ in the aqueous copper-catalyzed borylation of α,β-acetylenic esters. This account details the development of an efficient and aqueous-based method for generating 1,8-diaminonaphthalene protected β-boryl-α,β-unsaturated carbonyl compounds, including primary and secondary amides (Scheme 4.5). This strategy take advantage of the more Lewis acidic boron center in Bpin by chemoselectively activating it with a Lewis base (either water or 4-picoline) to form an sp²-sp³

![Scheme 4.5. Approach to Bdan vinylboronates. * Reproduced with permission.](image-url)
diboron intermediate, which thereby facilitates the transfer of Bdan.\textsuperscript{53-55,88,89} Based on previous \(\beta\)-borylation of alkynoates with \(\text{B}_2\text{pin}_2\)\textsuperscript{59} and \(\text{Me}_2\text{PhSi}—\text{Bpin}\),\textsuperscript{58} it was expected that this reaction proceeds stereoselectively to afford the (\(Z\))-isomer, complementary to the reported (\(E\))-isomer synthesis accessible \textit{via} a stereoselective Heck coupling reaction of 4.6.\textsuperscript{78}

4.4. Results and Discussion

4.4.1. Optimization and Characterization of the Acetylenic Ester Borylation

Preliminary studies utilized commercially available 2-butynoate and the previously established aqueous borylation protocol of alkynoates with \(\text{B}_2\text{pin}_2\).\textsuperscript{59} Under these conditions, no reaction was observed due to the insolubility of the pinB–Bdan diboron reagent 4.7 in water (Table 4.2, entry 1). Addition of an environmentally benign alcohol, such as ethanol or 2-propanol, aided in the solubility of the diboron reagent (entry 2-7). As such, the reaction proceeds smoothly to provide the (\(Z\))-\(\beta\)-boryl-\(\alpha,\beta\)-unsaturated ester 4.10, as a single regio- and stereoisomer. 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. The optimal percentage of alcohol in the aqueous solvent system was determined by monitoring the percent conversion over time (entry 2-5). A high conversion was observed 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 (entry 4-5). Unlike the copper(I)-catalyzed borylation reaction developed by Yun \textit{et al.},\textsuperscript{50} in which a methanol additive increased the rate of the reaction, no reaction was observed with this additive (entry 6). This observation further supports the inference that the role of the alcohol is to promote solubility, rather than serving to reduce
copper.\textsuperscript{90,91} Isopropanol, on the other hand, was an adequate additive, resulting in complete conversion (entry 7). Next, the use of a nanomicellar surfactant, 2 wt% TPGS-750-M,\textsuperscript{5,13} as an alternative aqueous reaction medium was examined and these conditions proved to be similar to the H\textsubscript{2}O/EtOH mixture (entries 8-9). Comparatively, no improvement to the yield was observed.

**Table 4.2.** Screening of aqueous solvent systems for the borylation of alkynoates with pinB—Bdan.\textsuperscript{a,*}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aqueous Solvent</th>
<th>Time (h)</th>
<th>% Conversion\textsuperscript{c} (% Yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H\textsubscript{2}O</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>5% EtOH</td>
<td>6</td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td>10% EtOH</td>
<td>4</td>
<td>100 (86)</td>
</tr>
<tr>
<td>4</td>
<td>15% EtOH</td>
<td>6</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>20% EtOH</td>
<td>6</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>10% MeOH</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>10% iPrOH</td>
<td>4</td>
<td>100 (85)</td>
</tr>
<tr>
<td>8</td>
<td>2 wt% TPGS-750-M</td>
<td>6</td>
<td>94</td>
</tr>
<tr>
<td>9</td>
<td>2 wt% TPGS-750-M, 10% Ethanol</td>
<td>6</td>
<td>100 (86)</td>
</tr>
<tr>
<td>10</td>
<td>10% EtOH/H\textsubscript{2}O\textsuperscript{d}</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>10% EtOH/H\textsubscript{2}O\textsuperscript{e}</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Reaction conditions: pinB—Bdan \textbf{4.7} (0.52 mmol), 2-butynoate (0.625 mmol), 4-picoline (5 mol\%), CuSO\textsubscript{4} (1 mol\%).\textsuperscript{b} Exclusive stereoselectivity was obtained, as determined by GC-MS of the crude material and confirmed by nOe of the isolated product.\textsuperscript{c} Conversion determined by monitoring the consumption of pinB—Bdan using GC-MS.\textsuperscript{d} Without copper.\textsuperscript{e} Without 4-picoline.

* Reproduced with permission.
with the addition of the surfactant. Therefore, the simpler conditions were determined to be optimal (entries 3 and 9). As expected, the copper catalyst and the base, 4-picoline (Scheme 4.2), were both necessary components for the reaction (entries 10 and 11).

Monitoring the reaction progress by GC-MS and analyzing the crude material by \(^1\)H NMR verified that only one product was formed. After purification, the final product was fully characterized as a single regio- and stereoisomer by correlating a nuclear Overhauser effect (nOe) between the amino and alpha protons. This protocol was used to authenticate the product distribution, as well as the absolute regio- and stereochemistry of the compounds given herein.

4.4.2. Alkynoate Substrate Scope

Under these optimized conditions (entry 3, Table 4.2), the functional group tolerance and scope of the reaction was examined (Table 4.3). Overall, the borylation reaction rapidly installed the Bdan functionality 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\(^1\) position provided the products in high yields with short reaction times (4.10-13). The more sterically hindered tert-butyl substituent affected neither the yield nor the selectivity of the product (4.14). Next, various cyclic substituents on the alkyne (entries 6-9) were borylated and high yields for the cyclopropyl (4.15) and cyclohexyl (4.17) derivatives. Unfortunately, the borylated product for ethyl 3-cyclopentylpropiolate (4.16) was only isolated in 48% yield. Regioselectivity for $\beta$-borylation was demonstrated by subjecting the conjugated cyclohex-3-en-1-yn-1-yl ester to the reaction conditions and isolating the (Z)-$\alpha,\beta,\gamma,\delta$-unsaturated diene (4.18) in a 78% yield. When R\(^1\) contained an ether substituent, the borylation proceeded smoothly to give 4.19 in a 77% yield. Next, substituent tolerance in the R\(^2\) position was examined. Substrates containing sterically bulky substituents, such as a phenyl ring or a branched isobutyl group, are readily borylated to provide
Table 4.3. Borylation of alkyanoates with pinB—Bdan\(^{a, *}\)

\[
\text{pinB—Bdan (4.7)} \\
\text{1 mol\% CuSO}_4 \\
\text{5 mol\% 4-picoline} \\
\text{10\% EtOH/H}_2\text{O} \\
\text{50 °C, 4-8 h}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yield(^c) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[\text{H}_3\text{C} \equiv \text{O}\text{OEt}]</td>
<td>[\text{danB} \quad \text{4.10}]</td>
<td>4</td>
<td>86</td>
</tr>
<tr>
<td>2</td>
<td>[\text{C}_3\text{H}_7 \equiv \text{O}\text{OEt}]</td>
<td>[\text{danB} \quad \text{4.11}]</td>
<td>4</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>[\text{C}<em>4\text{H}</em>{13} \equiv \text{O}\text{OMe}]</td>
<td>[\text{danB} \quad \text{4.12}]</td>
<td>4</td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td>[\text{C}<em>7\text{H}</em>{15} \equiv \text{O}\text{OEt}]</td>
<td>[\text{danB} \quad \text{4.13}]</td>
<td>4</td>
<td>82</td>
</tr>
<tr>
<td>5</td>
<td>[\text{O} \equiv \text{O}\text{OEt}]</td>
<td>[\text{danB} \quad \text{4.14}]</td>
<td>6</td>
<td>81</td>
</tr>
<tr>
<td>6</td>
<td>[\text{O} \equiv \text{O}\text{OEt}]</td>
<td>[\text{danB} \quad \text{4.15}]</td>
<td>4</td>
<td>83</td>
</tr>
<tr>
<td>7</td>
<td>[\text{O} \equiv \text{O}\text{OEt}]</td>
<td>[\text{danB} \quad \text{4.16}]</td>
<td>8</td>
<td>48</td>
</tr>
<tr>
<td>8</td>
<td>[\text{O} \equiv \text{O}\text{OEt}]</td>
<td>[\text{danB} \quad \text{4.17}]</td>
<td>4</td>
<td>72</td>
</tr>
</tbody>
</table>
good yields of the respective (Z)-β-boryl-α,β-unsaturated esters (4.20-21). Finally, the chemoselectivity of this reaction was demonstrated by examining unsaturation at the R² position. The borylation of hexynoate derivatives bearing the allyl (4.22) and propargyl (4.23) groups resulted in high yields of the β-borylated products, thus verifying that the reaction occurs exclusively at the electron-deficient alkyne.

\[ \text{Reaction conditions: pinB–Bdan 4.7 (0.52 mmol), alkynoate (0.625 mmol), 4-picoline (5 mol %) and CuSO₄ (1 mol %).} \]

\[ b \text{ Exclusive stereoselectivity was obtained, as determined by GC-MS of the crude material and confirmed by nOe of the isolated product.} \]

\[ c \text{ Averaged from 2 or more experiments.} \]

\[ * \text{ Reproduced with permission.} \]
4.4.3. **Optimization of the Acetylenic Amide Borylation**

Prompted by the great success of the alkynoate substrates, the substrate scope was expanded to include acetylenic amide derivatives. Amides have received minimal attention as substrates due to their inherently low reactivity towards 1,4-conjugate additions. In fact, methods to access \((Z)-\beta\)-boryl-\(\alpha,\beta\)-unsaturated amides directly are not available. However, it has been suggested that acetylenic amides and esters undergo 3,4-syn addition reactions. Gratifyingly, the Weinreb amide reacted readily under the 10% ethanol aqueous conditions to provide the desired product \(4.24\) in an 82% yield (Table 4.4, entry 1). The use of a surfactant was revisited, striving to increase in the reaction yield. When ethanol was replaced by the 2 wt% TPGS-750-M surfactant, 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 \(4.24\) was obtained (91%, entry 3). As expected, the reaction remained stereoselective for the \((Z)\)-isomer.

**Table 4.4.** Screening of solvent system for the borylation of Weinreb amide.\(^a,\)\(^b\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aqueous Solvent</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10% EtOH/H(_2)O</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td>2 wt % TPGS-750-M/H(_2)O</td>
<td>61</td>
</tr>
<tr>
<td>2</td>
<td>10% EtOH/H(_2)O, 2 wt % TPGS-750-M</td>
<td>91</td>
</tr>
</tbody>
</table>

\(^a\) Reaction conditions: pinB—Bdan \(4.7\) (0.625 mmol), alkynamide (0.520 mmol), 4-picoline (5 mol %) in ethanol (0.1 mL) and CuSO\(_4\) (1 mol %). \(^b\) Determined by \(^1\)H NMR of the crude material and confirmed by nOe of the isolated product.

* Reproduced with permission.
4.4.4. Alkynamide Substrate Scope

As the addition of the 2 wt % TPGS-750-M surfactant improved the yield, this aqueous-based medium was used to explore the scope and limitations of alkynamide substrates. A comparable, but slightly lower yield was obtained when the alkyl chain of the Weinreb amide was reduced from a hexyl to a methyl substituent (entries 1-2, Table 4.5).

A series of \( N,N \)-dimethyl amide substrates were synthesized to further explore the effects of substitutions on the alkyne. Substrates with aliphatic substituents on the \( R^1 \) position, such as hexyl or propyl groups, undergo \( \beta \)-borylations in good yields (entries 3-4). The branched \( \text{tert} \)-butyl derivative also gave the desired product \( 4.28 \) stereoselectively. Although this reaction does not reach completion after 48 h, an acceptable yield (71%) was obtained. Additionally, the borylation of amides containing cyclic \( R^1 \) substituents proceeded smoothly and provided the desired products in excellent yields (entries 6-7). Even 3-cyclopentyl-\( N,N \)-dimethylpropiolamide afforded the borylation product \( 4.29 \) in an 89% yield, which was surprising given that the ester equivalent was low yielding. The conjugated cyclohex-3-en-1-yne substituted \( N,N \)-dimethylpropiolamide was regioselectively borylated at the \( \beta \)-position, providing the (Z)-\( \alpha,\beta,\gamma,\delta \)-unsaturated diene, \( 4.31 \), in a 79% yield. Borylation of the methylene phenyl ether also afforded the desired product in a good yield (entry 9). Finally, the steric bulk of the tertiary amide was shown to be well tolerated with an alkynamide derivative of \( \text{D} \)-proline (entry 10). This substrate readily undergoes \( \beta \)-borylation to give \( 4.33 \) in excellent yield (92%) and without racemization of the chiral center.

The acidic hydrogen of the amide functionality is also tolerated under these mild conditions, as evidenced by \( 4.34-38 \). To the best of our knowledge, the borylation of secondary and primary amides has never been reported.\(^{95} \) The secondary amides were regio- and stereoselectively borylated in good to excellent yields \( (4.34-35) \). When steric demand of the amide
Table 4.5. Borylation of alkynamides with pinB—Bdan.\textsuperscript{a,*}

\[
\begin{align*}
\text{R}^1 & \quad \text{R}^2 & \quad \text{R}^3 \\
\text{Me} & \quad \text{Me} & \quad \text{Me} \\
\text{C}_6\text{H}_{13} & \quad \text{Me} & \quad \text{Me} \\
\text{C}_4\text{H}_{13} & \quad \text{Me} & \quad \text{Me} \\
\text{C}_6\text{H}_{13} & \quad \text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} & \quad \text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} & \quad \text{O}
\end{align*}
\]

\[
\begin{align*}
\text{N} & \quad \text{N} & \quad \text{N} \\
\text{N} & \quad \text{N} & \quad \text{N} \\
\text{N} & \quad \text{N} & \quad \text{N} \\
\text{N} & \quad \text{N} & \quad \text{N} \\
\text{N} & \quad \text{N} & \quad \text{N} \\
\text{N} & \quad \text{N} & \quad \text{N}
\end{align*}
\]

\[
\begin{align*}
\text{Me} & \quad \text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} & \quad \text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{1} & \quad \text{2} & \quad \text{3} & \quad \text{4} & \quad \text{5} & \quad \text{6} & \quad \text{7}
\end{align*}
\]

\[
\begin{align*}
\text{Entry} & \quad \text{Substrate} & \quad \text{Product} & \quad \text{Time (h)} & \quad \text{Yield\textsuperscript{c} (\%)} \\
1 & \quad \text{Me} & \quad \text{N} & \quad \text{O} & \quad \text{Me} & \quad \text{Me} & \quad \text{10} & \quad \text{85} \\
2 & \quad \text{C}_6\text{H}_{13} & \quad \text{N} & \quad \text{O} & \quad \text{Me} & \quad \text{Me} & \quad \text{4} & \quad \text{88} \\
3 & \quad \text{C}_3\text{H}_7 & \quad \text{N} & \quad \text{O} & \quad \text{Me} & \quad \text{Me} & \quad \text{15} & \quad \text{76} \\
4 & \quad \text{C}_6\text{H}_{13} & \quad \text{N} & \quad \text{O} & \quad \text{Me} & \quad \text{Me} & \quad \text{10} & \quad \text{86} \\
5 & \quad \text{C}_6\text{H}_{13} & \quad \text{N} & \quad \text{O} & \quad \text{Me} & \quad \text{Me} & \quad \text{48} & \quad \text{71} \\
6 & \quad \text{Me} & \quad \text{N} & \quad \text{O} & \quad \text{Me} & \quad \text{Me} & \quad \text{12} & \quad \text{89} \\
7 & \quad \text{Me} & \quad \text{N} & \quad \text{O} & \quad \text{Me} & \quad \text{Me} & \quad \text{15} & \quad \text{93}
\end{align*}
\]
<table>
<thead>
<tr>
<th>No.</th>
<th>Reaction Conditions</th>
<th>Product Structure</th>
<th>Yields</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>piB—Bdan (0.625 mmol), alkynamide (0.520 mmol), 4-picoline (5 mol %) in ethanol (0.1 mL) and CuSO₄ (0.9 mL, 1 mol % dissolved in an aqueous solution of 2 wt % TPGS-750-M).</td>
<td><img src="structure.png" alt="Structure 4.31" /></td>
<td>28 79</td>
</tr>
<tr>
<td>9</td>
<td>Determined by ¹H NMR of the crude material and confirmed by nOe of the isolated product.</td>
<td><img src="structure.png" alt="Structure 4.32" /></td>
<td>15 82</td>
</tr>
<tr>
<td>10</td>
<td><img src="structure.png" alt="Structure 4.33" /></td>
<td>9 92</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td><img src="structure.png" alt="Structure 4.34" /></td>
<td>12 76</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td><img src="structure.png" alt="Structure 4.35" /></td>
<td>12 96</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td><img src="structure.png" alt="Structure 4.36" /></td>
<td>15 41</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td><img src="structure.png" alt="Structure 4.37" /></td>
<td>16 90</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td><img src="structure.png" alt="Structure 4.38" /></td>
<td>9 93</td>
<td></td>
</tr>
</tbody>
</table>

* Reaction conditions: piB—Bdan (0.625 mmol), alkynamide (0.520 mmol), 4-picoline (5 mol %) in ethanol (0.1 mL) and CuSO₄ (0.9 mL, 1 mol % dissolved in an aqueous solution of 2 wt % TPGS-750-M). * Determined by ¹H NMR of the crude material and confirmed by nOe of the isolated product. * Averaged from 2 or more experiments. * Reproduced with permission.
substituent was increased from a methyl to a benzyl group, the borylation product was obtained nearly quantitatively (96%, 4.35). Gratifyingly, the less reactive carboxamides readily undergo borylation as well (entries 13-15). Excellent yields were obtained when the R⁰ position was substituted with a propyl (4.37) or hexyl (4.38) alkyl chain while a modest yield was obtained for methyl substituent (4.36). Interestingly, a trend of increasing product yield was observed with larger and more nonpolar substituents, presumably as a consequence of the hydrophobic effect.²⁴,²⁸

4.4.5. Proposed Mechanism

Activation of the nonpolar B—B bond is essential to borylation processes with diboron reagents. It is well established that the formation of an sp²-sp³ hybridized diboron adduct polarizes the boron–boron bond, which increases the electron density at the sp² hybridized boron center and imparts nucleophilic character capable of transmetallating with a transition metal catalyst.⁵⁴,⁸⁸,⁹⁶-⁹⁸ In the hallmark disclosure of a copper(II)-catalyzed aqueous borylation, ¹¹B NMR and solvent kinetic isotope studies were used to establish that water is essential in activating B₂pin₂ for a transmetallation with copper.⁵³ No evidence of 4-picoline coordinating to B₂pin₂ has been observed, which further corroborates that water activates the diboron reagent.⁹⁹ Based on this precedent, a plausible mechanism is proposed in Scheme 4.6. The chemoselective coordination of water to the Bpin moiety in 4.39 is inferred on the basis of DFT calculations, which established that coordination of a methoxide ion to the Bpin moiety is 7.4 kcal mol⁻¹ lower in energy than the alternative coordination to the Bdan moiety.⁷⁹,⁸⁴ Borner and Kleeberg also attributed the higher Lewis acidity of Bpin relative to B(NRR’)₂ moieties to explain the observation that copper(I) diaminoboryl complexes are selectively formed from unsymmetrical pinB–B(NRR’)₂ diboron reagents.¹⁰⁰ Thus, it is reasonable to conclude that water chemoselectively activates the Bpin moiety. Transmetallation of the Bdan group to the copper catalyst gives 4.40. For both the ester
and amide substrates, 4.40 undergoes syn-addition across the triple bond to provide the β-borylated copper intermediate, 4.41. Protonation of 4.41 leads to the formation of the (Z)-stereoisomer, which was observed in all examples.

**4.5. Conclusions**

In summary, a mild and efficient copper-catalyzed β-borylation of alkynoates and alkynamides was developed using the differentially protected diboron reagent, pinB—Bdan. The
chemoselective activation of this reagent is achieved under aqueous conditions which are environmentally friendly and conducted open-to-air. Catalytic amounts of an inexpensive copper catalyst and commercially available amine base also makes this approach cost effective. The 1,8-diaminonaphthalene protected boryl group is selectively transferred to deliver the (Z)-isomer of β-boryl α,β-unsaturated esters and amides. This regio-, stereo-, and chemoselective protocol provides access to a wide scope of derivatives. Excellent yields are obtained for most substrates and a diverse functional group tolerance is exhibited. Due to the added protection of the boron center, it is possible to further functionalize these compounds prior to the transformation of the boron center. As such, having direct access to structurally diverse derivatives will certainly aid in their exploration as synthetic intermediates, and these studies are currently underway.

4.6. References


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(99) Dang, L.; Zhao, H.; Lin, Z.; Marder, T. B. Understanding the Higher Reactivity of B$_2$cat$_2$ versus B$_2$pin$_2$ in Copper(I)-Catalyzed Alkene Diboration Reactions. *Organometallics* **2008**, *27*, 1178-1186.

Chapter 5. Current and Future Directions

5.1. Contributions

The research described herein was conceived by the collaborative efforts of Dr. Webster Santos and Prof. Todd Marder. Based on their ideas funded by IUPAC, the author submitted a proposal that received external support courtesy of the Fulbright Scholar Program. The duration of this research was conducted in the laboratories of Dr. Marder at the Universität Würzburg, Germany. This opportunity provided an exchange of ideas that facilitated the advancement of the work presented in this chapter as well as the endeavors of our colleagues abroad. The author gratefully acknowledges the financial support provided by IUPAC and the Fulbright Association. These experiments were conducted solely by the author of this chapter. Project direction and intellectual contributions were communicated by both advisors.
5.2. Introduction

There is only a finite quantity of palladium in the earth’s crust, which renders catalysts based on this metal extremely expensive (1g = $24 USD, based on current market value). Additionally, palladium compounds are highly toxic and pose serious harm to the environment. It has therefore become of utmost interest to discover and develop catalytic systems capable of replacing palladium with earth abundant transition metals. The development of copper catalysts as sustainable alternatives to palladium has led to the emergence of new methods for organoboron transformations. Being an earth abundant metal, copper catalysts address the needs of modern preparative chemistry to be non-toxic, environmentally benign, and economical (1g = $0.007 USD, based on current market value). The current and future directions of this work are searching for new modes of copper-catalyzed transformations that replace catalysts based on palladium and other rare earth metals.

The electronic properties of the metal are determinate factors regarding the activity of a catalyst. Since the metal is charged with carrying out a specific role, conferring noble metal catalysis to a base metal is not as straightforward as replacing a palladium reagent with a copper salt. For one, copper can access oxidation states ranging from 0 to +3, which enables this metal to carry out both one- and two-electron processes. Conversely, palladium only has two stable oxidation states (0 and +2) at its disposal. Due to its smaller size, copper forms shorter bonds than palladium complexes, making insertion processes much more challenging. It is also a hard Lewis acid, which renders weak organocopper bonds and strong metal–heteroatom linkages. Furthermore, copper has a much smaller coordination sphere than palladium, so it cannot accommodate large ancillary ligands for stabilizing intermediates or directing the selectivity of a given reaction. To address these challenges, thorough screenings of reaction conditions are needed.
5.3. Copper-Catalyzed Cross-Coupling Reactions

5.3.1. Screening of Reaction Conditions for a Carbon–Carbon Cross-Coupling

As described in Chapter 1, efficient methods for carrying out copper-catalyzed cross-coupling reactions are highly desirable. As part of a collaborative project, the author joined the research labs of Dr. Todd Marder at the Universität Würzburg. The proposed project sought to identify reaction conditions that enable copper to cross-couple the carbon–boron bond of β-boryl carbonyl compounds with alkyl halides (Scheme 5.1). The pinacolato β-boryl derivative of chalcone and the pinacolato β-boryl derivative of methyl 3-phenylpropionate, and their corresponding trifluoroborate salts were chosen as exploratory substrates. Aryl and methyl iodide were selected as simple coupling partners. Many reactions conditions were screened, however, no suitable conditions were identified for the desired conversion. In most cases, protodeboronation was observed. In the absence of other reagents, the alkoxide bases protodeboronated the pinacolato β-boryl substrates with the following trend LiO’Bu < NaO’Bu < KO’Bu. The substrates were stable towards sodium acetate and cesium carbonate, however, these bases were ineffective at facilitating transmetallation. The trifluoroborate β-boryl derivatives were also explored. Unfortunately, no conversion to product was observed under the conditions analyzed. A full tabulation of these experiments is found in Section 6.6.2.

Scheme 5.1. Summary of unsuccessful reaction conditions.
5.3.2. Future Directions

The next stage of this research will analyze the neopentyl glycolato β-boryl derivatives (Bneop). These substrates are more reactive than the corresponding pinacolato derivatives and have found more success in copper-catalyzed cross-coupling reactions.\(^1\)\(^-\)\(^5\) A protocol for obtaining the neopentyl glycolato β-boryl derivative from the trifluoroborate salt, as outlined in Scheme 5.2, has been developed for this undertaking.

![Scheme 5.2](image)

**Scheme 5.2.** Conversion of trifluoroborate salt into the neopentyl glycolato β-boryl derivative.

It is possible that these reactions were not conducted at an appropriate temperature. In reviewing the literature, it is observed that these reactions are often conducted at elevated temperature as high as 125 °C. It would be worthwhile to revisit a select few of these reactions and screen them at higher temperatures. Table 5.1 outlines the promising reactions that gave the least side-products at 80 °C, which should be reassessed.

**Table 5.1.** Outline of the proposed experiments to be conducted at 125 °C.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Base</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Organohalide</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>IPr</td>
<td>LiO'Bu</td>
<td>DMF</td>
<td>125</td>
<td>Ar—I</td>
</tr>
<tr>
<td>2</td>
<td>ICy</td>
<td>LiO'Bu</td>
<td>DMF</td>
<td>125</td>
<td>Ar—I</td>
</tr>
<tr>
<td>3</td>
<td>IPr</td>
<td>LiO'Bu</td>
<td>DMSO</td>
<td>125</td>
<td>Ar—I</td>
</tr>
<tr>
<td>4</td>
<td>ICy</td>
<td>LiO'Bu</td>
<td>DMSO</td>
<td>125</td>
<td>Ar—I</td>
</tr>
</tbody>
</table>
The reaction conditions outlined in Table 5.1 would be conducted with all six substrates. If no conditions are identified, it would be of interest to explore the boranes (e.g. 9-BBN). These derivatives have been very successful in copper-catalyzed sp\(^3\)-sp\(^3\) cross-coupling reactions.\(^6\)

5.3.3. Carbon–Heteroatom Transformations from C—B Bonds

The Chan-Evans-Lam protocol was described in extensive detail in Chapter 1. Presently, there lacks a generalizable method for this transformation. Many reactions are hampered by undesired side-products or unreactive substrates. Moreover, homo-coupling and autoxidation of the organoboron reagents are commonly encountered. A colleague in Dr. Marder’s research lab is currently examining one example wherein the attempted Chan-Lam reaction provides only homo-

![Scheme 5.3](image-url)

**Scheme 5.3.** Unsuccessful Chan-Lam cross-coupling reaction.
coupling side-products (Scheme 5.3). More study in this area to identify ways to circumvent these problems will aid the development of generalizable methods.

5.4. **Synthetic Applications of 1,8-Diaminonaphthalene β-Boryl α,β-Unsaturated Esters and Amides**

5.4.1. **Preliminary Results and Future Directions**

The future work of the project described in Chapter 4 is to explore the utility of these compounds. It is believed that the transformative power and synthetic utility of these compounds has been thwarted by the limited access to structurally diverse derivatives. The research described in Chapter 4 provides a facile and direct access to such compounds. Therefore, the exploration of these compounds as synthetic intermediates should be demonstrated.

Hall *et al.* has published several examples of the utility of these compounds (Scheme 5.4).[7,8] The stereoselective alkylation reaction has been attempted with compound 4.10. A 30% yield of compound 5.1 was observed by NMR of the crude mixture. These conditions were unoptimized, but the proof of concept has been established (Scheme 5.5).

![Scheme 5.4. Stereoselective reactions developed by Hall *et al.*](image)

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**Scheme 5.4.** Stereoselective reactions developed by Hall *et al.*[7,8]
The addition of a Bpin moiety to compound 4.10 was also explored as outlined in Scheme 5.6. No product was observed under the optimized conditions developed by Hall et al. nor with the aqueous conditions developed by Santos et al. Both reactions were performed on the bench top and in the microwave. When the latter was heated to 100 °C, the copper catalyst plated out onto wall of the microwave tube. A more detailed study of these reactions conditions will be necessary to realize this transformation.

The subsequent SMC reactions with palladium catalysts should not be hindered by steric interactions. However, a well-developed copper-catalyzed procedure would be ideal. If catalytic conditions are identified with the chalcone substrate in section 5.2, this method may be extendable to carrying out these chemoselective cross-coupling transformations. The future direction of this project has the ultimate goal of chemoselective borylations and transformations by copper catalysts.

**Scheme 5.5.** Unoptimized alkylation of compound 4.10.

**Scheme 5.6.** Unsuccessful borylation attempts of 4.10.
5.5. Other Investigations

5.5.1. Metal-Free Diboration of Allenes

As mentioned in Chapter 1, the diboration of an allenic substrate has been noted to proceed under metal-free conditions. Fernández et al. found that treating a mixture of B₂pin₂ and methanol with a catalytic amount of sodium tert-butoxide at 45 °C in THF was effective for the diboration of the terminal double bond of 5.3 (Scheme 5.7).\(^{10}\) This reaction would be an interesting project to explore because it provides complementary access to a regioselective diboration on the terminal double bond of mono-substituted allenes. However, only one example was explored in this report and the stereochemistry was not provided.

![Scheme 5.7. Transition metal-free diboration of 1-cyclohexyl-1,2-propadiene.\(^{10}\)](image)

In Chapter 2, a palladium-catalyzed protocol for the diboration of allenes using an alkenyl iodide co-catalyst was described. Yang and Cheng found that mono-substituted substrates were regioselective for addition to the terminal double bond and stereoselective for the (Z)-isomer.\(^{11}\) It would be interesting to develop a metal-free variation of this reaction using the aforementioned precedent. Firstly, the stereochemistry of 5.4 would need to be established. It is expected that this reaction provides a racemic mixture of \(E\) and \(Z\) products; however, a modest stereoselectivity may arise from steric interactions. Building off of the NHC-catalyzed stereoselective borylations developed by Hoveyda et al., a screening of chiral NHCs is expected to lead to the identification of stereoselective conditions.\(^{12-16}\)
5.5.2. Crystal Structure of PDAN Diboron

The PDAN diboron used in Chapters 2 and 4 has not yet been characterized by X-ray crystallography. This diboron is easily prepared in large quantities as outlined in Section 6.3.1. The recrystallization is easily performed by dissolving the compound in warm hexanes and cooling. However, this often provides fluffy sheets of solid rather than quality crystals. A slow crystallization using methanol and hexanes should result in the formation of analyzable crystals. Chlorinated solvents, like chloroform and dichloromethane, must be avoided in the presence of light. All recrystallizations should take precautions to avoid exposure to light.

On the note of exposure to light, it has been observed many times that chlorinated solvents, most especially, cause the solution of PDAN diboron to turn green and then purple, but only when exposed to light. Eventually black solid precipitates out of solution. The colored solutions are indistinguishable from the colorless solutions of PDAN diboron using GC-MS and NMR spectroscopy. Thus, the decomposition pathway and products are unclear. It would be of interest to explore this further. If purple crystals can be obtained and analyzed by crystallography, this may provide insight into the nature of this process.

5.6. References


Chapter 6. Experimental

6.1. General Information

All reactions in Chapters 2-5 were carried out in oven-dried glassware using standard Schlenk techniques, unless otherwise noted. All aqueous borylation reactions were carried out open-to-air. All reported borylation reactions were performed in triplicate. Milli-Q water was obtained using a Barnstead EASYpure UV water system. De-ionized water was used straight from the house DI water tap and was not degassed or further purified. Solvents were purchased from Fischer Scientific or Spectrum Chemicals. Tetrahydrofuran, toluene, acetonitrile, dichloromethane, and dimethylformamide were dried using an Innovative Technology Pure Solv-MD solvent purification system. Bis(pinacolato)diboron was purchased from Boron Molecular or donated by Allychem. Copper sulfate pentahydrate, 4-picoline, TPGS-750-M, and other commercially available reagents and substrates not characterized herein were purchased and used as received. CuSO₄ stock solutions were prepared by dissolving 2.6 mg CuSO₄ in 1 mL Milli-Q water or 2 wt% TPGS-750-M. TLC analyses were performed using either EMD silica gel 60F254 plates, Agela Technologies silica gel MF₂54 plates, or Silicycle aluminum backed silica gel F-254 plates and spots were visualized with UV light and KMnO₄ stain.

6.2. Instrumentation

¹H NMR spectra were recorded on a Bruker Advance II-500 (500 MHz), Agilent MR 400 MHz, Agilent DD2 400 MHz, or Bruker Avance III 600 MHz spectrometer. Chemical shifts are reported in ppm with the solvent resonance as the internal standard (CDCl₃: 7.26 ppm, (CD₃)₂SO: 2.50 ppm, (CD₃)₂CO: 2.05 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, dd = doublet of doublets, dt
= doublet of triplets, br = broad), coupling constants (Hz), and integration. $^{13}$C NMR spectra were recorded on a Bruker Advance II-500 (125 MHz), Agilent MR 400 MHz (100 MHz), Agilent DD2 400 MHz (100 MHz), or Bruker Avance III 600 (150 MHz) MHz spectrometer. Chemical shifts are reported in ppm with the solvent resonance as the internal standard (CDCl$_3$: 77.16, (CD$_3$)$_2$SO: 39.51, (CD$_3$)$_2$CO: 206.68 ppm). The carbon atoms directly attached to boron are not observed due to quadruple relaxation. $^{11}$B NMR spectra were recorded on a Bruker Advance II-500 (160 MHz), Agilent 400-MR (128 MHz), or Agilent DD2 400 MHz (128 MHz) spectrometer. Chemical shifts are reported in ppm with boron trifluoride diethyl etherate as an external standard (BF$_3$(OC$_2$H$_5$)$_2$: 0 ppm). High resolution mass spectra (HRMS) were performed on an Agilent LC-ESI-TOF. Gas chromatography (GC) analyses were performed on either a Hewlett Packard 6890 Series GC system coupled to a HP 5973 Mass Selective Detector or on an Agilent 7890B Series GC system coupled to an Agilent 5977A Mass Selective Detector and Agilent 7693 autosampler. In both instruments, the column was an Agilent DB-5MS with a length of 30 m, I.D. of 250 μm, and film thickness of 0.25 μm. Elemental Microanalyses were performed by Atlantic Microlab, Georgia. Optical rotation was determined using a JASCO P-2000 Polarimeter. Melting points were measured on Büchi Melting Point B-540 and are uncorrected.

6.3. Synthetic Procedures and Characterizations for Chapter 2

6.3.1. Synthesis and Characterization of PDAN Diboron

By stirring PDIPA diboron and 1,8-diaminonaphthalene in acetic acid for 1-3 hours, followed by extraction and column chromatography, delivers PDAN diboron as a white solid in 69% yield. This methodology is scalable to produce large quantities (1-2 g). Scheme 6.1 outlines this the approach developed in the Santos Laboratory.
To a solution of bis(pinacolato)diboron (10 g, 39.4 mmol) in diethyl ether (160 mL) was added bis(2-hydroxypropyl)amine (5.73 g, 43.3 mmol) in CH$_2$Cl$_2$ (20 mL) under a blanket of nitrogen. After 5 minutes, a white precipitate appeared and the reaction mixture was stirred at room temperature for 24 hours. The white solid was filtered and washed with copious amount of diethyl ether to provide the desired product 2 (6.6g, 62%, trans:cis 1:1.2). This compound is sufficiently pure for the subsequent synthesis of PDAN. Recrystallization from CH$_2$Cl$_2$ and EtOAc (1:2) affords analytically pure product. Unreacted B$_2$pin$_2$ starting material may be recovered by purification with column chromatography over silica gel, eluting with a 1:1 mixture of hexanes and EtOAc (3.1g, 31%). Spectral data are consistent with the literature.$^{1,2}$

PDIPA diboron (0.56 g, 2.08 mmol) and 1,8-diaminonaphthalene (0.299 g, 1.89 mmol) were added to a nitrogen-purged flask. These reagents were stirred in acetic acid (6.50 ml, 114 mmol) at room temperature for 1-3 h. The mixture was concentrated in vacuo, and then diluted with EtOAc. The organic mixture was washed with water (5 x 25 mL), dried over sodium sulfate, filtered, and concentrated. Purification by column chromatography over silica gel, eluting with a 9:1 mixture of hexanes and EtOAc, yields pinB—Bdan (0.383 g, 69%) as a white solid. Spectral data are consistent with the literature.$^3$

**Scheme 6.1.** Synthesis of PDIPA diboron and PDAN diboron.
6.3.2. General Procedures for Optimization of the Metal-Catalyzed Diboration of Phenyl Allene (Table 2.2)

**Method 1, entries 1-3:**

Pt(dba)$_3$ (4.8 mg, 5.35 µmol) catalyst was added to a two-neck round-bottomed flask and purged with nitrogen. Toluene (1 mL) was added and the suspension was stirred for 15 min. Next, pinB—Bdan (40 mg, 0.136 mmol) and phenyl allene (19.0 mg, 0.163 mmol) were added sequentially. The reaction mixture was heated to 80 °C and followed by TLC until the starting material had been consumed completely. The resulting solution was analyzed by GC-MS to determine the isomeric ratio. The contents were then concentrated *in vacuo* and purified by flash chromatography on silica gel. Recrystallization for X-ray crystallography was performed by dissolving the mixture of isomer in warm hexanes and cooling the solution. An $^1$H NMR was taken of the collected solid to confirm exclusive presence of the major isomer.

**Method 2, entries 4-13:**

Pt(dba)$_3$ (4.8 mg, 5.35 µmol) and ligand (8.16 µmol) were added to a two-neck round-bottomed flask and purged with nitrogen. Toluene (1 mL) was added and the suspension was stirred for 15 min, producing a purple mixture. Next, pinB—Bdan (40 mg, 0.136 mmol) and phenyl allene (19.0 mg, 0.163 mmol) were added sequentially. The reaction mixture was heated to 80 °C and followed by TLC until the starting material had been consumed completely. The resulting solution was analyzed by GC-MS to determine the isomeric ratio. The contents were then concentrated *in vacuo* and purified by flash chromatography on silica gel.

**Method 3, entries 14-15:**

[IrCl(cod)]$_2$ (2.3 mg, 3.40 µmol) and ligand (0 or 8.16 µmol) were added to a two-neck round-bottomed flask and purged with nitrogen. Toluene (1 mL) was added and the suspension
was stirred for 15 min. Next, pinB—Bdan (40 mg, 0.136 mmol) and phenyl allene (19.0 mg, 0.163 mmol) were added sequentially. The reaction mixture was heated to 80 °C and followed by TLC until the starting material had been consumed completely. The resulting solution was analyzed by GC-MS to determine the isomeric ratio. The contents were then concentrated in vacuo and purified by flash chromatography on silica gel.

**Method 4, entries 16-17:**

[RhCl(cod)]₂ (1.7 mg, 3.40 µmol) and ligand (0 or 8.16 µmol) were added to a two-neck round-bottomed flask and purged with nitrogen. Toluene (1 mL) was added and the suspension was stirred for 15 min. Next, pinB—Bdan (40 mg, 0.136 mmol) and phenyl allene (19.0 mg, 0.163 mmol) were added sequentially. The reaction mixture was heated to 80 °C and followed by TLC until the starting material had been consumed completely. The resulting solution was analyzed by GC-MS to determine the isomeric ratio. The contents were then concentrated in vacuo and purified by flash chromatography on silica gel.

**Method 5, entry 18:**

Pd₂(dba)₃ (3.1 mg, 3.40 µmol) was added to a two-neck round-bottomed flask and purged with nitrogen. Toluene (1 mL) was added and the suspension was stirred for 15 min. Next, pinB—Bdan (40 mg, 0.136 mmol) and phenyl allene (19.0 mg, 0.163 mmol) were added sequentially. The reaction mixture was heated to 80 °C and followed by TLC until the starting material had been consumed completely. The resulting solution was analyzed by GC-MS to determine the isomeric ratio. The contents were then concentrated in vacuo and purified by flash chromatography on silica gel.
6.3.3. **General Procedure for the Optimization of Reaction Conditions (Table 2.3)**

Pt(dba)$_3$ (4.8 mg, 5.35 µmol) and P[3,5-(CF$_3$)$_2$C$_6$H$_3$]$_3$ (5.5 mg, 8.16 µmol) were added to a two-neck round-bottomed flask and purged with nitrogen. Toluene (1 mL) was added and the suspension was stirred for 15 min, producing a purple mixture. Next, pinB—Bdan (40 mg, 0.136 mmol) and phenyl allene (0.163 mmol) were added sequentially. The contents were heated to 80 °C and followed by TLC until the starting material had been consumed completely. The resulting solution was analyzed by GC-MS or $^1$H NMR to determine the isomeric ratio. The reaction mixture was concentrated in vacuo and purified by flash column chromatography to yield the diboration product.

6.3.4. **General Procedure for the Ligand Screening of Disubstituted Allenes (Table 2.4)**

Pt(dba)$_3$ (4.8 mg, 5.35 µmol) and SPhos (3.4 mg, 8.16 µmol) or P[3,5-(CF$_3$)$_2$C$_6$H$_3$]$_3$ (5.5 mg, 8.16 µmol) were added to a two-neck round-bottomed flask and purged with nitrogen. Toluene (1 mL) was added and the suspension was stirred for 15 min, producing a purple mixture. Next, pinB—Bdan (40 mg, 0.136 mmol) and disubstituted allene (0.163 mmol) were added sequentially. The contents were heated to 80 °C and followed by TLC until the starting material had been consumed completely. The resulting solution was analyzed by GC-MS or $^1$H NMR to determine the isomeric ratio. The reaction mixture was concentrated in vacuo and purified by flash column chromatography to yield the diboration product.

6.3.5. **General Procedure for the Diboration of Disubstituted Allenes (Table 2.5)**

Pt(dba)$_3$ (4.8 mg, 5.35 µmol) and SPhos (3.4 mg, 8.16 µmol) were added to a two-neck round-bottomed flask and purged with nitrogen. Toluene (1 mL) was added and the suspension was stirred for 15 min, producing a purple mixture. Next, pinB—Bdan (40 mg, 0.136 mmol) and disubstituted allene (0.163 mmol) were added sequentially. The contents were heated to 80 °C and
followed by TLC until the starting material had been consumed completely. The resulting solution was analyzed by GC-MS or $^1$H NMR to determine the isomeric ratio. The reaction mixture was concentrated in vacuo and purified by flash column chromatography to yield the diboration product. Recrystallization for X-ray crystallography was performed by dissolving the mixture of isomer in warm hexanes and cooling the solution. An $^1$H NMR was taken of the collected solid to confirm exclusive presence of the major isomer.

### 6.3.6. Characterizations of the Bis(boryl) Products

$2$-(1-phenyl-$2$-($4,4,5,5$-tetramethyl-$1,3,2$-dioxaborolan-$2$-yl)allyl)-$2,3$-dihydro-$1H$-naphtho[$1,8$-$de$][$1,3,2$]diazaborinine (2.14):

- Compound 2.14 was synthesized using General Procedure 6.3.1. White solid; mp $172 – 174\, ^\circ C$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.25 – 7.08 (m, 5H), 7.01 (dd, $J = 8.1$, 7.4 Hz, 2H), 6.92 (d, $J = 8.1$ Hz, 2H), 6.18 (d, $J = 7.4$ Hz, 2H), 5.85 (d, $J = 2.9$ Hz, 1H), 5.81 (br s, 2H), 5.47 (m, 1H), 3.42 (s, 1H), 1.15 (s, 6H), 1.12 (s, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 142.1, 141.4, 136.4, 129.8, 129.7, 128.6, 127.7, 125.8, 119.8, 117.5, 105.8, 84.0, 25.0, 24.6; $^{11}$B NMR (128 MHz, CDCl$_3$) $\delta$ 30.60; HRMS (ESI+): Calcd for C$_{25}$H$_{29}$B$_2$N$_2$O$_2$ [M+H]$^+$: 411.2410, Found 411.2425; TLC: 19:1 / Hexanes:EtOAc, R$_f$ 0.35.

(E)-$2$-($3$-phenyl-$2$-($4,4,5,5$-tetramethyl-$1,3,2$-dioxaborolan-$2$-yl)but-$2$-en-$1$-yl)-$2,3$-dihydro-$1H$-naphtho[$1,8$-$de$][$1,3,2$]diazaborinine (2.21a):

- Compound 2.21a was synthesized using General Procedure 6.3.4. White solid; mp $139 – 140\, ^\circ C$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.30 – 7.26 (m, 1H), 7.26 – 7.20 (m, 4H), 7.09 (dd, $J = 8.2$, 7.3 Hz, 2H), 6.99 (d, $J = 8.3$ Hz, 2H), 6.30 (d, $J = 7.3$ Hz, 2H), 6.05 (br s, 2H), 2.06 (s,
3H), 1.98 (s, 2H), 1.11 (s, 12H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 146.3, 145.9, 141.6, 136.5, 128.0, 127.9, 127.7, 126.8, 119.8, 117.4, 105.6, 83.5, 24.7, 20.4; $^{11}$B NMR (128 MHz, CDCl$_3$) δ 31.00; HRMS (ESI+): Calcd for C$_{26}$H$_{31}$B$_2$N$_2$O$_2$ [M+H]$^+$: 425.2566, Found 425.2572; TLC: 9:1 / Hexanes:EtOAc, R$_f$ 0.4.

2-(3,3-diphenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)-2,3-dihydro-1H-naphtho[1,8-de][1,3,2]diazaborinine (2.23a):

![Compound 2.23a](image)

Compound 2.23a was synthesized using General Procedure 6.3.4. White solid; mp 183 – 185 °C; $^1$H NMR (500 MHz, CDCl$_3$) δ 7.34 – 7.28 (m, 2H), 7.26 – 7.18 (m, 6H), 7.17 – 7.06 (m, 4H), 7.00 (d, $J$ = 8.0 Hz, 2H), 6.26 (d, $J$ = 7.1 Hz, 2H), 5.90 (br s, 2H), 1.95 (s, 2H), 1.18 (s, 12H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 150.6, 144.5, 142.3, 141.5, 136.5, 129.6, 129.4, 128.3, 127.9, 127.7, 127.2, 127.0, 119.8, 117.4, 105.6, 83.9, 24.8; $^{11}$B NMR (128 MHz, CDCl$_3$) δ 35.51; HRMS (ESI+): Calcd for C$_{31}$H$_{33}$B$_2$N$_2$O$_2$ [M+H]$^+$: 487.2723, Found 487.2734; TLC: 9:1 / Hexanes:EtOAc, R$_f$ 0.38.

(E)-2-(5-methyl-3-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-2-en-1-yl)-2,3-dihydro-1H-naphtho[1,8-de][1,3,2]diazaborinine (2.25a):

![Compound 2.25a](image)

Compound 2.25a was synthesized using General Procedure 6.3.4. White solid; mp 147 – 149 °C; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.30 – 7.26 (m, 1H), 7.26 – 7.19 (m, 4H), 7.09 (dd, $J$ = 8.4, 7.3 Hz, 2H), 6.99 (dd, $J$ = 8.4, 1.0 Hz, 2H), 6.31 (dd, $J$ = 7.3, 1.0 Hz, 2H), 6.06 (br s, 2H), 2.36 (d, $J$ = 7.3 Hz, 2H), 2.02 (s, 2H), 1.49 (m, 1H), 1.06 (s, 12H), 0.82 (d, $J$ = 6.6 Hz, 6H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 149.7, 145.3, 141.6, 136.5, 128.6, 127.9, 127.7, 126.7, 119.8, 117.3, 105.6, 83.5, 42.2, 27.0, 24.7, 22.7; $^{11}$B NMR (128 MHz, CDCl$_3$) δ 31.15; HRMS (ESI+): Calcd
for C_{29}H_{37}B_{2}N_{2}O_{2} [(M+H)]^+: 467.3036, Found 467.3064; Calcd for C_{29}H_{36}B_{2}N_{2}O_{2} [(M+Na)]^+: 489.2855, Found 489.2875; TLC: 19:1 / Hexanes:EtOAc, R_f 0.29.

2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,3-di-p-tolylallyl)-2,3-dihydro-1H-naphtho[1,8-de][1,3,2]diazaborinine (2.26a):

![Structure](image)

Compound **2.26a** was synthesized using General Procedure 6.3.4. White solid; mp 215 – 217 °C; ¹H NMR (500 MHz, CDCl₃) δ 7.13 – 6.97 (m, 12H), 6.26 (dd, J = 7.3, 0.9 Hz, 2H), 5.90 (br s, 2H), 2.33 (s, 3H), 2.32 (s, 3H), 1.95 (s, 2H), 1.19 (s, 12H); ¹³C NMR (126 MHz, CDCl₃) δ 150.6, 142.0, 141.7, 139.8, 136.7, 136.6, 136.5, 129.5, 129.3, 129.0, 128.5, 127.7, 119.9, 117.4, 105.6, 83.9, 24.9, 21.3, 21.3; ¹¹B NMR (128 MHz, CDCl₃) δ 31.21; HRMS (ESI+): Calcd for C_{31}H_{31}B_{2}N_{2}F_{2}O_{2} [(M+H)]^+: 515.3036, Found 515.3060; TLC: 9:1 / Hexanes:EtOAc, R_f 0.35.

2-(3,3-bis(4-chlorophenyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)-2,3-dihydro-1H-naphtho[1,8-de][1,3,2]diazaborinine (2.27a):

![Structure](image)

Compound **2.27a** was synthesized using General Procedure 6.3.4. White solid; mp 185 – 187 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.31 – 7.27 (m, 2H), 7.25 – 7.20 (m, 2H), 7.14 – 6.99 (m, 8H), 6.27 (d, J = 7.2 Hz, 2H), 5.89 (br s, 2H), 1.93 (s, 2H), 1.20 (s, 12H); ¹³C NMR (101 MHz, CDCl₃) δ 148.0, 142.5, 141.3, 140.2, 136.4, 133.3, 133.1, 131.0, 130.7, 128.6, 128.1, 127.7, 119.8, 117.6, 105.7, 84.2, 24.8; ¹¹B NMR (128 MHz, CDCl₃) δ 35.69; HRMS (ESI+): Calcd for C_{31}H_{31}B_{2}Cl_{2}N_{2}O_{2} [(M+H)]^+: 555.1943, Found 555.1958; TLC: 9:1 / Hexanes:EtOAc, R_f 0.30.
2-(3,3-bis(4-fluorophenyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)-2,3-dihydro-
1H-naphtho[1,8-de][1,3,2]diazaborinine (2.28a):

Compound 2.28a was synthesized using General Procedure 6.3.4. White solid; mp 190 – 191.5 °C; 1H NMR (400 MHz, CDCl₃) δ 7.19 – 7.14 (m, 2H), 7.13 – 7.06 (m, 4H), 7.04 – 6.91 (m, 6H), 6.27 (dd, J = 7.3, 1.0 Hz, 2H), 5.90 (br s, 2H), 1.93 (s, 2H), 1.19 (s, 12H); 13C NMR (101 MHz, CDCl₃) δ 163.4 (d, J = 42.0 Hz), 160.9 (d, J = 42.2 Hz), 148.4, 141.3, 140.5 (d, J = 3.3 Hz), 138.0 (d, J = 3.3 Hz), 136.5, 131.2 (d, J = 7.9 Hz), 131.0 (d, J = 8.0 Hz), 127.7, 119.8, 117.6, 115.3 (d, J = 21.3 Hz), 114.8 (d, J = 21.3 Hz), 105.7, 84.1, 24.8; ¹¹B NMR (128 MHz, CDCl₃) δ 31.01; HRMS (ESI+): Calcd for C₃₁H₃₁B₂F₂N₂O₂ [M+H]⁺: 523.2534, Found 523.2538; TLC: 9:1 / Hexanes:EtOAc, R_f 0.30.

2-(3,3-bis(4-methoxyphenyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)-2,3-
dihydro-1H-naphtho[1,8-de][1,3,2]diazaborinine (2.29a):

Compound 2.29a was synthesized using General Procedure 6.3.4. White solid; mp 181 – 182 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.17 – 7.03 (m, 6H), 7.02 – 6.98 (m, 2H), 6.87 – 6.82 (m, 2H), 6.81 – 6.77 (m, 2H), 6.27 (dd, J = 8.2, 0.9 Hz, 2H), 5.92 (br s, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 1.97 (s, 2H), 1.21 (s, 12H); ¹³C NMR (101 MHz, CDCl₃) δ 159.0, 158.6, 149.9, 141.6, 137.6, 136.5, 135.0, 130.9, 130.6, 127.7, 119.8, 117.4, 113.6, 113.3, 105.6, 83.8, 55.4, 55.3, 24.9; ¹¹B NMR (128 MHz, CDCl₃) δ 31.40; HRMS (ESI+): Calcd for C₃₃H₃₇B₂N₂O₄ [M+H]⁺: 547.2934, Found 547.2963; Calcd for C₃₃H₃₆B₂N₂NaO₄ [M+Na]⁺: 569.2753, Found 569.2744; TLC: 9:1 / Hexanes:EtOAc, R_f 0.20.
2-(3,3-bis(4-ethoxyphenyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)-2,3-dihydro-1H-naphtho[1,8-de][1,3,2]diazaborinine (2.30a):

Compound 2.30a was synthesized using General Procedure 6.3.4.

White solid; mp 163.5 – 165 °C; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.13 – 7.07 (m, 4H), 7.04 – 6.97 (m, 4H), 6.85 – 6.78 (m, 2H), 6.80 – 6.73 (m, 2H), 6.27 (dd, \(J = 7.3, 0.9\) Hz, 2H), 5.91 (br s, 2H), 4.01 (q, \(J = 7.0\) Hz, 4H), 1.96 (s, 2H), 1 .40 (td, \(J = 7.0, 1.9\) Hz, 6H), 1.20 (s, 12H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 158.3, 157.9, 150.0, 141.6, 137.5, 136.5, 134.8, 130.9, 130.6, 127.7, 119.8, 117.3, 114.0, 113.9, 105.6, 83.8, 63.6, 63.5, 24.9, 15.0, 15.0; \(^{11}\)B NMR (128 MHz, CDCl\(_3\)) \(\delta\) 31.19; HRMS (ESI\(^+\)): Calcd for C\(_{35}\)H\(_{41}\)B\(_2\)N\(_2\)O\(_4\) [M+H]\(^+\): 575.3247, Found 575.3289; Calcd for C\(_{35}\)H\(_{40}\)B\(_2\)N\(_2\)O\(_4\NaO\(_4\) [M+Na]\(^+\): 597.3066, Found 597.3099; TLC: 9:1 / Hexanes:EtOAc, R\(_f\) 0.25.

2-(3,3-bis(4-propoxyphenyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)-2,3-dihydro-1H-naphtho[1,8-de][1,3,2]diazaborinine (2.31a):

Compound 2.31a was synthesized using General Procedure 6.3.4.

White solid; mp 179.5 – 181 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.15 – 6.97 (m, 8H), 6.87 – 6.78 (m, 2H), 6.81 – 6.74 (m, 2H), 6.27 (dd, \(J = 7.3, 0.6\) Hz 2H), 5.91 (br s, 2H), 3.90 (t, \(J = 6.6\) Hz, 4H), 1.96 (s, 2H), 1.80 (hd, \(J = 7.5, 1.6\) Hz, 4H), 1.20 (s, 12H), 1.03 (td, \(J = 7.4, 2.5\) Hz, 6H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 158.6, 158.1, 150.1, 141.6, 137.5, 136.5, 134.8, 130.9, 130.6, 127.7, 119.8, 117.3, 114.1, 113.9, 105.6, 83.8, 69.7, 69.6, 24.9, 22.8, 22.8, 10.7, 10.7; \(^{11}\)B NMR (128 MHz, CDCl\(_3\)) \(\delta\) 31.62; HRMS (ESI\(^+\)):

2-(3,3-di([1,1'-biphenyl]-4-yl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)-2,3-dihydro-1H-naphtho[1,8-de][1,3,2]diazaborinine (2.32a):

Compound 2.32a was synthesized using General Procedure 6.3.4.

White solid; mp 186 – 187 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.64 – 7.56 (m, 6H), 7.52 (d, J = 7.7 Hz, 2H), 7.44 (t, J = 7.6 Hz, 4H), 7.37 – 7.32 (m, 4H), 7.27 (d, J = 7.7 Hz, 2H), 7.11 (t, J = 7.8 Hz, 2H), 7.02 (d, J = 8.3 Hz, 2H), 6.29 (d, J = 7.3 Hz, 2H), 5.96 (br s, 2H), 2.05 (s, 2H), 1.23 (s, 12H); ¹³C NMR (101 MHz, CDCl₃) δ 149.8, 143.5, 141.5, 141.2, 141.1, 140.9, 140.1, 139.8, 136.5, 130.1, 129.9, 128.9, 128.9, 127.7, 127.4, 127.3, 127.2, 127.1, 127.0, 126.7, 119.8, 117.5, 105.7, 84.0, 24.9; ¹¹B NMR (128 MHz, CDCl₃) δ 31.73; HRMS (ESI+): Calcd for C₄₃H₄₁B₂N₂O₄ [M+H]⁺: 639.3349, Found 639.3392; TLC: 9:1 / Hexanes:EtOAc, Rₜ 0.24.

2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,3-di-o-tolylallyl)-2,3-dihydro-1H-naphtho[1,8-de][1,3,2]diazaborinine (2.33a):

Compound 2.33a was synthesized using General Procedure 6.3.4.

White solid; mp 183 – 188 °C (decomp); ¹H NMR (500 MHz, CDCl₃) δ 7.28 – 7.25 (m, 1H), 7.18 – 7.03 (m, 9H), 6.98 (dd, J = 8.3, 0.9 Hz, 2H), 6.21 (dd, J = 7.3, 0.9 Hz, 2H), 5.92 (br s, 2H), 2.23 (s, 3H), 2.22 (s, 3H), 1.81 (br s, 2H), 1.07 (s, 12H); ¹³C NMR (126 MHz, CDCl₃) δ 149.5, 143.5, 141.6, 140.7, 136.5, 136.1, 131.3, 130.5, 130.4, 130.2, 127.7, 127.0, 126.9, 125.4, 125.1, 119.7, 117.2,
195.5, 83.6, 24.7, 21.1, 20.7; $^{11}$B NMR (128 MHz, CDCl$_3$) δ 30.87; HRMS (ESI+): Calcd for C$_{33}$H$_{37}$B$_2$N$_2$O$_2$ [M+H]$^+$: 515.3036, Found 515.3067; TLC: 9:1 / Hexanes:EtOAc, R$_f$ 0.38.

2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,3-bis(3-(trifluoromethyl)phenyl)allyl)-2,3-dihydro-1H-naphtho[1,8-de][1,3,2]diazaborinine (2.34a):

Compound 2.34a was synthesized using General Procedure 6.3.4. White solid; mp 182.5 – 184.5 °C; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.59 – 7.30 (m, 8H), 7.11 (dd, $J = 8.3$, 7.3 Hz, 2H), 7.02 (dd $J = 8.3$, 0.9 Hz, 2H), 6.28 (dd, $J = 7.3$, 0.9 Hz, 2H), 5.94 (br s, 2H), 1.93 (s, 2H), 1.18 (s, 12H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 147.7, 144.2, 142.4, 141.2, 136.5, 132.9 – 132.8 (m), 132.8 (d, $J = 1.1$ Hz), 131.1, 130.8, 130.6, 130.2, 129.1, 128.6, 127.7, 126.3 – 125.9 (m), 125.6 (d, $J = 14.1$ Hz), 124.4 – 124.0 (m), 122.9 (d, $J = 14.4$ Hz), 119.8, 117.7, 105.8, 84.3, 24.8; $^{11}$B NMR (128 MHz, CDCl$_3$) δ 30.76; HRMS (ESI+): Calcd for C$_{33}$H$_{31}$B$_2$F$_6$N$_2$O$_2$ [M+H]$^+$: 623.2470, Found 623.2501; Calcd for C$_{33}$H$_{30}$B$_2$F$_6$N$_2$NaO$_2$ [M+Na]$^+$: 645.2290, Found 645.2273; TLC: 9:1 / Hexanes:EtOAc, R$_f$ 0.35.

6.3.7. Procedures and Characterizations for Synthetic Applications of the Bis(boryl) Compounds

2-(3,3-diphenyl-2-(p-tolyl)allyl)-2,3-dihydro-1H-naphtho[1,8-de][1,3,2]diazaborinine (2.42):

Tetrakis(triphenylphosphine) palladium(0) (3.6 mg, 3.09 µmol), cesium carbonate (60.3 mg, 0.185 mmol), 1-bromo-4-methylbenzene (15.2 µl, 0.123 mmol) and diboration product 2.23a (30 mg, 0.062 mmol) were placed in a flask and purged with nitrogen. Then toluene (1 mL) was added, and the mixture was stirred at 80 °C overnight. The reaction mixture was concentrated in vacuo and purified by flash column chromatography (hexanes/EtOAc = 19:1) to
yield the title compound (22.2 mg, 80%) as a white solid. mp 153 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.38 – 7.32 (m, 2H), 7.29 – 7.23 (m, 4H), 7.12 (d, $J = 8.1$ Hz, 2H), 7.08 – 6.91 (m, 10H), 6.14 dd, $J = 7.3, 0.9$ Hz, 2H), 5.42 (br s, 2H), 2.29 (s, 3H), 2.23 (s, 2H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 144.0, 143.2, 141.2, 140.9, 138.5, 137.5, 136.5, 136.4, 131.1, 130.0, 129.5, 129.2, 128.5, 127.7, 127.6, 126.8, 125.9, 119.7, 117.6, 105.7, 21.3; $^{11}$B NMR (128 MHz, CDCl$_3$) $\delta$ 31.17; HRMS (ESI+): Calcd for C$_{32}$H$_{28}$BN$_2$ [M+H]$^+$: 451.234, Found 451.2322; TLC: 19:1 / Hexanes:EtOAc, $R_f$ 0.31.

3,3-diphenyl-2-(p-tolyl)prop-2-en-1-ol (2.43):

To a solution of cross-coupling product 2.42 (40 mg, 0.089 mmol) in THF (0.8 ml) was added 6 M hydrochloric acid (89 µl, 0.533 mmol). The mixture was stirred at r.t. for a few hours until the coupling product was reacted completely by TLC. Water was added and the resulting mixture was extracted with diethyl ether. The organic layer was dried over magnesium sulfate, filtered, and concentrated in vacuo. The crude mixture was dissolved in MeOH (1.4 mL) and THF (1.4 mL), and then hydrogen peroxide 35% (272 µl, 8.87 mmol) was added in an ice bath. The contents were stirred in ice bath for 30 min and then at room temperature overnight. Aqueous sodium thiosulfate was added to the reaction mixture, and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered, concentrated, and purified by flash chromatography (hexanes/EtOAc = 9:1) to yield the title compound (17.3 mg, 65%) as a white solid. mp 134 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.39 – 7.27 (m, 5H), 7.13 – 6.99 (m, 7H), 6.96 – 6.91 (m, 2H), 4.47 (d, $J = 6.1$ Hz, 2H), 2.28 (s, 3H), 1.47 – 1.42 (t, $J = 6.2$ Hz, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 142.5, 142.5, 138.6, 137.2, 136.7, 130.8, 129.9, 129.8, 129.2, 128.4,
127.7, 127.4, 126.5, 65.2, 21.3; HRMS (ESI+): Calcd for C_{22}H_{19} [M-OH]^+: 283.1481, Found 283.1475; TLC: 9:1 / Hexanes:EtOAc, R_f 0.25.

2-(3,3-diphenyl-2-(p-tolyl)allyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.44):

The following procedure was a slight modification from the literature. The cross-coupling product 2.42 (42 mg, 0.093 mmol) was dissolved in THF (1 mL), and then 2M sulfuric acid (0.28 mL, 0.56 mmol) and pinacol (55.1 mg, 0.466 mmol) were added sequentially. The contents were stirred at room temperature for 24 h. Water was added and the mixture was extracted with diethyl ether. The organic layer was dried over magnesium sulfate, filtered, concentrated in vacuo and purified by flash chromatography (hexanes/EtOAc = 19:1) to yield the title compound (26.8 mg, 70%) as a white solid; mp 107 °C; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.37 – 7.29 (m, 4H), 7.25 – 7.20 (m, 1H), 7.06 – 6.97 (m, 5H), 6.95 – 6.90 (m, 4H), 2.24 (s, 3H), 2.14 (s, 2H), 1.10 (s, 12H); \(^1^3\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 144.2, 143.6, 141.1, 137.8, 137.3, 135.5, 131.1, 130.2, 129.6, 128.4, 128.2, 127.4, 126.5, 125.5, 83.3, 24.8, 21.3; \(^{11}\)B NMR (128 MHz, CDCl\(_3\)) \(\delta\) 33.40; HRMS (ESI+): Calcd for C\(_{28}\)H\(_{32}\)BO\(_2\) [M+H]^+: 411.2490, Found 411.2493; TLC: 19:1 / Hexanes:EtOAc, R_f 0.34.

(2-(p-tolyl)prop-1-ene-1,1-diyl)dibenzene (2.45):

\(O\)-Methylhydroxylamine solution\(^5\) (1.4 mL, 0.132 mmol, 0.094 M in THF) was added to a flame-dried flask, and the mixture was cooled to -78 °C. A solution of \(n\)-butyl lithium in hexanes (0.012 mL, 0.132 mmol, 2.5 M) was added dropwise and the reaction was stirred at -78°C for 30 min. Compound 2.44 (18 mg, 0.044 mmol) in THF (0.5 mL) solution was added dropwise to the deprotonated \(O\)-methylhydroxylamine solution. The reaction mixture was warmed to room temperature and heated to 60 °C for 10 h. Water was added and the mixture was extracted with ethyl acetate. The organic
layer was dried over sodium sulfate, filtered, concentrated and purified by flash column chromatography (100% hexane) to yield the title compound (12 mg, 97%). Spectral data are consistent with the literature.\(^6\)

**\((2-(p\text{-tolyl})\text{prop-2-ene-1,1-diyl})\text{dibenzene (2.46)}:\)**

\[
\text{Cesium carbonate (42.9 mg, 0.132 mmol) and compound 2.44 (18 mg, 0.044 mmol) were placed in a flask and purged with nitrogen. Toluene (0.5 mL) was added, and the reaction mixture was stirred at 80 °C for 3 h. The crude mixture was concentrated } \text{in vacuo and purified by flash chromatography (100% hexane) to yield } \text{the title compound (12.1 mg, 97%). Spectral data are consistent with the literature.} \(^7\)

**Potassium (3,3-diphenyl-2-(p-tolyl)allyl)trifluoroborate (2.47):**

The following procedure was a slight modification from the literature.\(^4\)

\[
\text{Compound 2.44 (48.4 mg, 0.118 mmol) was dissolved in acetonitrile (1 mL), and then saturated aqueous KHF}_2 \text{ (4.5 M, 105 µl, 0.472 mmol) was added dropwise. The reaction mixture was stirred at r.t. for 3 h. The solvent was removed } \text{in vacuo, and the residual solid was dried under high vacuum overnight. The resulting mixture was then extracted with hot acetonitrile, filtered, and concentrated } \text{in vacuo. Diethyl ether was added to the crude mixture, and it formed a suspension of white solid in the solution. The white solid was filtered off, washed thoroughly with diethyl ether and dried under vacuum (27.4 mg, 60%). mp > 280 °C; } \text{\(\text{^1H NMR (500 MHz, acetone-d}_6\)) } \delta 7.51 – 7.47 \text{ (m, 2H), 7.22 – 7.17 \text{ (m, 2H), 7.12 – 7.07 \text{ (m, 1H), 7.06 – 7.01 \text{ (m, 2H), 6.94 – 6.89 \text{ (m, 2H), 6.88 – 6.77 \text{ (m, 5H), 2.16 \text{ (s, 3H), 1.71 – 1.65 \text{ (m, 2H); } \text{^13C NMR (126 MHz, acetone-d}_6\)) } \delta 146.7, 146.5, 146.2, 144.8, 134.3, 134.0, 132.3, 131.7, 130.7, 128.3, 128.0, 127.7, 125.9, 125.1, 21.1; } \text{^11B NMR (128 MHz, acetone-}}
\]
4,4'-((3,3-diphenylprop-2-ene-1,2-diyl)bis(methylbenzene) (2.48):

The following procedure was a slight modification from the literature.\(^8\)
Pd\(_2\)(dba)\(_3\) (3.57 mg, 3.89 \(\mu\)mol), sodium tert-butoxide (28.1 mg, 0.292 mmol), Ruphos (3.63 mg, 7.79 \(\mu\)mol) and trifluoroborate 3.57 (38 mg, 0.097 mmol) were placed in a flask and purged with nitrogen. Then toluene (1 mL), water (0.1 mL), and 1-bromo-4-methylbenzene (24 \(\mu\)l, 0.195 mmol) were added. The contents were stirred at 80 °C overnight. The reaction mixture was then concentrated in vacuo and purified by flash column chromatography (100% hexanes) to yield the title compound (8.4 mg, 23%) as a white solid. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.33 – 7.26 (m, 4H), 7.25 – 7.22 (m, 1H), 7.07 – 6.93 (m, 11H), 6.89 – 6.84 (m, 2H), 3.84 (s, 2H), 2.27 (s, 3H), 2.20 (s, 3H); \(^13\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 143.5, 143.3, 141.3, 139.2, 138.1, 137.3, 135.8, 135.2, 130.9, 129.9, 129.6, 129.0, 128.7, 128.6, 128.3, 127.6, 126.9, 126.0, 41.1, 21.3, 21.1; HRMS (EI+): Calcd for C\(_{29}\)H\(_{26}\) [M]\(^+\): 374, Found 374; TLC: 98:2 / Hexanes:EtOAc, \(R_f\) 0.41.
precipitate formed and was collected by vacuum filtration. This solid was washed with water (100 mL) and then dissolved in ethyl acetate (25 mL). The organic solution was washed with water (50 mL) and brine (50 mL), and then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to quantitatively provide either 1,1-Bis(4-ethoxyphenyl)methanone (0.624 g, 2.308 mmol) or 1,1-Bis(4-ethoxyphenyl)methanone (0.688 g, 2.306 mmol) as a white solid. All other ketones were purchased from Sigma Aldrich and used as received.

(1-Isobutyl-vinyl)-benzene:

Bromination of α-Methylstyrene was performed according to the literature procedure. Under nitrogen, in a 50 mL round-bottomed flask, isopropylmagnesium bromide (8.42 ml, 21.06 mmol) was added dropwise to (3-bromoprop-1-en-2-yl)benzene (3.32 g, 16.85 mmol) in THF (Volume: 16.85 mL) and stirred at room temperature for 24 hours. The reaction was quenched with water. The suspension of magnesium salt in the water layer was dissolved with a small addition of 6M hydrochloric acid and the product was extracted with diethyl ether (3 x 10mL). The combined organic layer was dried over anhydrous sodium sulfate and then the solvent was evaporated in vacuo. The product was purified by flash chromatography over 50g silica and eluted with hexane (Rf = 0.60) to afford (1-Isobutyl-vinyl)-benzene as a colorless liquid (1.84 g, 11.48 mmol, 68.2 % yield). 1H NMR and 13C NMR match the previously reported spectra. All other alkenes were purchased from Sigma Aldrich and used as received.

6.4.2. General Procedure for the Methyllithium Addition–Dehydration of Ketones (Table 3.1)

In a two-neck, 25 mL round-bottomed flask, the benzophenone derivative (1.210 mmol) was stirred in THF (12.0 mL) at room temperature. Methyllithium (1.6 M in diethyl ether, 0.832
mL, 1.331 mmol) was added dropwise to the vessel and stirring was continued for 5 minutes. The reaction was quenched with saturated ammonium chloride (10 mL) and the product was extracted with diethyl ether (3 x 5 mL). The organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure to quantitatively provide corresponding alcohol (quantitative yields).

The alcohol was generally pure and used directly. In a 10 mL round-bottom flask, the 1,1-diphenylethanol derivative (1.197 mmol) was dissolved in toluene (2.0 mL) at room temperature. Then, 4-methylbenzenesulfonic acid (0.041 g, 0.239 mmol) was added to the flask and the reaction was heated to 80°C. After 4-6 hours, when the reaction was deemed complete by TLC, the solution was quenched with saturated sodium bicarbonate (10 mL). The product was extracted with diethyl ether (3 x 5 mL). The organic layer was then washed with water (20 mL) and brine (20 mL), and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the product was eluted from a silica plug with hexanes to provide desired alkenes (83-97% yields).

6.4.3. **General Procedure for the Synthesis of gem-Dibromocyclopropanes (Table 3.2)**

The following procedure was a slight modification from the literature. Alkene (1 equiv.) were dissolved in methylene chloride and added to a round-bottomed flask containing bromoform (1.5 equiv.), and triethylbenzylammonium chloride (0.2 equiv.). A solution of 25 M sodium hydroxide was added dropwise to keep the reaction temperature below 50 °C. The solution was stirred vigorously at 40 – 45 °C overnight. After the reaction mixture was cooled to room temperature, water was added to quench the reaction. The crude material was extracted with methylene chloride. The organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The 1,1-dibromocyclopropanes 3.32-3.38 were purified by column chromatography, eluting with hexanes/EtOAc (70-92% yields).
6.4.4. General Procedure for the Synthesis of Allenes (Table 3.2)

The following procedure was a slight modification from the literature. To a stirred solution of 1,1-dibromocyclopropane (1 equiv.) in dry THF was added ethyl magnesium bromide (0.9 M in THF, 1.7 equiv.) under nitrogen. The contents were stirred at room temperature for 0.5 h. The reaction was quenched with 6 M hydrochloric acid. The resulting mixture was extracted with ethyl acetate. The organic layer was washed with water, dried over magnesium sulfate, filtered, concentrated in vacuo, and purified by column chromatography to yield the allenes 3.39-3.45 (75-94%).

6.4.5. Temperature Calibration of 600 MHz Instrument

Several proton VT NMR spectra were acquired of HPLC grade methanol. The following equation is used to calculate the corrected temperature:

\[
\text{Corrected Kelvin} = 403 - 29.46(\Delta\delta) - 23.832(\Delta\delta)^2
\]

(Eq. 6.1)

where, \(\Delta\delta\) is the measured difference between the OH signal and the CH\(_3\) signal. A standard linear regression analysis provides a calibration curve for correcting the NMR study temperatures (Figure 6.1) with an error in corrected temperatures of \(\pm 0.34\) K.

![Low Temperature Calibration of 600 mHz NMR with MeOH](image)

**Figure 6.1.** Linear Regression Curve for Low Temperature Calibration of the 600 mHz NMR with neat MeOH.
### 6.4.6. Complete Line Shape Analysis of VT NMR Spectra

#### Linear Regression Analysis for Eyring Plot

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#### Regression Statistics

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Observations   13  

#### ANOVA

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### Regression Statistics

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- R Square: 0.995338
- Adjusted R Square: 0.994914
- Standard Error: 0.133778
- Observations: 13

### ANOVA

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6.4.7. Characterizations of Compounds

1,1-Bis(4-ethoxyphenyl)ethyline (3.27):

Compound 3.27 was synthesized according to General Procedure 6.4.2. White solid; mp 142 – 143 °C (lit.13 mp 142 °C); 1H NMR, 13C NMR, and MS match the previously reported spectra.14 TLC: 95:5 / Hexanes:EtOAc, Rf 0.43.

1,1-Bis(4-propoxyphenyl)ethyline (3.28):

Compound 3.28 was synthesized according to General Procedure 6.4.2. White solid; mp 133 – 134 °C (lit.13 mp 134 °C); 1H NMR (400 MHz, CDCl3) δ 7.29 – 7.24 (m, 4H), 6.90 – 6.81 (m, 4H), 5.28 (s, 2H), 3.94 (t, J = 6.6 Hz, 4H), 1.81 – 1.73 (m, 4H), 1.05 (t, J = 7.4, 6H); 13C NMR (101 MHz, cdcl3) δ 10.5, 22.6, 69.5, 111.4, 114.0, 129.4, 134.1, 149.1, 158.8; TLC: 95:5 / Hexanes:EtOAc, Rf 0.48.

1,1-Bis(4-biphenylyl)ethyline (3.29):

Compound 3.29 was synthesized according to General Procedure 6.4.2. White solid; mp 210 – 211 °C (lit.15 mp 211 °C); 1H NMR (400 MHz, CDCl3) δ 7.65 – 7.58 (m, 8H), 7.50 – 7.42 (m, 8H), 7.39 – 7.33 (m, 2H), 5.55 (s, 2H); 13C NMR (101 MHz, CDCl3) δ 114.3, 126.9, 127.0, 127.3, 128.7, 128.8, 140.3, 140.6, 140.7; TLC: 90:10 / Hexanes:DCM, Rf 0.26.

1,1-Bis(4-fluorophenyl)ethyline (3.30):

Compound 3.30 was synthesized according to General Procedure 6.4.2. White solid; mp 47 – 48 °C (lit.16 48 °C); 1H NMR (400 MHz, CDCl3) δ 7.34 – 7.27 (m, 4H), 7.06 – 6.99 (m, 4H), 5.40 (s, 2H); 13C NMR (101 MHz, CDCl3) δ 113.9 –
114.3 (m), 115.1 (d, $J = 21.3$ Hz), 129.8 (d, $J = 7.8$ Hz), 137.3 (d, $J = 3.6$ Hz), 148.0, 161.3, 163.8; TLC: 100% Hexanes $R_f$ 0.45.

1,1-Bis(3-(trifluoromethyl)phenyl)ethylene (3.31):

$$\begin{align*}
\text{F}_3\text{C} & \quad \begin{array}{c}
\text{Br} \\
\text{Br}
\end{array} \\
\text{O} & \quad \begin{array}{c}
\text{O}
\end{array} \\
\text{Ph} & \quad \begin{array}{c}
\text{Ph}
\end{array}
\end{align*}$$

Compound 3.31 was synthesized according to General Procedure 6.4.2. Colorless oil. $^1$H NMR, $^{13}$C NMR and MS match the previously reported spectra.$^{17}$ TLC: 100% Hexanes $R_f$ 0.45.

4,4’-(2,2-dibromocyclopropane-1,1-diyl)bis(ethoxybenzene) (3.32):

$$\begin{align*}
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\text{Br}
\end{array} \\
\text{O} & \quad \begin{array}{c}
\text{O}
\end{array} \\
\text{Ph} & \quad \begin{array}{c}
\text{Ph}
\end{array}
\end{align*}$$

Compound 3.32 was synthesized according to General Procedure 6.4.3. White solid; mp 122.5 – 124 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.40 – 7.35 (m, 4H), 6.85 – 6.79 (m, 4H), 3.98 (q, $J = 7.0$ Hz, 4H), 2.40 (s, 2H), 1.37 (t, $J = 7.0$ Hz, 6H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 14.8, 34.5, 35.3, 43.8, 63.3, 114.2, 130.1, 134.3, 157.9; TLC: 90:10 / Hexanes:EtOAc, $R_f$ 0.40.

4,4’-(2,2-dibromocyclopropane-1,1-diyl)bis(propoxybenzene) (3.33):

$$\begin{align*}
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\text{Br}
\end{array} \\
\text{O} & \quad \begin{array}{c}
\text{O}
\end{array} \\
\text{Ph} & \quad \begin{array}{c}
\text{Ph}
\end{array}
\end{align*}$$

Compound 3.33 was synthesized according to General Procedure 6.4.3. White solid; mp 93.5 – 95 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.41 – 7.35 (m, 4H), 6.86 – 6.80 (m, 4H), 3.87 (t, $J = 6.5$ Hz, 4H), 2.40 (s, 2H), 1.81 – 1.73 (m, 4H), 1.00 (t, $J = 7.4$ Hz, 6H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 10.5, 22.5, 34.5, 35.4, 43.8, 69.4, 114.3, 130.0, 134.3, 158.1; TLC: 95:5 / Hexanes:EtOAc, $R_f$ 0.35.

4,4”-(2,2-dibromocyclopropane-1,1-diyl)di-1,1’-biphenyl (3.34):

$$\begin{align*}
\text{Br} & \quad \begin{array}{c}
\text{Br}
\end{array} \\
\text{Ph} & \quad \begin{array}{c}
\text{Ph}
\end{array}
\end{align*}$$

Compound 3.34 was synthesized according to General Procedure 6.4.3. White solid; mp 200 – 202 °C; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.64 – 7.60 (m, 8H), 7.59 – 7.54 (m, 8H), 7.44 – 7.39 (m, 4H), 7.36 – 7.31 (m, 2H), 2.55
(s, 2H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 33.9, 34.6, 44.6, 127.0, 127.2, 127.4, 128.7, 129.6, 140.2, 140.5, 140.8; TLC: 75:25 / Hexanes:DCM, $R_f$ 0.30.

**4,4'-(2,2-dibromocyclopropane-1,1-diyl)bis(fluorobenzene) (3.35):**

![Chemical structure](image)

Compound **3.35** was synthesized according to General Procedure 6.4.3. White solid; mp 127 – 128 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.47 – 7.41 (m, 4H), 7.04 – 6.97 (m, 4H), 2.43 (s, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 33.4, 34.8, 43.6, 115.4, 115.5 (d, $J$ = 21.8 Hz), 130.7 (d, $J$ = 8.5 Hz), 137.5 (d, $J$ = 4.3 Hz), 160.6, 163.1; TLC: 95:5 / Hexanes:EtOAc, $R_f$ 0.35.

**3,3'-(2,2-dibromocyclopropane-1,1-diyl)bis((trifluoromethyl)benzene) (3.36):**

![Chemical structure](image)

Compound **3.36** was synthesized according to General Procedure 6.4.3. White solid; mp 122 – 123 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.77 – 7.70 (m, 4H), 7.56 – 7.45 (m, 4H), 2.54 (s, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 31.63, 34.68, 44.29, 122.37, 124.59 (q, $J$ = 3.8 Hz), 125.9 (q, $J$ = 3.8 Hz), 129.2, 131.1 (d, $J$ = 32.5 Hz), 132.7 (q, $J$ = 1.3 Hz), 142.0; TLC: 95:5 / Hexanes:EtOAc, $R_f$ 0.38.

**2,2'-(2,2-dibromocyclopropane-1,1-diyl)bis(methylbenzene) (3.37):**

![Chemical structure](image)

Compound **3.37** was synthesized according to General Procedure 6.4.3. White solid; mp 141 – 142 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.80 (s, br, 2H), 7.25 – 7.10 (m, 6H), 2.53 (s, 6H), 2.49 (s, br, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 21.83, 35.14, 37.07, 41.97, 124.72, 127.48, 131.25, 131.58, 137.34, 138.58; TLC: 100% Hexanes, $R_f$ 0.31.
(2,2-dibromo-1-isobutylcyclopropyl)benzene (3.38):

Compound 3.38 was synthesized according to General Procedure 6.4.3. White solid; mp 28.5 – 30 °C; 1H NMR (400 MHz, CDCl3) δ 7.44 – 7.26 (m, 5H), 2.44 – 2.34 (m, 2H), 2.27 (d, J = 7.5 Hz, 1H), 1.84 (d, J = 7.5 Hz, 1H), 1.42 (dd, J = 13.2, 10.3 Hz, 1H), 1.34 (m, 1H), 0.90 (d, J = 6.3 Hz, 3H), 0.85 (d, J = 6.3 Hz, 3H). 13C NMR (101 MHz, CDCl3) δ 21.3, 23.7, 27.2, 33.4, 36.3, 38.4, 48.7, 127.1, 128.2, 128.9, 140.7; TLC: 100% Hexanes, Rf 0.57.

4,4'-(propa-1,2-diene-1,1-diyl)bis(ethoxybenzene) (3.39):

Compound 3.39 was synthesized according to General Procedure 6.4.4. Beige solid; mp 70.5 – 72 °C; 1H NMR (400 MHz, CDCl3) δ 7.26 (dd, J = 6.4, 2.3 Hz, 5H), 6.90 – 6.83 (m, 4H), 5.21 (s, 2H), 4.05 (q, J = 7.0 Hz, 4H), 1.42 (t, J = 7.0 Hz, 6H); 13C NMR (101 MHz, CDCl3) δ 78.4, 107.5, 115.3, 115.5, 129.8, 129.9, 132.0, 132.1, 160.9, 163.3, 209.5; HRMS (ESI+): Calcd for C19H21O2 [M+H]+: 281.1536, Found 281.1548; TLC: 95:5 / Hexanes:EtOAc, Rf 0.34.

4,4'-(propa-1,2-diene-1,1-diyl)bis(propoxybenzene) (3.40):

Compound 3.40 was synthesized according to General Procedure 6.4.4. Yellow solid, mp 59 – 60.5 °C; 1H NMR (400 MHz, CDCl3) δ 7.33 – 7.23 (m, 4H), 6.97 – 6.83 (m, 4H), 5.22 (s, 2H), 3.95 (t, J = 6.6 Hz, 4H), 1.83 (sex, J = 7.1 Hz, 4H), 1.06 (t, J = 7.4 Hz, 6H); 13C NMR (101 MHz, CDCl3) δ 10.5, 22.6, 69.5, 77.6, 108.2, 114.4, 128.5, 129.4, 158.4, 209.4; HRMS (ESI+): Calcd for C21H25O2 [M+H]+: 309.1849, Found 309.1862; TLC: 95:5 / Hexanes:EtOAc, Rf 0.45.
4,4''-(propa-1,2-diene-1,1-diyl)di-1,1'-biphenyl (3.41):

Compound 3.41 was synthesized according to General Procedure 6.4.4. White solid; mp 150 – 151 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.65 – 7.58 (m, 8H), 7.50 – 7.42 (m, 8H), 7.38 – 7.32 (m, 2H), 5.34 (s, 1H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 78.4, 108.7, 127.1, 127.2, 127.4, 128.8, 128.9, 135.2, 140.2, 140.8, 210.1; HRMS (Mixed EIC): Calcd for C$_{27}$H$_{21}$ [M+H]$^+$: 345.1638, Found 345.1643; TLC: 80:20 / Hexanes:DCM, R$_f$ 0.35.

4,4'-(propa-1,2-diene-1,1-diyl)bis(fluorobenzene) (3.42):

Compound 3.42 was synthesized according to General Procedure 6.4.4. White solid; mp 68 – 69 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.33 – 7.27 (m, 4H), 7.07 – 7.01 (m, 4H), 5.26 (s, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 78.4, 107.5, 115.4 (d, $J$ = 21.5 Hz), 129.9 (d, $J$ = 8.0 Hz) 132.04 (d, $J$ = 3.4 Hz), 160.9, 163.3, 209.5; HRMS (APCI+): Calcd for C$_{15}$H$_{11}$F$_2$ [M+H]$^+$: 229.0823, Found 229.0823; TLC: 100% Hexanes, R$_f$ 0.43.

3,3'-(propa-1,2-diene-1,1-diyl)bis((trifluoromethyl)benzene) (3.43):

Compound 3.43 was synthesized according to General Procedure 6.4.4. Yellow, viscous oil; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.63 – 7.46 (m, 8H), 5.40 (s, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 42.0, 79.6, 122.6, 124.3 (q, $J$ = 3.8 Hz), 125.0 (q, $J$ = 3.8 Hz), 129.0, 131.1 (d, $J$ = 32.3 Hz), 131.4 (q, $J$ = 1.3 Hz), 136.5, 210.0; TLC: 100% Hexanes, R$_f$ 0.45.

2,2'-(propa-1,2-diene-1,1-diyl)bis(methylbenzene) (3.44):

Compound 3.44 was synthesized according to General Procedure 6.4.4. White solid; mp 74.5 – 76 °C; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.22 – 7.06 (m, 8H), 5.03
(s, 2H), 2.26 (s, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 20.6, 76.0, 106.3, 125.9, 127.2, 129.5, 130.7, 136.5, 136.9, 209.1; TLC: 100% Hexanes, R$_f$ 0.43.

**[(5-methylhexa-1,2-dien-3-yl)benzene (3.45):]**

Compound **3.45** was synthesized according to General Procedure 6.4.4.

Colorless liquid; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.41 – 7.36 (m, 2H), 7.33 – 7.27 (m, 2H), 7.20 – 7.15 (m, 1H), 5.02 (t, $J$ = 2.8 Hz, 2H), 2.30 (dt, $J$ = 7.0, 2.8 Hz, 2H), 1.85 (dp, $J$ = 13.4, 7.0 Hz, 1H), 0.96 (d, $J$ = 6.3 Hz, 3H), 0.94 (d, $J$ = 6.3 Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 22.6, 26.8, 39.3, 77.1, 103.8, 126.1, 126.5, 128.3, 136.5, 209.2; TLC: 100% Hexanes, R$_f$ 0.57.

**2,2'-(2-bromocyclopropane-1,1-diyl)bis(methylbenzene) (3.37b):**

Compound **3.37b** was prepared from **3.37** following literature precedent.$^{12}$

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.52 (ddd, $J$ = 7.1, 5.1, 1.6 Hz, 2H), 7.22 – 7.08 (m, 5H), 7.04 (ddt, $J$ = 7.1, 1.6, 0.7 Hz, 1H), 3.97 (dd, $J$ = 8.0, 4.4 Hz, 1H), 2.33 (s, 3H), 2.28 (s, 3H), 1.96 (dd, $J$ = 6.3, 4.4 Hz, 1H), 1.58 ((dd, $J$ = 6.3, 4.4 Hz, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 20.8, 21.7, 23.2, 28.0, 29.7, 30.3, 124.9, 125.0, 127.0, 127.3, 130.1, 131.1, 131.1, 131.7, 137.2, 139.0, 139.5, 139.7.

**2,2'-(cyclopropane-1,1-diyl)bis(methylbenzene) (3.37c):**

The following procedure for synthesizing compound **3.37c** was a slight modification from the literature.$^{12}$

$n$-Butyllithium (1.6 M in Hexanes, 0.11mL, 0.179 mmol) was added to a solution of **3.37b** (0.036g, 0.120 mmol) in dry THF (0.239mL) at −78 °C and stirred for 30 minutes. Methanol was slowly added to the solution and it was warmed to 0 °C before quenching with water. The product was extracted with diethyl ether and eluted from a silica plug with hexanes to provide 0.021g (0.094 mmol) of **3.37c** as a white
solid. $^1$H NMR (600 MHz, CDCl$_3$) δ 7.57 (dd, $J = 7.7$, 1.4 Hz, 2H), 7.16 (tdd, $J = 7.7$, 1.6, 0.8 Hz, 2H), 7.11 (td, $J = 7.4$, 1.6 Hz, 2H), 7.07 – 7.03 (m, 2H), 2.36 (s, 6H), 1.27 (s, 4H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 13.8, 21.1, 29.1, 29.7, 30.4, 124.9, 126.4, 130.5, 130.8, 139.5, 141.5.

6.4.8. Other Allenes

**buta-2,3-dien-2-ylbenzene:**

The title compound and the corresponding 1,1-dibromocyclopropyl intermediate were synthesized according to General Procedures 6.4.3 and 6.4.4., respectively. Spectral data are consistent with the literature.$^{12}$

**propa-1,2-diene-1,1-diyldibenzene:**

The title compound and the corresponding 1,1-dibromocyclopropyl intermediate were synthesized according to General Procedures 6.4.3 and 6.4.4., respectively. Spectral data are consistent with the literature.$^{18}$

**4,4'-(propa-1,2-diene-1,1-diyl)bis(methylbenzene):**

The title compound and the corresponding 1,1-dibromocyclopropyl intermediate were synthesized according to General Procedures 6.4.3 and 6.4.4., respectively. Spectral data are consistent with the literature.$^{11}$

**4,4'-(propa-1,2-diene-1,1-diyl)bis(chlorobenzene):**

The title compound and the corresponding 1,1-dibromocyclopropyl intermediate were synthesized according to General Procedures 6.4.3 and 6.4.4., respectively. Spectral data are consistent with the literature.$^{11}$
4,4’-(propa-1,2-diene-1,1-diyl)bis(methoxybenzene) (3.43g):

The title compound and the corresponding 1,1-dibromocyclopropyl intermediate were synthesized according to General Procedures 6.4.3 and 6.4.4., respectively. Spectral data are consistent with the literature.11

6.5. Synthetic Procedures and Characterizations for Chapter 4

6.5.7. General Procedures for the Synthesis of Acetylenic Ester Substrates

General Procedure 1:

\[
\begin{align*}
R^1 \equiv & \quad 1. \text{^7BuLi, THF,} \\
& -78 \degree C, 30 \text{ min} \\
\quad & 2. \text{Cl} \quad \text{O} \\
& -78 \degree C \text{ to rt, } 24 \text{ h} \\
\end{align*}
\]

Dry THF (5.98 mL, 0.612 M) and non-1-yne (600 µL, 3.66 mmol, 1.0 equiv.) were cooled to \(-78 \degree C\) using a dry ice-acetone cold bath. Next, \(n\)-butyllithium (1.54 mL of 2.5 M in hexanes, 3.84 mmol, 1.05 equiv.) was added dropwise to the flask and allowed to stir for 30 minutes. To the flask, ethyl carbonochloridate (361 µL, 3.66 mmol, 1.0 equiv) was then slowly added dropwise. The reaction temperature was held at \(-78 \degree C\) for 8-9 hours and allowed to warm to room temperature overnight. The reaction was quenched with saturated aqueous ammonium chloride (30 mL) and extracted with hexanes (3 x 5 mL). The organic layer was then washed with DI water (5 x 10 mL), dried over sodium sulfate, filtered, and concentrated \textit{in vacuo}. Column chromatography was used to purify the product, eluting with hexanes and ethyl acetate.
General Procedure 2:

\[
\text{Hex-2-ynoic acid (500 mg, 4.46 mmol, 1.3 equiv.) in methylene chloride (32.4 mL, 0.1 M), but-2-yn-1-ol (0.26 mL, 3.43 mmol, 1.0 equiv.) was added followed by the solution of 4-Dimethylaminopyridine (41.9 mg, 0.343 mmol, 0.1 equiv.) in methylene chloride (1.8 mL, 0.2 M). The solution was cooled to 0 °C and stirred for 15 minutes prior to the addition of } N,N'-
\text{Dicyclohexylcarbodiimide (0.751 mL, 4.80 mmol, 1.4 equiv.). The consumption of the starting material was monitored by TLC. After 6 hours, the reaction mixture was filtered through}
\]
a short plug of silica, which was rinsed with hexanes (3 x 10 mL). The filtrate was concentrated in vacuo to provide the final product as a colorless liquid in a 93% yield.

6.5.8. General Procedures for the Synthesis of Acetylenic Amide Substrates

**General Procedure 4:**

![Diagram]

Dry THF (27.2 mL, 0.2 M), methyl non-2-ynoate (1.0 mL, 5.44 mmol, 1.0 equiv.), and N,O-dimethylhydroxylamine (997 mg, 16.32 mmol, 3.0 equiv.) were cooled to -20 °C using a sodium chloride ice bath and kept cold for 1 hour prior to the dropwise addition of isopropyl magnesium chloride (12.0 mL of 2 M in diethyl ether, 24.0 mmol, 4.4 equiv.). The consumption of the starting material was monitored by TLC. The reaction was quenched with saturated aqueous ammonium chloride (20 mL). The mixture was extracted with diethyl ether (3 x 10 mL). The combined extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The product was purified using column chromatography, eluting with hexanes and ethyl acetate.

**General Procedure 5:**

![Diagram]

Dry THF (10 mL, 0.5 M) and oct-1-yne (500 mg, 4.54 mmol, 1.0 equiv.) were cooled to -78 °C using a dry ice-acetone cold bath. Next, n-butyllithium (1.8 mL of 2.5 M in hexanes, 4.50 mmol, 1.0 equiv.) was added dropwise to the flask and allowed to stir 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 °C for 6 hours and allowed to warm to room temperature overnight. The reaction was quenched with DI water (10 mL) and extracted with hexanes (10 x 3 mL). The organic layer was then washed with DI water (5 x 15 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. Column chromatography was used to purify the product, eluting with hexanes and diethyl ether (4c) or hexanes and ethyl acetate.

**General Procedure 6:**

\[ \text{HO} \quad \text{1. TEA, Pivaloyl Chloride, DCM, 0 °C} \]
\[ \text{\quad 2. } R^1 \quad R^2 \quad \text{TEA, DCM, 0 °C to rt, overnight} \]

Dry methylene chloride (45.3 mL, 0.1 M) and hexynoic acid (0.50 mL, 4.53 mmol, 1.0 equiv.) were cooled to 0 °C. Triethylamine (0.63 mL, 4.53 mmol, 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, 4.98 mmol, 1.1 equiv.). The consumption of starting material was monitored by TLC. Triethylamine (917 mg, 9.06 mmol, 2.0 equiv.) was added dropwise to a separate nitrogen-purged flask containing dry DCM (45.3 mL, 0.1 M) and methyl D-proline hydrochloride (585 mg, 4.53 mmol, 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. DI water (15 mL) was used to quench the reaction. Subsequently, the product(s) were extracted with methylene chloride (3 x 10 mL). The organic layer was then washed with DI water (2 x 10 mL), 10% NaOH (3 x 10 mL) and brine. The extract was dried over sodium sulfate, filtered, and concentrated in vacuo. Column chromatography was used to purify the
product, eluting with hexane and ethyl acetate. The resulting product was > 97% pure and used as is for the β-borylation reaction.

**General Procedure 7: 19**

![Chemical Structure](image)

Methyl non-2-ynoate (600 mg, 3.57 mmol, 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, 267 mmol, 75 equiv.) was added dropwise and allowed to stir at room temperature for 6 h (17 h, when \( R_1 = \text{CH}_3 \)). The consumption of the starting material was monitored by TLC. The aqueous based solvent from the crude reaction mixture was concentrated *in vacuo* to provide an off-white colored solid. The mixture was dissolved in ethyl acetate and rinsed with DI water (3 x 10 mL). The combined extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The solid was solubilized in a minimal amount of diethyl ether at room temperature then hexanes was added slowly until the solution became cloudy. The crude solution was sealed with parafilm and stored at 5 °C overnight. The precipitate was filtered and the obtained crystals were washed with cold hexanes. After being dried on high vacuum, the final product was obtained as white crystals.

6.5.9. **General Procedure for the β-Borylation of Alkynoates (Tables 4.2-4.3)**

In a 2 dram vial were pinB—Bdan 4.7 (153 mg, 0.520 mmol, 1.0 equiv.), 4-picoline (2.55 \( \mu \)L, 0.026 mmol, 0.05 equiv.) and ethyl but-2-ynoate (66 \( \mu \)L, 0.625 mmol, 1.2 equiv.). Then, 0.5 mL of 2.6 mg/mL CuSO₄ stock solution (prepared with Milli-Q water), 0.4 mL of Milli-Q water, and 0.1 mL of 200 proof ethanol (9:1 ratio, 0.52 M) were added down the sides of the reaction vessel. Care was taken to ensure that solid reagents were not splashed on the sides of the vial. The
reaction mixture was heated to 50 °C and stirred vigorously. The reaction was monitored for completion by TLC. In many cases, the product and borylating reagent exhibited the same Rf; therefore, GC-MS was used to determine complete consumption of the borylating reagent in these cases. After the reaction was found to be complete, 2 mL of ethyl acetate was added to quench the reaction. The product was extracted using ethyl acetate (3 x 10 mL). The combined extracts were then washed with DI water (7 x 10 mL) and brine. The organic layer was dried over sodium sulfate, filtered, and concentrated in vacuo. Column chromatography was used to purify the borylated product, eluting with hexanes and ethyl acetate.

6.5.10. General Procedure for the β-Borylation of Alkynamides (Tables 4.4-4.5)

In a 2 dram vial were pinB—Bdan 4.7 (183 mg, 0.624 mmol, 1.2 equiv.), 4-picoline (2.55 μL, 0.026 mmol, 0.05 equiv.), N-methoxy-N-methylene-2-ynamide (103 mg, 0.520 mmol, 1.0 equiv.). Then, 0.5 mL of 2.6 mg/mL CuSO4 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 reaction vessel. Care was taken to ensure that solid reagents were not splashed on the sides of the vial. The reaction mixture 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 Rf; therefore, GC-MS was used to determine the complete consumption of the starting material in these cases. After the reaction was found to be complete, 2 mL of ethyl acetate was added to quench the reaction. The product(s) were extracted using ethyl acetate (3 x 10 mL). The combined extracts were then washed with DI water (7 x 10 mL) and brine. The organic layer was dried over sodium sulfate, filtered, and concentrated in vacuo. Column chromatography was used to purify the borylated product(s), eluting with hexanes and ethyl acetate (4.24-4.35) or diethyl ether and ethyl acetate (4.36-4.38).
6.5.11. Characterization of the Substrates

**Ethyl dec-2-ynoate:**

Synthesized according to general procedure 1. The title compound was isolated in a 96% yield as a yellow liquid. $^1$H and $^{13}$C NMR are consistent with literature.$^{20}$ TLC: 100% Hexanes, R$_f$ 0.33.

**Ethyl 4,4-dimethylpent-2-ynoate:**

Synthesized according to general procedure 1. The title compound was isolated in a 66% yield as a colorless liquid; bp 182.7 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 4.20 (q, $J = 7.1$ Hz, 2H), 1.29 (t, $J = 7.1$ Hz, 3H), 1.27 (s, 9H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 154.3 (C), 96.5 (C), 72.0 (C), 61.9 (CH$_2$), 30.1 (CH$_3$), 27.6 (C), 14.2 (CH$_3$); HRMS (APCI+): Calcd for C$_9$H$_{14}$O$_2$ [M+H]$^+$: 155.1067, Found 155.1059; TLC: 100% Hexanes, R$_f$ 0.31.

**Ethyl 3-cyclopropylpropiolate:**

Synthesized according to general procedure 1. The title compound was isolated in an 87% yield as a yellow liquid; bp 148.9 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 4.15 (q, $J = 7.1$ Hz, 2H), 1.39 – 1.28 (m, 1H), 1.25 (t, $J = 7.1$ Hz, 3H), 0.93 – 0.81 (m, 4H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 153.9 (C), 93.1 (C), 68.6 (C), 61.8 (CH$_2$), 14.1 (CH$_3$), 9.3 (CH$_2$), -0.5 (CH); HRMS (APCI+): Calcd for C$_8$H$_{11}$O$_2$ [M+H]$^+$: 139.0754, Found 139.0753; TLC: 19:1 / Hexanes:EtOAc, R$_f$ 0.35.

**Ethyl 3-cyclopentylpropiolate:**

Synthesized according to general procedure 1. The title compound was isolated in a 61% yield as a colorless liquid; bp 207.1 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 4.18 (q, $J = 7.1$ Hz, 2H), 2.74 – 2.67 (m, 1H), 1.94 – 1.89
(m, 2H), 1.75 – 1.61 (m, 4H), 1.60 – 1.49 (m, 2H), 1.27 (t, J = 7.1 Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 154.1 (C), 93.4 (C), 72.8 (C), 61.8 (CH$_2$), 33.1 (CH$_2$), 29.8 (CH), 25.3 (CH$_2$), 14.2 (CH$_3$); HRMS (APCI+): Calcd for C$_{10}$H$_{15}$O$_2$ [M+H]$^+$: 167.1067, Found 167.1065; TLC: 19:1 / Hexanes:EtOAc, R$_f$ 0.41.

**Ethyl 3-cyclohexylpropionate:**

Synthesized according to general procedure 1. The title compound was isolated in a 63% yield as a colorless oil; bp 249.8 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 4.21 (q, J = 7.1 Hz, 2H), 2.55 – 2.46 (m, 1H), 1.88 – 1.80 (m, 2H), 1.76 – 1.67 (m, 2H), 1.55 – 1.46 (m, 3H), 1.35 – 1.27 (m, 3H), 1.30 (t, J = 7.1 Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 154.2 (C), 93.0 (C), 73.2 (C), 61.9 (CH$_2$), 31.6 (CH$_2$), 29.0 (CH), 25.7 (CH$_2$), 24.8 (CH$_2$), 14.2 (CH$_3$); HRMS (ESI+): Calcd for C$_{11}$H$_{17}$O$_2$ [M+H]$^+$: 180.1150, Found 180.1119; TLC: 9:1 / Hexanes:EtOAc, R$_f$ 0.58.

**Ethyl 3-(cyclohex-1-en-1-yl)propionate:**

Synthesized according to general procedure 1. The title compound was isolated in a 78% yield as a yellow liquid. $^1$H and $^{13}$C NMR are consistent with literature.$^{20}$ TLC: 19:1 / Hexanes:EtOAc, R$_f$ 0.44.

**Ethyl 4-phenoxybut-2-ynoate:**

Synthesized according to general procedure 1. The title compound was isolated in a 55% yield as a white solid. $^1$H and $^{13}$C NMR are consistent with literature.$^{21}$ TLC: 9:1 / Hexanes:EtOAc, R$_f$ 0.46.

**Phenyl hex-2-ynoate:**

Synthesized according to general procedure 2. The title compound was isolated in a 75% yield as a pale yellow liquid; bp 283.9 °C. $^1$H NMR
(400 MHz, CDCl$_3$) $\delta$ 7.42 – 7.36 (m, 2H), 7.30 – 7.23 (m, 1H), 7.15 – 7.12 (m, 2H), 2.38 (t, $J$ = 7.1 Hz, 2H), 1.71 – 1.60 (m, 2H), 1.05 (t, $J$ = 7.4 Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 152.2 (C), 150.3 (C), 129.6 (CH), 126.4 (CH), 121.6 (CH), 92.3 (C), 73.0 (C), 21.2 (CH$_2$), 20.9 (CH$_2$), 13.6 (CH$_3$); HRMS (APCI+): Calcd for C$_{12}$H$_{13}$O$_2$ [M+H]$^+$: 189.0910, Found 189.0902; TLC: 19:1 / Hexanes:EtOAc, $R_f$ 0.36.

**Isobutyl hex-2-ynoate:**

![Isobutyl hex-2-ynoate](image)

Synthesized according to general procedure 2. The title compound was isolated in an 86% yield as a pale yellow liquid; bp 219.1 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.93 (d, $J$ = 6.8 Hz, 2H), 2.31 (t, $J$ = 7.1 Hz, 2H), 2.02 – 1.92 (m, 1H), 1.66 – 1.55 (m, 2H), 1.00 (t, $J$ = 7.4 Hz, 3H), 0.94 (d, $J$ = 6.8 Hz, 6H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 154.2 (C), 89.4 (C), 73.4 (C), 71.9 (CH$_2$), 27.7 (CH), 21.2 (CH$_2$), 20.8 (CH$_2$), 19.2 (CH$_3$), 13.6 (CH$_3$); HRMS (APCI+): Calcd for C$_{10}$H$_{17}$O$_2$ [M+H]$^+$: 169.1223, Found 169.1217; TLC: 19:1 / Hexanes:EtOAc, $R_f$ 0.48.

**Allyl hex-2-ynoate:**

![Allyl hex-2-ynoate](image)

Synthesized according to general procedure 2. The title compound was isolated in a 67% yield as a yellow liquid; bp 208.9 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.98 – 5.87 (m, 1H), 5.30 – 5.25 (m, 1H), 5.39 – 5.32 (m, 1H), 4.65 (dt, $J$ = 5.9, 1.3 Hz, 2H), 2.31 (t, $J$ = 7.1 Hz, 2H), 1.67 – 1.56 (m, 2H), 1.0 (t, $J$ = 7.4 Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 153.7 (C), 131.4 (CH), 119.3 (CH$_2$), 90.0 (C), 73.2 (C), 66.4 (CH$_2$), 21.2 (CH$_2$), 20.8 (CH$_2$), 13.6 (CH$_3$); HRMS (APCI+): Calcd for C$_9$H$_{13}$O$_2$ [M+H]$^+$: 153.0910, Found 153.0901; TLC: 19:1 / Hexanes:EtOAc, $R_f$ 0.42.

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**But-2-yn-1-yl hex-2-ynoate:**

Synthesized according to general procedure 3. The title compound was isolated in an 80% yield as a colorless liquid; bp >235 °C (decomp). $^1$H NMR (400 MHz, CDCl$_3$) δ 4.71 (q, $^5$J = 2.4 Hz, 2H), 2.31 (t, $^1$J = 7.1 Hz, 2H), 1.85 (t, $^2$J = 2.4 Hz, 3H), 1.66 – 1.55 (m, 2H), 1.01 (t, $^1$J = 7.4 Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 153.4 (C), 90.9 (C), 84.3 (C), 73.0 (C), 72.7 (C), 54.2 (CH$_2$), 21.3 (CH$_2$), 21.0 (CH$_2$), 13.8 (CH$_3$), 4.0 (CH$_3$); HRMS (APCI+): Calcd for C$_{10}$H$_{13}$O$_2$ [M+H]$^+$: 165.0910, Found 165.0907; TLC: 19:1 / Hexanes:EtOAc, R$_f$ 0.38.

**N-Methoxy-N-methylnon-2-ynamide:**

Synthesized according to general procedure 4. The title compound was isolated in a 90% yield as a pale yellow oil. $^1$H and $^{13}$C NMR are consistent with the literature. $^{22}$ TLC: 4:1 / Hexanes:EtOAc, R$_f$ 0.40.

**N-Methoxy-N-methylbut-2-ynamide:**

Synthesized according to general procedure 4. The title compound was isolated in a 55% yield as a colorless oil. $^1$H and $^{13}$C NMR are consistent with the literature. $^{23}$ TLC: 3:2 / Hexanes:EtOAc, R$_f$ 0.34.

**N,N-Dimethylhex-2-ynamide:**

Synthesized according to general procedure 5. The title compound was isolated in a 91% yield as a pale yellow oil; bp <210 °C (decomp). $^1$H NMR (400 MHz, CDCl$_3$) δ 3.19 (s, 3H), 2.95 (s, 3H), 2.33 (t, $^1$J = 7.1 Hz, 2H), 1.60 (m, 2H), 1.01 (t, $^1$J = 7.3 Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 155.0 (C), 93.1 (C), 74.3 (C), 38.5 (CH$_3$), 34.2 (CH$_3$), 21.5 (CH$_2$), 21.0 (CH$_2$), 13.7 (CH$_3$); HRMS (ESI+): Calcd for C$_8$H$_{14}$NO [M+H]$^+$: 140.1070, Found 140.1075; TLC: 7:3 / Hexanes:EtOAc, R$_f$ 0.26.
**N,N-Dimethylnon-2-ynamide:**

Synthesized according to general procedure 5. The title compound was isolated in a 78% yield as a yellow oil. \(^1\)H and \(^{13}\)C NMR are consistent with the literature.\(^{19}\) TLC: 1:1 / Hexanes:EtOAc, R\(_f\) 0.18.

**N,N-4,4-Tetramethylpent-2-ynamide:**

Synthesized according to general procedure 5. The title compound was isolated in a 68% yield as an off-white solid; mp 64.0 – 64.8 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 3.17 (s, 3H), 2.94 (s, 3H), 1.27 (s, 9H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 155.0 (C), 100.3 (C), 72.7 (C), 38.5 (CH\(_3\)), 34.2 (CH\(_3\)), 30.3 (CH\(_3\)), 27.8 (C); HRMS (ESI\(^+\)): Calcd for C\(_9\)H\(_{16}\)NO [M+H]\(^+\): 154.1226, Found 154.1222; TLC: 3:2 / Hexanes:EtOAc, R\(_f\) 0.39.

**3-Cyclopentyl-N,N-dimethylpropiolamide:**

Synthesized according to general procedure 5. The title compound was isolated in an 85% yield as a light brown liquid; bp >250 °C (decomp). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 3.16 (s, 3H), 2.93 (s, 3H), 2.75 (p, \(J\) = 7.3 Hz, 1H), 2.00 – 1.88 (m, 2H), 1.77 – 1.62 (m, 4H), 1.61 – 1.53 (m, 2H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 155.0 (C), 97.1 (C), 73.6 (C), 38.4 (CH\(_3\)), 34.1 (CH\(_3\)), 33.3 (CH\(_2\)), 30.1 (CH), 25.1 (CH\(_2\)); HRMS (ESI\(^+\)): Calcd for C\(_{10}\)H\(_{16}\)NO [M+H]\(^+\): 166.1226, Found 166.1227; TLC: 3:2 / Hexanes:EtOAc, R\(_f\) 0.34.

**3-Cyclohexyl-N,N-dimethylpropiolamide:**

Synthesized according to general procedure 5. The title compound was isolated in a 64% yield as a white solid; mp 51.0 – 51.8 °C. \(^1\)H NMR (400 MHz, 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); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 155.0 (C), 96.7 (C), 74.0 (C), 38.5
(CH$_3$), 34.1 (CH$_3$), 31.8 (CH$_2$), 29.2 (CH), 25.8 (CH$_2$), 24.8 (CH$_2$); HRMS (ESI+): Calcd for C$_{11}$H$_{18}$NO [M+H]$^+$: 180.1383, Found 180.1387; TLC: 3:2 / Hexanes:EtOAc, R$_f$ 0.35.

3-(Cyclohex-1-en-1-yl)-N,N-dimethylpropiolamide:

Synthesized according to general procedure 5. The title compound was isolated in a 94% yield as an off-white solid; mp 41.6 – 42.6 °C. $^1$H NMR (400 MHz, 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); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 155.1 (C), 139.8 (CH), 119.2 (C), 92.4 (C), 79.5 (C), 38.5 (CH$_3$), 34.2 (CH$_3$), 28.5 (CH$_2$), 26.0 (CH$_2$), 22.1 (CH$_2$), 21.3 (CH$_2$); HRMS (ESI+): Calcd for C$_{11}$H$_{15}$NO [M+H]$^+$: 178.1226, Found 178.1224; TLC: 3:2 / Hexanes:EtOAc, R$_f$ 0.36.

$N,N$-Dimethyl-4-phenoxybut-2-ynamide:

Synthesized according to general procedure 5. The title compound was isolated in a 21% yield as a yellow oil; bp <180 °C (decomp). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.33 – 7.27 (m, 2H), 7.03 – 6.95 (m, 2H), 4.85 (s, 2H), 3.07 (s, 3H), 2.94 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 157.4 (C), 153.7 (C), 129.7 (CH), 122.0 (CH), 115.1 (CH), 86.0 (C), 79.9 (C), 55.9 (CH$_2$), 38.3 (CH$_3$), 34.2 (CH$_3$); HRMS (ESI+): Calcd for C$_{13}$H$_{14}$NO$_2$ [M+H]$^+$: 204.1019, Found 204.1023; TLC: 1:1 / Hexanes:EtOAc, R$_f$ 0.41.

Methyl hex-2-ynoyl-$d$-prolinate:

Synthesized according to general procedure 5. The title compound was isolated in a 64% yield (1:1 mixture of rotamers) as a colorless viscous oil; bp > 235 °C (decomp). In the NMR spectra, the second rotamer is designated by * and the overlapping rotamer peaks are designated by †. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.63 (dd, $J = 8.7, 3.2$ Hz, 1H), 4.50* (dd, $J = 8.7, 3.8$ Hz, 1H), 3.84 – 3.54† (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† (m, 7H), 1.66–1.51† (m, 4H), 1.02 (t, $J = 7.3$ Hz, 3H), 0.98* (t, $J = 7.3$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 172.4 (C), 172.0* (C), 153.1 (C), 152.9* (C), 92.3 (C), 92.1* (C), 74.8 (C), 74.7* (C), 60.7 (CH), 57.9* (CH), 52.3 (CH$_3$), 52.2* (CH$_3$), 48.4 (CH$_2$), 45.7* (CH$_2$), 30.6 (CH$_2$), 29.7* (CH$_2$), 24.1 (CH$_2$), 23.1* (CH$_2$), 21.2 (CH$_2$), 21.1* (CH$_2$), 20.7 (CH$_2$), 20.6* (CH$_2$), 13.4 (CH$_3$), 13.3* (CH$_3$); HRMS (ESI+): Calcd for C$_{12}$H$_{18}$NO$_3$ [M+H]$^+$: 224.1281, Found 224.1297; TLC: 3:2 / Hexanes:EtOAc, R$_f$ 0.37.

N-Methylhex-2-ynamide:

Synthesized according to general procedure 6. The title compound was isolated in a 68% yield (9:1 mixture of rotamers) as a white solid. $^1$H and $^{13}$C NMR are consistent with the literature.$^{24}$ TLC: 1:1 / Hexanes:EtOAc, R$_f$ 0.41.

N-Benzylhex-2-ynamide:

Synthesized according to general procedure 6. The title compound was isolated in a 53% yield (9:1 mixture of rotamers) as a white solid; mp 44.2 – 45.1 °C. In the NMR spectra, the minor rotamer is designated by * and the overlapping rotamer peaks are designated by †. $^1$H NMR (400 MHz, CDCl$_3$) δ 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); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 153.6† (C), 137.7* (C), 137.5 (C), 128.9* (CH), 128.8 (CH), 128.0 (CH), 127.9* (CH), 127.8 (CH), 127.2* (CH), 87.9† (C), 75.6† (C), 47.4* (CH$_2$), 43.9 (CH$_2$), 21.4 (CH$_2$), 21.3* (CH$_2$), 21.0* (CH$_2$), 20.7 (CH$_2$), 13.7 (CH$_3$), 13.6* (CH$_3$); HRMS (ESI+): Calcd for C$_{13}$H$_{16}$NO [M+H]$^+$: 202.1226, Found 202.1234; TLC: 4:1 / Hexanes:EtOAc, R$_f$ 0.29.
But-2-ynamide:

Synthesized according to general procedure 7. The title compound was isolated in a 65% yield as off-white crystals. $^1$H and $^{13}$C NMR are consistent with the literature.\textsuperscript{25} TLC: 1:1 / Hexanes:EtOAc, $R_f$ 0.48.

Hex-2-ynamide:

Synthesized according to general procedure 7. The title compound was isolated in a 43% yield as white crystals; mp 80.5 – 81.5 °C. $^1$H NMR (400 MHz, CDCl\textsubscript{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); $^{13}$C NMR (101 MHz, CDCl\textsubscript{3}) $\delta$ 155.3 (C), 89.0 (C), 75.1 (C), 21.3 (CH\textsubscript{2}), 20.7 (CH\textsubscript{2}), 13.6 (CH\textsubscript{3}); HRMS (ESI+): Calcd for C\textsubscript{6}H\textsubscript{10}NO [M+H]$^+$: 112.0757, Found 112.0755; TLC: 1:1 / Hexanes:EtOAc, $R_f$ 0.28.

Non-2-ynamide:

Synthesized according to general procedure 7. The title compound was isolated in an 81% yield as white crystals. $^1$H and $^{13}$C NMR are consistent with the literature.\textsuperscript{19} TLC: 1:1 / Hexanes:EtOAc, $R_f$ 0.40.

6.5.12. Characterization of the $\beta$-Borylated Products

Ethyl (Z)-3-(1H-naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-yl)but-2-enoate (4.10):

Synthesized according to general procedure A. Yellow solid; mp 85.7 – 87.2 °C; $^1$H NMR (400 MHz, CDCl\textsubscript{3}) $\delta$ 7.11 (dd, $J = 8.2$, 7.4 Hz, 2H), 7.04 (dd, $J = 8.2$ Hz, $^4J = 1.0$ Hz, 2H), 6.35 (dd, $J = 7.4$ Hz, $^4J = 1.0$ Hz, 2H), 6.22 (q, $^4J = 1.7$ Hz, 1H), 5.80 (br s, 2H), 4.22 (q, $J = 7.2$ Hz, 2H), 2.30 (d, $^4J = 1.7$ Hz, 3H), 1.33 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl\textsubscript{3}) $\delta$ 166.2 (C), 140.7 (C), 136.4 (C), 127.7 (CH), 125.7 (CH), 120.2 (C), 118.3 (CH), 106.3 (CH), 60.1 (CH\textsubscript{2}), 16.6 (CH\textsubscript{3}), 14.5 (CH\textsubscript{3});
$^{11}$B NMR (128 MHz, CDCl$_3$) δ 28.58; HRMS (ESI+): Calcd for C$_{16}$H$_{18}$BN$_2$O$_2$ [M+H]$^+$: 281.1456, Found 281.1450; TLC: 9:1 / Hexanes:EtOAc, R$_f$ 0.34.

**Ethyl (Z)-3-(1H-naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-yl)hex-2-enoate (4.11):**

Synthesized according to general procedure A. Yellow solid; mp 102.5 – 104 °C; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.12 (dd, $J = 8.3, 7.2$ Hz, 2H), 7.05 (dd, $J = 8.3$ Hz, $^4J = 1.0$ Hz, 2H), 6.35 (dd, $J = 7.2$ Hz, $^4J = 1.0$ Hz, 2H), 6.19 (t, $^4J = 0.7$ Hz, 1H), 5.78 (br s, 2H), 4.22 (q, $J = 7.2$ Hz, 2H), 2.80 – 2.72 (m, 2H), 1.58 – 1.47 (m, 2H), 1.33 (t, $J = 7.2$ Hz, 3H), 0.99 (t, $J = 7.3$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 166.0 (C), 140.7 (C), 136.4 (C), 127.7 (CH), 125.2 (CH), 120.1 (C), 118.2 (CH), 106.3 (CH), 60.1 (CH$_2$), 32.4 (CH$_2$), 23.2 (CH$_2$), 14.5 (CH$_3$), 14.4 (CH$_3$); $^{11}$B NMR (128 MHz, CDCl$_3$) δ 28.86; HRMS (ESI+): Calcd for C$_{18}$H$_{22}$BN$_2$O$_2$ [M+H]$^+$: 309.1769, Found 309.1759; TLC: 9:1 / Hexanes:EtOAc, R$_f$ 0.44.

**Methyl (Z)-3-(1H-naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-yl)non-2-enoate (4.12):**

Synthesized according to general procedure A. Yellow solid; mp 75.1 – 76.3 °C; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.14 (dd, $J = 8.3, 7.3$ Hz, 2H), 7.07 (dd, $J = 8.3$ Hz, $^4J = 1.0$ Hz, 2H), 6.36 (dd, $J = 7.3$ Hz, $^4J = 1.0$ Hz, 2H), 6.19 (t, $^4J = 0.7$ Hz, 1H), 5.83 (br s, 2H), 3.78 (s, 3H), 2.83 – 2.76 (m, 2H), 1.54 – 1.28 (m, 8H), 0.94 – 0.88 (m, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 166.4 (C), 140.6 (C), 136.3 (C), 127.6 (CH), 124.3 (CH), 120.1 (C), 118.1 (CH), 106.3 (CH), 51.2 (CH$_3$), 31.7 (CH$_2$), 30.5 (CH$_2$), 29.9 (CH$_2$), 29.7 (CH$_2$), 22.7 (CH$_2$), 14.2 (CH$_3$); $^{11}$B NMR (128 MHz, CDCl$_3$) δ 28.85; HRMS (ESI+): Calcd for C$_{20}$H$_{26}$BN$_2$O$_2$ [M+H]$^+$: 337.2082, Found 337.2078; TLC: 9:1 / Hexanes:EtOAc, R$_f$ 0.44.
**Ethyl (Z)-3-(1H-naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-yl)dec-2-enoate (4.13):**

Synthesized according to general procedure A. Yellow solid; mp 40 – 41 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.12 (dd, \(J = 8.3, 7.3\) Hz, 2H), 7.05 (dd, \(J = 8.3\) Hz, \(^4J = 1.0\) Hz, 2H), 6.35 (dd, \(J = 7.3\) Hz, \(^4J = 1.0\) Hz, 2H), 6.17 (t, \(^4J = 0.7\) Hz, 1H), 5.79 (br s, 2H), 4.22 (q, \(J = 7.2\) Hz, 2H), 2.80 – 2.73 (m, 2H), 1.55 – 1.22 (m, 13H), 0.91 – 0.86 (m, 3H);

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 166.0 (C), 140.7 (C), 136.4 (C), 127.7 (CH), 125.0 (CH), 120.2 (C), 118.2 (CH), 106.3 (CH), 60.1 (CH\(_2\)), 31.9 (CH\(_2\)), 30.5 (CH\(_2\)), 30.1 (CH\(_2\)), 30.0 (CH\(_2\)), 29.3 (CH\(_2\)), 22.8 (CH\(_2\)), 14.4 (CH\(_3\)), 14.2 (CH\(_3\)); \(^{11}\)B NMR (128 MHz, CDCl\(_3\)) \(\delta\) 28.90; HRMS (ESI+): Calcd for C\(_{22}\)H\(_{30}\)BN\(_2\)O\(_2\)[M+H]\(^+\): 365.2395, Found 365.2382; TLC: 9:1 / Hexanes:EtOAc, R\(_f\) 0.55.

**Ethyl (Z)-4,4-dimethyl-3-(1H-naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-yl)pent-2-enoate (4.14):**

Synthesized according to general procedure A. White solid; mp 102.3 – 103.3 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.13 (dd, \(J = 8.4, 7.3\) Hz, 2H), 7.06 (dd, \(J = 8.4\) Hz, \(^4J = 1.0\) Hz, 2H), 6.33 (dd, \(J = 7.3\) Hz, \(^4J = 1.0\) Hz, 2H), 5.95 (s, 1H), 5.66 (br s, 2H), 4.23 (q, \(J = 7.2\) Hz, 2H), 1.34 (t, \(J = 7.2\) Hz, 3H), 1.30 (s, 9H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 168.2 (C), 140.7 (C), 136.3 (C), 127.7 (CH), 124.0 (CH), 119.7 (C), 118.0 (CH), 106.1 (CH), 60.7 (CH\(_2\)), 36.1 (C), 30.7 (CH\(_3\)), 14.3 (CH\(_3\)); \(^{11}\)B NMR (128 MHz, CDCl\(_3\)) \(\delta\) 29.76; HRMS (ESI+): Calcd for C\(_{19}\)H\(_{24}\)BN\(_2\)O\(_2\)[M+H]\(^+\): 323.1925, Found 323.1927; TLC: 9:1 / Hexanes:EtOAc, R\(_f\) 0.51.
Ethyl (Z)-3-cyclopropyl-3-(1H-naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-yl)acrylate (4.15):

Synthesized according to general procedure A. White solid; mp 125.7 – 127.2 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.10 (dd, \(J = 8.3, 7.2\) Hz, 2H), 7.04 (dd, \(J = 8.3\) Hz, \(^4\)J = 1.0 Hz, 2H), 6.31 (dd, \(J = 7.2\) Hz, \(^4\)J = 1.0 Hz, 2H), 6.03 (d, \(^4\)J = 0.9 Hz, 1H), 5.62 (br s, 2H), 4.21 (q, \(J = 7.1\) Hz, 2H), 3.04 – 2.96 (m, 1H), 1.31 (t, \(J = 7.1\) Hz, 3H), 1.03 – 0.97 (m, 2H), 0.72 – 0.67 (m, 2H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 166.6 (C), 140.4 (C), 136.3 (C), 127.7 (CH), 123.6 (CH), 120.0 (C), 118.3 (CH), 106.3 (CH), 60.0 (CH\(_2\)), 14.5 (CH\(_3\)), 13.6 (CH), 8.7 (CH\(_2\)); \(^{11}\)B NMR (128 MHz, CDCl\(_3\)) \(\delta\) 28.75; HRMS (ESI+): Calcd for C\(_{18}\)H\(_{20}\)BN\(_2\)O\(_2\) [M+H]\(^{+}\): 307.1612, Found 307.1599; TLC: 9:1 / Hexanes:EtOAc, R\(_f\) 0.37.

Ethyl (Z)-3-cyclopentyl-3-(1H-naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-yl)acrylate (4.16):

Synthesized according to general procedure A. White solid; mp 112.5 – 113.2 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.12 (dd, \(J = 8.3, 7.2\) Hz, 2H), 7.05 (dd, \(J = 8.3\) Hz, \(^4\)J = 1.0 Hz, 2H), 6.33 (dd, \(J = 7.2\) Hz, \(^4\)J = 1.0 Hz, 2H), 6.03 (d, \(^4\)J = 1.0 Hz, 1H), 5.66 (br s, 2H), 4.20 (q, \(J = 7.1\) Hz, 2H), 3.93 – 3.81 (m, 1H), 2.04 – 1.94 (m, 2H), 1.80 – 1.63 (m, 4H), 1.52 – 1.39 (m, 2H), 1.32 (t, \(J = 7.1\) Hz, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 166.1 (C), 140.5 (C), 136.3 (C), 127.7 (CH), 124.2 (CH), 119.9 (C), 118.2 (CH), 106.2 (CH), 60.0 (CH\(_2\)), 41.6 (CH), 33.4 (CH\(_2\)), 25.9 (CH\(_2\)), 14.4 (CH\(_3\)); \(^{11}\)B NMR (128 MHz, CDCl\(_3\)) \(\delta\) 29.55; HRMS (ESI+): Calcd for C\(_{20}\)H\(_{24}\)BN\(_2\)O\(_2\) [M+H]\(^{+}\): 335.1925, Found 335.1922; TLC: 9:1 / Hexanes:EtOAc, R\(_f\) 0.47.
Ethyl (Z)-3-cyclohexyl-3-(1H-naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-yl)acrylate (4.17):

Synthesized according to general procedure A. White solid; mp 137.1 – 137.6 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.12 (dd, \(J = 8.3, 7.2\) Hz, 2H), 7.05 (dd, \(J = 8.3\) Hz, \(^4\)J = 1.0 Hz, 2H), 6.33 (dd, \(J = 7.2\) Hz, \(^4\)J = 1.0 Hz, 2H), 5.96 (d, \(^4\)J = 0.9 Hz, 1H), 5.63 (br s, 2H), 4.20 (q, \(J = 7.2\) Hz, 2H), 3.57 – 3.45 (m, 1H), 1.82 – 1.67 (m, 5H), 1.46 – 1.12 (m, 8H); \(^13\)C NMR (101 MHz CDCl\(_3\)) \(\delta\) 166.0 (C), 140.5 (C), 136.3 (C), 127.7 (CH), 123.2 (CH), 119.9 (C), 118.1 (CH), 106.2 (CH), 60.0 (CH\(_2\)), 40.5 (CH), 33.0 (CH\(_2\)), 26.3 (CH\(_2\)), 26.1 (CH\(_2\)), 14.4 (CH\(_3\)); \(^{11}\)B NMR (128 MHz, CDCl\(_3\)) \(\delta\) 29.35; HRMS (ESI+): Calcd for C\(_{21}\)H\(_{26}\)BN\(_2\)O\(_2\) [M+H]\(^+\): 349.2082, Found 349.2068; TLC: 9:1 / Hexanes:EtOAc, \(R_f\) 0.50.

Ethyl (Z)-3-(cyclohex-1-en-1-yl)-3-(1H-naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-yl)acrylate (4.18):

Synthesized according to general procedure A. Dark yellow solid; mp 120 – 121.5 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.11 (dd, \(J = 8.3, 7.3\) Hz, 2H), 7.03 (dd, \(J = 8.3\) Hz, \(^4\)J = 1.0 Hz, 2H), 6.34 (dd, \(J = 7.3\) Hz, \(^4\)J = 1.0 Hz, 2H), 6.11 (s, 1H), 5.81 (br s, 2H), 5.42 (m, 1H), 4.19 (q, \(J = 7.2\) Hz, 2H), 2.20 – 2.06 (m, 4H), 1.78 – 1.64 (m, 4H), 1.30 (t, \(J = 7.2\) Hz, 3H); \(^13\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 156.9 (C), 140.8 (C), 138.1 (C), 136.5 (C), 127.7 (CH), 125.0 (CH), 122.4 (CH), 120.2 (C), 118.2 (CH), 106.3 (CH), 60.3 (CH\(_2\)), 28.6 (CH\(_2\)), 25.3 (CH\(_2\)), 23.0 (CH\(_2\)), 22.2 (CH\(_2\)), 14.5 (CH\(_3\)); \(^{11}\)B NMR (128 MHz, CDCl\(_3\)) \(\delta\) 27.95; HRMS (ESI+): Calcd for C\(_{21}\)H\(_{24}\)BN\(_2\)O\(_2\) [M+H]\(^+\): 347.1925, Found 347.1915; TLC: 9:1 / Hexanes:EtOAc, \(R_f\) 0.45.
Ethyl (Z)-3-(1H-naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-yl)-4-phenoxybut-2-enoate (4.19):

Synthesized according to general procedure A. Yellow solid; mp 114.5 – 116 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.34 – 7.22 (m, 2H), 7.11 (dd, J = 8.3, 7.2 Hz, 2H), 7.03 (dd, J = 8.3 Hz, ⁴J = 1.0 Hz, 2H), 7.01 – 6.96 (m, 3H), 6.32 (dd, J = 7.2 Hz, ⁴J = 1.0 Hz, 2H), 6.30 (t, ⁴J = 2.1 Hz, 1H), 6.14 (br s, 2H), 5.41 (d, ⁴J = 2.1 Hz, 2H), 4.25 (q, ⁴J = 7.2 Hz, 2H), 1.35 (t, ⁴J = 7.2 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 165.6 (C), 158.3 (C), 140.8 (C), 136.4 (C), 129.8 (CH), 127.7 (CH), 126.1 (CH), 121.5 (CH), 120.3 (C), 118.1 (CH), 114.8 (CH), 106.2 (CH), 68.3 (CH₂), 60.7 (CH₂), 14.4 (CH₃); ¹¹B NMR (128 MHz, CDCl₃) δ 28.33; HRMS (ESI+): Calcd for C₂₂H₂₂BN₂O₃ [M+H]⁺: 373.1718, Found 373.1718; TLC: 9:1 / Hexanes:EtOAc, Rf 0.36.

Phenyl (Z)-3-(1H-naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-yl)hex-2-enoate (4.20):

Synthesized according to general procedure A. Orange solid; mp 116.3 – 116.8 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.44 – 7.38 (m, 2H), 7.28 – 7.22 (m, 1H), 7.16 – 7.11 (m, 4H), 7.07 (dd, J = 8.3 Hz, ⁴J = 1.0 Hz, 2H), 6.41 (t, ⁴J = 0.8 Hz, 1H), 6.38 (dd, J = 7.2 Hz, ⁴J = 1.0 Hz, 2H), 5.82 (br s, 2H), 2.85 – 2.79 (m, 2H), 1.61 – 1.50 (m, 2H), 1.00 (t, J = 7.3 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 164.1 (C), 150.6 (C), 140.6 (C), 136.4 (C), 129.6 (CH), 127.7 (CH), 125.9 (CH), 124.1 (CH), 121.8 (CH), 120.2 (C), 118.4 (CH), 106.4 (CH), 32.7 (CH₂), 23.2 (CH₂), 14.5 (CH₃); ¹¹B NMR (128 MHz, CDCl₃) δ 28.97; HRMS (ESI+): Calcd for C₂₂H₂₂BN₂O₂ [M+H]⁺: 357.1769, Found 357.1768; TLC: 9:1 / Hexanes:EtOAc, Rf 0.47.
**Isobutyl (Z)-3-(1H-naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-yl)hex-2-enoate (4.21):**

Synthesized according to general procedure A. Yellow solid; mp 86.9 – 88.1 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.12 (dd, \(J = 8.3, 7.3\) Hz, 2H), 7.05 (dd, \(J = 8.3\) Hz, \(^4\)J = 1.0 Hz, 2H), 6.36 (dd, \(J = 7.3\) Hz, \(^4\)J = 1.0 Hz, 2H), 6.20 (s, 1H), 5.77 (br s, 2H), 3.94 (dd, \(J = 6.6, 0.6\) Hz, 2H), 2.79 – 2.71 (m, 2H), 2.05 – 1.93 (m, 1H), 1.58 – 1.46 (m, 2H), 1.02 – 0.96 (m, 9H); \(^13\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 166.2 (C), 140.7 (C), 136.4 (C), 127.7 (CH), 125.2 (CH), 120.1 (C), 118.2 (CH), 106.3 (CH), 70.4 (CH\(_2\)), 32.4 (CH\(_2\)), 27.9 (CH), 23.3 (CH\(_2\)), 19.3 (CH\(_3\)), 14.5 (CH\(_3\)); \(^{11}\)B NMR (128 MHz, CDCl\(_3\)) \(\delta\) 28.89; HRMS (ESI\(^+\)): Calcd for C\(_{20}\)H\(_{26}\)BN\(_2\)O\(_2\) [M+H]\(^+\): 337.2082, Found 337.2084; TLC: 9:1 / Hexanes:EtOAc, R\(_f\) 0.57.

**Allyl (Z)-3-(1H-naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-yl)hex-2-enoate (4.22):**

Synthesized according to general procedure A. Yellow solid; mp 65.0 – 65.9 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.13 (dd, \(J = 8.3, 7.3\) Hz, 2H), 7.06 (dd, \(J = 8.3\) Hz, \(^4\)J = 1.0 Hz, 2H), 6.35 (dd, \(J = 7.3\) Hz, \(^4\)J = 1.0 Hz, 2H), 6.23 (s, 1H), 6.05 – 5.94 (m, 1H), 5.80 (br s, 2H), 5.42 – 5.36 (m, 1H), 5.32 – 5.27 (m, 1H), 4.70 – 4.66 (m, 2H), 2.81 – 2.74 (m, 2H), 1.59 – 1.48 (m, 2H), 1.00 (t, \(J = 7.4\) Hz, 3H); \(^13\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 165.5 (C), 140.6 (C), 136.4 (C), 132.3 (CH), 127.7 (CH), 124.7 (CH), 120.1 (C), 118.5 (CH\(_2\)), 118.2 (CH), 106.3 (CH), 64.9 (CH\(_2\)), 32.4 (CH\(_2\)), 23.2 (CH\(_2\)), 14.4 (CH\(_3\)); \(^{11}\)B NMR (128 MHz, CDCl\(_3\)) \(\delta\) 28.92; HRMS (ESI\(^+\)): Calcd for C\(_{19}\)H\(_{22}\)BN\(_2\)O\(_2\) [M+H]\(^+\): 321.1769, Found 321.1768; TLC: 9:1 / Hexanes:EtOAc, R\(_f\) 0.72.
But-3-yn-1-yl (Z)-3-((1H-naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-yl)hex-2-enoate (4.23):

Synthesized according to general procedure A. Yellow solid; mp 132.8 – 133.5 °C; 1H NMR (400 MHz, CDCl3) δ 7.11 (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), 6.21 (t, 4J = 0.9 Hz, 1H), 5.75 (br s, 2H), 4.72 (q, 5J = 2.4 Hz, 2H), 2.80 – 2.74 (m, 2H), 1.88 (t, 5J = 2.4 Hz, 3H), 1.57 – 1.46 (m, 2H), 0.99 (t, J = 7.3 Hz, 3H); 13C NMR (101 MHz, CDCl3) δ 165.0 (C), 140.6 (C), 136.4 (C), 127.7 (CH), 124.2 (CH), 120.2 (C), 118.3 (CH), 106.3 (CH), 83.3 (C), 73.3 (C), 52.5 (CH2), 32.4 (CH2), 23.2 (CH2), 14.4 (CH3), 3.8 (CH3); 11B NMR (128 MHz, CDCl3) δ 28.91; HRMS (ESI+): Calcd for C20H22BN2O [M+H]+: 333.1769, Found 333.1770; TLC: 19:1 / Hexanes:EtOAc, Rf 0.35.

(Z)-N-Methoxy-N-methyl-3-(1H-naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-yl)non-2-enamide (4.24): Note: β-carbon observed with 3 second delay

Synthesized according to general procedure B. Yellow solid; mp 85.6 – 86.5 °C; 1H NMR (400 MHz, CDCl3) δ 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); 13C NMR (151 MHz, CDCl3) δ 167.6 (C, br), 153.4 (C–B, br), 140.8 (C), 136.5 (C), 127.7 (CH), 124.6 (CH, br), 120.1 (C), 118.1 (CH), 106.2 (CH), 61.7 (CH3), 32.3 (CH3, br), 31.9 (CH2), 31.0 (CH2), 30.1 (CH2), 29.8 (CH2), 22.8 (CH2), 14.2 (CH3); 11B NMR (128 MHz, CDCl3) δ 28.98; HRMS (ESI+): Calcd for C21H29BN3O2 [M+H]+: 366.2347, Found 366.2361; TLC: 3:2 / Hexanes:EtOAc, Rf 0.39.
(Z)-N-Methoxy-N-methyl-3-(1H-naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-yl)but-2-enamide (4.25): Note: β-carbon observed with 3 second delay

Synthesized according to general procedure B. Yellow solid; mp 99.2 – 100.1 °C; 1H NMR (400 MHz, CDCl3) δ 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); 13C NMR (101 MHz, CDCl3) δ 167.6 (C, br), 147.3 (C–B, br), 140.8 (C), 136.4 (C), 127.7 (CH), 125.5 (CH, br), 120.1 (C), 118.1 (CH), 106.2 (CH), 61.8 (CH3), 32.2 (CH3, br), 16.7 (CH3); 11B NMR (128 MHz, CDCl3) δ 28.69; HRMS (ESI+): Calcd for C16H19BN3O2 [M+H]+: 296.1565, Found 295.1562; TLC: 3:2 / Hexanes:EtOAc, Rf 0.24.

(Z)-N,N-Dimethyl-3-(1H-naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-yl)hex-2-enamide (4.26):

Synthesized according to general procedure B. Beige solid; mp 197.3 – 198.3 °C; 1H NMR (400 MHz, (CD3)2CO) δ 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); 13C NMR (101 MHz, (CD3)2CO) δ 168.8 (C), 143.0 (C), 137.4 (C), 131.4 (CH), 128.4 (CH), 121.1 (C), 117.7 (CH), 106.6 (CH), 37.7 (CH3), 34.2 (CH3), 33.3 (CH2), 23.7 (CH2), 14.5 (CH3); 11B NMR (128 MHz, (CD3)2CO) δ 28.94; HRMS (ESI+): Calcd for C18H23BN3O [M+H]+: 309.1929, Found 309.1938; TLC: 1:1 / Hexanes:EtOAc, Rf 0.33.
(Z)-N,N-Dimethyl-3-(1H-naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-yl)non-2-enamide

(4.27):

Synthesized according to general procedure B. Beige solid; mp 50.4 – 51.2 °C; ^1H NMR (400 MHz, CDCl3) δ 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), 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); ^13C NMR (101 MHz, CDCl3) δ 168.9 (C), 140.9 (C), 136.4 (C), 129.6 (CH), 127.7 (CH), 120.0 (C), 117.9 (CH), 106.1 (CH), 38.0 (CH3), 34.5 (CH3), 31.8 (CH2), 31.5 (CH2), 29.8 (CH2), 29.7 (CH2), 22.7 (CH2), 14.2 (CH3); ^11B NMR (128 MHz, CDCl3) δ 28.92; HRMS (ESI+): Calcd for C21H29BN3O [M+H]^+: 350.2398, Found 350.2420; TLC: 3:2 / Hexanes:EtOAc, Rf 0.28.

(Z)-N,N-4,4-Tetramethyl-3-(1H-naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-yl)pent-2-enamide (4.28):

Synthesized according to general procedure B. Beige solid; mp > 195 °C (decomp); ^1H NMR (400 MHz, CDCl3) δ 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); ^13C NMR (101 MHz, CDCl3) δ 170.8 (C), 140.9 (C), 136.3 (C), 127.7 (CH), 127.0 (CH), 119.7 (C), 117.9 (CH), 106.0 (CH), 38.5 (CH3), 36.6 (C), 34.3 (CH3), 30.6 (CH3); ^11B NMR (128 MHz, CDCl3) δ 29.67; HRMS (ESI+): Calcd for C19H25BN3O [M+H]^+: 322.2085, Found 322.2081; TLC: 1:1 / Hexanes:EtOAc, Rf 0.23.
(Z)-3-Cyclopentyl-N,N-dimethyl-3-(1H-naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-yl)acrylamide (4.29):

Synthesized according to general procedure B. Beige solid; mp > 185 °C (decomp); $^1$H NMR (400 MHz, 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); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 169.1 (C), 140.8 (C), 136.3 (C), 128.7 (CH), 127.7 (CH), 119.9 (C), 118.0 (CH), 106.1 (CH), 43.0 (CH), 38.3 (CH$_3$), 34.5 (CH$_3$), 33.3 (CH$_2$), 25.8 (CH$_2$); $^{11}$B NMR (128 MHz, CDCl$_3$) $\delta$ 29.35; HRMS (ESI+): Calcd for C$_{20}$H$_{25}$BN$_3$O [M+H]$^+$: 334.2085, Found 334.2086; TLC: 1:1 / Hexanes:EtOAc, R$_f$ 0.25.

(Z)-3-Cyclohexyl-N,N-dimethyl-3-(1H-naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-yl)acrylamide (4.30):

Synthesized according to general procedure B. White solid; mp 175.2 – 177.5 °C; $^1$H NMR (400 MHz, 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); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 168.8 (C), 140.8 (C), 136.4 (C), 127.66 (CH), 127.67 (CH), 119.8 (C), 118.0 (CH), 106.0 (CH), 42.2 (CH), 38.2 (CH$_3$), 34.5 (CH$_3$), 33.1 (CH$_2$), 26.3 (CH$_2$), 26.1 (CH$_2$); $^{11}$B NMR (128 MHz, CDCl$_3$) $\delta$ 29.45; HRMS (ESI+): Calcd for C$_{21}$H$_{27}$BN$_3$O [M+H]$^+$: 348.2242, Found 348.2247; TLC: 1:1 / Hexanes:EtOAc, R$_f$ 0.43.
(Z)-3-(Cyclohex-1-en-1-yl)-N,N-dimethyl-3-(1H-naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-yl)acrylamide (4.31):

Synthesized according to general procedure B. Light brown solid; mp > 155 °C (decomp); $^1$H NMR (400 MHz, CDCl$_3$) δ 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), 5.78 (br s, 2H), 5.63 (p, $J = 1.8$ Hz, 1H), 3.02 (s, 3H), 2.98 (s, 3H), 2.15 – 2.08 (m, 4H), 1.71 – 1.59 (m, 4H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 169.5 (C), 141.0 (C), 137.7 (C), 136.4 (C), 128.3 (CH), 127.7 (CH), 126.6 (CH), 120.0 (C), 117.9 (CH), 106.1 (CH), 38.2 (CH$_3$), 34.4 (CH$_3$), 28.3 (CH$_2$), 25.7 (CH$_2$), 23.0 (CH$_2$), 22.1 (CH$_2$); $^{11}$B NMR (128 MHz, CDCl$_3$) δ 28.66; HRMS (ESI+): Calcd for C$_{21}$H$_{25}$BN$_3$O$_2$ [M+H]$^+$: 346.2085, Found 346.2090; TLC: 1:1 / Hexanes:EtOAc, R$_f$ 0.21.

(Z)-N,N-Dimethyl-3-(1H-naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-yl)-4-phenoxybut-2-enamide (4.32):

Synthesized according to general procedure B. Beige solid; mp > 153 °C (decomp); $^1$H NMR (400 MHz, CDCl$_3$) δ 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), 6.35 (dd, $J = 7.3$ Hz, $^4J = 1.0$ Hz, 2H), 4.94 (d, $^4J = 1.3$ Hz, 2H), 3.03 (s, 6H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 167.7 (C), 158.3 (C), 141.0 (C), 136.5 (C), 132.2 (CH), 129.8 (CH), 127.7 (CH), 121.4 (CH), 120.2 (C), 117.9 (CH), 114.8 (CH), 106.2 (CH), 68.4 (CH$_2$), 38.1 (CH$_3$), 34.8 (CH$_3$); $^{11}$B NMR (128 MHz, CDCl$_3$) δ 28.42; HRMS (ESI+): Calcd for C$_{22}$H$_{25}$BN$_3$O$_2$ [M+H]$^+$: 372.1878, Found 372.1886; TLC: 20:1 / Et$_2$O:EtOAc, R$_f$ 0.29.
Methyl (Z)-(3-(1H-naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-yl)hex-2-enoyl)-o-prolinate (4.33): Note: β-carbon observed with 3 second delay

Synthesized according to general procedure B. The title compound was isolated as a 76:24 mixture of rotamers. Yellow solid; mp 149.9 – 151.4 °C; [α]D +35.7 (c 0.038, CH3OH). In the NMR spectra, minor rotamer is designated by * and the overlapping rotamer peaks are designated by †. 1H NMR (400 MHz, CDCl3) δ 7.11† (dd, J = 8.3, 7.3 Hz, 2H), 7.03† (dd, J = 8.3 Hz, 4H), 6.38 – 6.33 (m, 5H), 6.20* (s, 1H), 5.79 (br s, 2H), 5.77* (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); 13C NMR (126 MHz, CDCl3) δ 173.1* (C), 172.9 (C), 166.9* (C), 166.6 (C), 150.3† (C–B, br), 140.9 (C), 140.9* (C), 136.4† (C), 128.4* (CH), 128.2 (CH), 127.7† (CH), 120.1† (C), 118.0* (CH), 117.9 (CH), 106.2 (CH), 106.1 (CH), 60.1* (CH), 58.5 (CH), 52.7* (CH3), 52.3 (CH3), 47.7 (CH2), 46.1* (CH2), 33.1* (CH2), 32.9 (CH2), 31.5* (CH2), 29.4 (CH2), 25.0 (CH2), 23.2 (CH2), 23.1* (CH2), 23.0* (CH2), 14.5* (CH3), 14.4 (CH3); 11B NMR (128 MHz, CDCl3) δ 29.79; HRMS (ESI+): Calcd for C22H27BN3O3 [M+H]+: 392.2140, Found 392.2102; TLC: 1:1 / Hexanes:EtOAc, Rf 0.40.

(Z)-N-Methyl-3-(1H-naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-yl)hex-2-enamide (4.34):

Synthesized according to general procedure B. Yellow solid; mp >157 °C (decomp); 1H NMR (400 MHz, CDCl3) δ 7.11 (dd, J = 8.3, 7.3 Hz, 2H), 7.03 (dd, J = 8.3 Hz, 4H), 6.34 (dd, J = 7.3 Hz, 4J = 0.8 Hz, 2H), 6.11 (s, 1H), 5.76 (br s, 2H), 5.60 (br d, J = 4.9 Hz, 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); 13C NMR (101 MHz, CDCl3) δ 167.5 (C), 140.8 (C), 136.3 (C), 128.3 (CH), 127.7 (CH), 120.0 (C), 118.0
(CH), 106.2 (CH), 32.2 (CH₂), 26.2 (CH₃), 23.4 (CH₂), 14.4 (CH₃); ¹¹B NMR (128 MHz, CDCl₃) δ 28.83; HRMS (ESI+): Calcd for C₁₇H₂₁BN₃O [M+H]+: 294.1772, Found 294.1772; TLC: 1:1 /Hexanes:EtOAc, Rᵣ 0.27.

(Z)-N-Benzyl-3-(1H-naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-yl)hex-2-enamide (4.35):

Synthesized according to general procedure B. Yellow solid; mp 113.5 – 114.8 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.26 – 7.39 (m, 5H), 7.10 (dd, J = 8.3, 7.3 Hz, 2H), 7.03 (dd, J = 8.3 Hz, ⁴J = 0.8 Hz, 2H), 6.33 (dd, J = 7.3 Hz, ⁴J = 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); ¹³C NMR (101 MHz, CDCl₃) δ 166.4 (C), 140.8 (C), 138.3 (C), 136.4 (C), 128.9 (CH), 128.1 (CH), 128.0 (CH), 127.7 (CH), 127.7 (CH), 120.1 (C), 118.1 (CH), 106.2 (CH), 43.6 (CH₂), 32.4 (CH₂), 23.5 (CH₂), 14.5 (CH₃); ¹¹B NMR (128 MHz, CDCl₃) δ 29.14; HRMS (ESI+): Calcd for C₂₃H₂₅BN₃O [M+H]+: 370.2085, Found 370.2086; TLC: 4:1 /Hexanes:EtOAc, Rᵣ 0.18.

(Z)-3-(1H-Naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-yl)but-2-enamide (4.36):

Synthesized according to general procedure B. Yellow solid; mp 164.8 – 165.6 °C; ¹H NMR (400 MHz, (CD₃)₂SO) δ 7.89 (s, 2H), 7.31 (s, 1H), 7.04 (dd, J = 8.3, 7.4 Hz, 2H), 6.97 – 6.93 (s, 1H), 6.87 (dd, J = 8.3, ⁴J = 0.9 Hz, 2H), 6.50 (dd, J = 7.4, ⁴J = 0.9 Hz, 2H), 6.34 (q, ⁴J = 1.6 Hz, 1H), 2.16 (d, ⁴J = 1.6 Hz, 3H); ¹³C NMR (101 MHz, (CD₃)₂SO) δ 168.4 (C), 142.2 (CH), 135.9 (C), 130.4 (C), 127.6 (CH), 119.8 (C), 116.3 (CH), 105.6 (CH), 16.2 (CH₃); ¹¹B NMR (128 MHz, (CD₃)₂SO) δ 30.04; HRMS (ESI+): Calcd for C₁₄H₁₅BN₃O [M+H]+: 252.1303, Found 252.129; TLC: 1:1 /Hexanes:EtOAc, Rᵣ 0.47.

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(Z)-3-(1H-Naphtho[1,8-de][1,3,2]diazaborin-2(3H)-yl)hex-2-enamide (4.37):

Synthesized according to general procedure B. Yellow solid; mp 133.5 – 134.3 °C; \(^1\)H NMR (400 MHz, 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), 6.35 (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); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 168.3 (C), 140.7 (C), 136.4 (C), 127.7 (CH), 127.2 (CH), 120.1 (C), 118.2 (CH), 106.3 (CH), 32.4 (CH\(_2\)), 23.3 (CH\(_2\)), 14.5 (CH\(_3\)); \(^{11}\)B NMR (128 MHz, CDCl\(_3\)) \(\delta\) 29.07; HRMS (ESI+): Calcd for C\(_{16}\)H\(_{19}\)BN\(_3\)O [M+H]\(^+\): 280.1616, Found 280.1621; TLC: 2:1 / Et\(_2\)O:EtOAc, \(R_\text{f}\) 0.23.

(Z)-3-(1H-Naphtho[1,8-de][1,3,2]diazaborin-2(3H)-yl)non-2-enamide (4.38):

Synthesized according to general procedure B. Yellow solid; mp 98.6 – 99.3 °C; \(^1\)H NMR (400 MHz, 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), 6.35 (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); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 168.7 (C), 140.8 (C), 136.4 (C), 127.7 (CH), 127.0 (CH), 120.1 (C), 118.1 (CH), 106.2 (CH), 31.8 (CH\(_2\)), 30.4 (CH\(_2\)), 30.1 (CH\(_2\)), 29.7 (CH\(_2\)), 22.7 (CH\(_2\)), 14.2 (CH\(_3\)); \(^{11}\)B NMR (128 MHz, CDCl\(_3\)) \(\delta\) 28.97; HRMS (ESI+): Calcd for C\(_{19}\)H\(_{25}\)BN\(_3\)O [M+H]\(^+\): 322.2085, Found 322.2080; TLC: 2:1 / Et\(_2\)O:EtOAc, \(R_\text{f}\) 0.33.
6.6. Synthetic Procedures for Chapter 5

6.6.7. General Procedure for Screening Copper-Catalyzed Cross-Coupling Conditions

In the glovebox, an oven-dried Schlenk tube with magnetic stir-bar was charged with copper catalyst (0.05 equiv.), ligand (0.05 equiv.), base (0.10 equiv.), and substrate (1 equiv.). The reaction vessel was removed and connected to a Schlenk line. Under positive pressure of Argon, 1 mL of dry solvent was added through a septum via syringe. The reaction mixture was stirred for 30 mins before the organohalide was subsequently added via syringe. The contents were heated at the designated temperature and monitored by GC-MS and TLC analysis. Samples were withdrawn with a purged needle. Every 1-3 h, the reaction progress was checked. After 4 h, the solvent was removed in vacuo and the contents of the flask were analyzed via $^1$H NMR and GC-MS.

Copper sources were purified prior to use through standard methods. Copper catalysts were prepared following literature procedures.26

6.6.8. Tabulation of Experiments

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<td>DMF</td>
<td>80</td>
<td>Ar—I</td>
<td>NR</td>
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<tr>
<td>18</td>
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$R^3 = \text{Me, Ph}$

Diagram:

```
MeO       Ph
O----------BF3
```

Reaction conditions:

- [Cu], base, Solvent, temp

Result:

- NR

Organohalides:

- Ar—I
- Me—I
<table>
<thead>
<tr>
<th></th>
<th>Reagent 1</th>
<th>Reagent 2</th>
<th>Solvent</th>
<th>Temp</th>
<th>Substrate</th>
<th>Regioselectivity</th>
<th>Yield</th>
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<tr>
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<td>NR</td>
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<tr>
<td>21</td>
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<td>NR</td>
<td></td>
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<tr>
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<td>80</td>
<td>Ar—I</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>(IPr)CuCl</td>
<td>NaOAc</td>
<td>DMF</td>
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<td>Me—I</td>
<td>NR</td>
<td></td>
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<tr>
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<td>Me—I</td>
<td>NR</td>
<td></td>
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<tr>
<td>25</td>
<td>CuCN</td>
<td>CsCO₃</td>
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<td>NR</td>
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<td>Ar—I</td>
<td>NR</td>
<td></td>
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<td>DMF</td>
<td>80</td>
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<td>NR</td>
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<td>CsCO₃</td>
<td>DMF</td>
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<td>Ar—I</td>
<td>NR</td>
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<tr>
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<td>NR</td>
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<td>80</td>
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<td>NR</td>
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<tr>
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<td>DMF</td>
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<td>Ar—I</td>
<td>NR</td>
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<tr>
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<td></td>
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<tr>
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<td>LiO'Bu</td>
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<td>NR</td>
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<td>80</td>
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<td>NR</td>
<td></td>
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<tr>
<td>42</td>
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<td>NR</td>
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<td>CuCl / BiPy</td>
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<td>Me—I</td>
<td>NR</td>
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6.7. References


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Appendix – Spectral Data

[Chemical structure image]

2.14
Appendix – Spectral Data for Chapter 2

2.14
Appendix – Spectral Data for Chapter 2

Z-2.17

255
Appendix – Spectral Data for Chapter 2

2.21a
Appendix – Spectral Data for Chapter 2
Appendix – Spectral Data for Chapter 2

2.23a
Appendix – Spectral Data for Chapter 2

2.23a
Appendix – Spectral Data for Chapter 2

![Spectral Data](image)

2.25a

ppm

-31.15
Appendix – Spectral Data for Chapter 2

2.26a
Appendix – Spectral Data for Chapter 2

2.27a
Appendix – Spectral Data for Chapter 2

2.27a
Appendix – Spectral Data for Chapter 2

2.28a
Appendix – Spectral Data for Chapter 2

2.29a

\[
\begin{align*}
\text{ppm} & \quad 8.0 \quad 7.5 \quad 7.0 \quad 6.5 \quad 6.0 \quad 5.5 \quad 5.0 \quad 4.5 \quad 4.0 \quad 3.5 \quad 3.0 \quad 2.5 \quad 2.0 \quad 1.5 \quad 1.0 \quad 0.5 \\
186.99 & \quad 149.87 \quad 141.55 \quad 137.64 \quad 136.48 \quad 134.97 \quad 130.48 \quad 119.71 \quad 117.35 \quad 113.56 \quad 113.28 \quad 105.61 \quad -83.80 \quad 55.44 \quad 55.34 \quad 24.88
\end{align*}
\]
Appendix – Spectral Data for Chapter 2

2.30a

![Spectral Data Graph]

ppm
Appendix – Spectral Data for Chapter 2

2.31a
Appendix – Spectral Data for Chapter 2

2.31a
Appendix – Spectral Data for Chapter 2

2.34a
Appendix – Spectral Data for Chapter 2

2.34a
Appendix – Spectral Data for Chapter 2

![Chemical Structure](image)

2.42
Appendix – Spectral Data for Chapter 2

![Chemical structure and spectra graphs]

2.44
Appendix – Spectral Data for Chapter 2

\[ \text{2.44} \]
Appendix – Spectral Data for Chapter 2

2.47

-135.65

ppm


55 50 45 40 35 30 25 20 15 10 5 0 -5 -10 -15 -20

ppm
Appendix – Spectral Data for Chapter 3
Appendix – Spectral Data for Chapter 3

3.28

- 1.03
- 1.75
- 1.78
- 1.80
- 1.81
- 1.83
- 1.83
- 1.84
- 1.85
- 3.91
- 3.94
- 6.82
- 6.82
- 6.83
- 6.83
- 6.84
- 6.85
- 7.23
- 7.24
ed3
- 7.24
d
- 7.25
- 7.26
- 7.27
- 2.03
- 3.92
- 4.06c
- 4.06c
- 6.00a
- 6.00a
- 9.0
- 8.0
- 8.5
- 8.0
- 7.5
- 7.0
- 6.5
- 6.0
- 5.5
- 5.0
- 4.5
- 4.0
- 3.5
- 3.0
- 2.5
- 2.0
- 1.5
- 1.0
- 0.0

ppm

- 158.84
- 149.07
- 134.11
- 129.36
- 114.04
111.38
- 69.50
- 22.60
- 10.51

ppm
Appendix – Spectral Data for Chapter 3
Appendix – Spectral Data for Chapter 3

F₃C—\(\text{CH}_2\)—CF₃

3.31
Appendix – Spectral Data for Chapter 3

3.34

ppm

140.81
140.24
129.58
128.72
127.55
127.35
127.03

2.55
7.26 CDCl3

295
Appendix – Spectral Data for Chapter 3

3.35
Appendix – Spectral Data for Chapter 3
Appendix – Spectral Data for Chapter 3

3.39
Appendix – Spectral Data for Chapter 3

3.40

ppm

209.41
158.40
129.41
128.49
114.39
108.24
77.60 edc8
69.53
22.57
10.49

ppm
Appendix – Spectral Data for Chapter 3

[Diagram of a molecule with spectral data annotations]

[Chemical shifts and other spectral data values]
Appendix – Spectral Data for Chapter 3

3.42

![NMR spectrum image]

ppm

209.50 163.34 160.89 132.05 120.90 115.47 115.26 107.46 78.35

ppm

185 175 165 155 145 135 125 115 105 95 85 7

1, 2, 3, 4, 5, 6
Appendix – Spectral Data for Chapter 3

\[ \text{F}_3C\text{C} = \text{C} \text{C} \text{CF}_3 \]

**3.43**

**ppm**

9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0

200.99

136.54 131.38 131.36 131.28 130.86 130.06 126.31 125.06 124.94 124.28 124.24 124.21 122.60

210 200 190 180 170 160 150 140 130 120 110 100 90 80

304
Appendix – Spectral Data for Chapter 3

3.45
Appendix – Spectral Data for Chapter 3

3.37c
Appendix – Spectral Data for Chapter 4

ethyl dec-2-ynoate

[Chemical structure image]
Appendix – Spectral Data for Chapter 4

ethyl 4,4-dimethylpent-2-ynoate

![NMR spectrum of ethyl 4,4-dimethylpent-2-ynoate]
Appendix – Spectral Data for Chapter 4

ethyl 3-cyclopropylpropionate

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Appendix – Spectral Data for Chapter 4

ethyl 3-cyclopentylpropionate
Appendix – Spectral Data for Chapter 4

ethyl 3-cyclohexylpropionate

[Diagram of a chemical structure with various peaks indicating chemical shifts in ppm]

ppm

80  170  160  150  140  130  120  110  100  90  80  70  60  50  40  30  20  10
Appendix – Spectral Data for Chapter 4

ethyl 3-(cyclohex-1-en-1-yl)propionate
Appendix – Spectral Data for Chapter 4

ethyl 4-phenoxybut-2-ynoate
Appendix – Spectral Data for Chapter 4

phenyl hex-2-ynoate
Appendix – Spectral Data for Chapter 4

isobutyl hex-2-ynoate

1H NMR (CDCl₃, 300 MHz): 
- 7.46 (dd, J = 11.0, 17.8 Hz, 1H)
- 3.94 (s, 1H)
- 3.32 (s, 3H)
- 2.22 (s, 3H)
- 1.99 (s, 3H)
- 1.97 (s, 3H)
- 1.93 (s, 3H)
- 1.92 (s, 3H)
- 1.65 (s, 1H)
- 1.64 (s, 1H)
- 1.62 (s, 1H)
- 1.60 (s, 1H)
- 1.58 (s, 1H)
- 1.56 (s, 1H)
- 1.03 (s, 3H)
- 1.01 (s, 3H)
- 0.95 (s, 3H)

13C NMR (CDCl₃, 75 MHz): 
- 184.20 (s, C=O)
- 89.43 (s, CH)
- 73.41 (s, CH)
- 71.91 (s, CH)
- 27.72 (s, CH₃)
- 21.23 (s, CH₃)
- 20.76 (s, CH₃)
- 19.15 (s, CH₃)
- 13.61 (s, CH₃)
Appendix – Spectral Data for Chapter 4

allyl hex-2-ynoate
but-2-yn-1-yl hex-2-ynoate

Appendix – Spectral Data for Chapter 4
Appendix – Spectral Data for Chapter 4

N-methoxy-N-methylnon-2-ynamide
Appendix – Spectral Data for Chapter 4

N-methoxy-N-methylbut-2-ynamide

ppm

170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

154.54 89.52 72.44 62.06 32.30 4.11

3.76 3.57 3.49 3.45 3.44 3.39 3.22 3.04 2.02
Appendix – Spectral Data for Chapter 4

N,N-dimethylhex-2-ynamide

- 7.26 edd3

\[ \text{ppm} \]

- 3.19
- 2.95
2.93
2.91
2.35
2.33
2.31
1.63
1.61
1.60
1.58
1.56
1.01

1.89

3.06

154.96

93.06

74.34

- 38.45
- 34.16
- 21.51
- 21.02
- 13.66

\[ \text{ppm} \]

- 80
- 170
- 160
- 150
- 140
- 130
- 120
- 110
- 100
- 90
- 80
- 70
- 60
- 50
- 40
- 30
- 20
- 10
- 0
Appendix – Spectral Data for Chapter 4

N,N,4,4-tetramethylpent-2-ynamide
Appendix – Spectral Data for Chapter 4

3-cyclopentyl-N,N-dimethylpropiolamide

[Chemical structure image]

[Chemical spectrum image]
Appendix – Spectral Data for Chapter 4

3-cyclohexyl-\textit{N},\textit{N}-dimethylpropilamide
Appendix – Spectral Data for Chapter 4

3-(cyclohex-1-en-1-yl)-N,N-dimethylpropilamide
Appendix – Spectral Data for Chapter 4

3-cyclohexyl-\(N,N\)-dimethylpropiolamide
Appendix – Spectral Data for Chapter 4

methyl hex-2-ynoyl-D-proline

ppm

1.00 0.95 1.24 2.40 7.46 7.40 24.06 4.02 1.04 1.53 1.55 1.58

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Appendix – Spectral Data for Chapter 4

N-methylhex-2-ynamide
Appendix – Spectral Data for Chapter 4

but-2-ynameide
Appendix – Spectral Data for Chapter 4

hex-2-yamide

[Chemical structure and spectral data diagram]
Appendix – Spectral Data for Chapter 4

4.10
Appendix – Spectral Data for Chapter 4
Appendix – Spectral Data for Chapter 4

![Spectral Data Diagram](image)

337
Appendix – Spectral Data for Chapter 4

4.11

Spectral data for compounds 4.11 is shown in the figure. The spectrum includes peaks at 28.86 and -0.00 ppm.
Appendix – Spectral Data for Chapter 4
Appendix – Spectral Data for Chapter 4
Appendix – Spectral Data for Chapter 4

![Spectral Diagram](image_url)
Appendix – Spectral Data for Chapter 4

348
Appendix – Spectral Data for Chapter 4

[Chemical Structure Image]

[1H NMR Spectrum Image]

[13C NMR Spectrum Image]
Appendix – Spectral Data for Chapter 4

4.18

[Chemical structure image]

[Graphical representation of spectral data]
Appendix – Spectral Data for Chapter 4

4.18
Appendix – Spectral Data for Chapter 4
Appendix – Spectral Data for Chapter 4

4.21

[Chemical Structure Image]

[1H NMR Spectral Data]

[13C NMR Spectral Data]
Appendix – Spectral Data for Chapter 4

![Spectral Data Diagram]

358
Appendix – Spectral Data for Chapter 4

4.22
Appendix – Spectral Data for Chapter 4
Appendix – Spectral Data for Chapter 4
Appendix – Spectral Data for Chapter 4

![Spectral Data Diagram](image-url)

4.25
Appendix – Spectral Data for Chapter 4
Appendix – Spectral Data for Chapter 4

Solvent = Acetone-$d_6$
Appendix – Spectral Data for Chapter 4

Solvent = Acetone-d$_6$
Appendix – Spectral Data for Chapter 4

[Chemical structure image and spectrum graph]

371
Appendix – Spectral Data for Chapter 4

4.30

ppm

7.26 dddd
7.13
7.11
7.09
7.04
7.02
7.04
6.34
6.33
6.13
5.68
3.01
2.64
2.62
2.61
2.60
1.75
1.75
1.70
1.69
1.67
1.66
1.62
1.42
1.30
1.18
1.17
1.15
1.14
1.0
0.85
0.80
0.75
0.70
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0

ppm

168.85
140.70
136.86
127.67
119.84
117.96
106.04
-42.23
-38.19
-34.51
-33.07
-26.34
-26.05

127.70
127.65
127.60

fi (ppm)
Appendix – Spectral Data for Chapter 4
Appendix – Spectral Data for Chapter 4

![Spectral Data Image]
Appendix – Spectral Data for Chapter 4
Appendix – Spectral Data for Chapter 4

![Chemical Structure](image)

[Chemical Structure]

-28.83

0.00

130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 ppm

![Spectral Data](image)

![Spectral Data](image)
Appendix – Spectral Data for Chapter 4

4.35
Appendix – Spectral Data for Chapter 4
Appendix – Spectral Data for Chapter 4

![Spectral Data Diagram]

---

388
Appendix – Spectral Data for Chapter 4
Appendix – Spectral Data for Chapter 4
Appendix – Spectral Data for Chapter 4

4.38
Appendix – Spectral Data for Chapter 4

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