Selective Additions to Unsaturated Carbon-Carbon Bonds by the Use of N-Heterocyclic Carbene-Copper(I) Catalysts

Brian A. Ondrusek
SELECTIVE ADDITIONS TO UNSATURATED CARBON-CARBON BONDS BY THE USE
OF N-HETEROCYCLIC CARBENE-COPPER(I) CATALYSTS

By

BRIAN A. ONDRUSEK

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The members of his supervisory committee were:

D. Tyler McQuade
Professor Directing Dissertation

Bruce Locke
University Representative

Michael Roper
Committee Member

Gregory Dudley
Committee Member

Igor Alabugin
Committee member

The Graduate School has verified and approved the above-named committee members, and certifies that the dissertation has been approved in accordance with university requirements.
I dedicate this effort to my family, without whose support I could never have accomplished all that I have.
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The development of easily-accessible and densely-functionalized synthetic intermediates is a longstanding goal of the organic chemistry community. The use of transition metal catalysts has allowed many synthetic targets to be produced with minimal waste. Copper(I) has distinct advantages to its use as a catalyst for organic transformations, in that it is relatively cheap and non-toxic by comparison to other metals which see frequent use. Hydroboration chemistry, in particular, has seen some of these benefits, as copper(I) catalyst systems for hydroboration have been the source of much research in the past 15 years, enabling the production of a wide variety of complex boron-containing synthetic intermediates via addition reactions to unsaturated bonds. The research contained herein describes our efforts to improve the methods for functionalization of unsaturated carbon-carbon bonds using N-heterocyclic carbene-copper(I) catalysts.

The formation of chiral allylboronates via allylic substitution is an important class of reactions owing to the versatile products that result, which can be used subsequently to produce allylic alcohols, homoallylic alcohols as well as to form C-C bonds via coupling reactions. Previously, only a few examples of chiral allylboronates have been described by the asymmetric addition of boron, therefore this was designated a good starting point for our research into this area. Through the use of a copper(I) catalyst with a 6-membered N-heterocyclic carbene (6-NHC) ligand, we have demonstrated the ability to produce chiral allylboronates with a high degree of selectivity. Additionally, this system was found to be stereoconvergant, meaning that both the E and Z-isomeric starting materials resulted in products with the same absolute stereochemistry.

In addition to polarized allylic alkenes, we also investigated the hydroboration of alkenes
which are strained but otherwise unactivated, a class of substrates understudied for copper-catalyzed hydroboration. Through the use of a 5-NHC ligand pioneered by Glorius, we were able to achieve the selective hydroboration of unfunctionalized strained alkenes in the presence of non-strained alkenes for a variety of norbornene and styrenic substrates.

In addition to the hydroboration of C-C double bonds, we then became interested in the addition of boron to alkynyl species to produce functionalized vinylboronates. Regioselective hydroborations utilizing copper(I) catalysis have been reported for terminal alkynes and for some internal alkyne systems, however propargylic substrates have been understudied and the ability to access any desired regioisomer remains elusive. Our efforts have shown that boron addition to propargylic alcohols can be controlled by the careful selection of catalyst and O-protecting group. Specifically, we have demonstrated that the use of a 6-NHC-Cu(I) complex with a m-nitrophenyl propargyl ether results in selectivity for the alpha position with a high degree of selectivity. The use of a 5-NHC-Cu(I) complex to an unprotected propargylic alcohol produced the desired beta-borylated material, also with good selectivity. In this way we have been able to produce a variety of functionalized vinylboronates to which we then turned our attention.

In an effort to showcase the utility of these vinylboronate species, we have also developed an ate-mediated allylic substitution, or AMAS, which can produce tertiary allylboronates by the simple addition of organomagnesium reagent. A variety of Grignard reagents were employed, and it was demonstrated that the AMAS procedure is compatible with most functional groups that are stable under Grignard conditions. To showcase the synthetic viability of this procedure we performed a total synthesis of the sugar molecule methyl axenoside from entirely achiral starting materials. This natural product was synthesized in 9 steps with an overall yield of 10%.
CHAPTER 1

INTRODUCTION

1.1 Layman’s Introduction

The work contained herein describes our efforts to improve upon current methods in organic chemistry toward the addition of boron to double and triple bonds. From a general perspective, such controlled additions allow us to perform specific transformations to desired substrates, yielding large quantities of product. This kind of progress is important for several different reasons. The medicinal chemist will use such transformations to create libraries of derivatives of biologically-active compounds which can then be screened for their effectiveness toward disease. Reactions which are selective for one product over another competing product may open new synthetic routes toward valuable natural products of which the synthetic organic chemist will take advantage. Additionally, the development of reactions which are environmentally and atom economic may enable valuable compounds to be produced on an industrial scale.

More fundamentally, the study of new organometallic complexes, such as the copper(I)-N-heterocyclic carbene complexes described in this work, provide insight into the chemistry of the metals themselves. The studies described in this work focus on copper because of the differing reactivity that copper shows compared to other transition metals commonly encountered in this field of study such as platinum, palladium and iridium. These fundamental studies add to the current body of knowledge in organic chemistry, creating the potential for even more methods of producing desired compounds. The work contained herein is our contribution to this area of organic chemistry, where we describe the use of copper(I)-NHC complexes for the
catalytic addition of boron to unsaturated double and triple bonds, and our applications of the materials produced by these newly-developed methods.

1.2 Alkene Functionalization in Organic Chemistry

Many methods exist for the functionalization of alkenes, including the Sharpless asymmetric epoxidation, Simmons-Smith cyclopropanation and Sharpless asymmetric dihydroxylation. While many other alkene functionalization strategies exist, the use of transition metals link these three particular methods. The pairing of organometallic catalysts with alkene chemistry has enabled a wide range of reactivity to be possible.

What is oftentimes less considered is the difference between one alkene and another. The reactivity of a polarized alkene will be considerably different than that of an isolated olefin, likewise an unstrained olefin will have very different reactivity than a unstrained one. The ability to match a catalyst species to the features of a particular alkene would allow one to perform very specific transformations to it, thereby adding valuable techniques to the chemist’s “toolbox.” The work described herein utilizes a series of copper(I) – N-heterocyclic carbene catalysts to exploit the different reactivities of different types of alkenes. We begin with the development of a stereoconvergent method for the allylic substitution of allyl aryl ethers, and move toward the chemoselective hydroboration of strained and styrenic double bonds. Moving on to alkynes, we explore a regioselective hydroboration of propargylic alcohols and aryl ethers, and finish with the development of a method for the ate-mediated allylic substitution (or AMAS) of the resulting vinylboronate products.

Our choice of copper for the forthcoming studies is due to the interest in the McQuade group of developing low-cost and efficient chemical processes. Many catalysts rely on metals such as platinum, palladium, iridium and rhodium which can be toxic and expensive. Copper is
an attractive alternative for these metals due to its relative abundance and lower cost. While research into copper-catalyzed process has exploded in the past few decades, much of this work has been accomplished with copper-complexes of phospine ligands. More recently, the discovery of N-heterocyclic carbenes as stable ligands has caused another leap forward in the development of copper(1)-catalyzed chemistry. The following section will attempt to understand the differences between these two ligands and shed light on the origins of the differing reactivity profiles of their copper(I) complexes.

1.3 N-Heterocyclic Carbenes as Useful Ligands for Cu(I) Catalysts

For the development of catalytic organometallic reactions, the metal center alone is not the only factor to be considered. Many reactions involve transition metals paired with ligands which affect the reactivity of the metals. The careful matching of metal and ligand properties is essential in controlling the reactivity of a catalyst. These ligands can have one of two roles: they can be direct participants in the catalytic cycle, or so-called spectator ligands which simply provide steric and electronic bias to the metal center while avoiding any structural changes during the course of a reaction. In modern copper(I) chemistry, two classes of spectator ligands have found broad utility owing to the tunable nature of their steric and electronic properties, phosphine and N-heterocyclic carbene (NHC) ligands. Phosphine ligands are undoubtedly the most commonly encountered ligands, due to their well-understood tunability thanks to the seminal work by Tolman,\(^3\) as well as the commercial availability of a large number of compounds which facilitates quick screening of potential ligands.

\(N\)-heterocyclic carbenes, on the other hand, are a much newer class of ligands that have only begun to see major use in the last ten years. While these compounds are relatively easy to
synthesize, their commonplace use is still hindered by lack of commercial availability and detailed understand of how structure impacts their steric and electronic properties. However, processes are continually being discovered in which NHC-Cu(I) complexes outperform phosphine-Cu(I) complexes, which has led to a surge of interest in these valuable compounds.

1.3.1 Synthesis of Phosphine and NHC ligands

One of the major disadvantages to the use of NHC ligands for routine transition metal catalysis is the lack of a variety of commercially available ligands. Phosphines, while sometimes difficult to prepare, can be purchased in wide variety or even as a kit from many commercial suppliers. Fortunately, the preparation of NHC complexes is relatively straightforward, and can be accomplished either by functionalization of a preexisting imidazole ring or by the construction of an imidazolium salt from corresponding arylamine and triethyl orthoformate (Figure 1.1).

Additionally, metallation of the imidazolium salt has proven problematic for some transition metals. However in the case of copper(I) this can be accomplished either by direct treatment with CuCl in the presence of base, or simply by continuous flow of the imidazolium salt through a packed bed of Cu$_2$O at elevated temperatures. With isolation of these compounds achieved by simple trituration with hot toluene, a wide variety of NHC-Cu(I) complexes can be easily prepared for use. A major advantage of this class of compounds over other varieties of organometallic catalysts is their stability. These compounds can easily be stored at the benchtop for months at a time without any noticeable decrease in effectiveness.
1.3.2 Steric and Electronic Properties of NHCs

$N$-heterocyclic carbenes, like their phosphine counterparts, are 2-electron ligands with limited pi-backbonding ability, and therefore share some of the same properties.$^6$ Notable differences involve the effects of $N$- and $P$-substituents on the properties of the Cu(I) complex as a whole.

Geometrically speaking, the substituents attached to a phosphine ligand will point away from the metal center, forming a “cone” shape and giving these substituents little direct interaction with the metal center (Figure 1.2, bottom). NHC ligands instead form a “fan” shape, with substituents attached to nitrogen partially enveloping the metal center (Figure 1.2, top). It can be assumed then that the substituents of an NHC will play a large role in the steric environment of the reactive metal site, whereas phosphine substituents have less of a direct steric effect.

From the standpoint of electronics, it is well understood that the properties of a phosphine ligand can be tuned by exchange of the substituents attached to phosphorous center. This tunability is a result of the substituents attaching directly to the phosphorous atom which is
donating to the metal center. The *N*-substituents of an NHC, however, are not directly attached to the carbene donor center, and therefore play less of a role in the electronic properties of the overall complex. Further differences between phosphine and NHC ligands involve their binding strength with the metal center. NHC ligands, in this case, bind much more strongly to the metal center and are therefore less likely to be exchanged. The irreversible binding of NHCs is influenced less by the electronic nature of the NHC as it is by the desire for the NHC to retain aromaticity.

![Figure 1.2 Graphical illustration of the different steric environments created by NHC ligands and phosphine ligands](image)

Although tuning of *N*-substituents is a less-efficient way to tune the electronic properties of an NHC ligand, one understudied method involves the use of a 6-membered imidazolinium ring as opposed to the more common 5-membered imidazolium. It is understood that 6-membered *N*-heterocyclic carbene species are stronger donor ligands than corresponding 5-membered NHCs, which are stronger donors still than corresponding phosphine ligands. The donor abilities of phospine, 5-NHC and 6-NHC ligands have been briefly examined by comparing the carbonyl stretching frequencies (v(CO)) for the corresponding LRuCO complexes.
(Figure 1.3), although to our knowledge, no extensive study to this effect has been performed. The donor ability of the 6-NHC ligand developed in our group lies somewhere in between that of the typical 6-NHC and 5-NHC ligands. Much of the work contained herein describes our efforts to understand the reactivity of 6-membered NHCs by examining a unique 6-NHC Cu(I) complex developed in our lab.

![Diagram of LRu(CO)2 NHC complexes]

**Figure 1.3** Donation ability of some LRu(CO)2 NHC complexes, from ref 7

### 1.4 Allylic Substitution

The advent of asymmetric forms of allylic substitution reactions came about in response to an increasing demand for enantiopure compounds for natural product and pharmaceutical production. The use of transition metal catalysts bearing chiral ligands has revolutionized this area of research, making it one of the simplest and powerful carbon-carbon bond forming processes. As a result, a multitude of methods have been developed, many having the advantage of producing the desired enantiopure compounds from relatively cheap and commercially available prochiral materials. Additionally, copper-catalyzed allylic substitution reactions have
become popular due to the low cost of the copper salts and the normally high regio- and enantioselectivity. The copper-catalyzed allylic substitution works by the attack of a strong nucleophile onto an allylic olefin, which then causes the elimination of a leaving group at the allylic position.

Bäckvall

äs

15 mol % CuSAr
n-BuMgl
Et₂O, 0 °C, 120 min
100 % yield
42 % ee

κ

Knochel

82 % yield
96 % ee
98:2 S₉₂²:S₉₂

Figure 1.4 Early examples of copper-catalyzed asymmetric allylic substitution reactions

Copper has an advantage over other metals of interest in that it allows the use of unstabilized carbon nucleophiles, and a great deal of work has been dedicated to the development of allylic substitution systems utilizing Grignard, organozinc and organoaluminum nucleophiles catalyzed by copper. One of the first examples by Bäckvall and van Koten involved Grignard reagents, a chiral copper catalyst and substituted allylic acetates, though it only showed moderate enantioselectivity (Figure 1.4, top). A later system developed by the Knochel group relied upon dialkylzinc reagents and a chiral amine ligand paired to copper bromide to perform allylic substitution reactions on allylic halides (Figure 1.4, bottom). These two early
examples showcase the variety of conditions under which such a reaction can take place, in that the Knochel system requires a polar solvent and the van Koten system works better when the Grignard is in a non-polar solvent. Additionally, allylic acetates are the starting materials of choice for the Grignard substitution, whereas allylic chlorides work best for the Knochel substitution. Research in this field has made use of a great number of carbon and non-carbon nucleophiles. The work contained in the upcoming chapters will utilize diboron reagents as non-carbon nucleophiles, and additional information regarding allylic substitutions with non-carbon nucleophiles can be found at the beginning of those chapters.

1.5 Addition Reactions to Strained Alkenes

Alkenes which are distorted from optimal geometry but otherwise unactivated can undergo addition reactions in the presence of isolated olefins. The driving force for these reactions is the relief of ring strain, and a number of recent publications have taken advantage of the strained properties of this class of alkene. Specifically, a number of recent publications by the Lautens group have used strained olefins in the production of polycyclic heterocycles. In 2007, they described a palladium(0) catalyzed annulation of aryl heterocycles for which the key step was palladium insertion into a norbornenyl double bond. A subsequent intramolecular C-H activation reaction of a pendant heterocycle enabled the production of a variety of polycyclic heterocycles. The following year, the Lautens group published a report detailing the formation of polycyclic heterocycles of benzothiophene. These reactions were catalyzed by a rhodium(I) complex employing a bulky phosphine ligand (Figure 1.5, top). Several examples from this manuscript showed that transition metal catalyzed coupling took place exclusively at the electron-rich double bond in cases where others were available. Similar examples of selectivity were encountered in a subsequent publication where they describe a rhodium-catalyzed
vinylecyclopropanation reaction of dienylboronate esters with strained alkenes (Figure 1.5, bottom). In addition to preferential rhodation to the more electron-rich olefin, as was seen in the previous report, they also observed with some examples a preference for strained olefins over relatively unactivated ones. This kind of selectivity is an interesting feature of reactions involving strained alkene systems and is an important step forward regarding the selective functionalization of alkenes.

**Chemoselectivity for Electron Rich Alkenes**

![Chemoselectivity for Electron Rich Alkenes](image)

**Strained Alkene Chemoselectivity**

![Strained Alkene Chemoselectivity](image)

**Figure 1.5** Examples of addition to strained alkenes from the Lautens group showing chemoselectivity for electron rich (top) and strained (bottom) olefins

These reactions behave as they do because of the approximately 100 kcal/mol strain energy present in a norbornenyl double bond, and other types of addition reactions should be possible as well. The addition of boron to strained alkenes is not unheard of, though most examples of transition metal catalyzed processes involve rhodium and iridium. Additionally, while these metals can catalyze the monoboration of strained alkenes under some circumstances,
diboration products are most often observed. Our work in Chapter 3 explores the use of copper(I) catalysts in the chemoselective hydroboration of strained alkenes, a metal for which very few examples of this type exist.

1.6 Regioselective Functionalization of Alkynes

The functionalization of alkynes is intimately related to the functionalization of alkenes. Regioselective methods to functionalize alkynes produce substituted alkenes with a variety of properties, and methods to achieve this also constitute a significant part of the work contained herein. Alkynes are generally less reactive than their olefin counterparts, often requiring stronger conditions and elevated temperatures to react. Transition metal catalysis is a common way that researchers have found to circumvent these issues, and thus alkynes have come to hold an important place in organic synthesis. Common methods for the functionalization of alkynes include the Glaser coupling, a copper-catalyzed process by which one can produce homocoupled 1,3-diynes, or heterocoupled diynes if using a palladium catalyst. The Sonogashira cross-coupling reaction is a palladium catalyzed process which has become the standard for C-C bond forming processes with alkynes.

The Glaser and Sonogashira coupling reactions all functionalize at the acetylenic position, however many methods also exist for manipulation of the pi-system. Performing a Diels-Alder cycloaddition with alkynes is a useful way to produce functionalized 1,4-cyclohexadienes. Another example which has gained popularity since the discovery of a copper-catalyzed methodology is “click” chemistry, or the copper-catalyzed alkyne-azide cycloaddition reaction (CuAAC). This reaction produces 1,2,3-triazoles with exclusively the 1,4-regiochemistry. Many other methods for alkyne functionalization exist, but the focus of this work is specifically on hydroboration.
The hydroboration of alkynes is a reaction that any second-year undergraduate should know, however we are only now just scratching the surface of the potential that these methods hold. The classical methods for alkyne functionalization have become known as the Brown hydroboration method. Relying on the addition of simple boranes and heat, the Brown hydroboration method can produce vinylboronates from their corresponding alkynes with respectable regioselectivity (for the \textit{anti}-Markovnikov product) and exclusively \textit{syn}-geometry due to the nature of the intermediate. A great leap forward with this chemistry was taken as transition metal complexes were used to catalyze the process. The advantages gained were decreased reaction times and further control over regio- and chemoselectivity.

Despite the promise of transition metal catalyzed hydroboration of alkynes, this research is still quite young. Many of the methods that currently exist apply exclusively to terminal alkynes, showing no reactivity or selectivity for internal triple bonds. Moreover, methods for the regioselective hydorboration of internal alkynes are somewhat limited to specific substrates. Chapter 4 describes our contributions to this field in the development of a method for the regioselective hydroboration of propargyl alcohols or propargyl ary1 ethers using NHC-Cu(I) catalysts. The resulting vinylboronates serve as useful synthetic intermediates and their application in an ate-mediated allylic substitution reaction is described in Chapter 5. In Chapter 6, this useful allylic substitution method is further applied as a key step toward the total synthesis of a naturally-occurring saccaride.
CHAPTER 2

A STEREOCONVERGENT SYNTHESIS OF CHIRAL ALLYLBORONATES VIA ASYMMETRIC ALLYLIC SUBSTITUTION

2.1 Background

Stereochemically pure compounds are indispensable in the production of pharmaceuticals and natural products. Chiral allylboronates are important synthetic intermediates due to the versatility of the C-B bond. Reactions which transform allylboronates into allylic alcohols, amines and homoallylic alcohols are well known, and even C-C bonds can be formed from them by Suzuki-Miyaura coupling. Their synthesis can be achieved by a variety of methodologies. The Hall group has shown that chiral allylboronates can be easily produced via the $S_N2'$ alkylation of a vinylboronate with an allylic leaving group using an iridium or copper catalyst. Other methods for allylboronate production include the use of chiral auxiliaries, 1,4-silaboration and diboration.

The work described in this chapter creates allylboronates from allylic aryl ethers. These compounds can be prepared in several different ways, though most methods offer poor stereocontrol about the double bond. This can be a problem because the majority of transition metal catalyzed allylation reactions display stereodivergence, or rather that the $E$ and $Z$-isomers of a particular substrate produce different enantiomeric products (Figure 2.1). In situations where only one enantiomeric product is desired a stereoconvergent reaction would be preferred, in which both $E$ and $Z$-isomers of a starting material lead to the same stereochemical product. Unfortunately, because enantioconvergence requires a catalyst that can discriminate between
enantiomers, examples of reactions showing enantioconvergence are rare. Such an innovation would expand the available methods for starting material production, thereby improving the utility of such a transformation.

**Figure 2.1** Stereoconvergence versus stereodivergence in asymmetric allylic substitution

Enantioconvergence has been previously reported for allylic substitution reactions. The Ito and Sawamura groups observed enantioconvergence for the asymmetric allylic substitution of cyclic allylic alkyl ethers where the allylic position is racemic, however this method displays enantiodivergence when applied to *E/Z* mixtures of acyclic substrates.\(^{19}\) The Hoveyda group has expanded on the substrate scope of these Cu-catalyzed allylic substitution reactions by showing that tertiary allylic alcohols can be produced from their corresponding trisubstituted allylic carbonates in high yield and selectivity,\(^ {20}\) however this method also displays enantiodivergence, with *E* and *Z* allylic carbonates yielding different stereochemical products. This chapter reports the development of the first enantioconvergent route toward linear chiral allylboronates via the asymmetric allylic substitution of allyl aryl ethers utilizing a 6-membered *N*-heterocyclic carbene (6-NHC) copper(I) catalyst species previously developed in our lab.
2.2 Initial Studies and Optimization

Recently we reported that 6-NHC-Cu(I) complex 1a was an efficient catalyst for the asymmetric β-borylation of a variety of α,β-unsaturated esters.\textsuperscript{21} When applied to a substrate possessing an allyl aryl ether, however, we observed unique chemoselectivity for the corresponding allylboronate instead of the expected β-borylated product. This discovery led us to examine the reaction using other copper(I) ligands which are known to participate in β-borylation. As Table 2.1 shows, 6-membered NHC complex 1a produces the allylic substitution product almost exclusively (entry 1). Conversely, the 5-membered N-heterocyclic carbene complex 2 (SIMes) produced the β-borylated product 5b exclusively (entry 2), while the phosphine-Cu(I) complex 3 produced a low-yielding mixture of 5a and 5b. These data indicate a chemoselectivity difference between 6-NHC complex 1a and other phosphine and NHC ligands commonly used for allylic substitution reactions.

![Chemical structures and reaction scheme]

Table 2.1 Comparison of Allylic Substitution versus β-Borylation Chemoselectivity

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Temp (°C)</th>
<th>Time</th>
<th>5a/5b ratio\textsuperscript{a}</th>
<th>Yield (%\textsuperscript{b})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>-20</td>
<td>10 min</td>
<td>25/1</td>
<td>88 (5a) (70)</td>
</tr>
</tbody>
</table>
### Table 2.1 continued

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Temp (°C)</th>
<th>Time</th>
<th>5a/5b ratio&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>2</td>
<td>-20</td>
<td>20 min</td>
<td>1/24</td>
<td>88 (5b) (71)</td>
</tr>
<tr>
<td>3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>3</td>
<td>rt</td>
<td>6 h</td>
<td>1/1.5</td>
<td>65 (5a + 5b) (16&lt;sup&gt;d&lt;/sup&gt;)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Ratios were determined by <sup>1</sup>H NMR spectroscopy. <sup>b</sup> Yields were determined by <sup>1</sup>H NMR spectroscopy; isolated yields are shown in parentheses. <sup>c</sup> The reaction was run in THF. <sup>d</sup> Isolated yield of 5a.

### 2.2.1 Optimization Studies

#### 2.2.1.1 Catalyst Comparison for Allylic Substitution.

Having established the unique chemoselectivity of 6-NHC complex 1a, we sought to explore this allylic substitution reaction by comparing catalyst activity of a simpler system. Using the setup depicted in Table 2.2, and comparing the same ligands as in Table 2.1, we established that once again the 6-NHC catalyst 1a produced only the branched allylboronate product in high yield (entry 1). The 5-NHC catalyst 2 also produced the branched allylboronate exclusively, albeit in low yield. The phospine-based catalyst 3 (entry 3) produced a low-yielding mixture of branched and linear product.

Despite the excellent chemoselectivity of 1a, the observed enantioselectivity was disappointing. On the basis of molecular models, we hypothesized that increasing the steric constraints of the system at the para position might lead to greater discrimination between the favored and unfavored transition states (see Figure 2.4 below), and because the modular synthesis of our 6-NHC ligand allows for adjustments to be made in a simple fashion we are able to easily introduce a tert-butyl group onto the steric blockade of catalyst 1a. When the allylic substitution was performed with catalyst 1b, possessing a tert-butyl group in the para position, we observed much improved enantioselectivity (84 %, Table 2.2, entry 4), with no loss in
chemoselectivity (>99:1 of 6a/6b). Thus, catalyst 1b was chosen for further examination of this allylic substitution reaction.

Table 2.2 Catalyst Comparison for an Allylic Substitution Reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol %)</th>
<th>Time</th>
<th>6a/6b&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a (1)</td>
<td>20 min</td>
<td>&gt;99:1</td>
<td>91 (47)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>2 (1)</td>
<td>3 h</td>
<td>&gt;99:1</td>
<td>17</td>
</tr>
<tr>
<td>3&lt;sup&gt;d&lt;/sup&gt;</td>
<td>3 (3)</td>
<td>22 h</td>
<td>14/1</td>
<td>11</td>
</tr>
<tr>
<td>4</td>
<td>1b (1)</td>
<td>10 min</td>
<td>&gt;99:1</td>
<td>91 (84)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Ratios were determined by GC analysis. <sup>b</sup> Yields were determined by GC using an internal standard. <sup>c</sup> Product ee. <sup>d</sup> The reaction was carried out in THF at room temperature.

2.2.1.2 Leaving Group Optimization for Allylic Substitution. The performance of any substitution reaction can be highly dependent on the properties of the leaving group, thus a screen of potential allyl aryl ethers was performed, attempting to maximize the enantioselectivity of the reaction. The same hex-2-enyl aryl ether (E-7 or Z-7) was used for all screening reactions, varying only the steric and electronic nature of the aryl leaving group (Table 2.3).

The nature of the aryl ring had little impact on the yield and selectivity of the allylic
substitution, though some trends were observed nonetheless. The experiments above show that modestly electron rich aryl groups such as phenyl, 2-methylphenyl and 3,5-dimethyl (entries 1-3) provide good yields but only modest enantioselectivity. Electron rich aryl rings (entry 9) provide somewhat lower enantioselectivity. Electron-poor arenes, with the exception of 3,5-bis(trifluoromethyl)phenyl (entry 4), provide the highest levels of enantioselectivity (entries 5-8). More surprising were the results of entries 5 and 6, wherein we observed that both the pure (E) and (Z)-substrates of our 3-nitrophenyl ether provided the same enantiomeric product, the (S)-enantiomer. These results are opposite what was observed by the Ito, Sawamura and Hoveyda groups, who observed stereodivergence in that the linear (E) and (Z)-isomers resulted in different enantiomeric products. These observations served as our first indications that direct enantioconvergence may be at work, though more experiments needed to be performed to rule out other possibilities.

Table 2.3 Leaving Group Optimization for the Asymmetric Allylic Substitution Reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate (Ar)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>E-7a (phenyl)</td>
<td>91</td>
<td>84 (S)</td>
</tr>
<tr>
<td>2</td>
<td>E-7b (2-methylphenyl)</td>
<td>91</td>
<td>80 (S)</td>
</tr>
<tr>
<td>3</td>
<td>E-7c (3,5-dimethylphenyl)</td>
<td>86</td>
<td>88 (S)</td>
</tr>
<tr>
<td>4</td>
<td>E-7d (3,5-bis(trifluoromethyl)phenyl)</td>
<td>95</td>
<td>64 (S)</td>
</tr>
<tr>
<td>5</td>
<td>E-7e (3-nitrophenyl)</td>
<td>79</td>
<td>89 (S)</td>
</tr>
</tbody>
</table>

1b (1 mol %) B$_2$(pin)$_2$ (1.1 equiv.)
NaOFtBu (0.3 equiv.)
MeOH (2 equiv.)
Et$_2$O, 0°C, 10 min

Bpin

7 (E or Z)
Table 2.3 continued

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate (Ar)</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td><em>Z</em>-7e (3-nitrophenyl)</td>
<td>47</td>
<td>91 (S)</td>
</tr>
<tr>
<td>7</td>
<td><em>E</em>-7f (4-nitrophenyl)</td>
<td>94</td>
<td>87 (S)</td>
</tr>
<tr>
<td>8</td>
<td><em>E</em>-7g (3-methyl-4-nitrophenyl)</td>
<td>74</td>
<td>84 (S)</td>
</tr>
<tr>
<td>9</td>
<td><em>E</em>-7h (4-methoxyphenyl)</td>
<td>92</td>
<td>62 (S)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Determined by GC analysis using an internal standard. <sup>b</sup> Determined by GC analysis after oxidation and acetylation of the allylboronate products.

2.2.2 Mechanistic Considerations for Stereoconvergence

Direct enantioconvergence as a result of catalyst control is only one way to interpret the results above in entries 5 and 6 of Table 2.3, therefore we needed to investigate other hypotheses as well. Our initial hypothesis was that *E/Z*-isomerization may be occurring through an intermediate π-allyl complex derived from an η<sup>3</sup> bond between copper and the allyl group of our starting material (Figure 2.2). This phenomenon would also yield a stereoconvergent procedures by formation of the more stable isomer (likely trans), which would lead to a single enantiomeric product.

![Figure 2.2 Graphical representation of our hypothesized π-allyl-copper intermediate responsible for the observed stereoconvergence.](image)

This hypothesis was examined by monitoring the reaction of the pure *cis*-isomer by <sup>1</sup>H
NMR. If isomerization was indeed occurring, we predicted that we should detect the more stable \textit{trans}-isomer at early conversion, however during the course of the reaction no isomerization was observed. Additionally, it was expected that a \( \pi \)-allyl-copper intermediate should produce some amount of the linear product, however none was observed during the course of the reaction. While these observations cannot conclusively rule out the presence of a \( \pi \)-allyl intermediate, it seemed to give credence to the idea that our observed stereoconvergence was catalyst-based.

Once we had shown that isomerization does not occur, we began to speculate about the differing reaction rates of the two isomers, which led us to monitor the relative rates of product formation of both the \( (E) \) and \( (Z) \)-isomeric substrates. To accomplish this, we performed an allylic substitution on a 1:1 mixture of the isomeric alkenes and monitored the rates of this reaction by GC (Figure 2.3). The data show that the \textit{trans}-isomer reacts quickly relative to the \textit{cis}-isomer, explaining the low yield of the \textit{cis}-isomer in Table 2.3 (entry 6). Additionally, the overall enantiomeric excess of the reaction was 94 \% (95 \% GC yield), which is intermediate between the \textit{ee}'s of each isomer reacted alone (see Table 2.4, entry 1). These data provided further evidence for direct enantioconvergence induced by catalyst 1b.

![Figure 2.3 Reaction profiles for the \textit{trans} and \textit{cis}-substrates.](image-url)
Having established that direct enantioconvergence is occurring, we considered the steric constraints of our catalyst species in an effort to reconcile our observations (Figure 2.4). We first considered that all bottom-side approaches (with respect to Figure 2.4) to the catalyst would be blocked by orientation of the phenyl ring proximal to the metal center. With that established, we reasoned that the remaining four approach options (above) would be dominated by the interaction between the R-group of the substrate and the steric blockade of the 6-NHC-Cu(I) catalyst. If all approaches rendering the R-group in close proximity to the steric blockade of the catalyst are unfavorable (Figure 2.4, right side), then this leaves only two approaches viable, resulting in the addition of boron to the same face of the substrate regardless of the geometry of the alkene. Furthermore, it seems likely that the differential consumption rates of the trans and cis-substrates would be due to the proximity of the aryl group with the phenyl ring on the far side.
of the ligand (Figure 2.4, left side).

2.3 Substrate Synthesis and Reaction Scope

Our observation of stereoconvergence enables us to produce allyl aryl ether starting materials by a variety of methods. With the stereodivergent allylic substitution methods of Ito, Sawamura and Hoveyda, any method that provides poor $E/Z$ selectivity, such as cross metathesis, would be unsuitable because one would obtain a mixture of enantiomers upon substitution. The stereoconvergent method provided by catalyst 1b enables the use of starting material produced by any method, regardless of the ratio of isomers, without the need for tedious purifications.

![Chemical Reaction Diagram]

**Figure 2.5** Stereoconvergence allows for diversity of methods for substrate production.

As Figure 2.5 illustrates, when not concerned about the isomeric ratio of the resulting ethers, any number of methods can be used. The method used can depend upon the cost of reagents or any other criterion for the production of a desired compound. For example, the
substrates used in Table 2.4 below were produced by a number of different methods such as Buchwald’s modification of the classical Ullmann coupling (entry 9), cross-metathesis (entries 3-9), nucleophilic aromatic substitution (entries 1 and 2) and even simple $S_{N}2$ substitution conditions via the Williamson ether synthesis (entry 10). These methods provide products with a range of isomeric purity, as detailed in Table 2.4 below, and such freedom in synthesis is valuable.

Thus, starting materials with a range of isomeric purity were used to explore the functional group compatibility of our system under the optimized reaction conditions. When treated with 1 mol % of catalyst 1b, $E/Z$ isomeric mixtures of all substrates were well tolerated, resulting in uniformly high yields and high enantioselectivities.

![Diagram](image)

Table 2.4 Substrate Scope for Asymmetric Allylic Substitution Using Catalyst 1b

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>$E/Z$ of 10</th>
<th>Yield of 11 (%)$^a$</th>
<th>ee (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Substrate 10a" /></td>
<td>&gt;30/1</td>
<td>90</td>
<td>93 (S)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;1/30</td>
<td>80</td>
<td>96 (S)</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Substrate 10b" /></td>
<td>26/1</td>
<td>84$^d$</td>
<td>&gt;99 @</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Substrate 10c" /></td>
<td>4.7/1$^c$</td>
<td>95</td>
<td>93 (S)</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="Substrate 10d" /></td>
<td>5.5/1$^c$</td>
<td>87</td>
<td>92</td>
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</table>
Table 2.4 continued

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>$E/Z$ of 10</th>
<th>Yield of 11 (%)$^a$</th>
<th>ee (%)$^b$</th>
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</thead>
<tbody>
<tr>
<td>5</td>
<td><img src="image" alt="10e" /></td>
<td>6.6/1$^c$</td>
<td>95</td>
<td>93 (S)</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="10f" /></td>
<td>3.3/1$^c$</td>
<td>92</td>
<td>93</td>
</tr>
<tr>
<td>7</td>
<td><img src="image" alt="10g" /></td>
<td>3.2/1$^c$</td>
<td>50</td>
<td>94</td>
</tr>
<tr>
<td>8</td>
<td><img src="image" alt="10h" /></td>
<td>1.1/1$^c$</td>
<td>&gt;95</td>
<td>94</td>
</tr>
<tr>
<td>9</td>
<td><img src="image" alt="10i" /></td>
<td>12/1$^c$</td>
<td>83</td>
<td>93 (S)</td>
</tr>
<tr>
<td>10</td>
<td><img src="image" alt="10j" /></td>
<td>&gt;30/1</td>
<td>92$^d$</td>
<td>90</td>
</tr>
</tbody>
</table>

$^a$ Isolated yields. $^b$ Determined by GC analysis after oxidation and acetylation of allylboronate. $^c$ Synthesized by cross-metathesis. $^d$ Isolated yield of 12.

Enantioselectivity was determined by oxidation of the product allylboronate and subsequent acetylation, and where possible, absolute configurations were determined by comparison with known compounds. The pure cis and pure trans isomers of a product were compared in entry 1, which shows that the pure cis-10a (96 % ee) gave a higher enantioselectivity than trans-10a (93 % ee). Allylic substitution of a compound with a bulky substituent attached to the double bond (entry 2) produced an allylboronate with >99 % enantioselectivity. Interestingly, the product obtained in entry 2 is of the opposite predicted stereochemistry, verified by comparison to known data. While we hypothesize that this
phenomenon is due to the bulkiness of the cyclohexyl side chain, additional experiments would be necessary to support this hypothesis, as a bulky side chain (Figure 2.4) should serve to increase the selectivity for the S-enantiomer. Substrates with mixed E/Z ratios were produced by cross metathesis (entries 3 – 9). These substrates show that the asymmetric allylic substitution method is tolerant of TBS-protected alcohols and boc-protected amines. These observations show that a library of chiral allylboronates could be easily created by a variety of methods, and with high stereochemical purity.

As a final substrate, we wished to establish the electronic preference of 1b between di- or tri-substituted allylic aryl ethers. In order to examine this question, compound 10k was prepared (Figure 2.6), and the reaction was run under standard allylic substitution conditions with 6-NHC-Cu(I) catalyst 1b, before analyzing the crude reaction mixture by ¹H NMR. Our analysis showed that the reaction went to 80 % conversion, and that only the disubstituted alkene reacted. These results indicate that not only is 1b chemoselective toward allylic substitution over β-borylation, but also that it reacts preferentially with disubstituted double bonds in the presence of trisubstituted ones.

![Figure 2.6](image-url)  
**Figure 2.6** Competition study between di- and trisubstituted allylic aryl ethers for asymmetric allylic substitution reaction.

### 2.4 Conclusions

An asymmetric method was described for the allylic substitution of a variety of allyl aryl ethers. 6-membered N-heterocyclic carbene copper(I) catalysts 1a and 1b have demonstrated
unique reactivity compared to copper(I) complexes of other 5-membered NHC and phosphine ligands. Complex 1b shows exceptional chemoselectivity and enantioselectivity for the addition of bis(pinacolato)diboron to allylic aryl ethers, showing preference for allylic substitution over other available reaction pathways, as well as a strong preference for disubstituted alkenes. Most notable, however, is the observance of stereoconvergence with catalyst 1b, which contrasts with the stereodivergence observed for other methods of allylic substitution for linear substrates. This observation enables substrate preparation by a variety of methods because $E$ and $Z$ substrate mixtures will produce the same stereochemical outcome. The observed stereoconvergence was rationalized by consideration of catalyst geometry after the existence of a $\pi$-allyl-copper complex was deemed unlikely. This method serves as a useful addition into the existing literature because of the ease with which one can produce highly enantiopure chiral allylboronates, which can be valuable intermediates toward the synthesis of a variety of pharmaceutical and natural compounds.
CHAPTER 3

REACTIVITY OF A FUSED N-HETEROCYCLIC CARBENE-COPPER(I) SYSTEM TOWARD STRAINED AND STYRENIC ALKENES

3.1 Background

Copper(I) catalysts employing \( N \)-heterocyclic carbene ligands have emerged as promising tools for the addition of boron reagents to unsaturated carbon-boron bonds, as evidenced by their utility in the \( \beta \)-borylation of \( \alpha,\beta \)-unsaturated esters and the asymmetric allylic substitution of allyl aryl ethers.\(^{21,24}\) In addition to polarized unsaturated bonds, methods toward the borylation of unactivated or strained alkenes would be synthetically useful. The Fernández group has demonstrated the ability of palladium catalysts to perform efficient diboration of a number of styrenic substrates.\(^{25}\) This group has also reported on the Rh(cod)(NHC)-catalyzed selective diboration of unsubstituted cyclic olefins.\(^{26}\) The Miyaura group has used iridium-based catalysts to hydroborate a number of unactivated alkenes with pinacolborane.\(^{27}\) Additionally, the Srebnik group has shown that both rhodium and zirconium catalysts are efficient in the hydroboration and addition of \( \text{CCl}_4 \) to strained, styrenic and even some unactivated olefins.\(^{28}\) Copper-based methods hold additional promise in this area, from the use of commercially available bis(pinacolato)diboron instead of pinacol borane, as well as the potential for both hydroboration and carboration. While some literature precedent exists, copper-based methods for these transformations remain relatively unexplored. Previously, the borylation of styrene was reported by the Fernández group, who found that the choice of Cu(I)-NHC complex and ratio of styrene to diboron reagent had a large effect on the selectivity of diborylation versus hydroboration.\(^{29}\) A report published by the Hoveyda group likewise illustrates the potential of
Cu(I)-NHC species to selectively hydroborate 1,1-disubstituted aryl olefins.\textsuperscript{30} We hypothesized that the appropriate choice of NHC ligand might expand on current knowledge and allow us to perform a selective hydroboration of modestly activated and styrenic olefins.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{ligands.png}
\caption{A series of pyridine carboxylate-derived NHC ligands prepared by Glorius, et. al.}
\end{figure}

We sought to find a suitable \(N\)-heterocyclic ligand which is both easy to prepare and highly active toward the selective hydroboration of strained or styrenic olefins in the presence of unstrained and unactivated ones. In 2005, Glorius, et. al reported the synthesis and characterization of a unique class of fused \(N\)-heterocyclic carbene ligands derived from commercially available pyridine carboxylates.\textsuperscript{31} These ligands were easily prepared (Figure 3.1) and subsequently shown to be highly efficient ligands for the palladium-catalyzed Suzuki cross-coupling of aryl chlorides. Herein we show that the Cu(I)-NHC complex of this ligand can be easily formed in a continuous flow process, and demonstrate that it is an active catalyst for the hydroboration of strained and styrenic olefins.

### 3.2 Preparation of the Cu(I)-NHC Complex

Recently we described a procedure for the efficient formation of Cu(I)-NHC complexes by continuous flow, and successfully produced a series of 5- and 6-membered N-heterocyclic
This method was utilized for the synthesis of the copper(I) complex used in this study starting from the commercially available chloride salt of the Glorius ligand (Figure 3.2, 13). Our continuous flow method involved flowing a solution of imidazolium salt (13) through a packed column of Cu$_2$O and molecular sieves, with additional molecular sieves at the ends of the column. By heating the column to 110 °C, the solution of 13 could be passed through the column at a steady rate and isolated by simple trituration with toluene. In this way, multigram quantities of the copper(I) complex 14 could be formed in a short amount of time with an isolated yield of 94%. Additionally, this complex, like many NHC-Cu(I) complexes that we have developed, is air stable and easily handled.

A single crystal of complex 14 was obtained by vapor diffusion of diethyl ether into a solution of 14 in dichloromethane, and the resulting crystals were analyzed by single-crystal X-ray crystallography. Figure 3.3 shows the resulting X-ray crystal structure. The observed carbene-copper bond is consistent with other known NHC-Cu(I)Cl complexes. Interestingly, the N-C-Cu bond angles illustrate the pocket produced by the heterocycle substituent in that the bond angle is larger on the side of the mesityl group and smaller on the side of the heterocycle. Additionally, this ligand possesses several unique features among NHC ligands that we hoped to explore. The 5,6-fused ring system appears to be aromatic based upon planarity and bond lengths in the crystal structure. The large relative difference in steric congestion from one side of the
ligand to the other may also confer unique properties onto Cu(I)-species with this ligand. We hypothesized that this property would produce an active catalyst and our examination of its reactivity is described below.

![Figure 3.3 X-ray crystal structure of 14, showing two crystallographically independent molecules. Selected distances [Å] and angles [°]: Cu-Cl 2.0982(6) and 2.1046(6). The mesityl fragment leads to a larger N-C-Cu angle as compared to the N-C-Cu angle on the opposite side of the C-Cu-Cl line (132.9° vs. 123.8° and 124.7°).](image)

### 3.3 Optimization Studies and the Role of Methanol

As the hydroboration of polarized olefins, such as α,β-unsaturated esters and allylic species, is already well understood and the logical next step is the functionalization of strained, but otherwise nonpolar double bonds. The few methods that currently exist utilize transition metals which are often toxic and expensive, but more importantly the application of copper-based methods will endow flexibility in the methods by pulling from the extensive library of copper based C-Y bond formation reactions. To test our hypothesis that the Cu(I)-NHC complex utilizing the Glorius ligand would be an active catalyst toward the hydorboration of strained double bonds, we chose norbornene (15) as our representative substrate.
Previous work in the Yun group has demonstrated that methanol is necessary as a proton source for high conversions of NHC-Cu(I) catalyzed reactions. Our conditions screen focused on control experiments which would discern the role of methanol as well as identify a suitable base and boron source. As Table 3.1 demonstrates, using Glorius-Cu(I) complex 14, bis(pinacolato)diboron as a boron source and sodium tert-butoxide as a base (entry 1) the reaction proceeds to 82 % isolated yield of the desired product. Omitting methanol (entry 2) stalls the reaction at only 4 % conversion, which we attribute to minute traces of water in the system. Further control experiments show that omitting catalyst 14, or omitting base (entries 3 and 4) gives no reaction. Furthermore, due to the recent development of metal-free carbene catalyzed reactions, we exchanged the active catalyst 14 with the imidazolium salt 13, but saw no conversion (entry 5). Thus, the active Cu(I)-NHC is required for a reaction to take place, and the addition of methanol as a proton source is necessary for regeneration of the catalyst.

To further understand the role of methanol in our system, we then attempted deuterium-incorporation studies. The reaction was carried out under optimized reaction conditions using methanol-d₄ in place of methanol. The deuterated product 17 was isolated with yields equivalent
to those reported for 16. These date, plus information gained from the literature and our control experiments led us to propose the catalytic cycle depicted in Figure 3.4 below.

Figure 3.4 Proposed catalytic cycle for the hydroboration of norbornene with Cu(I) complex 14.

In this proposed catalytic cycle, CuCl is first exchanged with NaOtfBu, which is presumed to be the resting state. Transmetallation with bis(pinacolato)diboron leads to the active Cu-B species which then undergoes oxidative addition with norbornene. The resulting organocuprate intermediate then undergoes methanolysis to yield the desired product (either protonated or deuterated) and regenerates the starting Cu-alkoxide intermediate. Kinetic isotope effect experiments were undertaken in order to discern the rate-determining step, unfortunately these
were unsuccessful. Both dilution of the reaction and decreasing catalyst loading were attempted in order to obtain usable data, however even under these conditions the reaction was found to be too fast for accurate analysis. Based, however, on the strong dependence of the reaction on the presence of methanol, we propose that methanolysis of the organocuprate intermediate is the rate determining step of this cycle. It remained to be seen, however, if this system is general in its reactivity toward strained or styrenic olefins.

3.4 Reaction Scope

A representative, though not exhaustive, list of strained and styrenic olefins were chosen to examine the potential scope of this system. The following substrates were chosen because they represent olefins with a range of strain, from unactivated to highly-strained. Additionally, a few examples of styrenic olefins were chosen to represent the range of these substrates that would prove active in our system. The results of our hydroboration experiments with 14 is depicted in Table 3.2 below.

![Diagram](image)

Table 3.2 Hydroboration Scope for Strained and Styrenic Alkenes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (a)</td>
<td><img src="image" alt="Substrate 1" /></td>
<td><img src="image" alt="Product 1" /></td>
<td>89^b</td>
</tr>
<tr>
<td>2 (b)</td>
<td><img src="image" alt="Substrate 2" /></td>
<td><img src="image" alt="Product 2" /></td>
<td>81</td>
</tr>
<tr>
<td>3 (c)</td>
<td><img src="image" alt="Substrate 3" /></td>
<td><img src="image" alt="Product 3" /></td>
<td>76</td>
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</table>
Table 3.2 continued

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
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<td><img src="image1" alt="Substrate" /></td>
<td><img src="image2" alt="Product" /></td>
<td>85&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>5 (e)</td>
<td><img src="image3" alt="Substrate" /></td>
<td><img src="image4" alt="Product" /></td>
<td>82</td>
</tr>
<tr>
<td>6 (f)</td>
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<td><img src="image6" alt="Product" /></td>
<td>95</td>
</tr>
<tr>
<td>7 (g)</td>
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</tr>
<tr>
<td>8 (h)</td>
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</tr>
<tr>
<td>9 (i)</td>
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<td><img src="image12" alt="Product" /></td>
<td>NR&lt;sup&gt;d&lt;/sup&gt;</td>
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</tbody>
</table>

<sup>a</sup> Isolated Yield. <sup>b</sup> Isolated as a 79:21 mixture of regioisomers. <sup>c</sup> Isolated as a 69:31 mixture of regioisomers. <sup>d</sup> No reaction was observed even after 24 hours.

Entry 1 showcases the selectivity of our system for strained alkenes, as the mono-borylated product was obtained in 89 % yield as a mixture of regioisomers, while the product resulting from hydroboration of the unactivated alkene was not observed. Likewise, in entry 34 the norbornene olefin was hydroborated preferentially in the presence of an olefin contained within a five-membered ring, though once again the product was isolated as a mixture of regioisomers. This system works well in the presence of other functional groups, as norbornene olefins were hydroborated efficiently in the presence of silyl ethers and methyl esters (entries 2 and 5, respectively). Styrenic alkenes were also borylated efficiently, as the products of hydroboration of styrene and acenaphthalene were isolated in high yield (entries 3 and 6). Additionally, in the case of styrene only the primary boronic ester was isolated, showing
selectivity for the terminal carbon of styrene. Hydroboration of the modestly-strained double bonds of cyclohexene, 1-methylcyclopentene and 1,5-cyclooctadiene (entries 7-9) did not show any conversion even after 24 hours, displaying the excellent selectivity offered by our system. We have therefore shown that a variety of strained and styrenic double bonds can be borylated in high yields, even in the presence of other competing olefins even if they themselves are modestly strained.

Based upon the selectivity of the Glorius-Cu(I) system for strained olefins versus unactivated ones, future work in this area would almost certainly involve a theoretical study of these systems. Discerning the minimum amount of strain energy for such a reaction to occur may allow us to match additional NHC-copper complexes to an olefin of our choosing. Additionally, matching unstrained alkenes to an even more active catalyst might allow for the selective functionalization of unstrained double bonds, which would provide further flexibility to an already promising method.

3.5 Conclusions

In order to examine the reactivity of Cu(I)-NHC complexes toward the borylation of strained and stryenic olefins we have synthesized an N-heterocyclic carbene-copper(I) complex using a ligand introduced by Glorius. Complex 14 was prepared by continuous flow through a packed column of Cu$_2$O and a single crystal was obtained that shows the unequivalent N-C-Cu bond angles that form a pocket in the structure of the complex. This NHC-Cu(I) complex was used successfully in the hydroboration of a number of strained and styrenic olefins, demonstrating excellent selectivity for these double bonds over less-activated ones. Control experiments yielded a proposed mechanism where the role of methanol is elucidated and
emphasized. This method for the functionalization of strained olefins broadens the scope of substrates which can be functionalized with current copper-based methods. Future experiments wherein the reactivity of unpolarized and unstrained double bonds are functionalized would further expand this growing area of research.
CHAPTER 4

REGIOSELECTIVE CATALYTIC HYDROBORATIONS OF PROPARGYLIC SPECIES USING COPPER(I)-NHC COMPLEXES

4.1 Background

Multifunctional intermediates enable efficient synthesis of complex natural products and/or pharmaceuticals. Vinylboronates are ideal examples of multifunctional intermediates because of the versatility of the C-B bond and the diverse reactivity of the double bond. The Walsh group reported the synthesis of compact, functional group rich-vinylboronates via a three-step process from an alkynyl boronic ester. The process begins with the hydroboration of the alkyn followed by transmetallation with dimethylzinc, culminating with addition to an aldehyde (Figure 4.1). These compounds are then used to make several different kinds of compounds by exploiting the chemoselectivity of the zinc and boron moieties, resulting in compounds such as cyclopropylboronate esters (via Simmons-Smith cyclopropanation of the alkene), allylic amines, \( \alpha \)-substituted ketones and 2-keto-\textit{anti}-1,3-diols. While the Walsh approach is powerful, the process begins with alkynyl boronates that must be prepared because few are commercially available. A streamlined approach leading to Walsh’s intermediates would further expand this area of chemistry.

An alternative synthesis of Walsh-type vinylboronate intermediates might be achieved via catalytic hydroboration of internal alkynes. Although alkyne hydroborations of this type have are known using boranes, the hydroboration of internal alkynes often leads to regioisomeric mixtures. Recently developed hydroboration methods using diboron/methanol as reducing agents
and transition metal catalysts represent a new strategy for selective hydroboration of internal alkynes. Despite the promise of these catalytic methods, no one has yet realized a practical approach to regioselective hydroboration of internal alkynes.

Figure 4.1 A series of heterobimetallics pioneered by Walsh were used to create a variety of complex molecules.

Alkyne hydroboration methods which produce desired vinylboronates have been around for nearly 30 years, however access to all desired regioisomers remains a challenge. While no general method is yet known, several examples of selective hydroboration have been reported involving copper catalysis (Figure 4.2). The first such reaction was reported by Yun, who was able to selectively borylate acetylenic esters and phenylacetylene using catalytic copper and a phosphine ligand. The regioselectivity in these cases was driven by substrate control rather than catalyst control. Catalyst controlled methods for regioselective hydroborations are also starting to emerge. The Hoveyda group has used N-heterocyclic carbene copper(I) complexes to provide both α- and β-vinylboronates of terminal alkynes using a 5-membered NHC complex with
While the Hoveyda method is attractive and demonstrates that ligands surrounding copper can alter regioselectivity, the method is only useful for terminal alkynes. More recently, the Carretero group reported the use of Cu(I)-phosphine complexes for the regioselective hydroboration of propargylic dialkyl substrates, producing \( \beta \)-borylated \((Z)\)-allylic alcohols.\(^{41}\) The Carretero method represents another step forward but regioselectivity erodes as the small group (the position occupied by the methyl group) increases in size. Regardless of limitations, these methods demonstrate that when ligand and substrate are matched regioselective hydroborations can occur. Recognizing that our 6-NHC-Cu(I) complexes provided unique selectivity in context of \( \beta \)-borylations and allylic substitutions, we began to study the reactions using internal alkyne substrates. As we describe in more detail below, our efforts have yielded a new approach to regioselective hydroboration of internal alkynes.

### 4.2 Selectivity and Protection Group Screen

#### 4.2.1 Initial Experiments

Figure 4.2 illustrates two different reaction manifolds by which copper(I)-catalyzed hydroborations can proceed. The first pathway is direct hydroboration (e.g., Yun, Hoveyda, Carretero) and the second pathway is a substitution reaction yielding an allene (Sawamura). The substitution reaction appears to be favored when a leaving group is present in the propargylic position. Based on these prior observations, we predicted that 6-NHC-Cu(I) catalyst 1b would react with propargylic carbonates to yield allene products (Figure 4.2). As presented below, 1b does not behave as predicted but instead provides a mixture of allene and regioselective catalytic hydroboration. The catalytic hydroboration products dominated the product distribution. The following section describes that alteration of protection groups on the propargylic alcohol and
ligand match provides excellent regioselectivity whereby the ligand on the copper center and the protecting group can be matched to favor one regioisomer over the other.

**Figure 4.2** Copper(I) catalyzed borylations of propargylic species showing different reactivity between phosphine and NHC-ligand based complexes.

4.2.2 Screen of O-Protection Groups and Incorporation of a 5-NHC

Analysis of prior work in the field and our observations allowed us to develop a model for internal hydroborations. We hypothesized that the following design principles guide the
reaction:

(1) The strength of the leaving group (OP) controlled allene vs. internal hydroboration when NHC-Cu(I) were used as the catalyst. Strong leaving groups were predicted to favor allene formations whereas weak leaving groups would favor hydroboration.

(2) Matching the polarity of the alkyne with that of the copper(I) catalyst by tuning the NHC ligand attached to copper could control the regioselectivity.

These hypotheses were tested by running the experiments defined in Table 4.1. Experiments were run using two different catalysts and the same substrate where only the protection group was varied. Our results are summarized in Table 4.1 below.

Table 4.1 Screen of O-Protection Groups for Alkyne Hydroboration Study

<table>
<thead>
<tr>
<th>Entry</th>
<th>P</th>
<th>Conv. (%)(^a)</th>
<th>(\alpha:\beta)(^a)</th>
<th>Conv. (%)(^a)</th>
<th>(\alpha:\beta)(^a)</th>
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<td>TBS</td>
<td>55</td>
<td>65:45</td>
<td>78</td>
<td>19:81</td>
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<tr>
<td>3</td>
<td>Bn</td>
<td>100</td>
<td>53:47</td>
<td>100</td>
<td>11:89</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>100</td>
<td>69:31</td>
<td>100</td>
<td>33:67</td>
</tr>
<tr>
<td>5</td>
<td>(p)-MeOC(_6)H(_4)</td>
<td>6</td>
<td>71:29</td>
<td>76</td>
<td>39:61</td>
</tr>
<tr>
<td>6</td>
<td>(m)-NO(_2)C(_6)H(_4)</td>
<td>100</td>
<td>88:12</td>
<td>100</td>
<td>79:21</td>
</tr>
<tr>
<td>7</td>
<td>(p)-NO(_2)C(_6)H(_4)</td>
<td>100</td>
<td>85:15(^b)</td>
<td>100</td>
<td>75:25(^c)</td>
</tr>
<tr>
<td>8(^d)</td>
<td>(p)-NO(_2)C(_6)H(_4)</td>
<td>100</td>
<td>96:4</td>
<td>87</td>
<td>95:5</td>
</tr>
</tbody>
</table>

\(^a\) Determined by \(^1\)H NMR analysis of crude product mixtures. \(^b\) Reaction contains 8.6% allene product. \(^c\) Reaction contains 9.8% allene product. \(^d\) Reaction carried out at -55 °C for 14 hours.
A variety of O-protected propargyl alcohols were synthesized in order to derive the relationship between alkyne and catalyst. Electron-rich (entry 4), electron-poor (entries 6-8) and more neutral (entries 1-4) protection groups were used to alter the electronics of the alkyne. We hypothesized that an electron-rich protecting group would result in an electron rich alkyne, and vice-versa for an electron-withdrawing protecting group. Silyl protection groups were predicted to increase the electron density by polarizing the triple bond in the β-position, the alkyne carbon farthest from the propargyl alcohol moiety. To test the impact of NHC-donor properties on the regioselectivity, we tested the 5-NHC-Cu(I) complex 2 as our weak donor ligand and our 6-NHC (1b) as the strong donor ligand, based upon donor strength data gathered previously.\(^7\)

The data in Table 4.1 supports our hypothesis that matching alkyne/catalyst electronics can affect the regioselectivity of the hydroboration reaction. Several interesting trends were uncovered from these experiments. Firstly, silyl, benzyl and phenyl protecting groups (unsubstituted and 4-MeO-substituted), all predicted to provide electron-rich alkynes, did not provide useful selectivity using either catalyst (entries 2–5, 1b). However, for all protection groups tested, 6-NHC-Cu(I) catalyst 1b provides the α-borylated product dominantly. This trend is reversed for 2, which provides the β-substituted materials preferentially whenever the alkyne is electron rich or neutral (entries 2-5, 2). When employing the para-NO\(_2\) substituted arene both catalysts provide the α-borylated product (entries 7 and 8), though both selectivity and conversion are superior with catalyst 1b, especially at -55 °C. Catalyst 2 has optimal selectivity when reacted with the propargyl alcohol (entry 1), providing the β-borylated product with high conversion and selectivity.

These observations indicate that alkyne and catalyst electronics can be matched to achieve optimal regioselectivity in the hydroboration of these internal alkynes. The method
developed by Walsh is useful, but suffers from a lack of commercially-available starting materials for the reaction. By comparison, our method has the potential to perform regioselective hydroborations for a wide scope of internal propargylic species (see below), which are easily synthesized from any number of commercially-available terminal alkynes and aldehydes. Additionally, our method provides access to both vinylboronate regioisomers by matching of alkyne/catalyst electronics, which is a level of control previously unknown for this kind of transformation. The results in Table 4.1 indicate that we can preferentially obtain the α-borylated product by reacting catalyst 1b with a propargyl p-nitrophenyl ether, while the β-borylated product can be prepared by the reaction of 5-NHC catalyst 2 with the appropriate propargyl alcohol.

4.3 Substrate Screen

4.3.1 Regioselectivity of Hydroborations Performed with 6-NHC (1b)

The next step for demonstrating the utility of our hydroboration method is to explore the scope of the reaction. As we show in the coming paragraphs, our method functions well for many different propargyl species that are easily synthesized from commercially-available terminal alkynes and aldehydes. Because the substrate scope seemed so vast, we chose to focus our demonstration around specific cases of steric bulk and functional group tolerance. Our results for 6-NHC-Cu(I) catalyst 1b are displayed in Figure 4.3 below.

As shown in Figure 4.3, most cases of steric congestion and functional groups were well-tolerated. As predicted by our results in Table 4.1, pairing an electron-poor alkyne with catalyst 1b allowed for the selective α-borylation of all substrates. The selectivity for the α-position was excellent for all except primary ether 21a, which formed α-vinylboronate 22a with moderate...
preference over the $\beta$-isomer in a ratio of 85:15. Secondary aryl propargyl ethers 22b-22i provide the corresponding $\alpha$-vinylboronates with excellent selectivity.

![Chemical structures and reaction scheme](image)

$\text{Ar} = \rho$-NO$_2$C$_6$H$_4$

$\text{R}^1 \equiv \text{OAr}

\text{Bpin} + \text{R}^1 \text{R}^2$

$\alpha$-addition

$\beta$-addition

22 $\alpha$:$\beta$ (isolated yield)

$\text{ArO-R}^1 \text{R}^2$

$\text{Bpin}$

$\text{ArO-R}^1 \text{R}^2$

$\text{Bpin}$

$a$ Selectivity data obtained by $^1$H NMR analysis of the crude product. $^b$ Isolated with unknown product.

**Figure 4.3** Regioselectivity and yield data for a set of propargyl aryl ethers using 1b

Steric congestion is tolerated except in the most bulky of substrates, such as 22c and 22i, which showed poor conversion. In comparing vinylboronates 22c and 22h, it appears that steric bulk is only a problem when located proximal to the propargyl ether moiety (22c), rather than on the other side of the triple bond, where yield and selectivity remained high (22h). A variety of functional groups were also well-tolerated, such as the chloro and silyl ether substrates 22d and
22f, which provided α-borylated products in high yield. Carbamate derivative 22e, however, was unable to be isolated. Lastly, vinylboronate 22g shows that there is no competition between the propargyl nitroaryl ether moiety and a similar functional group elsewhere in the substrate. Yield and selectivity for the α-position were excellent, supporting our hypothesis that tuning the electronic properties of the triple bond via O-protection is the source of this observed selectivity.

![Deprotection of the p-nitrophenyl protection group](image)

**Figure 4.4** Deprotection of the p-nitrophenyl protection group

We have shown that catalytic hydroboration of p-nitrophenyl propargyl ethers provides easy access to a variety of α-vinylboronates. However, the use of p-nitrophenyl as a protection group for alcohols is rare, and to enhance the synthetic utility of this α-borylation procedure, we sought a strategy for the efficient removal of the p-nitrophenyl moiety (Figure 4.4). This was accomplished as a modification of a procedure developed by Fukase, where we reduce the nitro group using indium rather than palladium, which provided selectivity so that the desired double bond was not reduced. The resulting aniline was oxidatively cleaved using ceric ammonium nitrate in acetonitrile/water. This method provides the desired allylic alcohol in 71% yield over 2 steps, and provides an efficient new strategy for the protection of alcohols that is useful in its own right.

The procedure described in this section pairs aryl propargyl ethers with the 6-NHC Cu(I) catalyst 1b to selectively yield α-vinylboronates of the type previously described by Walsh.
These substrates are produced easily from a variety of readily-available materials, and can be selectively borylated so that they can be used in ways previously described by Walsh and others for this type of bifunctional substrate.

4.3.2 Regioselectivity of Hydroborations Performed with 5-NHC (2)

Having determined that our method provides ready access to α-vinylboronates (Figure 4.3), we sought to show that our method is also capable of selectively producing β-vinylboronates of the type produced by the Yun group (Figure 4.2) because these substrates are valuable allylation and Suzuki coupling substrates. Having already shown promising β-selectivity by pairing an unprotected propargyl alcohol with 5-NHC Cu(I) complex 2 (Table 4.1, entry 1, 2) we set out to test the scope of this transformation using the same test substrates as described in Figure 4.3.

Our initial attempts at applying our method to propargyl alcohols were confounded by poor isolated yields of the desired products. Following the reaction by $^1$H NMR revealed the reason to be two-fold (Figure 4.5). Firstly, the crude product mixture showed that in addition to the desired allylic alcohol, we were also producing the boronic ester of the corresponding
product in approximately a 3:1 ratio. Addition of triethanolamine to the crude reaction mixture at room temperature was successful in hydrolyzing the boronic ester, while leaving the vinylboronate moiety intact. Secondly, the resultant allylic alcohols were unstable to silica gel chromatography and thus we were initially unable to isolate them. This problem was easily remedied by the one-pot acetylation of the allylic alcohols with acetic anhydride and 4-(dimethylamino)pyridine.

![Diagram of reaction](image)

Figure 4.6 Regioselectivity and yield data for a set of propargyl alcohols using 2. Isolated yields in parentheses after conversion to the allylic acetate.

With the ability to isolate the desired β-vinylboronates, we were now ready to explore the
scope of our system (Figure 4.6). The results of the substrate study involving SIMes 5-NHC-Cu(I) complex 2 show a tolerance for functional groups and sterics as good as, if not better than, the system utilizing 6-NHC-Cu(I) complex 1b. Primary allylic alcohol 23a shows similar, but reversed selectivity as was reported using complex 1b, though with an improved yield. Isolated yields of the reactions were excellent in all cases except for 24h and 24i where, opposite the results observed when using 1b (Figure 4.3), steric congestion on the distal side of the triple bond is not well-tolerated. Additionally, products 24h and 24i display a reversal of selectivity, favoring the α-vinylboronate over the expected β-product. Unfavorable interactions between the bulky group on the side farthest from the alcohol and the pinacol-moiety is likely the cause, and α-borylation is thus preferred. Functional groups also appear to be well-tolerated, as the chloro-, carbamate-, silyl ether and p-nitrophenyl ether products 24d-g are all produced with excellent yields and selectivity.

By pairing easily synthesized propargyl alcohols with 5-NHC Cu(I) complex 2, we were able to regioselectively hydroborate at the β-position to produce β-vinylboronates of the type described by the Yun group. The scope of the reaction demonstrates that a wide variety of propargyl alcohols can be reacted in this fashion with high yields and excellent selectivity. As was the case with the Walsh-type products, the substrates for this transformation are easily produced from commercially-available starting materials and provide a product that can be used in a number of important chemical transformations. While these results are exciting, the origin of the observed selectivity was not entirely clear. In the next section, we attempt to understand the origin of selectivity.
4.4 Regioselectivity Experiments and Rationale

We developed a selectivity hypothesis by examining the results of our O-protection group study in Table 4.1. When using 6-NHC-Cu(I) complex 1b, a preference for the α-vinylboronates occurs in all cases. This preference is enhanced when the alcohol is protected as an aryl ether (entry 5), and enhanced further when the arene is electron-poor (entries 6-8). When using 5-NHC-Cu(I) complex 2 a similar gradient is observed, with selectivity for the β-vinylboronate strongest in the case of the propargyl alcohol (entry 1), and decreasing selectivity as the protection groups become increasingly electron-deficient or when an aromatic ring is used. In the case of 2, the use of an electron-poor arene reverses selectivity in favor of the α-vinylboronate. The origin of this kind of selectivity is due to the matching of steric and electronic effects between the substrate and catalyst, though the specifics are not entirely clear. With this in mind, we prepared substrates 25a and 25b to represent sterically free and sterically congested propargylic alcohols, respectively, as well as 25c and 25d to represent the respective p-nitrophenyl ethers. Each of these substrates were tested using catalysts 1b (Figure 4.7) and 2 (Figure 4.8) in an attempt to further explain the origin of selectivity for these systems.

![Diagrams showing selectivity](image)

**Figure 4.7** Electronic and steric effects participating in the observed selectivity with 2.
As shown in Figure 4.7, when using 5-NHC-Cu(I) complex 2, a preference for β-borylation is observed for both propargylic alcohols 25a and 25b. This would seem to indicate that steric do not play an important role in catalyst orientation in this case, but that selectivity may instead arise due to electronic factors such as the polarizing effect that the alcohol has upon the triple bond. With p-nitrophenyl ethers 25c and 25d, however, the branched ether shows high selectivity for α-borylation and the linear ether shows almost no selectivity at all. We have interpreted these data to mean that in this case steric have overruled the electronic effects of the alcohol. Substitution with a p-nitrophenyl moiety reduces the electron-donating character of the alcohol, likewise reducing the selectivity for the β-position. In the case of branched ether 25d, steric dominate further, and the preferred orientation delivers α-selectivity.

![Chemical structure](image.png)

**Figure 4.8** Observed regioselectivity with complex 1b

In the reactions of 6-NHC-Cu(I) complex 1b with compounds 25a-d we are shown a different story altogether. Here the reaction shows α-selectivity in all cases, though the effect is enhanced with compounds 25c and 25d. This indicates that the catalyst choice controls the
selectivity of the hydroboration, though to what extent steric and electronic characteristics play a role is as yet unknown. Ab initio calculations will be required to help better understand these observations and to help model the catalytic system, and these experiments are currently underway.

4.5 Conclusions

Vinylboronates are versatile compounds that are highly valuable to the synthetic chemist. We have described a method for the regioselective hydroboration of propargylic aryl ethers and alcohols using, respectively, the 6-NHC-Cu(I) and 5-NHC-Cu(I) complexes 1b and 2. Both of these methods yield the respective α- and β-vinylboronates in high yield and with excellent selectivity, and display excellent functional group tolerance. The products of the reaction with 2 can be isolated as their respective allylic acetates, and the products of reaction with 1b can be deprotected using a modified Fukase approach to yield the allylic alcohols. The synthetic utility of some selected compounds are explored in subsequent chapters.
CHAPTER 5

PREPARATION OF TERTIARY ALLYLBORONATES FROM VINYLBORONATES VIA “ATE-MEDIATED ALLYLIC SUBSTITUTION” (AMAS)

5.1 Background

Allylboronates are a useful subset of compounds which possess orthogonally reactive functional groups. They are often benchtop stable compounds which can undergo chemistry at the boron center, such as C-C bond forming reactions, oxidations and aminations, as well as forming organotrifluoroborates that have found increased use in transition metal C-C bond forming processes due to their increased nucleophilicity. Alternatively, the reactivity of the allyl moiety presents a number of synthetic opportunities, most notably the ability to form homoallylic alcohols. Allylboronates can be prepared in a number of different ways, most notably by Matteson homologation which is useful in forming secondary and tertiary boronates. This method relies on the formation of an intermediate “ate” complex of boron, and subsequent 1,2-metallate rearrangement to yield the desired products (Figure 5.1), and asymmetric applications of this reaction are well understood. While useful, the required cryogenic conditions and dangerous (halomethyl)lithium reagents prevent this reaction from widespread use on large scale. Another route toward allylboronate formation was recently reported by the Aggarwal group (figure 5.1). Starting from an optically active carbamate, the Aggarwal method performs an α-lithiation and subsequent addition of allylboronate. The resulting ate-complex undergoes a similar 1,2-metallate rearrangement to yield a tertiary allylboronate.
Yet another strategy toward the formation of functionalized allylboronates is allylic substitution from vinylboronates. As is the case with homologation chemistry, this method involves the formation of a boron ate complex, which then displaces a leaving group in an $S_{N}2'$ fashion to yield the desired allylboronate. The Lombardo group studied this strategy, especially the conditions under which a 1,3-borotropic shift might occur, en route toward the synthesis of anti-homoallylic alcohols (Figure 5.1). The Hoffmann and Hall groups have also contributed to this work in their efforts to produce secondary allylboronates from vinylboronates with an allylic halogen, though tertiary allylboronates were problematic under their conditions (Figure 5.1).

**Figure 5.1** Recent and common methods for the synthesis of allylboronates.

Having recently described our copper(I)-NHC catalyzed method for the production of $\beta$-vinylboronates via regioselective hydroboration of propargylic alcohols, this work seeks to
utilize these compounds to access tertiary allylboronates via an “ate-mediated allylic substitution,” or AMAS, methodology. The method is attractive because of the ubiquity of terminal alkynes and aldehydes which are commercially available. Likewise, the tertiary allylboronate products could be formed in a modular nature, allowing flexibility in synthetic planning that does not currently exist. Herein we explore this methodology for the synthesis of valuable tertiary allylboronates.

5.2 Optimization Studies

In the previous chapter we established that using a 5-membered NHC-Cu(I) catalyst in the hydroboration of propargylic alcohols yields β-vinylboronates with high yield and selectivity. This procedure is useful because of the variety of commercially-available terminal alkynes and aldehydes that can be used to prepare the propargylic alcohol starting materials. These products are isolated as allylic acetates, and we hypothesized that treatment of these vinylboronate allylic acetates with an organometallic nucleophile may result in an allylic substitution reaction (Figure 5.2). The results of our optimization studies are compiled in Table 5.1.

We first attempted to react a representative vinylboronate (26) with phenyllithium solution at 0 °C (entry 1). Analysis of the crude $^1$H NMR spectrum after quenching with saturated ammonium chloride solution showed that the starting material had been consumed, though the result was instead the formation of trisubstituted olefin via protodeboronation, as well as a considerable amount of unidentified by-products.

Reacting the less nucleophilic phenylmagnesium bromide in the same manner provided the desired product (entry 2), though with a similar amount of unidentified by-products. Proton NMR analysis of the reaction mixture revealed that by-product formation occurred during
quenching. The reaction was repeated with several proton-donating quench solutions (entries 2 – 4), all of which resulted in the formation of by-products. Desired product was finally formed, in >95 % conversion (entry 5), after simply filtering the crude reaction mixture through a pad of silica gel.

\[
\text{R} + \text{H} \rightarrow \text{AcO} \quad \text{26}
\]

![Figure 5.2 Preparation of tertiary allylboronates from easily-accessible vinylboronates.](image)

**Table 5.1** Optimization Studies for AMAS

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile</th>
<th>Quench Reagent</th>
<th>Results¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhLi</td>
<td>NH₄Cl</td>
<td>Mixture</td>
</tr>
<tr>
<td>2</td>
<td>PhMgBr</td>
<td>NH₄Cl</td>
<td>Mixture</td>
</tr>
<tr>
<td>3</td>
<td>PhMgBr</td>
<td>H₂O</td>
<td>Mixture</td>
</tr>
<tr>
<td>4</td>
<td>PhMgBr</td>
<td>HCl</td>
<td>Mixture</td>
</tr>
<tr>
<td>5</td>
<td>PhMgBr</td>
<td>None ²</td>
<td>Full conv.</td>
</tr>
<tr>
<td>6</td>
<td>NaOMe</td>
<td>None ²</td>
<td>NR</td>
</tr>
<tr>
<td>7</td>
<td>NaO₃Bu</td>
<td>None ²</td>
<td>NR</td>
</tr>
<tr>
<td>8</td>
<td>NaCN</td>
<td>None ²</td>
<td>NR</td>
</tr>
</tbody>
</table>

¹ Results obtained by ¹H NMR analysis of crude reaction mixture. ² Reaction was worked-up before sampling by filtering through a pad of silica gel.
silica gel, omitting any proton-donating solutions. Organolithium reagents failed to provide the desired product even under these conditions. A few other experiments were performed, utilizing weaker bases and non-carbon nucleophiles such as sodium methoxide (entry 6), sodium tert-butoxide (entry 7) and sodium cyanide (entry 8), though none of these reactions showed any consumption of starting material. Although we desired to expand upon the nucleophilic landscape of this procedure, we opted instead to move forward by examining the scope of organomagnesium reagents that are compatible with this reaction.

5.3 Nucleophile Scope

The identification of appropriate reaction conditions for the preparation of tertiary allylboronates then prompted us to examine the range of Grignard reagents which could be used (Table 5.2). The large number of commercially available Grignard reagents facilitated this process and is an additional advantage to this procedure.

![Reaction scheme](image)

Table 5.2 Scope of Tertiary Allylboronates Prepared from Vinylboronates

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>RMgX</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27a</td>
<td>MeMgCl</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>27b</td>
<td>MeMgBr</td>
<td>97</td>
</tr>
<tr>
<td>3</td>
<td>27c</td>
<td>CH3MgBr</td>
<td>94</td>
</tr>
<tr>
<td>4</td>
<td>27d</td>
<td>MeMgBr</td>
<td>81</td>
</tr>
<tr>
<td>5</td>
<td>27e</td>
<td>MeMgCl</td>
<td>98</td>
</tr>
<tr>
<td>6</td>
<td>27f</td>
<td>MgCl</td>
<td>76</td>
</tr>
</tbody>
</table>
Table 5.2 continued

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>RMgX</th>
<th>Yield (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>27g</td>
<td><img src="image" alt="diagram" /></td>
<td>68</td>
</tr>
<tr>
<td>8</td>
<td>27h</td>
<td><img src="image" alt="diagram" /></td>
<td>86</td>
</tr>
<tr>
<td>9</td>
<td>27i</td>
<td><img src="image" alt="diagram" /></td>
<td>89</td>
</tr>
<tr>
<td>10</td>
<td>27j</td>
<td><img src="image" alt="diagram" /></td>
<td>71</td>
</tr>
<tr>
<td>11</td>
<td>27k</td>
<td><img src="image" alt="diagram" /></td>
<td>88</td>
</tr>
</tbody>
</table>

$^a$ 1.5 equiv. RMgX, 0.2 M in diethyl ether. $^b$ Isolated yield.

The results in Table 5.2 suggest that a wide range of Grignard reagents are compatible. Both aryl and alkyl organomagnesium species performed well, as did sterically congested reagents (entries 2, 9 – 10) which suggests that this method would be useful in the production of bulky tertiary allylboronates. Entries 9 and 10 are particularly interesting, in that they suggest that magnesium bromide Grignards outperform the analogous magnesium chlorides. The cause of this observed counterion difference is unknown, though it may reflect a competition between allylic substitution and 1,2-addition to the acetate.

Another feature of this reaction is that the allylboronate products formed were exclusively the $E$-geometry. This was verified by $^1$H NMR spectroscopy of the crude and pure products where the coupling constants of the vinyl proton peaks were in the range of 15 – 16 Hz, well-established to be a feature of $trans$-alkenes (Figure 5.3, top). We hypothesize that the observed $E$-selectivity is due to the avoidance of allylic strain as the double bond is formed and the acetate is eliminated (Figure 5.3, bottom). The discovery of this $E$-selectivity was fortuitous as it would allow for more predictable downstream reactivity in any case where $cis$- and $trans$-isomers may react differently, such as asymmetric dihydroxylations, epoxidations and other transition metal catalyzed transformations.
**Figure 5.3** $^1$H NMR evidence for $E$-selectivity in AMAS process (top, $J = 6.3, 15.8$ Hz and $J = 1.6, 15.8$ Hz), as well as a rationale for observed selectivity involving the avoidance of allylic strain (bottom).

### 5.4 Representative AMAS Substrates

With the nucleophilic landscape regarding commercially available Grignards established, we then examined how the substrate might affect the AMAS procedure. As mentioned before, the number of available terminal alkynes and aldehydes is large, therefore instead of an exhaustive study we opted to select a few example substrates which will establish how the
reaction proceeds in a variety of circumstances (Figure 5.4).

![Chemical Structures](image)

**Figure 5.4** Representative vinylboronate substrates for AMAS.

As we had observed previously, all of the products obtained were the \(E\)-isomers. Substrate 28 demonstrates that protected alcohol functionalities are well tolerated, indicating that the allylic substitution reaction is preferred over competing \(S_N2\) substitution. Additionally, allylboronate 30 verifies again that bulky organomagnesium reagents are compatible with the reaction conditions. Modestly acidic protons such as benzylic protons are tolerated as depicted by substrate 31. We suspect that the loss of yield in generating allylboronate 32 may be due to the additional bulk of the benzyl group distal to the acetate, but the desired product was still
obtained in acceptable yields. Lastly, primary allylic acetate 33 was reacted smoothly with phenylmagnesium bromide to produce the terminal allylboronate 34 in 69% yield, which opens the door for a variety of interesting and functionalized metathesis and Heck coupling substrates to be easily produce by the AMAS approach. This study is certainly not exhaustive, however it does suggest that the production of allylboronates by AMAS should be limited only by the stability of the substrates toward the organomagnesium reagents used.

This chapter details our initial investigations into the scope of this potentially versatile method, however several more directions remain to be explored. As described in the following chapter, our initial attempts to make this reaction stereoselective by using an optically-active propargyl alcohol were unsuccessful. Future attempts to achieve stereoselectivity will focus on using bulky chiral boronate esters and/or chiral NHC ligands to induce asymmetry into the reaction. Additional effort will be directed toward expanding upon the nucleophilic landscape of the AMAS protocol. While we have shown that organomagnesium species outperform organolithium reagents, it remains to be seen if other metals are viable options such as organocuprates, zincates and mixed organometallic reagents which have proven useful in deprotonative metallation and metal-halogen exchange reactions. Furthermore, experiments to reveal the behavior of this system toward non-carbon nucleophiles and intramolecular AMAS cyclization reactions are currently underway.

5.5 Conclusions

Tertiary allylboronates represent a useful subset of orthogonally-reactive compounds that can be challenging to produce. Leveraging the regioselective hydroboration of propargylic alcohols discussed in Chapter 4, we utilized these β-vinylboronates in “ate-mediated allylic
substitution,” or AMAS, reactions. This simple method has the advantage of the ubiquity of starting materials as commercially available terminal alkynes and aldehydes, as well as the procedure which requires only the addition of organomagnesium reagent, many of which are also commercially-available. At the moment, the nucleophilic landscape of this procedure is limited to Grignard reagents, though studies are still underway in this area. Other ongoing work involves expanding both the nucleophilic and substrate landscape of this reaction, so that we can fully understand the limits of this process.
CHAPTER 6

SYNTHESIS OF METHYL AXENOSIDE AND METHYL 3-EPI-AXENOSIDE VIA ATE-MEDIATED ALLYLIC SUBSTITUTION (AMAS)

6.1 Background

This chapter describes the application of the “ate-mediated allylic substitution (AMAS) reaction as a key reaction for the preparation of methyl axenoside and its epimer, methyl 3-epi-axenoside. Axenose is a naturally-occuring deoxy sugar found in several biologically active natural products, such as axenomycin, polyketomycin and dutomycin\(^5\) (Figure 6.1). This sugar has been synthesized several times, typically as its methyl glycoside, using a variety of strategies. Garegg and Norberg produced the desired compound using classical saccaride manipulations in 13 steps with 1.6 % overall yield starting from L-fucose.\(^5\) Likewise, the Giuliano group synthesized axenose from D-ribose, in this case with 4 % yield over 12 steps.\(^5\) More recently, the Myers group synthesized methyl axenoside en route toward a total synthesis of Trioxacarcinoside A.\(^5\) Unlike previous strategies, the synthesis performed by Myers began from linear, non-natural precursors instead of sugars. The introduction of stereochemistry at the C3 position of axenose was achieved by a diastereoselective addition of allylmagnesium chloride to a silyl-protected syn-\(\alpha,\beta\)-dihydroxyketone (Figure 6.2). The synthesis reported by Myers is the most efficient synthesis of methyl axenoside to date, with a yield of 18 % over 10 steps.

The Myers group synthesis of methyl axenoside represents the state of the art method for this compound, however their strategy still suffers from use of starting materials that require several steps to produce. A method toward methyl axenoside which begins from low cost and
commercially-available starting materials would be an improvement to the current methodologies. We envisioned that our recently described AMAS procedure could provide a simpler alternative, generating the tertiary alcohol by oxidation of the resulting allylboronate. The following sections detail our divergent synthesis of methyl axenoside and its C3 epimer, methyl 3-epi-axenoside.

**Figure 6.1** Selected biologically-active natural products containing the axenose motif, highlighted in red.

**Figure 6.2** Diastereoselective allylation as the key step in the Myers’ synthesis of methyl axenoside
6.2 Retrosynthetic Analysis

Synthesis of a tertiary alcohol often requires several steps to complete. Our choice of methyl axenoside as a target is derived from this functionality at the C3 position. Vinylboronates are potentially a convenient synthon for the formation of internal tertiary alcohols, requiring only the alkaline oxidation of the corresponding tertiary allylboronate. A retrosynthetic analysis of axenose was performed in order to plan a route toward this necessary intermediate.

The thermodynamically favored form of a deoxy sugar is the ring-closed form 35, resulting spontaneously from the ring-open form (36) by addition of an alcohol to the aldehyde (Figure 6.3). The vicinal sec-diol 36 should be accessible from a Sharpless dihydroxylation of the corresponding allylic alcohol (37), which itself can be accessed by oxidation of the corresponding allylboronate resulting from AMAS (38).

![Figure 6.3 Retrosynthetic analysis of axenose, utilizing AMAS methodology](image)

The synthesis of 38 can be accomplished in several different ways. Introduction of the methyl group by AMAS with methylmagnesium bromide would involve the use of a commercially-available Grignard reagent, but would require the aldehyde synthon to be present
from the beginning of the synthesis, possibly complicating the Grignard addition step. Instead, we chose to introduce a masked aldehyde synthon in the AMAS step (Figure 6.5), which would necessitate the synthesis of the relatively simple vinylboronate 39.

![Chemical structures](image.png)

**Figure 6.4** Retrosynthetic analysis of the axenose procedure described by Myers

A retrosynthetic analysis of axenose reveals how this synthetic methodology diverges from that of Myers (Figure 6.4). The greatest disadvantage to this method is in the production of starting materials, an endeavor which could be expensive and time-consuming. By contrast, the ubiquity of commercial terminal alkynes and aldehydes provides an attractive route toward the synthesis of vinylboronate 39 by our method. Additionally, the modular nature of the AMAS will allow us to examine alternative syntheses if the delivery of the aldehyde synthon does not function as planned.

### 6.3 Synthesis: Part 1

A number of aldehyde synthons exist and three were examined, but disappointingly, none provided the desired outcome (Figure 6.5). Synthesis of 39 went smoothly, further demonstrating that our copper(I) catalyzed hydroboration method works well. As described in Chapter 5, the
AMAS method works best when a Grignard nucleophile is added to vinylboronates such as \(39\), and therefore our efforts to introduce a 2-carbon aldehyde synthon focused on commercially available Grignards. Initially, we sought to introduce (1,3-dioxolan-2-ylmethyl)magnesium bromide (Figure 6.5, \(41\)), however the reaction mixture was comprised of a number of unidentified products resulting from decomposition of the dioxolane moiety after having formed the Grignard. Additionally, \textit{in situ} formation of the organomagnesium species via magnesium-halogen exchange failed under both Rieke and Knochel conditions, providing the same complex mixture of products. Furthermore, the literature suggests that this reagent is difficult to prepare and has a limited scope, therefore we instead began investigating the use of terminal alkynes as masked aldehydes. We attempted the AMAS reaction using both commercially available, as well as \textit{in situ} generated, ethynylmagnesium chloride and its TMS-protected analogue (Figure 6.5, \(42\) and \(43\)), however this procedure also yielded an unidentifiable mixtures of products.

\[ \text{H}_2\text{C} = \text{O} + \text{MgCl} \xrightarrow{\text{Et}_2\text{O}, -78 \, ^\circ\text{C}} \text{OH} \quad \xrightarrow{\text{1) 5-NHC, B_2(pin)_2, MeOH, NaOtfBu, Et}_2\text{O, 0}^\circ\text{C}} \text{AcO} \quad \xrightarrow{\text{2) Ac}_2\text{O, DMAP, DCM, rt}} \text{Bpin} \]

\[ \text{Bpin} \quad \text{Bpin} \quad \text{Bpin} \]

\[ \text{5-NHC: 2} \]

\[ \text{MgBr} \quad \text{MgCl} \quad \text{TMS} \]

\[ \text{EtO} \]

\[ \text{40} \]

\[ \text{39} \]

\[ \text{41} \]

\[ \text{42} \]

\[ \text{43} \]

\textbf{Figure 6.5} Strategies for the introduction of an aldehyde synthon via AMAS

Considering that a suitable aldehyde synthon could not be easily identified, we then decided to approach the problem from a different perspective. Due to the flexability of the
AMAS reaction, we opted to approach our target molecule from the opposite direction. Our new strategy elected to mask the aldehyde as a protected alcohol, which involves the introduction of a methyl group at the AMAS step. Methylmagnesium bromide has proven effective for AMAS reactions in the past, so the synthesis was carried out as detailed in Figure 6.6. The propargyl alcohol 44 was prepared in excellent yield from a commercially available terminal alkyne which carries the aldehyde moiety masked as a silyl ether. Treatment of 44 with 5-NHC under typical β-hydroboration conditions and subsequent acetate protection yielded vinylboronate 45. Ate-mediated allylic substitution of this vinylboronate by treatment with methylmagnesium bromide led smoothly to the desired allylboronic ester 46 with acceptable yield. Lastly, oxidation of 46 with hydrogen peroxide and sodium hydroxide led to the desired allylic alcohol 47.

Figure 6.6 Improved strategy toward allylic alcohol 47
6.4 Asymmetric Dihydroxylation

6.4.1 Performing the AD-Reaction

The allylic alcohol, 47, if successfully dihydroxylated could provide a product with the necessary stereochemistry to provide axenose and its C3 epimer. As per our retrosynthetic analysis, arrival at this intermediate would leave cyclization of the resulting polyol as the remaining challenge en route toward axenose. The Sharpless dihydroxylation is known to function on allylic substrates, so we selected this approach. The Sharpless dihydroxylation is osmium-catalyzed, typically utilizing the osmium salt $K_2O_2S_2•2H_2O$ for its lower toxicity compared to $OsO_4$, and asymmetric induction is achieved using the cinchona alkaloid-derived ligands $(DHQ)_2$PHAL and $(DHQD)_2$PHAL. These reaction components are commercially-available in pre-mixed forms as AD-mix-$\alpha$ and AD-mix-$\beta$, further simplifying the process.

![Figure 6.7](image)

**Figure 6.7** Sharpless mnemonic (a) and allylic alcohol considerations (b) for producing the desired syn-diol

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Dihydroxylation of the allylic alcohol 47 provided the next challenge en route toward our target molecule methyl axenoside. Using the Sharpless mnemonic for asymmetric dihydroxylations with PHAL ligands (Figure 6.7a)\textsuperscript{55a} we determined that (DHQ)$_2$PHAL would provide the desired $\textit{syn}$-diol selectivity. Additionally, the dihydroxylation of allylic alcohols imparts stereochemical factors which affect the outcome of the reaction (Figure 6.7b). In this case, due to coordination of the catalyst by the allylic hydroxyl group, the undesired ($S$)-isomer at the C3 position would form at a faster rate than the desired ($R$)-isomer. This implies that there will be a competition between the ($R$)-isomer, preferentially formed by the ligand, and the ($S$)-isomer, which is kinetically favored.

Dihydroxylation of allylboronate 46 was unsuccessful, likely due to interactions between the osmium catalyst and the allylic boronic ester. Dihydroxylation of allylic alcohols is well-understood for secondary allylic alcohols, but there are far fewer examples of successful reactions with tertiary alcohols, and treatment of 47 with commercially available AD-mix-$\alpha$ led to incomplete consumption of starting material. Adding the reaction components separately allowed us to control reaction stoichiometry. Starting material was completely consumed upon increasing the osmium precatalyst loading to 0.5 mol % and increasing ligand loading to 5 mol %. Thus, the desired triol was isolated in 78 % yield as a mixture of diastereomers that were inseparable at this stage.

**6.4.2 Establishing Dihydroxylation Enantioselectivity**

The asymmetric dihydroxylation reaction left us with a mixture of four possible stereoisomers (Figure 6.8). While two of these isomers would lead to the desired methyl
axenoside and methyl 3-epi-axenoside (48 and 49, respectively), it was important for us to establish the enantioselectivity of the dihydroxylation.

There are many different ways to establish the enantoiselectivity of a reaction. Gas chromatography and high-performance liquid chromatography with chiral columns are normally the methods first considered. GC analysis was unsuccessful in this instance due to the relatively high boiling point of the analyte. HPLC was not possible due to the lack of a chromophore that would allow for ultraviolet detection. Several derivitization methods were tested, from benzyl-protection of the secondary alcohol groups, to derivitization using Mosher’s acid chloride, failing in each case due to lack of selectivity between the syn-secondary alcohols. Deprotection of the silyl ether using tetra-\textit{n}-butylammonium fluoride, and subsequent derivitization of the resulting primary alcohol with Mosher’s acid chloride was also unable to provide us with data on the enantioselectivity because the introduced chirality center was too far away from the other chirality centers to cause effective diastereoselective separation.

The enantioselectivity of the asymmetric dihydroxylation was successfully established with the use of chiral lanthanide shift reagents. These chiral lanthanide complexes, typically of europium or praseodymium, coordinate to the heteroatoms in a substrate, and in the case of a pair of enantiomers they coordinate to different extents, resulting in a shift separation that can be

![Possible products of asymmetric dihydroxylation of allylic alcohol 47](image)
visualized with proton NMR. Literature precedent had indicated that the europium-camphorate based complex Eu(hfc)$_3$ should provide the best separation in deuterated acetonitrile, and therefore an $^1$H NMR spectrum of the dihydroxylation products (48 and 49, mixed) was taken in acetonitrile-$d_6$ as a reference (Figure 6.9, red). A small amount of Eu(hfc)$_3$ was dissolved in the NMR sample tube and the spectrum was retaken (Figure 6.9, violet).

![Figure 6.9](image)

**Figure 6.9** $^1$H NMR spectra of dihydroxylation products in MeCN-d$_3$ before (red) and after addition of Eu(hfc)$_3$. a) Product from dihydroxylation with (DHQ)$_2$PHAL. b) Catalyst only, no ligand. c) Product from dihydroxylation with (DHQD)$_2$PHAL.

At this point a number of peaks appeared as though they could be direct indicators of enantioselectivity, and the data therefore needed to be verified. Verification was provided by performing the dihydroxylation reaction twice more, once with osmium catalyst and without ligand, and once more with the opposite enantiomeric ligand (DHQD)$_2$PHAL (Figure 6.9, green and blue, respectively). As Figure 6.9 shows, the peaks indicated by the arrow display the kind of
pattern we would expect from opposite enantiomeric ligands (Figure 6.9, green). Integration of the peak areas allowed us to establish the enantiomeric ratio of the dihydroxylation reaction at approximately 76%, or 52% enantiomeric excess.

Desiring a higher level of enantioselectivity, we hypothesized that performing a stereoselective AMAS reaction might be possible if the substrate possessed an optically pure allylic acetate moiety. By setting the stereochemistry at the AMAS step, we hypothesized that the dihydroxylation might provide better results. This allylic acetate was derived from a chiral propargyl alcohol which was prepared by the asymmetric reduction of the corresponding alkyne-one with Noyori catalyst (Figure 6.10).56

\[
\text{HO}_\text{-} \xrightarrow{\text{PDC, DCM}} \text{O} \xrightarrow{\text{Noyori \([R,R]\), DCM, rt, 12 h}} \text{OH}
\]

**Figure 6.10** Preparation of an optically pure propargyl alcohol using Noyori catalyst

Regiospecific hydroboration of this optically pure propargyl alcohol, protection as the allylic acetate and subsequent allylic substitution provided the desired allylboronic ester cleanly, however without any observable optical activity. We attribute this observation to two things, free rotation of the B-C bond of the intermediate ate-complex, which allows the incoming carbon
nucleophile to be added to either side of the alkene without preference, as well as the distance from the reaction site to the chiral center. This topic is currently being explored in more detail.

6.5 Synthesis: Part 2

The optically enriched mixture of 48 and 49 were carried forward. While we felt that the Sharpless reaction might yield better results with more effort, we devised this synthesis to showcase the AMAS reaction and therefore returned our attention to the synthesis of methyl axenoside and its C3 epimer. While compounds 48 and 49 were inseparable after dihydroxylation, we hypothesized that separation would be possible at a later stage. Deprotection of the silyl ether was accomplished easily with TBAF, resulting in tetraol 50 (Figure 6.11). Isolation of this compound was accomplished with some difficulty using silica gel chromatography, due to the co-elution of tetrabutylammonium salts.

![Figure 6.11 Initial synthetic route toward axenose involving tetraol 50](image)

At this stage, we hypothesized that oxidation of the primary alcohol would result in spontaneous cyclization to form axenose. To accomplish this, we tried several methods for the selective oxidation of a primary alcohol in the presence of secondary alcohols, including Dess-Martin periodinane, chromium-based reagents and TEMPO oxidations with a number of co-oxidants, unfortunately none of these methods produced the desired product, and in only one case (TEMPO/bis(acetoxyiodo)benzene) was a small amount of the corresponding lactone
detected. Literature precedent suggests that oxidation conditions may have cleaved the gem-diol C-C bond and resulted in a number of by-products.

Reevaluating our synthetic strategy, we first protected tetraols 48 and 49 as their corresponding acetonide derivatives (Figure 6.12). In addition to decreasing the polarity of the products, it would provide a known intermediate downstream which had been previously reported by Myers (the aldehyde 53). Upon protection, the compounds were separated by silica gel chromatography, yielding compound 51 in 38 % yield (73 % yield combined isomers). The same silyl deprotection strategy was applied as before, yielding the primary alcohol 52 in 81 % yield, and it is noteworthy that isolation of this compound was much easier once the gem-diol moiety had been protected.

![Figure 6.12 Synthetic route toward methyl axenoside from tetraol 48](image)

Our efforts to oxidize the primary alcohol 52 involved the same range of conditions as before. Chromium-based reagents showed signs of aldehyde formation, but the crude product
mixture was a tar-like substance and difficult to work with. TEMPO-based oxidation strategies also showed signs of aldehyde formation, but product was lost upon work-up and purification. As it appeared that the resulting aldehyde 53 was unstable to silica gel chromatography, we chose to use Dess-Martin Periodinane as our oxidant. As the only reagent other than starting material, it was possible to dilute the reaction with hexanes upon completion and remove the solid iodinane by filtration through silica gel. Silica gel chromatography provided a relatively pure sample of 53 for characterization, though in practice the crude material was carried through without further purification.

We hypothesized that cyclization would occur spontaneously upon removal of the acetonide protection group. Traditional acidic conditions for the removal of this protecting group were unsuccessful, however, due to competing elimination of the tertiary alcohol as evidenced by the presence of the corresponding α,β-unsaturated aldehyde. As compound 53 had been previously reported by Myers during his synthesis of methyl axenoside, we employed the same acetonide deprotection strategy. This deprotection strategy was originally reported by the Hirama group,57 using a 5 % solution of triflic acid in 2,2,2-trifluoroethanol at -40 °C, efficient deprotection was achieved in under an hour, and crude characterization revealed the presence of the desired axenose. Axenose itself proved to be unstable to silica gel chromatography, but a one-pot formation of the methyl glycoside using acetyl chloride in methanol provided methyl axenoside. The product was easily purified by gentle washing with petroleum ether to yield the desired product (54) as a white solid in 90 % yield, as a 44:55 ratio of α and β-anomers, which matched reported spectral information upon separation (Figures 6.13 and 6.14). Methyl axenoside was synthesized with a final overall yield of 10 % over 9 steps.
6.6 Synthesis of Methyl 3-epi-Axenoside

Desiring a divergent route which would allow us to produce both methyl axenoside, and its anomer methyl 3-epi-axenoside, we carried out the same sequence of reactions starting with compound 49.

Compound 55 was separated from 51 following acetonide protection, as described above,
in 34% yield. Treatment with TBAF in THF provided the desired primary alcohol 56 in identical yields as previously reported. Aldehyde 57 was obtained by selective DMP oxidation of the primary alcohol, and used without purification in the deprotection/cyclization/methylation reaction to produce methyl 3-epi-axenoside 58 in identical yields as the previous strategy to form methyl axenoside. Unlike methyl axenoside, however, the epimer did not form an easily isolated solid which allowed for separation of the resulting anomers. Using a technique common to carbohydrate chemistry, the methyl glycoside was peracylated with acetic anhydride and DMAP, which allowed for chromatographic separation of the anomers and subsequent characterization. Methyl 3-epi-axenoside was thus synthesized in 9 steps with an overall yield of 9%.

**Figure 6.15** Synthetic route toward methyl 3-epi-axenoside from compound 49

### 6.7 Conclusions

In an effort to showcase the synthetic utility of the ate-mediated allylic substitution
developed previously, we chose to synthesize the epimeric methyl glycosides of axenose. Previous strategies toward axenose have relied mainly on saccharide-based starting materials, except for the method developed by the Myers group which started from acyclic precursors but suffers from starting materials which require several steps to produce. Our method began with commercially-available acyclic compounds, and we were able to successfully synthesize methyl axenoside and methyl 3-epi-axenoside in 9 steps with an overall yield of 10 and 9 %, respectively. These results compare favorably with previously-reported syntheses, specifically with Myers who achieved a higher overall yield, but over 18 steps. Additional studies involving the introduction of asymmetry into the AMAS process are needed to improve this process, and such investigations are currently underway.
APPENDIX A

SUPPORTING INFORMATION FOR CHAPTER 2

A.1 Characterization Data

A.1.1 General Procedures and Instrumentation

All commercially available reagents were used without further purification unless otherwise noted. Some substrates were synthesized according to literature procedure. Column chromatography was performed using silica gel from Merck (230 – 400 mesh). Visualization of the compounds was accomplished with UV light (254 nm), alkaline KMnO$_4$ solution followed by heating. $^1$H NMR and $^{13}$C NMR spectra were recorded in CDCl$_3$ on a 400 MHz spectrometer operating at 400.172 and 100.623 MHz, respectively, and 600 MHz instrument operating at 600.133 and 150.914 MHz, respectively. Proton chemical shifts are reported relative to the residual proton signals of the deuterated solvent CDCl$_3$ (7.26 ppm) or CD$_2$Cl$_2$ (5.32 ppm) or TMS. Carbon chemical shifts were internally referenced to the deuterated solvent signals in CDCl$_3$ (77.16 ppm) or CD$_2$Cl$_2$ (53.8 ppm). Data are represented as follows: chemical shift, multiplicity (bs = broad singlet, s = singlet, d = doublet, t = triplet, q = quartet, h = heptet, m = multiplet), coupling constant (Hz), and integration. Products were identified by comparison to spectral data reported in the literature. Gas chromatographic (GC) analyses were performed using a GC equipped with an autosampler, a flame ionization detector (FID), and a column (Astec CHIRALDEX™ β-DM: 30 m x 0.25 mm x 0.12 μm and γ-TA: 30 m x 0.25 mm x 0.12 μm). Elemental analyses were performed by Atlantic Microlabs, Inc.
A.1.2 Experimental Data

A.1.2.1 Synthesis of the 6-NHC copper complex (1b) Intermediates for the 6-NHC copper complex were synthesized according to literature procedure.

\[ (2S,3S)-(6-(4-\text{tert-butyl}-2,6\text{-dimethylphenyl})-2,3\text{-diphenyl}-2,3,5,6\text{-tetrahydroimidazo}[1,2-c]\text{quinazolin-5-yl})\text{copper(I) chloride} \ (1b) \]

Imidazoquinazolium salt (100 mg, 0.189 mmol) and CuCl (21.0 mg, 0.212 mmol) were charged to a schlenk flask and placed under high vacuum for 1 hour. After releasing the pressure, anhydrous THF was added to the mixture at 0 °C. KOrBu solution in THF (212 µL, 0.212 mmol, 1 M solution in THF) was added to the mixture dropwise. During the addition of KOrBu, a blue color appeared and immediately disappeared. After complete addition of KOrBu the blue color maintained for ten seconds and then changed to light brown. After 10 minutes, THF was carefully removed under vacuum and DCM was added to the reaction mixture. The reaction mixture was stirred for 18 hours. The reaction mixture was filtered through Celite and washed with DCM. The filtrate was reduced under high vacuum. The crude product was used for asymmetric reactions without further purification.

\(^1\)H NMR (600 MHz, CD\(_2\)Cl\(_2\)): \(\delta\) 9.13 (s, 1H) 7.76 (s, 1H) 7.67 (s, 1H) 7.50-7.42 (m, 10H) 7.33 (s, 1H) 7.28 (s, 1H) 6.79 (s, 1H) 5.63 (s, 1H) 5.48 (s, 1H) 2.18 (s, 3H) 1.98 (s, 3H) 1.38 (s, 9H).

\(^{13}\)C NMR (CD\(_2\)Cl\(_2\), 150 MHz) : \(\delta\) 196.7, 154.1, 152.1, 140.3, 139.7, 137.9, 137.2, 136.8, 134.9, 134.7, 130.3, 130.1, 129.8, 129.5, 128.7, 128.1, 127.20, 127.15, 127.1, 118.0, 113.1, 77.4, 75.1, 35.0, 31.4, 18.25, 18.18. IR (neat) 2961, 1655, 1624, 1471, 1456, 1389, 1276, 1063, 1033 \([\alpha]_D^{25} = -87.1^\circ \ (c=0.40, \text{CH}_2\text{Cl}_2) \]

A.1.2.2 Reaction Conditions for Chemoselectivity Comparisons

Typical reaction conditions are as follows:

Using 6-NHC Cu(I) complex (1a):

Substrate (51 mg, 0.22 mmol) and bis(pinacolato)diboron (51 mg, 0.20 mmol) were dissolved in Et₂O (1 mL). NaOrBu (6 mg, 0.060 mmol) was added to the reaction mixture and the reaction was cooled to -20 °C and MeOH (18 µL, 0.4 mmol) was added. After 5 minutes, 6-NHC 1a (1.1 mg, 0.0020 mmol) was added. After complete consumption of bis(pinacolato)diboron, the reaction mixture was filtered through silica gel and washed with ether. The filtrate was concentrated under rotory evaporator, proton NMR of crude product was taken for the determination of deallylated product to borylated product (25:1). The resulting residue was purified by column chromatography (Hexane:EtOAc = 6:1 to 4:1) to afford the shown product 5a (27 mg, 70 % yield). These data were used to generate Table 2.1. ¹H NMR (600 MHz, CDCl₃) 7.63 (d, J=15.3 Hz, 1H) 7.43 (d, J=8.9 Hz, 2H) 6.85 (d, J=8.6 Hz, 2H) 6.30 (d, J=16.0 Hz, 1H) 4.26 (q, J=7.1 Hz, 2H) 1.34 (t, J=7.1 Hz, 3H) ¹³C NMR (150 MHz, CDCl₃) δ 167.8, 157.9, 144.6, 130.2, 127.5, 116.1, 115.9, 60.7, 14.6. HRMS(EI) calcd for C₁₁H₁₂O₃: 192.07865 found : 192.0786.

Using 5-NHC Cu(I) complex (2):

Substrate (51 mg, 0.22 mmol) and bis(pinacolato)diboron (51 mg, 0.20 mmol) were dissolved in ether (1 mL). NaOrBu (6 mg, 0.060 mmol) was added to the reaction mixture and the reaction was cooled to -20 °C before adding MeOH (18 µL, 0.4 mmol). After 5 minutes, 5-NHC 2 (0.8 mg, 0.0020 mmol) was added. After complete consumption of bis(pinacolato)diboron, the reaction mixture was filtered through silica gel and washed with ether. The filtrate was concentrated under rotory evaporator. Proton NMR of crude product was
taken for the determination of the ratio of deallylated product to borylated product (1:24). The resulting residue was purified by column chromatography (Hexane:EtOAc = 50:1 to 20:1) to afford the illustrated product 5b (51 mg, 71 % yield). These data were used to generate Table 2.1. 

\[ ^1H\text{ NMR (600 MHz, } \text{CDCl}_3) \delta 7.13-7.11 (m, 2H) 6.83-6.80 (m, 2H) 6.08-6.02 (m, 1H) 5.40 (ddd, J=17.2 Hz, 3.1 Hz, 1.6 Hz, 1H) 5.26 (ddd, J=10.5 Hz, 2.8 Hz, 1.4 Hz, 1H) 4.49 (dt, J=5.3 Hz, 1.5 Hz, 2H) 4.11-4.06 (m, 2H) 2.82 (dd, J=16.2 Hz, 9.8 Hz, 1H) 2.67 (dd, J=9.8 Hz, 6.2 Hz, 1H) 2.61 (dd, J=16.2 Hz, 6.2 Hz, 1H) 1.22-1.20 (m, 9H) 1.17 (s, 6H) \]

\[ ^{13}C\text{ NMR (150 MHz, } \text{CDCl}_3) \delta 173.7, 157.0, 133.81, 133.77, 129.4, 117.7, 115.0, 83.7, 69.1, 60.5, 37.8, 24.8, 24.7, 14.5 \]

HRMS(EI) calcd for C\text{\textsubscript{20}H\textsubscript{29}BO\textsubscript{5}} 360.21081 found : 360.21141.

Using Xantphos (3):

Xantphos (8.7 mg, 0.015 mmol), CuCl (1.5 mg, 0.015 mmol) and NaO\text{\textsubscript{tBu}} (4.3 mg, 0.045 mmol) were dissolved in THF (0.4 mL) and the reaction mixture was stirred for 30 minutes. Bis(pinacolato)diboron (127 mg, 0.50 mmol) was added to the reaction. After 3 minutes, the substrate (128 mg, 0.55 mmol) in THF (1.6 mL) was added to the reaction mixture, followed by the addition of MeOH (45 µL, 1.0 mmol). After complete consumption of bis(pinacolato)diboron, the reaction mixture was filtered through silica gel and washed with ether. The filtrate was concentrated under rotory evaporator. Proton NMR of the crude product was taken to determine the ratio of deallylated product to borylated product (1:1.3). The resulting residue was purified by column chromatography (Hexane:EtOAc = 8:1) to afford the desired products (17 mg, 16 % yield). These data were used to generate Table 2.1.
A.1.2.3 Synthesis of Substrates for Leaving Group Screen

Representative Procedure A: A 7 mL screw-top vial was equipped with a stir bar and charged with aryl iodide (1 equiv.), allylic alcohol (2 equiv.), copper iodide (10 mol %), cesium carbonate (2 equiv.), 1,10-phenanthroline (20 mol %) and 1 mL toluene. The vial was sealed and heated to 110 °C with stirring for 48 hours, after which time it was cooled to room temperature and filtered through a pad of silica gel, using diethyl ether as an eluent. The solvent was removed under vacuum, and the crude product was purified by flash chromatography (9:1 Hexanes:EtOAc). Any remaining aryl iodide was removed by vacuum distillation to yield the pure desired compounds.

Representative Procedure B: Sodium hydride (1.3 equiv.) was carefully weighed out and placed in a 100 mL 3-necked round bottom flask fitted with a condenser and stir bar, then suspended in 10 mL dry DMF. A solution of the allylic alcohol (1 equiv.) in 10 mL dry DMF was added dropwise over 30 minutes, then the solution was stirred for an additional hour. A
solution of the aryl fluoride (2 equiv.) in 2 mL DMF was added dropwise and the entire solution
was stirred at room temperature for 1 hour, then stirred at 50 °C for 14 hours, after which time
the solution became a bright yellow. The reaction was quenched with 10 mL saturated
ammonium chloride solution, and extracted with diethyl ether (x4). The combined organic layers
were washed with 20 mL of 1 M HCl solution and brine, then dried over MgSO₄ and
concentrated under vacuum. Flash chromatography of the crude product, and subsequent vacuum
distillation yielded the pure desired compounds.

(E)-(hex-2-en-1-yloxy)benzene, **trans-7a**

Produced by procedure A. Isolated as a yellow oil in 78 % yield. R_f (9:1 Hexanes:EtOAc) = 0.67. ¹H NMR (CDCl₃, 600 MHz): δ = 0.92 (td, J = 7.4, 1.4, 3H), 1.44 (hd, J = 7.4, 1.0 Hz, 2H), 2.05–2.10 (m, 2H), 4.48 (dt, J = 5.9 Hz, 1.0 Hz, 2H), 5.67–5.75 (m, 1H), 6.91–6.96 (m, 3H), 7.26–7.30 (m, 2H). ¹³C NMR (CDCl₃, 150 MHz): δ = 159.0, 135.7, 129.6, 125.2, 120.9, 115.0, 69.0, 34.6, 22.3, 13.9. HRMS (EI) Calcd. For C₁₂H₁₆O 176.12012 found : 176.11988.

(E)-1-(hex-2-en-1-yloxy)-2-methylbenzene, **trans-7b**

Produced by procedure A. Isolated as a dark yellow oil in 62 % yield. R_f (9:1 Hexanes:EtOAc) = 0.68. ¹H NMR (CDCl₃, 600 MHz): δ = 0.92 (t, J = 7.4 Hz, 3H), 1.44 (sx, J = 7.4 Hz, 2H), 2.07 (dq, J = 1.0, 7.9, 14.7 Hz, 2H), 2.25 (s, 3H), 4.49 (dd, J = 1.0, 5.7 Hz, 2H), 5.69–5.86 (m, 2H), 6.83 (d, J = 8.4 Hz, 1H), 6.85 (dt, J = 0.9, 7.5 Hz, 1H), 7.14 (m, 2H). ¹³C NMR (CDCl₃, 150 MHz): δ 157.0, 134.5, 130.6, 127.0, 126.6, 125.4, 120.3, 111.6, 68.9, 34.4, 22.2, 16.3, 13.6. IR (neat, cm⁻¹): 3023, 2959, 2928, 2872, 1602, 1494, 1461, 1379, 1307, 1207, 1240, 1192, 1120, 1050, 1013. LRMS (m/z, CI⁺): Calcd. 190.28 found 191.2.

(E)-1-(hex-2-en-1-yloxy)-3,5-dimethylbenzene, **trans-7c**
Produced by procedure A. Isolated as a dark yellow oil in 95% yield. R_f (9:1 Hexanes:EtOAc) = 0.69. $^1$H NMR (CDCl$_3$, 600 MHz) δ = 0.91 (t, J = 7.4 Hz, 3H), 1.43 (sx, J = 7.4 Hz, 2H), 2.07 (dq, J = 0.9, 7.7 Hz, 2H), 2.28 (s, 6H), 4.44 (dd, J = 0.96, 6.0 Hz, 2H), 5.69 – 5.84 (m, 2H), 6.55 (s, 2H), 6.59 (s, 1H). $^{13}$C NMR (CDCl$_3$, 150 MHz) δ = 158.8, 139.1 (2), 135.2, 125.2, 122.4, 112.5 (2), 68.7, 34.4, 22.2, 21.4 (2), 13.7. IR (neat cm$^{-1}$): 3015, 2958, 2925, 2869, 1612, 1594, 1458, 1376, 1323, 1293, 1090. LRMS (m/z, CI+): Calcd. 204.3, found 205.2.

$^{(E)}$-1-(hex-2-en-1-yloxy)-3,5-bis(trifluoromethyl)benzene, $trans$-7d

Produced by procedure A. Isolated as a light yellow oil in 88% yield. R_f (9:1 Hexanes:EtOAc) = 0.79. $^1$H NMR (CDCl$_3$, 600 MHz) δ = 0.91 (t, J = 7.4 Hz, 3H), 1.43 (sx, J = 7.4 Hz, 2H), 2.08 (dq, J = 0.84, 7.4 Hz, 2H), 4.57 (dd, J = 0.90, 6.1 Hz, 2H), 5.67 – 5.90 (m, 2H), 7.30 (s, 2H), 7.44 (s, 1H). $^{13}$C NMR (CDCl$_3$, 150 MHz) δ = 159.4, 137.0 (2), 133.0, 132.8, 123.7 (2), 115.4 (2), 114.3, 69.7, 34.5, 22.2, 13.7. IR (neat, cm$^{-1}$): 2963, 2932, 2675, 1614, 1467, 1395, 1369, 1320, 1275, 1173, 1131, 1110, 1015. LRMS (m/z, EI+): Calcd. 312.09, found 312.0.

$^{(E)}$-1-(hex-2-en-1-yloxy)-3-nitrobenzene, $trans$-7e

Produced by procedure B. Isolated as a dark yellow oil in 90% yield. R_f (7:3 Hexanes:EtOAc) = 0.58. $^1$H NMR (CDCl$_3$, 600 MHz) δ = 0.91 (t, J = 7.3 Hz, 3H), 1.44 (sx, J = 7.4 Hz, 2H), 2.08 (dq, J = 0.96, 7.8, 14.7 Hz, 2H), 4.56 (dd, J = 1.0, 6.1 Hz, 2H), 5.66 – 5.91 (m, 2H), 7.23 (dq, J = 0.72, 2.5, 8.3 Hz, 1H), 7.41 (t, J = 8.2 Hz, 1H), 7.74 (t, J = 2.3 Hz, 1H), 7.81 (dq, J = 0.72, 1.2, 7.3 Hz, 1H). $^{13}$C NMR (CDCl$_3$, 150 MHz) δ = 159.4, 149.4, 136.8, 129.9, 123.9, 122.2, 115.8, 109.2, 66.6, 34.5, 22.2, 13.8. IR (neat, cm$^{-1}$): 2960, 2922, 2884, 1619, 1579, 1510, 1482, 1461, 1349, 1320, 1284, 1243, 1092, 1011. LRMS (m/z, EI+): Calcd. 221.1, found 221.1
(Z)-1-(hex-2-en-1-yloxy)-3-nitrobenzene, cis-7e

Prepared by procedure B. Isolated as a bright yellow oil in 91% yield. $^1$H NMR (CDCl$_3$, 600 MHz) $\delta = 0.95$ (t, $J = 7.4$ Hz, 3H), 1.46 (sx, $J = 7.4$ Hz, 2H), 2.15 (q, $J = 7.5$ Hz, 2H), 4.66 (d, $J = 6.1$, 2H), 5.65 – 5.76 (m, 2H), 7.23 (ddd, $J = 0.72$, 2.6, 8.3 Hz, 1H), 7.42 (t, $J = 8.2$, 1H), 7.73 (t, $J = 2.3$, 1H), 7.82 (ddd, $J = 0.72$, 2.0, 5.2 Hz, 1H). $^{13}$C NMR (CDCl$_3$, 150 MHz) $\delta = 159.4$, 149.4, 135.5, 130.0, 123.8, 122.2, 115.9, 109.1, 64.8, 30.0, 22.7, 13.9. IR (neat, cm$^{-1}$): 2960, 1607, 1592, 1511, 1496, 1461, 1381, 1255, 1173, 1111, 971, 861, 844, 752, 690. LRMS ($m/z$, EI+): Calcd. 221.1, found 221.0.

(E)-1-(hex-2-en-1-yloxy)-4-nitrobenzene, trans-7f

Prepared by procedure B. Isolated as a yellow oil in 89% yield. $R_f$ (9:1 Hexanes:EtOAc) = 0.42. $^1$H NMR (CDCl$_3$, 600 MHz) $\delta = 0.91$ (t, $J = 7.3$ Hz, 3H), 1.44 (sx, $J = 7.4$ Hz, 2H), 2.08 (dq, $J = 0.96$, 6.8, 13.6 Hz, 2H), 4.57 (dd, $J = 0.96$, 6.1 Hz, 2H), 5.65 – 5.70 (m, 1H), 5.85 – 5.90 (m, 1H), 6.95 (dd, $J = 3.4$, 5.5 Hz, 2H), 8.19 (dd, $J = 3.4$, 5.5 Hz, 2H). $^{13}$C NMR (CDCl$_3$, 150 MHz) $\delta = 163.8$, 141.5, 136.8, 125.9, 125.9, 123.6, 114.7, 114.7, 69.6, 34.3, 22.0, 13.6. IR (neat, cm$^{-1}$): 2960, 1607, 1592, 1511, 1496, 1461, 1381, 1255, 1173, 1111, 971, 861, 844, 752, 690. LRMS ($m/z$, EI+): Calcd. 221.1, found 221.0.

(E)-4-(hex-2-en-1-yloxy)-2-methyl-1-nitrobenzene, trans-7g

Prepared according to procedure B. Isolated as a dark yellow oil in 41% yield. $R_f$ (7:3 Hexanes:EtOAc) = 0.66. $^1$H NMR (CDCl$_3$, 600 MHz) $\delta = 0.91$ (t, $J = 7.3$ Hz, 3H), 1.43 (sx, $J = 7.4$ Hz, 2H), 2.08 (dq, $J = 1.0$, 7.4, 14.8 Hz, 2H), 2.62 (s, 3H), 4.54 (dd, $J = 1.0$, 6.1 Hz, 2H), 5.64 – 5.88 (m, 2H), 6.77 – 6.81 (m, 2H), 8.08 (d, $J = 8.8$ Hz, 1H). $^{13}$C NMR (CDCl$_3$, 150 MHz) $\delta = 162.4$, 142.3, 137.1, 136.7, 127.6, 123.9, 118.4, 112.6, 69.5, 34.5, 22.2, 21.8, 13.8. IR (neat, cm$^{-1}$): 2960, 1511, 1496, 1461, 1381, 1255, 1173, 1111, 971, 861, 844, 752, 690. LRMS ($m/z$, EI+): Calcd. 221.1, found 221.0.
\(\text{cm}^{-1}\): 2960, 2931, 2872, 1671, 1606, 1579, 1510, 1469, 1456, 1362, 1334, 1269, 1248, 1173, 1077, 1035. LRMS \((m/z, \text{EI}+)\): Calcd. 235.1, found 235.0.

\((E)-1-(\text{hex}-2\text{-en}-1\text{-yloxy})-4\text{-methoxybenzene, }\text{trans-7h}\)

Prepared according to procedure A. Isolated as a light yellow liquid in 80\% yield. \(^1\)H NMR (CDCl\(_3\), 600 MHz) \(\delta = 0.90 \text{ (t, } J = 7.3 \text{ Hz, } 3\text{H}), 1.43 \text{ (sx, } J = 7.4 \text{ Hz, } 2\text{H}), 2.06 \text{ (dq, } J = 0.9, 7.7, 14.7 \text{ Hz, } 2\text{H}), 3.76 \text{ (s, } 3\text{H}), 4.42 \text{ (dd, } J = 0.9, 6.1 \text{ Hz, } 2\text{H}), 5.67 - 5.83 \text{ (m, } 2\text{H}), 6.80 - 6.84 \text{ (m, } 4\text{H}). \(^1\)C NMR (CDCl\(_3\), 150 MHz) \(\delta = 154.0, 153.1, 135.4, 125.4, 115.9 \text{ (2), } 114.8 \text{ (2), } 69.7, 55.9, 34.6, 22.3, 13.8. \) LRMS \((m/z, \text{EI}+)\): Calcd 206.1, found 206.0.

A.1.2.4 Reaction Profile between trans and cis substrates

\((E)-1-(\text{hex}-2\text{-en}-1\text{-yloxy})-3\text{-nitrobenzene, }\text{trans-7e and cis-7e} \) (44 mg Each, 0.2 mol) and bis(pinacolato)diboron (51 mg, 0.2 mol) and cyclooctane (13 \(\mu\)L), as an internal standard, were dissolved in diethyl ether (1.5 \(\text{mL}\)). NaO\text{tBu} (6 mg, 0.06 mol) was added to the reaction mixture and cooled to -55 °C and MeOH (18 \(\mu\)L) was added. After 5 minutes the 6-NHC copper catalyst (1.2 mg, 0.002 mol), \(1b\) was added. The reaction was then monitored by talking aliquots of the reaction mixture at set intervals and analyzing the sample by GC and proton NMR after removing the solvent. All measurements taken were normalized by the internal standard. Internal standard calibration curve can be viewed in Figure A.2.
Figure A.2 Calibration curve of product 8 (1 equiv.) versus cyclooctane (0.5 equiv.)

Figure A.3 Reaction profile between trans and cis products 7e

Table A.1 GC Analysis for Reaction Yield.

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<tr>
<th>Time (min)</th>
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<th>Product</th>
<th>P/IS</th>
<th>Yield (%)(^a)</th>
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Table A.1 continued

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<th>Time (min)</th>
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<th>Product</th>
<th>P/IS</th>
<th>Yield (%)(^a)</th>
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\(^a\) Yield is based on a maximum value of P/IS = 2.94 based calibration curve.

Table A.2 \(^1\)H NMR Analysis for E/Z Ratio

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<th>Z (%)(^a)</th>
<th>E (%)(^b)</th>
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\(^a\) Ratio of specific isomer (E or Z) over total area (E+Z). \(^b\) Based on Formation of Product.
Figure A.4 GC chromatograms of reaction progress
Figure A.5 $^1$H NMR data for E/Z ratio dynamics

A.1.2.5 Synthesis of Substrates for Substrate Scope in Table 2.4 and Allylic Substitution Reactions

1-(Allyloxy)-3-nitrobenzene (Substrate for metathesis reactions):

A 250 mL round-bottom flask was charged with 3-nitrophenol (5 g, 35.9 mmol, 1 eq.), allyl bromide (4.67 mL, 53.9 mmol, 1.5 eq.), anhydrous K$_2$CO$_3$ (9.94 g, 71.9 mmol, 2 eq.) and 120 mL acetone (0.3 M) and stirred at room temperature for 14 hours. The reaction mixture was then filtered through Celite and concentrated by N$_2$ flow. The product was redissolved into hexanes, and filtered through Celite to remove KBr salt. Desired product was isolated as a bright yellow oil in 98 % yield. R$_f$ (7:3 Hexanes:EtOAc) = 0.66. $^1$H NMR (CDCl$_3$, 600 MHz) $\delta$ = 4.62 (m, 2H), 5.35 (dd, J = 1.2, 10.6 Hz, 1H), 5.45 (dd, J = 1.4, 17.3 Hz, 1H), 6.02 – 6.09 (m, 1H), 7.25 (ddd, J = 0.6, 2.5, 8.3 Hz, 1H), 7.42 (t, J = 8.2 Hz, 1H), 7.74 (t, J = 2.3 Hz, 1H), 7.83 (m, 1H). $^{13}$C NMR (CDCl$_3$, 150 MHz) $\delta$ = 159.1, 149.2, 132.1, 130.0, 121.9, 118.5, 115.9, 109.1, 69.4. IR (neat, cm$^{-1}$) = 3097, 2871, 1617, 1582, 1524, 1481, 1460, 1424, 1349, 1321, 1286, 1242, 1230, 1157, 1096, 1022. LRMS (m/z, EI+): Calcd. 179.1, found 179.1.

Representative Metathesis Procedure: A 50 mL round-bottom flask was flame-dried and kept under N$_2$ atmosphere. The flask was charged with 1-(allyloxy)-3-nitrobenzene (4 eq.), terminal olefin (1 eq.) and methylene chloride (0.2 M) and stirred at room temperature for 10 minutes. Grubbs’ 1$^{st}$ generation catalyst was added (5 mol %) and the reaction was heated to reflux (45 °C) for 14 hours, then cooled to room temperature. The crude material was adsorbed onto silica and flash chromatography was used to isolate the product (10% Et$_2$O in Hexanes). Remaining 1-(allyloxy)-3-nitrobenzene was then removed by Kügelrohr distillation (100 °C at 150 mTorr) to give the desired product.
1-((3-Cyclohexylallyl)oxy)-3-nitrobenzene, \textbf{10b}

Isolated as a brown oil in 37\% yield. $R_f = (9:1$ Hexanes:EtOAc) 0.49. $^1$H NMR (CDCl$_3$, 600 MHz, $E$-isomer only) $\delta = 1.07 – 1.35$ (m, 5H), $1.71 – 1.76$ (m, 5H), $2.00 – 2.05$ (m, 1H), $4.55$ (d, $J = 6.1$ Hz, 2H), $5.60 – 5.85$ (m, 2H), $7.23$ (ddd, $J = 0.72, 2.5, 8.9$ Hz, 1H), $7.41$ (t, $J = 8.2$ Hz, 1H), $7.73$ (t, $J = 2.3$ Hz, 1H), $7.81$ (ddd, $J = 0.60, 1.8, 7.9$ Hz, 1H). $^{13}$C NMR (CDCl$_3$, 150 MHz): $\delta = 159.4, 142.5, 129.9, 122.1, 121.3, 115.8, 109.3, 69.9, 40.6, 33.2, 32.7$ (2), $26.2, 25.9$ (2). IR (neat, cm$^{-1}$): 2924, 2851, 1620, 1579, 1523, 1481, 1448, 1348, 1285, 1244, 1075, 1012. LRMS ($m/z$, EI+): Calcd. 261.1, found 261.0.

1-Nitro-3-((4-phenylbut-2-en-1-yl)oxy)benzene, \textbf{10c}

Isolated as a dark brown oil in 31\% yield. $R_f (9:1$ Hexanes:EtOAc) = 0.33. $^1$H NMR (CDCl$_3$, 600 MHz, $E/Z = 4.6/1$) $\delta = 3.44$ (d, $J = 6.8$ Hz, 2H), $4.59$ (dd, $J = 1.0, 5.8$ Hz, 2H), $5.73 – 5.77$ (m, 1H), $6.02 – 6.06$ (m, 1H), $7.17 – 7.23$ (m, 4H), $7.30$ (t, $J = 7.6$ Hz, 2H), $7.31$ (t, $J = 8.2$ Hz, 1H), $7.73$ (t, $J = 2.3$ Hz, 1H), $7.81$ (ddd, $J = 0.78, 2.1, 8.2$ Hz, 1H). $^{13}$C NMR (CDCl$_3$, 150 MHz): $\delta = 159.3, 149.4, 139.5, 134.8, 130.0, 128.72$ (2), $128.67$ (2), $126.5, 125.3, 122.1, 115.9, 109.3, 69.2, 38.8$. IR (neat, cm$^{-1}$) 3028, 1617, 1581, 1528, 1494, 1481, 1453, 1347, 1321, 1286, 1244, 1093, 1012. LRMS ($m/z$, EI+): Calcd. 269.1, found 269.1.

1-Nitro-3-((5-phenylpent-2-en-1-yl)oxy)benzene, \textbf{10e}

Isolated as a light yellow oil in 79\% yield. $^1$H NMR (CDCl$_3$, 600 MHz, $E/Z = 3.3/1$): $\delta = 2.42$ (q, $J = 7.1$ Hz, 2H), $2.73$ (t, $J = 7.4$ Hz, 2H), $4.54$ (dd, $J = 0.84, 6.0$ Hz, 2H), $5.69 – 5.94$ (m, 2H), $7.17$ (t, $J = 7.0$ Hz, 3H), $7.21$ (dd, $J = 2.2, 7.7$ Hz, 1H), $7.27$ (t, $J = 7.6$ Hz, 2H), $7.41$ (t, $J = 8.2$ Hz, 1H), $7.72$ (t, $J = 2.3$ Hz, 1H), $7.81$ (ddd, $J = 0.72, 2.1, 8.2$ Hz, 1H). $^{13}$C NMR (CDCl$_3$, 150 MHz): $\delta = 159.3, 149.4, 141.5, 135.6, 130.0, 128.7, 128.6, 128.5, 128.5, 126.1, 124.5, 122.1,
(E)-1-((4-(4-Methoxyphenyl)but-2-en-1-yl)oxy)-3-nitrobenzene, **10d**

Isolated as a dark brown oil in 49% yield. R<sub>f</sub> = 0.27. \(^1\)H NMR (CDCl<sub>3</sub>, 600 MHz, E/Z = 5.5/1): δ = 3.38 (d, J = 6.7 Hz, 2H), 3.79 (s, 3H), 4.58 (dd, J = 1.0, 5.9 Hz, 2H), 6.04 – 5.70 (m, 2H), 6.84 (dt, J = 3.8, 6.8 Hz, 2H), 7.10 (dt, J = 2.9, 4.7 Hz, 2H), 7.22 (ddd, J = 0.72, 2.4, 8.3 Hz, 1H), 7.41 (t, J = 8.3 Hz, 1H), 7.30 (t, J = 2.3 Hz, 1H), 7.81 (ddd, J = 0.72, 2.0, 8.0 Hz, 1H). \(^{13}\)C NMR (CDCl<sub>3</sub>, 150 MHz): δ = 159.3, 158.3, 149.3, 135.3, 134.1, 129.7, 129.4 (2), 125.0, 122.1, 115.9, 114.2 (2), 109.3, 69.2, 55.4, 37.9. IR (neat, cm<sup>-1</sup>): 2918, 1611, 1581, 1523, 1511, 1482, 1463, 1349, 1321, 1299, 1286, 1244, 1177, 1094, 1034, 1012. LRMS (m/z, EI+): Calcd. 283.1, found 283.1.

1-((6-Bromohex-2-en-1-yl)oxy)-3-nitrobenzene, **10f**

Isolated as a bright orange oil in 47% yield. \(^1\)H NMR (CDCl<sub>3</sub>, 600 MHz, E/Z = 3.3/1): δ = 1.98 (p, J = 6.8 Hz, 2H), 2.28 (q, J = 7.0 Hz, 2H), 3.42 (t, J = 6.6 Hz, 2H), 4.57 (d, J = 5.8 Hz, 2H), 5.74 – 5.88 (m, 2H), 7.23 (dd, J = 2.3, 8.2 Hz, 1H), 7.42 (t, J = 8.2 Hz, 1H), 7.73 (d, 1.7 Hz, 1H), 7.82 (d, J = 8.1 Hz, 1H). \(^{13}\)C NMR (CDCl<sub>3</sub>, 150 MHz): δ = 159.3, 149.4, 134.1, 130.0, 125.5, 122.1, 116.0, 109.2, 69.2, 33.0, 31.8, 30.7. IR (neat, cm<sup>-1</sup>): 2941, 1619, 1579, 1528, 1482, 1459, 1349, 1321, 1285, 1242, 1093, 1011. HRMS (m/z, Cl+): Calcd. 299.02, found 300.1.

7-(3-Nitrophenoxy)hept-5-en-2-one, **10g**

Isolated as a dark brown oil in 51% yield. \(^1\)H NMR (CDCl<sub>3</sub>, 600 MHz, E/Z = 3.2/1): δ = 2.16 (s, 3H), 2.39 (q, J = 7.0 Hz, 2H), 2.57 (t, J = 7.0 Hz, 2H), 4.55 (d, J = 5.8, 2H), 5.66 – 5.91.
(m, 2H), 7.22 (dd, J = 2.1, 8.3 Hz, 1H), 7.42 (t, J = 8.2 Hz, 1H), 7.72 (s, 1H), 7.82 (d, J = 8.0 Hz, 1H). $^{13}$C NMR (CDCl$_3$, 150 MHz): $\delta = 207.5$, 159.1, 149.2, 134.4, 129.9, 124.8, 121.9, 115.8, 109.1, 69.1, 42.6, 29.9, 26.3. IR (neat, cm$^{-1}$): 3097, 2918, 1715, 1619, 1579, 1524, 1482, 1410, 1349, 1322, 1286, 1243, 1163, 1012. LRMS ($m/z$, EI+): Calcd. 249.1, found 249.1.

**Methyl 6-(3-nitrophenoxy)hex-4-enoate, 10h**

Isolated as a brown oil in 57% yield. $^1$H NMR (CDCl$_3$, 600 MHz, E/Z = 1.1/1) $\delta = 2.29 – 2.32$ (m, 1.3H), 2.35 – 2.39 (m, 2.5H), 2.44 (m, 4H), 2.46 – 2.51 (m, 3.4H), 3.68 (s, 3H), 3.69 (s, 3H), 4.56 (dd, J = 0.6, 5.8 Hz, 2H), 4.70 (dd, J = 0.6, 5.8 Hz, 1.8H), 5.66 – 5.92 (m, 2H), 7.23 (m, 1H), 7.42 (m, 1H), 7.73 (m, 1H), 7.82 (m, 1H). $^{13}$C NMR (CDCl$_3$, 150 MHz): $\delta = 173.3$, 159.3, 149.4, 134.1, 130.1, 130.0, 129.6, 129.2, 122.0, 116.0, 109.2, 69.6, 64.7, 51.7, 34.1, 33.6, 27.6, 23.5. IR (neat, cm$^{-1}$): 3023, 2952, 2913, 1736, 1617, 1580, 1523, 1482, 1437, 1349, 1321, 1286, 1243, 1196, 1167, 1093, 1011. LRMS ($m/z$, EI+): Calcd. 265.3, found 265.1.

**tert-Butyldimethyl((4-(3-nitrophenoxy)but-2-en-1-yl)oxy)silane, 10i**

Isolated as a dark brown oil in 47% yield. $R_f = 0.34$. $^1$H NMR (CDCl$_3$, 600 MHz, E/Z = 12/1) $\delta = 0.08$ (s, 6H), 0.91 (s, 9H), 4.23 (m, 2H), 4.62 (m, 2H), 5.91 – 6.00 (m, 2H), 7.27 (ddd, J = 0.72, 2.4, 8.3 Hz, 1H), 7.42 (t, J = 8.2 Hz, 1H), 7.73 (t, 2.3 Hz, 1H), 7.82 (ddd, J = 0.9, 2.1, 8.2 Hz, 1H). $^{13}$C NMR (CDCl$_3$, 150 MHz): $\delta = 159.3$, 149.3, 134.2, 130.0, 123.5, 122.0, 115.9, 109.3, 68.8, 62.9, 26.0 (3), 18.5, -5.2 (2). IR (neat, cm$^{-1}$): 2950, 2930, 2884, 2857, 1616, 1581, 1530, 1472, 1463, 1349, 1321, 1286, 1248, 1101, 1024. LRMS ($m/z$, CI+): Calcd. 323.1, found 324.2.

**tert-Butyl (4-(4-methoxyphenoxy)but-2-en-1-yl)carbamate, 10j**
Isolated as a light yellow solid. $^1$H NMR (CDCl$_3$, 600 MHz): δ = 1.45 (s, 9H), 3.82 (br s, 2H), 4.60 (dd, J = 1.1, 5.4 Hz, 2H), 5.82 – 5.93 (m, 2H), 7.23 (dd, J = 0.78, 2.6, 8.3 Hz, 1H), 7.43 (t, J = 8.2 Hz, 1H), 7.73 (t, J = 2.3 Hz, 1H), 7.83 (dd, J = 0.72, 2.2, 8.2 Hz, 1H). $^{13}$C NMR (CDCl$_3$, 150 MHz): δ = 159.2, 155.8, 149.4, 131.9, 130.1, 125.4, 121.9, 116.0, 109.2, 79.7, 68.6, 42.0, 28.5 (3). IR (neat, cm$^{-1}$): 3432, 3337, 2978, 1700, 1619, 1524, 1519, 1391, 1365, 1350, 1243, 1168, 1074, 1014. LRMS (m/z, EI+): Calcd. 308.1, found 309.1.

Typical conditions for allylic substitution reactions. Allylic aryl ethers (0.20 mmol) and bis(pinacolato)diboron (56 mg, 0.22 mmol) were dissolved in ether (1 mL). NaOrBu (6 mg, 0.060 mmol) was added to the reaction mixture and the reaction was cooled to -55 °C before adding anhydrous methanol (18 µL, 0.40 mmol). After 5 minutes, 6-NHC copper catalyst 1b (1.2 mg, 0.0020 mmol) was added. After complete consumption of allylic aryl ethers the reaction mixture was filtered through silica gel and washed with ether. The filtrate was concentrated under rotary evaporator. The resulting residue was purified by column chromatography (Hexane:Et$_2$O) to afford the desired products. Absolute configuration was determined with comparison to known data after oxidation and acetylation of the subsequent allylic boronic ester.

(S)-2-(hex-1-en-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, 11a

Borinate, 11a was prepared according to the general procedure from E and Z isomer substrates and purified by column chromatography (Hexanes to Hexanes: EtOAc 20:1). From the E isomer: 11a was isolated as clear oil (90 % yield, 93 % ee). From the Z isomer: 11a was isolated as a clear oil (80 % yield, 96 % ee). Rf (20:1 Hexanes:EtOAc) = 0.47. Ee was determined by GC analysis after oxidation and acetylation of the alcohol. $^1$H NMR (600 MHz, CDCl3): δ 5.79 (ddd, J=17.1 Hz, 10.1 Hz, 8.8z, 1H) 4.97 (ddd, J=17.1 Hz, 1.8 Hz, 1.2 Hz, 1H)
4.92 (ddd, J=10.1 Hz, 1.8 Hz, 0.7 Hz, 1H), 1.84 (q, J=7.8 Hz, 1H) 1.56-1.50 (m, 1H) 1.44-1.25 (m, 3H) 1.24 (s, 6H) 1.23 (s, 6H) 0.89 (t, J=7.3 Hz, 3H) 13C NMR (150 MHz, CDCl3): δ 140.0, 113.6, 83.3, 32.7, 24.94, 24.85, 22.3, 14.3. [α]D25 = +11.1° (c=1.5, DCM, 96 % ee). HRMS(EI) calcd for C12H23BO2 210.17912 found: 210.18004. Absolute configuration determined by comparison with known data of acetylated product. Observed data [α]D25 = -4.4° (c=0.3, CHCl3), known data for S configuration [α]D25 = -30.7° (c = 3.8, CHCl3).

(R)-1-Cyclohexylprop-2-en-1-ol, 11b

Boronate, 11b was prepared according to the general procedure. The boronate ester was oxidized to the alcohol, 11b and purified by column chromatography (Hexanes to Hexanes: Et2O 10:1). 11b was isolated as a clear oil (84 % yield, >99 % ee). Rf (10:1 Hexanes:EtOAc) = 0.12. Ee was determined by GC analysis (β-DM column, 110 °C, 4 mL/min) after acetylation of the alcohol. 1H NMR (600 MHz, CDCl3) δ 5.86 (ddd, J=6.5 Hz, 10.4 Hz, 17.0 Hz, 1H) 5.21 (dt, J=1.4 Hz, J=17.2 Hz, 1H) 5.15 (dt, J=1.3 Hz, J=10.4 Hz, 1H) 3.85 (t, J=6.1 Hz, 1H) 1.85 (d, J=12.7 Hz, 1H) 1.80-1.72 (m, 2H), 1.71-1.64 (m, 2H) 1.48-1.44 (br, 1H), 1.44-1.37 (m, 1H), 1.28-95 (m, 5H) 13C NMR (150 MHz, CDCl3) δ = 139.8, 115.5, 43.5, 28.8, 28.3, 26.5, 26.2, 26.1. [α]D25 = +14.7° (c=0.70, CHCl3). HRMS(CI+) calcd for C9H15O 139.11230 found: 139.11196. Absolute configuration was determined by comparison with known data for S configuration, [α]D25 = -16.04° (c=2.36, CHCl3,>99%,ee).

(S)-4,4,5,5-tetramethyl-2-(1-phenylbut-3-en-2-yl)-1,3,2-dioxaborolane, 11c

Boronate 11c was prepared according to the general procedure and purified by column chromatography (Hexanes to Hexanes:Et2O 20:1). 11c was isolated as a clear oil (95 % yield, 93
% ee). Rf (20:1 Hexanes:EtOAc) = 0.28. Ee was determined by GC (β-DM column, 110°C, 4mL/min) after oxidation to the alcohol. $^1$H NMR (600 MHz, CDCl$_3$) δ = 7.26 – 7.20 (m, 4H), 7.16 – 7.13 (m, 1H), 5.84 (ddd, J = 8.3, 9.4, 17.5 Hz, 1H), 5.00 (dt, J = 1.4, 17.2 Hz, 1H), 4.95 (dt, J = 1.02, 10.3 Hz, 1H), 2.89 (dd, J = 8.5, 13.7 Hz, 1H), 2.78 (dd, J = 7.6, 13.7 Hz, 1H), 2.20 (q, J = 8.1 Hz, 1H), 1.17 (s, 6H), 1.15 (s, 6H). $^{13}$C NMR (150 MHz, CDCl$_3$) δ = 141.6, 138.8, 128.9, 128.0, 125.7, 114.1, 83.3, 36.4, 24.6. $[\alpha]_D^{25} = +3.88^\circ$ (c = 1.34, CHCl$_3$). HRMS(CI+) calcd for C$_{16}$H$_{24}$BO$_2$ 259.1869, found: 259.1867. Absolute configuration was determined by comparison with known data of alcohol product.

2-(1-(4-Methoxyphenyl)but-3-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, 11d

Boronate 11d was prepared according to the general procedure and purified by column chromatography (Hexanes to Hexanes:Et$_2$O 10:1). 11d was isolated as a clear oil (87 % yield, 92 % ee). Rf (20:1 Hexanes:EtOAc) = 0.09. Ee was determined by GC (β-DM column, 90°C, 1.6 mL/min) after oxidation to the alcohol. $^1$H NMR (600 MHz, CDCl$_3$) δ = 7.13 (d, J = 8.6 Hz, 2H), 6.79 (d, J = 8.6 Hz, 2H), 5.82 (ddd, J = 8.3, 9.4, 17.8 Hz, 1H), 5.02 (dt, J = 1.4, 17.2 Hz, 1H), 4.94 (d, J = 10.2 Hz, 1H), 3.77 (s, 3H), 2.83 (dd, J = 8.5, 13.3 Hz, 1H), 2.72 (dd, J = 7.6, 13.9 Hz, 1H), 2.19 (q, J = 8.2 Hz, 1H), 1.17 (s, 6H), 1.15 (s, 6H). $^{13}$C NMR (150 MHz, CDCl$_3$) δ = 157.7, 138.8, 133.8, 129.8, 114.1, 113.5, 83.3, 55.2, 35.5, 24.7, 24.6. $[\alpha]_D^{25} = -1.03^\circ$ (c = 1.00, CHCl$_3$). HRMS(CI+) calcd for C$_{17}$H$_{26}$BO$_2$ 289.1975, found: 289.1971.

(S)-4,4,5,5-Tetramethyl-2-(5-phenylpent-1-en-3-yl)-1,3,2-dioxaborolane, 11e

Boronate 11e was prepared according to the general procedure and purified by column chromatography (Hexanes to Hexanes:Et$_2$O 20:1). 11e was isolated as a clear oil (88 % yield, 93 % ee). Rf (20:1 Hexanes:EtOAc) = 0.27. Ee was determined by GC (β-DM column, 110°C, 4
mL/min) after oxidation to the alcohol. $^1$H NMR (600 MHz, CDCl$_3$) $\delta = 7.28-7.15$ (m, 5H), 5.82 (ddd, J = 8.1, 10.2, 18.6 Hz, 1H), 5.04-4.98 (m, 2H), 2.68-2.54 (m, 2H), 1.92-1.89 (m, 2H), 1.79-1.70 (m, 1H), 1.24 (s, 12H). $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta = 142.7, 139.2, 128.5, 128.2, 125.6, 114.0, 83.2, 35.2, 24.7, 24.6. [\alpha]^{25}_D = -4.90^\circ$ (c = 1.00, DCM). HRMS(CI+) calcd for C$_{17}$H$_{26}$BO$_2$ 273.20259, found: 273.20373.

2-(6-Bromohex-1-en-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, **11f**

Boronate **11f** was prepared according to the general procedure and purified by column chromatography (Hexanes to Hexanes:Et$_2$O 20:1). **11f** was isolated as a clear oil (92 % yield, 93 % ee). R$_f$ (10:1 Hexanes:EtOAc) = 0.28. Ee was determined by GC ($\beta$-DM column, 110°C, 4 mL/min) after oxidation and acetylation of the alcohol. $^1$H NMR (600 MHz, CDCl$_3$) $\delta = 5.76$ (ddd, J = 8.7, 10.1, 17.1 Hz, 1H), 5.02-4.96 (m, 2H), 3.40 (td, J = 2.6, 8.0 Hz, 2H), 1.96-1.88 (m, 1H), 1.88-1.80 (m, 2H), 1.73-1.65 (m, 1H), 1.60-1.53 (m, 1H), 1.25 (s, 12H). $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta = 138.8, 114.2, 83.3, 33.7, 32.2, 28.7, 24.7, 24.6. [\alpha]^{25}_D = +5.96^\circ$ (c = 1.33, CHCl$_3$). HRMS(CI+) calcd for C$_{12}$H$_{23}$BO$_2$ 289.0974, found: 289.0968.

5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)hept-6-en-2-one, **11g**

Boronate **11g** was prepared according to the general procedure and purified by column chromatography (Hexanes to Hexanes:Et$_2$O 5:1). **11g** was isolated as a clear oil (50 % yield, 94 % ee). R$_f$ (5:1 Hexanes:EtOAc) = 0.16. Ee was determined by GC ($\beta$-DM column, 100°C, 4 mL/min) after oxidation and acetylation of the alcohol. $^1$H NMR (600 MHz, CDCl$_3$) $\delta = 5.74$ (ddd, J = 8.6, 10.2, 17.2, 1H), 5.01-4.97 (m, 2H), 2.50-2.38 (m, 2H), 2.13 (s, 3H), 1.87-1.68 (m, 3H), 1.24 (s, 12H). $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta = 209.1, 138.7, 114.4, 83.3, 42.9, 29.9, 24.7,
24.6, 24.0. \([\alpha]_D^{25} = +3.76^\circ\) (c = 0.90, CHCl₃). HRMS(CI+) calcd for C₁₂H₂₃BO₃ 289.0974, found: 289.0968.

**Methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-5-enoate, 11h**

Boronate 11h was prepared according to the general procedure and purified by column chromatography (Hexanes to Hexanes:Et₂O 10:1). 11h was isolated as a clear oil (>95 % yield, 94 % ee). Rₚ (5:1 Hexanes:EtOAc) = 0.52. Ee was determined by GC (β-DM column, 110°C, 4 mL/min) after oxidation and acetylation of the alcohol. \(^1\)H NMR (600 MHz, CDCl₃) δ = 5.78-5.72 (m, 1H), 5.02-4.98 (m, 2H), 3.66 (s, 3H), 2.39-2.34 (m, 1H), 2.33-2.28 (m, 1H), 1.93-1.87 (m, 1H), 1.93-1.87 (m, 1H), 1.83-1.73 (m, 2H), 1.24 (s, 12H). \(^1\)C NMR (150 MHz, CDCl₃) δ = 174.1, 138.4, 114.6, 83.3, 51.4, 33.3, 25.2, 24.7, 24.6. \([\alpha]_D^{25} = +5.1^\circ\) (c = 0.08, CHCl₃).

HRMS(CI+) calcd for C₁₃H₂₄BO₄ 255.1768, found: 255.1772.

**tert-Butyldimethyl((2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-yl)oxy)silane, 11i**

Boronate 11i was prepared according to the general procedure and purified by column chromatography (Hexanes to Hexanes:Et₂O 20:1). From the predominantly cis-isomer, 11i was isolated as a clear oil (91 % yield, 93 % ee). From the predominately trans-isomer, 11i was isolated as a clear oil (83 % yield, 93 % ee). Rₚ (20:1 Hexanes:EtOAc) = 0.26. Ee was determined by GC (β-DM column, 80°C, 4 mL/min) after oxidation. \(^1\)H NMR (600 MHz, CDCl₃) δ = 5.82 (ddd, J = 8.6, 10.2, 17.3 Hz, 1H), 5.04 (dt, J = 1.6, 16.9 Hz, 1H), 4.99 (dd, J = 1.56, 10.4 Hz, 1H), 3.78 – 3.72 (m, 2H), 2.12 (q, J = 7.4 Hz, 1H), 1.24 (s, 12H), 0.88 (s, 9H), 0.04 (s, 6H). \(^1\)C NMR (150 MHz, CDCl₃) δ = 136.6, 115.0, 83.2, 64.3, 25.9, 24.7, 18.3, -5.4.
\([\alpha]_D^{25} = +0.87^\circ \) (c = 1.2, CHCl\(_3\)). HRMS(CI+) calcd for C\(_{16}\)H\(_{34}\)BO\(_3\)Si 313.23704, found: 313.23701.

*tert*-Butyl (2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-yl)carbamate, 11\(j\)

Boronate 11\(j\) was prepared according to the general procedure. The boronate was oxidized to the alcohol 12\(j\) and purified by column chromatography (Hexanes to Hexanes:Et\(_2\)O 1:1). 12\(j\) was isolated as a clear oil (92 \% yield, 90 \% ee). R\(_f\) (1:1 Hexanes:Et\(_2\)O) = 0.32. Ee was determined by GC (\(\beta\)-DM column, 115°C, 4 mL/min) after oxidation. \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta = 5.86\) (ddd, \(J = 5.5, 10.5, 17.1\) Hz, 1H), 5.4 (dt, \(J = 1.4, 17.2\) Hz, 1H), 5.03 (d, \(J = 10.6\), 1H), 5.03-4.90 (br, 1H), 4.29 – 4.20 (br, 1H), 3.43-3.32 (br, 1H), 3.12-3.07 (m, 1H), 2.72-2.66 (br, 1H), 1.45 (s, 9H). \(^1^3\)C NMR (150 MHz, CDCl\(_3\)) \(\delta = 156.8, 138.0, 116.2, 79.7, 72.4, 46.3, 28.3.\) \([\alpha]_D^{25} = -2.69^\circ \) (c = 1.4, CHCl\(_3\)). HRMS(CI+) calcd for C\(_9\)H\(_{18}\)O\(_3\)N 188.12867, found: 188.12815.

**A.1.2.6 Testing the Reactivity of the Tri-Substituted Alkene vs. the Di-Substituted Alkene**

Allylic Aryl Ether, 10\(k\) (19 mg, 0.048 mmol) and bis(pinacolato)diboron (12 mg, 0.053 mmol) was dissolved in ether (1 mL). NaO\(_x\)Bu (1.5 mg, 0.015 mmol) was added to the reaction mixture, then the reaction was cooled to -55 °C and MeOH (5 \(\mu\)L, 0.1 mmol) was added. After 5 minutes, 6-NHC copper catalyst 1\(b\) (0.3 mg, 0.000480 mmol) was added. The reaction was quenched after 18 hours. Solvent was evaporated in vacuo and proton NMR was taken of the crude mixture (80 \% yield based on unreacted starting material).
Figure A.6 $^1$H NMR of crude reaction mixture following reaction of tri-substituted alkene.
Figure A.7 $^1$H NMR and $^{13}$C NMR of compound 1b
Figure A.8 $^1$H NMR and $^{13}$C NMR of compound 4
Figure A.9 $^1$H NMR and $^{13}$C NMR of compound 5a
Figure A.10 $^1$H NMR and $^{13}$C NMR of compound 5b
Figure A.11 $^1$H NMR and $^{13}$C NMR of compound 7a
Figure A.12 $^1$H NMR and $^{13}$C NMR of compound 7b
Figure A.13 $^1$H NMR and $^{13}$C NMR of compound 7c
Figure A.14 $^1$H NMR and $^{13}$C NMR of compound 7d
Figure A.15 $^1$H NMR and $^{13}$C NMR of compound trans-7e
Figure A.16 $^1$H NMR and $^{13}$C NMR of compound cis-7e
Figure A.17 $^1$H NMR and $^{13}$C NMR of compound 7f
Figure A.18 $^1$H NMR and $^{13}$C NMR of compound 7g
Figure A.19 $^1$H NMR and $^{13}$C NMR of compound 7h
Figure A.20 $^1$H NMR and $^{13}$C NMR of 1-(allyloxy)-3-nitrobenzene
Figure A.21 $^1$H NMR and $^{13}$C NMR of compound 10b
Figure A.22 $^1$H NMR and $^{13}$C NMR of compound 10c
Figure A.23 $^1$H NMR and $^{13}$C NMR of compound 10d
Figure A.24 $^1$H NMR and $^{13}$C NMR of compound 10e
Figure A.25 $^1$H NMR and $^{13}$C NMR of compound 10f
Figure A.26 $^1$H NMR and $^{13}$C NMR of compound 10g
Figure A.27 $^1$H NMR and $^{13}$C NMR of compound 10h
Figure A.28 \(^1\text{H}\) NMR and \(^{13}\text{C}\) NMR of compound \textit{trans-10i}
Figure A.29 $^1$H NMR and $^{13}$C NMR of compound cis-10i
Figure A.30 $^1$H NMR and $^{13}$C NMR of compound 10j
Figure A.31 $^1$H NMR and $^{13}$C NMR of compound 10k
Figure A.32 $^1$H NMR and $^{13}$C NMR of compound 11a
Figure A.33 $^1$H NMR and $^{13}$C NMR of compound 12b
Figure A.34 $^1$H NMR and $^{13}$C NMR of compound $11c$
Figure A.35 $^1$H NMR and $^{13}$C NMR of compound 11d
Figure A.36 $^1$H NMR and $^{13}$C NMR of compound 11e
Figure A.37 $^1$H NMR and $^{13}$C NMR of compound 11f
Figure A.38 $^1$H NMR and $^{13}$C NMR of compound 11g
Figure A.39 $^1$H NMR and $^{13}$C NMR of compound 11h
Figure A.40 $^1$H NMR and $^{13}$C NMR of compound 11i
Figure A.41 $^1$H NMR and $^{13}$C NMR of compound 12j
APPENDIX B

SUPPORTING INFORMATION FOR CHAPTER 3

B.1 Characterization Data

B.1.1 General Procedures and Instrumentation

Flash chromatography was performed using silica gel (230-400 mesh). For analytical thin layer chromatography (TLC), silica gel 60 F\textsubscript{254} plates were used. All commercial reagents were used without further purification, except sodium \textit{t}-butoxide which was purified by sublimation (180 °C at 200 mTorr) prior to use in the large scale synthesis. Proton nuclear magnetic resonance (\textsuperscript{1}H NMR) spectra and carbon nuclear magnetic resonance (\textsuperscript{13}C NMR) spectra were recorded on a 600 MHz spectrometer. Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane or referenced to residual solvent. Data are represented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, p=pentet, hept=heptet, m = multiplet), coupling constants in Hertz (Hz), integration. Percent conversion of crude reaction mixtures was determined by gas chromatography with integration relative in an internal standard.

Reactions performed in flow were performed with a commercially available Vapourtec R series reactor controlled by FlowCommander\textsuperscript{TM} software. Mixtures of solid copper(I) oxide and filler material were packed into a glass Omnifit column (6.6 mm diameter) fitted with Vapourtec end caps and PTFE frits. All tubing and fittings were supplied with the reactor, but the tubing was standard 1.00 mm bore PFA and standard PTFE fittings.

B.1.2 Catalyst Synthesis
Prepared according to general reactor setup described in reference 32 using 80% CH$_2$Cl$_2$/20% toluene. A flow rate of 0.800 mL/min was used. The solution was concentrated under reduced pressure and dried to yield 14 (66 mg, 94% yield). $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.39 (d, J = 9.2 Hz, 1H), 7.29 (s, 1H), 7.00 (s, 2H), 6.94 (dd, J = 9.3, 6.6 Hz, 1H), 6.58 (d, J = 6.5 Hz, 1H), 3.11 (s, 3H), 2.36 (s, 3H), 1.99 (s, 6H) ppm. $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 167.0, 139.6, 136.7, 136.2, 134.3, 131.9, 129.4, 123.3, 115.9, 114.0, 112.7, 22.4, 21.1, 17.7 ppm. Anal. Calcd. for C$_{17}$H$_{19}$ClCuN$_2$: C: 58.28; H:5.47; N:8.00. Found: C: 58.90; H: 5.08; N: 7.95.

B.1.3 Screening Conditions

A single stock solution of bicyclo[2.2.1]hept-2-ene (0.4 M, 1 eq) and bis(pinacolato)diboron (0.48 M, 1.2 eq) starting materials, with mesitylene (15 mol %) as an internal standard, was prepared in dry, inhibitor-free diethyl ether. A 1.86 mL portion of the stock solution (equivalent to a 70 mg scale reaction with respect to norbornene) was dispensed into a flame-dried Schlenk tube containing a stir bar under nitrogen, which was then fitted with a rubber septum. Powdered NaOtBu (21 mg, 0.223 mmol, 0.30 eq) is then added, and the sides of the reaction vessel are washed with an additional 0.930 mL diethyl ether. Anhydrous methanol was then added via syringe through the septum (60 $\mu$L, 1.49 mmol, 2 eq). Copper chloride complex 14 (2.60 mg, 7.43 $\mu$mol, 0.01 eq) is then added. An additional 0.930 mL of diethyl ether was then added to wash any residual catalyst into the flask. The reaction was allowed to stir for 30 minutes at room temperature. Reaction conversions were determined by comparing the ratio of peak area between norbornene and internal standard for the stock solution and crude reaction.
mixture after 30 minutes (GC Method: 75 °C hold 2 min, then ramp 5 °C/min to 100 °C then ramp 30 °C/min to 220 °C and hold 2 min. Flow rate: 1.3 mL/min).

**B.1.4 Reaction Scale-Up**

Bicyclo[2.2.1]hept-2-ene (268.8 mg, 2.85 mmol, 1 eq) and bis(pinacolato)diboron (869.8 mg, 3.43 mmol 1.2 eq) were weighed out into a vial and then transferred to a flame dried side armed round bottom using 10 mL of inhibitor-free diethyl ether. Powdered NaOrBu (82.3 mg, 0.856 mmol, 0.30 eq) was added followed by anhydrous methanol (230 μL, 5.71 mmol, 2 eq). Finally, copper chloride complex 14 (10 mg, 0.029 mmol, 0.01 eq) was added to initiate the reaction. The reaction was stirred for 40 minutes, filtered through silica gel and washed with additional ether and concentrated. The product was chromatographed (100 % hexanes) to afford product 16 (521 mg, 82% yield). The $^1$H NMR and $^{13}$C NMR data were in accordance with those described in the literature.

**B.1.5 Reaction Scope Studies**

A flame-dried Schlenk tube with magnetic stir bar was purged with nitrogen flow, then fitted with a rubber septum. Alkene (70 mg) in diethyl ether (0.2 M total, divided amongst washings) was charged to the vessel, followed by bis(pinacolato)diboron (1.2 eq) which was added by removing the septum and dumping under light nitrogen flow. Powdered NaOrBu (30 mol %) was added in the same manner, at which time the walls of the vessel were washed with ether. Anhydrous MeOH (2 eq) was added via syringe directly through the septum, causing the solution to become clear. Finally, copper chloride complex 14 (1 mol %) was added in one portion by under light nitrogen flow by removing the septum and dumping. The reaction was stirred at room temperature for 30 minutes before being filtered through a silica plug, eluting
with diethyl ether. This crude solution was concentrated under reduced pressure and the product was then purified by flash chromatography and dried under high vac before characterization.

4,4,5,5-Tetramethyl-2-((1R,4S)-5-vinylbicyclo[2.2.1]heptan-2-yl)-1,3,2-dioxaborolane, 19a

Starting material (18a) was purchased as a mixture of *endo* and *exo*, and the product was obtained as a 79:21 mixture of regioisomers. Isolated yield: 129 mg (89 %). R<sub>f</sub> (hexanes) = 0.59. ¹H NMR (600 MHz, CDCl₃) δ = 0.86 (m, 1H), 0.97 – 1.06 (m, 1H), 1.23 (s, 12H), 1.28 – 1.33 (m, 1H), 1.36 – 1.43 (m, 1H), 1.68 – 1.73 (m, 1H), 1.77 (dt, J = 4.4, 5.9 Hz, 1H), 2.18 – 2.22 (m, 1H), 2.24 – 2.31 (m, 1H), 2.46 – 2.53 (m, 1H), 4.96 – 5.02 (m, 2H), 5.82 – 5.91 (m, 1H). ¹³C NMR (150 MHz, CDCl₃) δ = 24.9, 25.7, 37.9, 39.8, 39.8, 42.6, 44.1, 45.7, 83.0, 113.9, 142.4 (The carbon attached to boron is not observed). IR (cm⁻¹, neat) = 3076, 2978, 2949, 2868, 2353, 1817, 1638, 1474, 1450, 1409, 1360, 1315, 1278, 1233, 1209, 1147, 1123, 1102, 1021. HRMS (EI+): Calcd for C₁₅H₂₅O₂B 248.19477, found 248.19532.

(((1S,3R,4S)-5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)bicyclo[2.2.1]heptane-2,3-diyl)bis(methylene))bis(oxy))bis(tert-butyldimethylsilane), 19b

The starting material for this transformation (18b) was synthesized according to known procedures. Isolated yield: 75 mg (81 %). R<sub>f</sub> (9:1 Hexanes:EtOAc) = 0.90. ¹H NMR (600 MHz, CDCl₃) δ = 0.02 (s, 12H), 0.87 (s, 18H), 1.08 – 1.11 (m, 1H), 1.22 (s, 12H), 1.31 – 1.35 (m, 1H), 1.37 (s, 2H), 1.64 (m, 1H), 2.08 – 2.09 (m, 2H), 2.31 – 2.34 (m, 2H), 3.52 – 3.59 (m, 2H), 3.69 – 3.76 (m, 2H). ¹³C NMR (150 MHz, CDCl₃) δ = 82.9, 61.2, 61.1, 44.3, 42.3, 41.7, 39.9, 39.4, 26.1, 25.2, 24.8, 24.8, 18.4, 18.3, -5.1, -5.2. IR (cm⁻¹, neat) = 2954, 2921, 2880, 2856, 2794, 2745, 2705, 1470, 1446, 1405, 1372, 1311, 1249, 1225, 1188, 1147, 1082, 1004.
4,4,5,5-Tetramethyl-2-phenethyl-1,3,2-dioxaborolane, 19c

Spectra match those reported previously.\(^{29}\) Isolated yield: 118 mg (76%, some product may have been lost during vacuum purification). \(R_f\) (9:1 Hexanes:EtOAc) = 0.41. \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta = 1.14\) (t, \(J = 8.2\) Hz, 2H), \(1.22\) (s, 12H), \(2.75\) (t, \(J = 8.1\) Hz, 2H), 7.14 – 7.16 (m, 1H), 7.21 – 7.22 (m, 2H), 7.24 – 7.27 (m, 2H). \(^13\)C NMR (150 MHz, CDCl\(_3\)) \(\delta = 144.6, 128.3, 128.1, 125.6, 83.2, 30.1, 25.0\) (The carbon attached to boron is not observed). LRMS (EI+) [M]\(^+\) = 232.2.

2-((3aR,4S,7S,7aR)-3a,4,5,6,7,7a-Hexahydro-1H-4,7-methanoinden-6-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, 19d

This product was obtained as a 69:31 mixture of regioisomers. Isolated yield: 117 mg (85%). \(R_f\) (9:1 Hexanes:EtOAc) = 0.53. \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta = 1.03 – 1.05\) (m, 1H), \(1.22\) (s, 12H), \(1.31 – 1.34\) (m, 1H), \(1.43 – 1.44\) (m, 3H), \(2.12 – 2.13\) (m, 1H), \(2.19 – 2.21\) (m, 3H), \(2.36 – 2.37\) (m, 1H), \(2.48 – 2.54\) (M, 1H), \(3.01 – 3.04\) (m, 1H), \(5.52 – 5.53\) (m, 1H), \(5.66 – 5.67\) (m, 1H). \(^13\)C NMR (150 MHz, CDCl\(_3\)) \(\delta = 133.1, 131.2, 82.9, 54.4, 43.4, 42.1, 41.1, 39.8, 32.4, 27.8, 24.9, 24.5\) (The carbon attached to boron is not observed). IR (cm\(^{-1}\), neat) = 3039, 2982, 2941, 2876, 2357, 1601, 1466, 1405, 1364, 1307, 1270, 1233, 1209, 1143, 1102, 1001. HRMS (EI+): Calcd for C\(_{16}\)H\(_{25}\)O\(_2\)B 260.19477, found 260.19520.

Dimethyl (1S,3R,4S)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)bicyclo[2.2.1]heptane-2,3-dicarboxylate, 19e

Isolated yield: 93 mg (82%). \(R_f\) (7:3 Hexanes:EtOAc) = 0.45. \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta = 1.22\) (d, \(J = 2.6\) Hz, 12H), \(1.38 – 1.40\) (m, 1H), \(1.44\) (dt, \(J = 1.6, 9.9\) Hz, 1H), \(1.47 – 1.51\) (m, 1H), \(1.62 – 1.65\) (m, 1H), \(1.84 – 1.88\) (m, 1H), \(2.56\) (br, 1H), \(2.62\) (m, 1H), \(2.94\) (dd, \(J =\)
3.8, 11.8 Hz, 1H), 3.00 (ddd, J = 1.8, 4.2, 11.8 Hz, 1H), 3.63 (d, J = 1.9 Hz, 6H). $^{13}$C NMR (150 MHz, CDCl$_3$) δ = 173.1, 173.1, 83.1, 51.5, 51.4, 48.0, 46.8, 42.1, 40.8, 39.9, 26.9, 24.9, 24.8 (The carbon attached to boron is not observed). IR (cm$^{-1}$, neat) = 2974, 2945, 2676, 1740, 1458, 1429, 1397, 1368, 1307, 1274, 1204, 1166, 1139, 1115, 1090, 1057, 1033.

2-(1,2-Dihydroacenaphthylene-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, 19f

Isolated yield: 87 mg (95 %). $R_f$ (100 % Hexanes) = 0.20. $^1$H NMR (600 MHz, CDCl$_3$) δ = 1.25 (d, J = 10.3 Hz, 12H), 3.27 (t, J = 6.7 Hz, 1H), 3.53 (d, J = 6.8 Hz, 2H), 7.26 – 7.32 (m, 1H), 7.30 – 7.32 (m, 1H), 7.40 – 7.43 (m, 2H), 7.53 – 7.57 (m, 2H). $^{13}$C NMR (150 MHz, CDCl$_3$) δ = 147.5, 146.5, 139.2, 131.9, 128.0, 127.8, 122.2, 121.8, 119.2, 119.1, 83.8, 32.2, 25.1, 24.8, 24.7. IR (cm$^{-1}$, neat) = 3035, 2974, 2929, 2361, 1916, 1715, 1601, 1507, 1462, 1450, 1388, 1360, 1319, 1270, 1217, 1143, 1098.

B.1.6 Deuterium Incorporation Experiment

Bicyclo[2.2.1]hept-2-ene (58 mg, 0.616 mmol, 1 eq) and bis(pinacolato)diboron (187.6 mg, 739 mmol, 1.2 eq) were weighed out into a 7 mL screw-top vial and transferred to an oven-dried schlenk tube with stir bar and rubber septum using inhibitor-free diethyl ether (1 mL). The reaction vessel was then charged with solid NaOrBu (17.75 mg, 185 μmol, 0.3 eq) by quickly removing the septum and adding under light nitrogen flow. Another 1 mL portion of diethyl ether was added. This was followed by methanol-d$_4$ (99.8%, 0.75 mL, 18.5 mmol, 30 eq). Lastly, copper chloride complex 14 (2.12 mg, 6.2 μmol, 0.01 eq) was added by removing the septum and adding under light nitrogen flow. Diethyl ether (1.1 mL) was then added. The reaction was stirred for ~30 minutes, filtered through silica gel with diethyl ether and concentrated under reduced pressure. The product was again filtered through silica gel with 100 % hexanes and
concentrated to afford crude product 17. See spectra section for comparison of \(^1\)H NMR spectra for both the deuterium (17) and hydrogen (16) products.

**B.1.7 Crystal Structure Determination of 14**

**B.1.7.1 Crystal Growth of C\textsubscript{17}H\textsubscript{18}N\textsubscript{2}ClCu (14)** All manipulations were performed under a dry nitrogen atmosphere using standard Schlenk techniques. Colorless block-shaped crystals of 14 were obtained by vapor diffusion of diethyl ether into a solution of 14 (38 mg, 0.10 mmol) in 1 mL of dichloromethane.

**B.1.7.2 Structure Description** X-ray diffraction study revealed that complex 14 crystallizes in the monoclinic space group C2/c. The asymmetric unit contains two crystallographically independent molecules of 14, which exhibit almost identical structural parameters. Symmetry tests did not reveal any additional symmetry elements. In each independent molecule, the Cu(I) ion has an almost linear coordination of one Cl\(^-\) ion and one NHC ligand, with the C–Cu–Cl angles of 178.35(7)° and 177.25(6)°. The Cu–C distances of 1.873(2) Å and 1.879(2) Å and the Cu–Cl distances of 2.0982(6) and 2.1046(6) fall within the ranges reported for other (NHC)CuCl complexes (1.86-1.90 Å and 2.09-2.12 Å, respectively).\(^6\) The presence of the methylphenylene fragment rigidly fused to the NHC results in a weak agostic interaction between the methyl H atoms and the Cu center. This steric effect leads to a larger N–C–Cu angle on the side of the interaction as compared to the N–C–Cu angle on the opposite side of the C–Cu–Cl line (132.9° and 131.6° vs. 123.8° and 124.7°).

**B.1.7.3 X-ray Crystallographic Procedures** A single crystal of 14 was suspended in Paratone-N oil (Hampton Research) and mounted on a cryoloop which was placed in an N\(_2\) cold stream and cooled down to 173(2) K. The data set was recorded as \(\omega\)-scans at 0.3° stepwidth and
integrated with the Bruker SAINT software package. A multi-scan absorption correction was applied based on fitting a function to the empirical transmission surface as sampled by multiple equivalent measurements (SADABS). The space group determination was performed with XPREP, while the solution and refinement of the crystal structures were carried out using the SHELX programs. The final refinement was performed with anisotropic atomic displacement parameters for all but H atoms. All H atoms were placed in calculated positions and refined in a riding model. A summary of pertinent information relating to the data collection and refinement is provided in Table B.1, while selected bond distances and angles appear in Table B.2.

<table>
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<th>Table B.1 Data Collection and Structural Refinement Parameters of 14</th>
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<td>R1, wR2, (all data)</td>
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<td>Goodness of fit</td>
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<td>Largest diff. peak/hole, e/Å³</td>
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\[ R1 = \sum \left| \frac{\Delta}{\sum |F_o|-|F_c|} \right|, \quad wR2 = \left( \sum \frac{w(F_o^2-F_c^2)^2}{\sum w(F_o^2)^2} \right)^{1/2} \]

\[ \text{Quality-of-fit} = \left( \sum \frac{w(F_o^2-F_c^2)^2}{N_{\text{obs}}-N_{\text{params}}} \right)^{1/2}, \text{based on all data.} \]
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B.2 Spectral Data

Figure B.1 $^1$H NMR and $^{13}$C NMR of compound 19a
Figure B.2 $^1$H NMR and $^{13}$C NMR of compound 19b
Figure B.3 $^1$H NMR and $^{13}$C NMR of compound 19c
Figure B.4 $^1$H NMR and $^{13}$C NMR of compound 19d
Figure B.5 $^1$H NMR and $^{13}$C NMR of compound 19e
Figure B.6 $^1$H NMR and $^{13}$C NMR of compound 19f
APPENDIX C

SUPPORTING INFORMATION FOR CHAPTER 4

C.1 Characterization Data

C.1.1 General Procedures and Instrumentation

All commercially available reagents were used without further purification, unless otherwise noted. Some substrates were synthesized according to literature procedures. Flash chromatography was performed using silica gel (230 – 400 mesh). TLC visualization of the materials was accomplished using UV light (254 nm) and an alkaline KMnO₄ solution followed by heating. ¹H NMR and ¹³C NMR were recorded in CDCl₃ unless otherwise noted. Spectra were obtained on a 400 MHz spectrometer operating at 400.170 and 100.623 MHz respectively, and a 600 MHz spectrometer operating at 600.130 and 150.903 MHz respectively. Proton chemical shifts are reported based upon the residual solvent signals of CDCl₃ (7.27 ppm) or TMS. Carbon chemical shifts were referenced to the deuterated solvent signal of CDCl₃ (77.16 ppm). ¹H NMR data are represented as follows: chemical shift, multiplicity (bs = broad singlet, s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sx = sextet, h = heptet, m = multiplet, etc.), coupling constant (Hz), and integration. Some products were identified by comparison to values reported in the literature.

C.1.2 Synthesis of Substrates for Leaving Group Screen
1-(Hex-3-yn-2-yloxy)-4-nitrobenzene, 20g

Sodium hydride (60% dispersion in mineral oil, 244 mg, 6.1 mmol, 3 equiv) was suspended in 2 mL dry DMF and cooled to 0 °C in a flame-dried 50 mL round-bottom flask. 3-Hexyn-2-ol (220 μL, 2 mmol, 1 equiv) was added slowly and the solution was stirred at 0 °C for 10 minutes, then 4-fluoronitrobenzene (433 μL, 4 mmol, 2 equiv) was added slowly. The reaction was warmed to room temperature and stirred for 2 hours. Once the reaction was complete, excess NaH was quenched with saturated ammonium chloride solution. The aqueous layer was extracted with diethyl ether (3 x 20 mL) and the combined organic layers were washed with 20 mL of each 1M HCl and brine, then dried over MgSO₄ and concentrated. The crude product was purified by flash chromatography, then distilled under reduced pressure (50 °C at 200 mTorr) to yield 363.6 mg desired product as a dark yellow oil (82% yield). Rf = 0.66 (7:3 Hexanes:EtOAc). ¹H NMR (600 MHz, CDCl₃): δ 1.10 (t, J = 7.3 Hz, 3H), 1.66 (d, J = 6.4 Hz, 3H), 2.19 (qd, J = 1.9, 7.5, 15 Hz, 2H), 4.93 (qt, J = 1.8, 6.5, 13 Hz, 1H), 7.06 (td, J = 2.7, 10.4 Hz, 2H), 8.20 (td, J = 2.7, 10.4, 2H). ¹³C NMR (150 MHz, CDCl₃): δ 162.8, 141.8, 125.8, 115.7, 89.4, 77.5, 65.0, 22.6, 13.7, 12.5. IR (neat, cm⁻¹): 2985, 2939, 2243, 1608, 1593, 1513, 1494, 1455, 1376, 1341, 1295, 1246, 1179, 1162, 1112, 1071, 1056, 1010. HRMS (Cl⁺): Calcd for C₁₂H₁₄O₃N 220.09737 found : 220.09665.

1-(Hex-3-yn-2-yloxy)-3-nitrobenzene, 20f

Sodium hydride (60% dispersion in mineral oil, 244 mg, 6 mmol, 3 equiv) was suspended in 2 mL of dry DMF and cooled to 0 °C in a flame-dried 50 mL round-bottom flask. 3-Hexyn-2-ol (220 μL, 2 mmol, 1 equiv) was added slowly and the solution was stirred at 0 °C for 10 minutes, then 4-fluoronitrobenzene (433 μL, 4 mmol, 2 equiv) was added slowly, causing the
solution to turn blue. The reaction was warmed to room temperature and stirred for 2 hours. Once complete, the reaction was quenched with saturated ammonium chloride solution. The aqueous layer was extracted with diethyl ether (4 x 20 mL) and the combined organic layers were washed with 1M HCl solution and brine. The organic layers were then dried over MgSO₄ and concentrated. The crude product was purified by flash chromatography, then distilled under reduced pressure (55 °C at 200 mTorr) to yield 363.4 mg desired product as a dark yellow oil (82% yield). R_f = 0.55 (7:3 Hexanes:EtoAc). ¹H NMR (600 MHz, CDCl₃): δ 1.09 (td, J = 1.7, 7.4 Hz, 3H), 1.66 (dd, J = 1.7, 6.5 Hz, 3H), 2.19 (qd, J = 1.7, 7.5 Hz, 2H), 4.91 (qt, 1H), 7.30 (d, J = 8.2 Hz, 1H), 7.42 (td, J = 1.7, 8.2, 1H), 7.83 (d, J = 8.1 Hz, 1H), 7.89 (d, J = 2.0 Hz, 1H). ¹³C NMR (150 MHz, CDCl₃): δ 158.1, 149.1, 129.7, 122.7, 116.0, 110.5, 89.2, 77.5, 64.9, 22.4, 13.6, 12.3. IR (neat, cm⁻¹): 2986, 2939, 2238, 1619, 1582, 1524, 1480, 1453, 1375, 1349, 1317, 1285, 1293, 1165, 1096, 1073, 1057, 1013. HRMS (CI+): Calcd for C₁₂H₁₄O₃N 220.09737 found: 220.09738.

(Hex-3-yn-2-yl)benzene, 20d

3-Hexyn-2-ol (440 µL, 4.5 mmol, 2 equiv), iodosobenzene (461 mg, 2.2 mmol, 1 equiv), copper(I) iodide (42.6 mg, 0.2 mmol, 10 mol%), cesium carbonate (1.46 g, 4.5 mmol, 2 equiv), 1,10-phenanthroline (80.7 mg, 0.45 mmol, 20 mol%) and 0.5 mL toluene were charged to a 7 mL screw-top vial, sealed and heated to 80 °C for 48 hours. The reaction was then cooled to room temperature and filtered through a pad of silica gel with diethyl ether. The crude reaction mixture was purified by flash chromatography to yield 157 mg desired product as a colorless oil (40% yield). R_f = 0.62 (9:1 Hexanes: EtoAc). ¹H NMR (600 MHz, CDCl₃): δ 1.10 (t, J = 7.5 Hz, 3H), 1.61 (d, J = 6.36 Hz, 3H), 2.19 qd, J = 1.9, 7.5, 14.9 Hz, 2H), 4.84 (qt, J = 1.9, 6.5 Hz, 1H), 6.95 (tt, J = 1.1, 3.7 Hz, 1H), 7.00 (m, 2H), 7.28 (m, 2H). ¹³C NMR (150 MHz, CDCl₃): δ 157.8,
129.4, 121.2, 116.0, 87.9, 78.9, 64.2, 22.8, 13.8, 12.5. IR (neat, cm\(^{-1}\)): 2984, 2938, 2872, 2243, 1598, 1494, 1373, 1331, 1235, 1161, 1081, 1057, 1013. HRMS (EI+): Calcd for C\(_{12}\)H\(_{14}\)O 174.10447 found : 174.10413.

**tert-Butyl(hex-3-yn-2-ylloxy)dimethylsilane, 20b**

3-Hexyn-2-ol (220 µL, 2 mmol, 1 equiv), triethylamine (369 µL, 2.7 mmol, 1.3 equiv) and DMAP (25 mg, 0.2 mmol, 10 mol%) were dissolved in 5 mL DCM in a 50 mL round-bottom flask. A solution of TBDMSCl (460 mg, 3 mmol, 1.5 equiv) in 5 mL DCM was added slowly and the reaction mixture was stirred at room temperature for 16 hours before being diluted with brine. The aqueous layer was extracted with 3 x 15 mL DCM, and then the combined organic layers were washed with brine, dried over MgSO\(_4\) and concentrated. The crude product was purified by flash chromatography to yield 411.6 mg desired product as a colorless oil with a small amount of HOTBDMS that was carried on to the next reaction (95% yield). \(R_f = 0.74\) (3:1 Hexanes:EtOAc). \(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta\) 0.11 (s, 3H), 0.12 (s, 3H), 0.91 (s, 9H), 1.12 (t, \(J = 7.5\) Hz, 3H), 1.38 (d, 6.5 Hz, 3H), 2.19 (qd, \(J = 1.9, 7.5, 15.0\) Hz, 2H), 4.50 (qt, \(J = 1.8, 6.4, 12.8\) Hz, 1H). \(^{13}\)C NMR (150 MHz, CDCl\(_3\)): \(\delta\) 85.2, 82.3, 59.4, 25.9, 26.0, 25.8, 18.4, 14.0, 12.5, -3.4, -4.4, -4.7. IR (neat, cm\(^{-1}\)): 2979, 2956, 2930, 2885, 2858, 1473, 1463, 1369, 1362, 1320, 1253, 1161, 1101, 1089, 1063, 1030, 1006. HRMS (CI+): Calcd for C\(_{12}\)H\(_{23}\)OSi 211.15183 found : 211.15224.

**1-(Hex-3-yn-2-ylloxy)-4-methoxybenzene, 20e**

3-Hexyn-2-ol (200 mg, 2 mmol, 1 equiv), 4-methoxyphenol (277 mg, 2.2 mmol, 1.1 equiv), and triphenylphosphine (532 mg, 2 mmol, 1 equiv) were dissolved in dry THF (10 mL) and cooled to 0 °C and stirred for 5 minutes before diisopropyl azodicarboxylate (DIAD, 480 µL,
2.4 mmol, 1.2 equiv) was added slowly. The reaction was warmed to 50 °C and stirred for 45 minutes before being concentrated and redissolved in EtOAc. The organic solution was washed with sodium hydroxide three times and once with saturated brine solution. The organic layers were dried over magnesium sulfate and concentrated. The reaction was purified by flash chromatography to yield the desired product as a light yellow oil (299 mg, 67% yield). \( R_f = 0.62 \) (20:1 Hexanes:EtOAc) \(^1\)H NMR (600 MHz, CDCl\(_3\)): \( \delta \) 1.10 (t, \( J = 5.0 \) Hz, 3H), 1.58 (d, \( J = 6.5 \) Hz, 3H), 2.19 (dq, \( J = 1.9, 2.5 \) Hz, 2H), 3.77 (s, 3H), 4.76 (tq, \( J = 1.8, 2.2 \) Hz, 1H), 6.83 (dt, \( J = 3.1, 10.6 \) Hz, 2H), 6.95 (dt, \( J = 3.1, 10.6 \) Hz, 2H). \(^{13}\)C NMR (150 MHz, CDCl\(_3\)): \( \delta \) 154.4, 151.9, 117.5, 114.6, 87.8, 79.2, 65.3, 55.8, 22.8, 13.9, 12.5. IR (neat, cm\(^{-1}\)): 2984, 2934, 2827, 2243, 1589, 1505, 1446, 1373, 1331, 1289, 1225, 1180, 1161, 1109, 1074, 1507, 1037, 1012. HRMS (Cl+): Calcd for C\(_{13}\)H\(_{16}\)O\(_2\) 204.1150 found : 204.1142.

\((\text{Hex-3-yn-2-yloxy})\text{methyl})\text{benzene, 20c}\)

Sodium hydride (175 mg, 4.3 mmol, 1.5 equiv, 60% disp. in mineral oil) was suspended in dry DMF and cooled to 0 °C. 3-hexyn-2-ol (473 µL, 2.9 mmol, 1.5 equiv) was added slowly, causing the mixture to turn yellow. Tetrabutylammonium iodide (TBAI, 108 mg, 0.3 mmol, 0.1 equiv) was added and the mixture was stirred for 5 minutes before adding benzyl bromide (348 µL, 2.9 mmol, 1 equiv), causing the reaction to turn green. The reaction was complete after 1 hour, monitoring by GC and was carefully quenched with saturated ammonium chloride solution resulting in an orange solution. The aqueous layer was extracted three times with diethyl ether and the combined organic layers were washed with 1M HCl solution and brine, then dried over magnesium sulfate and concentrated. The reaction was purified by flash chromatography to yield 251 mg desired product (46% yield) as a yellow oil. \( R_f = 0.69 \) (8:2 Hexanes:EtOAc) \(^1\)H NMR (600 MHz, CDCl\(_3\)): \( \delta \) 1.17 (t, \( J = 7.5 \) Hz, 3H), 1.44 (d, \( J = 6.8 \) Hz, 3H), 2.25 (dq, \( J = 1.9\), \( J = 7.2 \) Hz, 2H), 4.78 (tq, \( J = 1.8, 2.2 \) Hz, 1H), 6.84 (dt, \( J = 3.1, 10.6 \) Hz, 2H), 6.95 (dt, \( J = 3.1, 10.6 \) Hz, 2H). IR (neat, cm\(^{-1}\)): 2984, 2934, 2827, 2243, 1589, 1505, 1446, 1373, 1331, 1289, 1225, 1180, 1161, 1109, 1074, 1507, 1037, 1012. HRMS (Cl+): Calcd for C\(_{13}\)H\(_{16}\)O\(_2\) 204.1150 found : 204.1142.
2.5 Hz, 2H), 4.20 (tq, J = 1.9, 2.2 Hz, 1H), 4.49 (d, J = 11.7 Hz, 1H), 4.77 (d, J = 11.7 Hz, 1H), 7.28 (m, 1H), 7.34 (m, 4H). $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 138.4, 128.5, 128.1, 127.7, 87.3, 79.4, 70.3, 64.8, 22.3, 14.1, 12.6. IR (neat, cm$^{-1}$): 3060, 3028, 2981, 2936, 2861, 2377, 2227, 1723, 1691, 1603, 1495, 1453, 1371, 1319, 1269, 1163, 1089, 1063, 1027. HRMS (CI+): Calcd for C$_{13}$H$_{15}$O 187.11230 found : 187.11216.

C.1.3 Synthesis of Substituted Propargylic Aryl Ethers

Representative Procedure: Sodium hydride (3 equiv) was suspended in dry DMF (0.5 M solution with respect to the propargyl alcohol) in a 50 mL flame-dried round bottom flask and cooled to 0 °C under nitrogen flow. Propargyl alcohol (1 equiv, 21a - i) was added after ten minutes and the mixture was stirred for another 10 minutes at 0 °C. 4-Fluoronitrobenzene (2 equiv) was added slowly, and the reaction mixture was then warmed to room temperature with stirring for 2 hours. The reaction was quenched with saturated ammonium chloride solution, and the aqueous layer was extracted with 4 x 20 mL diethyl ether. The combined organic layers were washed with 1 M HCl and brine, then dried over MgSO$_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography (20:1 Hexanes: EtOAc), and any remaining 4-fluoronitrobenzene was removed by distillation under reduced pressure (typically 50 °C at 200 mTorr) to yield the desired propargylic ethers in 70 – 99% yield.

1-(Hept-2-yn-1-yl)-4-nitrobenzene, 21a

Obtained in 64% yield as a bright yellow oil. $R_f$ (9:1 Hexanes:Ethyl acetate) = 0.40. $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 0.89 (t, J = 7.3 Hz, 3H), 1.37 (sx, J = 7.4 Hz, 2H), 1.48 (p, J = 7.3 Hz, 2H), 2.22 (tt, J = 2.0, 3.5 Hz, 2H), 4.78 (t, J = 2.0 Hz, 2H), 7.05 (td, J = 2.7, 10.3 Hz, 2H), 8.21 (td, J = 2.7, 10.3 Hz, 2H). $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 162.9, 142.0, 125.9, 115.2, 89.9,
1-(Dodec-7-yn-6-yl)oxy)-4-nitrobenzene, 21b

Obtained in 78% yield as a dark yellow oil. R_t = 0.45 (9:1 Hexanes:EtOAc). ¹H NMR (600 MHz, CDCl₃): δ 0.87 (t, J = 7.3 Hz, 3H), 0.92 (t, J = 7.0 Hz, 3H), 1.35 (m, 6H), 1.45 (p, J = 7.3 Hz, 2H), 1.54 (m, 2H), 1.93 (m, 2H), 2.18 (dt, J = 1.9, 3.5 Hz, 2H), 4.77 (tt, J = 1.9, 3.2 Hz, 1H), 7.06 (td, J = 2.8, 10.5 Hz, 2H), 8.20 (td, J = 2.8, 10.5 Hz, 2H). ¹³C NMR (150 MHz, CDCl₃): δ 163.1, 141.7, 125.8, 115.8, 88.8, 69.3, 36.0, 31.5, 30.6, 25.0, 22.7, 22.0, 18.5, 14.1, 13.6. IR (neat, cm⁻¹): 2957, 2925, 2872, 1607, 1592, 1515, 1495, 1466, 1340, 1295, 1246, 1174, 1156, 1111. HRMS (CI⁺): Calcd for C₁₅H₁₅O₃N 234.11302 found : 234.11316.

1-Nitro-4-((1-phenylhept-2-yn-1-yl)oxy)benzene, 21c

1-Phenylhept-2-yn-1-ol (200 mg, 1.1 mmol, 1 equiv), 4-nitrophenol (163 mg, 1.2 mmol, 1.1 equiv) and triphenylphosphine (279 mg, 1.1 mmol, 1 equiv) were dissolved in THF (0.2 M) and cooled to 0 °C in a 50 mL round-bottom flask. Diisopropylazodicarboxylate (DIAD, 264 µL, 1.3 mmol, 1.2 equiv) was added slowly, then the reaction was fitted with a condenser and warmed to 50 °C. After 30 minutes, the reaction was extracted from 1 M sodium hydroxide using ethyl acetate (3 x 15 mL), then washed with saturated sodium bicarbonate solution and brine. The crude material was dried over MgSO₄ and concentrated. The crude product was purified by running flash chromatography on basic alumina, using gradient elution from 100% hexane to 9:1 Hexanes:Diethyl ether. The desired product was obtained as a light yellow oil (118 mg, 31% yield). R_t = 0.59 (8:2 Hexanes:Diethyl ether). ¹H NMR (600 MHz, CDCl₃): δ0.87 (t, J
=7.2 Hz, 3H), 1.36 (sx, J = 7.4 Hz, 2H), 1.49 (p, J = 7.1 Hz, 2H), 2.26 (t, J = 7.2 Hz, 2H), 2.89 (s, 1H), 7.15 (d, J = 8.7 Hz, 2H), 7.38 – 7.46 (m, 3H), 7.58 – 7.62 (m, 2H), 8.22 (d, J = 8.3 Hz, 2H).

$^{13}$C NMR (150 MHz, CDCl$_3$): δ 162.6, 147.2, 137.4, 129.2, 128.9, 127.6, 125.8, 116.2, 91.3, 71.2, 30.5, 22.0, 18.6, 13.6. IR (neat, cm$^{-1}$): 2958, 2932, 2864, 2226, 1743, 1608, 1592, 1515, 1494, 1455, 1341, 1299, 1243, 1172, 11367, 1111, 1078. HRMS (Cl+): Calcd for C$_{19}$H$_{19}$O$_3$N 309.1365 found : 309.1355.

1-((12-Chlorododec-7-yn-6-yl)oxy)-4-nitrobenzene, 21d

Obtained in 77% yield as an orange oil. R$_f$ = 0.44 (9:1 Hex:EtOAc). $^1$H NMR (600 MHz, CDCl$_3$): δ 0.92 (t, J = 6.9 Hz, 3H), 1.34 – 1.36 (m, 4H), 1.52 – 1.55 (m, 2H), 1.63 (p, J = 7.3 Hz, 2H), 1.81 (p, J = 7.1 Hz, 2H), 1.88 – 1.99 (m, 2H), 2.25 (dt, J = 1.8, 3.4 Hz, 2H), 3.50 (t, J = 6.5 Hz, 2H), 4.78 (tt, J = 1.8, 3.2 Hz, 1H), 7.06 (dt, J = 2.7, 10.5 Hz, 2H), 8.21 (dt, J = 2.7, 10.5 Hz, 2H). $^{13}$C NMR (150 MHz, CDCl$_3$): δ 162.9, 141.8, 125.8, 115.7, 87.7, 78.1, 69.1, 44.4, 35.9, 31.6, 31.5, 25.7, 25.0, 22.7, 18.1, 14.1. IR (neat, cm$^{-1}$): 2954, 2932, 2862, 2240, 1607,1592, 1514, 1494, 1456, 1341, 1298, 1249, 1174, 1156, 1111, 1051. HRMS (Cl+): Calcd for C$_{18}$H$_{25}$O$_3$NCl 338.15230 found : 338.15263.

Triisopropyl((7-(4-nitrophenoxy)dodec-5-yn-1-yl)oxy)silane, 21f

Obtained in 66% yield as an orange oil. R$_f$ = 0.65 (8:2 Hexanes:EtOAc). $^1$H NMR (600 MHz, CDCl$_3$): δ 0.91 (t, J = 7.0 Hz, 3H), 1.03 (s, 5H), 1.04 (s, 12H), 1.33 – 1.36 (m, 4H), 1.54 – 1.57 (m, 6H), 1.87 – 1.98 (m, 2H), 2.21 – 2.24 (m, 2H), 3.66 (t, J = 5.9 Hz, 2H), 4.77 (tt, J = 1.8, 3.2 Hz, 1H), 7.06 (dt, J = 2.8, 10.4 Hz, 2H), 8.20 (dt, J = 2.8, 10.4 Hz, 2H). $^{13}$C NMR (150 MHz, CDCl$_3$): δ 163.1, 141.7, 125.8, 115.7, 88.6, 77.5, 69.2, 62.9, 36.0, 32.1, 31.5, 25.1, 25.0, 22.7, 18.6, 18.1, 14.1, 12.4. IR (neat, cm$^{-1}$): 2941, 2865, 2230, 1607, 1592, 1517, 1495, 1463, 1381,
1341, 1250, 1174, 1110, 1068. HRMS (CI+): Calcd for C_{27}H_{46}O_4NSi 476.31961 found : 476.31891.

1-((12-(p-Nitrophenyl)dodec-7-yn-6-yl)oxy)-4-nitrobenzene, 21g

Obtained in 87% yield as a dark orange oil. R_f = 0.50 (9:1 Hexanes:EtOAc). ^1H NMR (600 MHz, CDCl_3): δ 0.91 (t, J = 7.1 Hz, 3H), 1.34 – 1.36 (m, 4H), 1.53 – 1.57 (m, 2H), 1.67 (p, J = 7.3 Hz, 2H), 1.83 – 1.87 (m, 2H), 1.89 – 1.99 (m, 2H), 2.30 (dt, J = 1.8, 3.5 Hz, 2H), 4.01 (t, J = 6.3 Hz, 2H), 4.79 (tt, J = 1.8, 3.2 Hz, 1H), 6.91 (dt, J = 2.8, 10.5 Hz, 2H), 7.06 (dt, J = 2.8, 10.5 Hz, 2H), 8.19 (dt, J = 2.8, 10.6 Hz, 4H). ^13C NMR (150 MHz, CDCl_3): δ 164.1, 162.9, 141.8, 141.6, 126.1, 125.8, 115.7, 114.5, 87.8, 78.1, 69.1, 68.2, 35.9, 31.5, 28.1, 25.0, 22.7, 18.5, 14.1. IR (neat, cm^{-1}): 2953, 2923, 2870, 2228, 1606, 1591, 1495, 1468, 1339, 1298, 1251, 1173, 1110, 1050. HRMS (CI+): Calcd for C_{24}H_{28}O_6N_4 441.20257 found : 441.20324.

1-Nitro-4-((1-phenyloct-1-yn-3-yl)oxy)benzene, 21h

Isolated in 85% yield as an orange oil. R_f = 0.37 (20:1 Hexanes:EtOAc). ^1H NMR (600 MHz, CDCl_3): δ 0.93 (t, J = 9.4 Hz, 3H), 1.38 – 1.40 (m, 4H), 1.60 – 1.63 (m, 2H), 2.01 – 2.11 (m, 2H), 5.02 (t, J = 9.4 Hz, 1H), 7.13 (d, J = 9.4 Hz, 2H), 7.28 – 7.33 (m, 3H), 7.38 (d, J = 7.7 Hz, 2H), 8.22 (d, J = 9.4 Hz, 2H). ^13C NMR (150 MHz, CDCl_3): δ 162.9, 141.9, 131.9, 129.0, 128.5, 125.9, 122.0, 115.7, 87.7, 86.0, 69.4, 35.8, 31.5, 25.0, 22.7, 14.1. IR (neat, cm^{-1}): 3420, 2954, 2928, 2860, 1607, 1591, 1513, 1493, 1443, 1340, 1298, 1247, 1173, 1111, 1070. HRMS (CI+): Calcd for C_{20}H_{21}O_3N 323.1521 found : 323.1517.

1-((1-Cyclohexyl-4,4-dimethylpent-1-yn-3-yl)oxy)-4-nitrobenzene, 21i
Isolated in 87% yield as an orange oil. \( R_f = 0.55 \) (20:1 Hexanes:EtOAc). \(^1\)H NMR (600 MHz, CDCl\(_3\)): \( \delta \) 1.11 (s, 9H), 1.25 – 1.33 (m, 3H), 1.38 – 1.47 (m, 3H), 1.61 – 1.64 (m, 2H), 1.70 – 1.73 (m, 2H), 2.41 (br t, \( J = 8.7 \) Hz, 1H), 4.41 (d, \( J = 1.9 \) Hz, 1H), 7.09 (dt, \( J = 2.7, 10.5 \) Hz, 2H), 8.20 (dt, \( J = 2.7, 10.5 \) Hz, 2H). \(^{13}\)C NMR (150 MHz, CDCl\(_3\)): \( \delta \) 163.5, 141.7, 125.7, 115.8, 93.4, 77.9, 75.9, 36.1, 32.5, 29.0, 25.9, 25.8, 24.7. IR (neat, cm\(^{-1}\)): 2931, 2854, 2226, 1606, 1591, 1514, 1495, 1448, 1394, 1365, 1341, 1298, 1250, 1172, 1150, 1111, 1038. HRMS (Cl\(^+\)): Calcd for C\(_{19}\)H\(_{26}\)O\(_3\)N 316.19127 found : 316.19183.

**C.1.3.1 Synthesis of tert-Butyl-(7-(4-nitrophenoxy)dodec-5-yn-1-yl)carbamate, 21e**

![Reaction scheme](image)

**Figure C.1** Reaction scheme followed to yield desired carbamate derivative 21e

1-((12-Iodododec-7-yn-6-yl)oxy)-4-nitrobenzene:

1-((12-Chlorododec-7-yn-6-yl)oxy)-4-nitrobenzene (above, 379 mg, 1.1 mmol, 1 equiv) was dissolved in acetone (0.2 M) with sodium iodide (68 mg, 4.5 mmol, 4 equiv) and heated to reflux for 14 hours, after which time the reaction was filtered through Celite and concentrated to yield the desired product in 85% yield. The product has 33% starting material impurity, but was
carried over into the next reaction without further purification. $R_f = 0.45$ (9:1 Hexanes:EtOAc).

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 0.91 (t, $J = 6.5$ Hz, 3H), 1.34 – 1.37 (m, 4H), 1.52 – 1.65 (m, 4H), 1.78 – 1.99 (m, 4H), 2.22 – 2.26 (m, 2H), 3.14 (t, $J = 6.9$ Hz, 1.29H, iodo-substrate), 3.50 (t, $J = 6.5$ Hz, 0.65H, chloro-substrate), 4.78 (tt, $J = 1.8$, 3.2 Hz, 1H), 7.06 (dt, $J = 2.7$, 10.5 Hz, 2H), 8.21 (dt, $J = 2.7$, 10.5 Hz, 2H). $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 162.9, 141.8, 125.9, 125.8, 115.7, 87.6, 78.1, 69.1, 44.4, 35.9, 31.5, 29.2, 25.0, 22.7, 17.8, 14.1. IR (neat, cm$^{-1}$): 2951, 2930, 2859, 1607, 1591, 1514, 1494, 1456, 1341, 1302, 1249, 1174, 1111. HRMS (Cl+): Calcd for C$_{18}$H$_{25}$NO$_3$I 430.08795 found : 430.08802.

1-((12-Azidododec-7-yn-6-yl)oxy)-4-nitrobenzene:

1-((12-Iodododec-7-yn-6-yl)oxy)-4-nitrobenzene (400 mg, 0.9 mmol, 1 equiv) was dissolved in DMAC (0.3M) in a 50 mL round bottom flask. Sodium azide (91 mg, 1.4 mmol, 1.5 equiv) was added, and the mixture was heated at 70 °C overnight. Full conversion achieved by GC after 2 hours, then the reaction was diluted with DCM and the organic layer was washed repeatedly with ice-cold water. The organic layer was washed once more with brine, dried over MgSO$_4$ and carefully concentrated to ¼ volume and used without further purification. $R_f = 0.54$ (7:3 Hexanes:EtOAc).

**tert-**Butyl (7-(4-nitrophenoxy)dodec-5-yn-1-yl)carbamate, **21e**

The crude 1-((12-Azidododec-7-yn-6-yl)oxy)-4-nitrobenzene from above (0.93 mmol, 1 equiv) was charged to a 50 mL round-bottom flask with triphenylphosphine (293 mg, 1.1 mmol, 1.2 equiv), water (0.7 mL) and ether (0.2 M) then stirred at room temperature for 16 hours. Di-*t*-butyl dicarbonate (1.71 mL, 7.5 mmol, 8 equiv) was added and the solution was stirred at room temperature for 4 hours before the reaction was diluted with water and the aqueous layer
extracted with diethyl ether (x3). The combined organic layers were washed with brine, dried over MgSO₄ and concentrated. The reaction was purified by flash chromatography to give the desired product in 34% yield. Rf = 0.62 (9:1 Hexanes:EtOAc). ¹H NMR (600 MHz, CDCl₃): δ 0.92 (t, J = 7.0 Hz, 3H), 1.34 – 1.36 (m, 4H), 1.44 (s, 9H), 1.49 – 1.51 (m, 4H), 1.51 – 1.55 (m, 2H, slightly obscured by water peak), 1.87 – 1.99 (m, 2H), 2.22 (td, J = 1.9, 3.2 Hz, 2H), 3.09 (d, 5.4 Hz, 2H), 4.46 (br s, 1H), 4.77 (tt, J = 1.8, 3.2 Hz, 1H), 7.06 (dt, J = 2.7, 10.4 Hz, 2H), 8.20 (dt, J = 2.7, 10.4 Hz, 2H). ¹³C NMR (150 MHz, CDCl₃): δ 162.8, 155.9, 141.6, 125.7, 115.6, 87.9, 79.2, 77.7, 69.0, 35.8, 31.3, 29.2, 28.4, 27.4, 25.6, 24.8, 22.5, 18.3, 14.0. IR (neat, cm⁻¹): 3375, 2933, 2863, 2236, 1809, 1770, 1704, 1592, 1515, 1495, 1455, 1391, 1366, 1341, 1298, 1249, 1212, 1172, 1112, 1071. HRMS (Cl-): Calcd for C₂₃H₃₄O₅N₂ 418.24677 found : 418.24689.

C.1.4 Hydroboration of Propargylic Aryl Ethers

Representative Procedure: Propargylic Aryl Ether (30 mg, 1 equiv, 21a - i) in diethyl ether (anhydrous, 0.2 M solution) was charged to a Schlenk tube and sealed under nitrogen flow on the bench. Bis(pinacolato)diboron (1.2 equiv) then sodium t-butoxide (0.3 equiv) were each separately charged to the reaction vessel by quickly removing the septum and dumping the solid material in one portion while under light nitrogen flow. The reaction vessel was then cooled to 0 °C after washing the sides of the vessel with additional diethyl ether through the septum. Methanol (anhydrous, 2 equiv) was injected into the system, and then the 6-NHC Cu(I) catalyst 1b was added (1 mol%). The system was reacted for 30 minutes, then diluted with diethyl ether and filtered through silica gel. After analysis of the crude mixture by TLC (9:1 Hexanes:diethyl ether, for visualization), the crude product was purified by silica gel chromatography to yield the pure products in yields ranging from 27 – 98%.
(Z)-4,4,5,5-Tetramethyl-2-(1-(4-nitrophenoxy)hept-2-en-2-yl)-1,3,2-dioxaborolane, **22a**

Isolated in 86% yield as a dark yellow oil ($\alpha:\beta = 85:15$). $R_f = 0.22$ (9:1 Hexane:EtOAc). $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 0.90 (t, $J = 7.3$ Hz, 3H), 1.26 (s, 12H), 1.31 – 1.38 (m, 2H), 1.39 – 1.45 (m, 2H), 2.27 (q, $J = 7.3$ Hz, 2H), 4.74 (s, 2H), 6.67 (t, $J = 7.4$ Hz, 1H), 7.00 (dt, $J = 2.7, 10.5$ Hz, 2H), 8.17 (dt, $J = 2.7, 10.5$ Hz, 2H). $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 164.3, 154.1, 141.4, 125.9, 115.0, 83.8, 83.1, 65.4, 31.1, 29.6, 24.9, 22.6, 14.1.(the vinyl carbon attached to the boron is not observed) IR (neat, cm$^{-1}$): 2977, 2954, 2931, 2863, 1632, 1606, 1592, 1514, 1497, 1467, 1413, 1371, 1340, 1311, 1259, 1234, 1170, 1141, 1111. HRMS (Cl+): Calcd for C$_{19}$H$_{29}$O$_{5}$BN 362.21388 found : 362.21399.

(Z)-4,4,5,5-Tetramethyl-2-(7-(4-nitrophenoxy)dodec-5-en-6-yl)-1,3,2-dioxaborolane, **22b**

Obtained in 85% yield as a dark yellow oil ($\alpha:\beta = 97:3$). $R_f = 0.38$ (9:1 Hexanes:EtOAc). $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 0.90 (t, $J = 7.0$ Hz, 6H), 1.19 (s, 6H), 1.21 (s, 6H), 1.22 – 1.28 (m, 2H), 1.30 – 1.36 (m, 9H), 1.46 – 1.51 (m, 1H), 1.70 – 1.76 (m, 1H), 1.96 – 2.01 (m, 1H), 2.18 – 2.24 (m, 1H), 2.29 – 2.35 (m, 1H), 5.05 (dd, $J = 5.9, 7.7$ Hz, 1H), 6.40 (t, $J = 7.3$ Hz, 1H), 6.87 (dt, $J = 2.7, 10.5$ Hz, 2H), 8.12 (dt, $J = 2.7, 10.5$ Hz, 2H). $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 163.9, 150.0, 141.0, 125.8, 115.6, 83.5, 78.1, 35.6, 31.8, 31.3, 29.85, 25.8, 24.9, 24.7, 22.8, 22.7, 14.1, 14.1. (the vinyl carbon attached to the boron is not observed) IR (neat, cm$^{-1}$): 2957, 2929, 2867, 2858, 1629, 1606, 1591, 1514, 1495, 1466, 1405, 1371, 1340, 1310, 1258, 1214, 1169, 1142, 1110. HRMS (Cl+): Calcd for C$_{24}$H$_{39}$O$_{5}$BN 432.29213 found : 432.29216.

(Z)-2-(1-Chloro-7-(4-nitrophenoxy)dodec-5-en-6-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, **22d**
Isolated in 92% yield as a yellow oil (α:β = 95:5). Rf = 0.42 (9:1 Hexanes:EtOAc). 

$^1$H NMR (600 MHz, CDCl$_3$): δ 0.90 (t, J = 6.5 Hz, 3H), 1.21 (s, 6H), 1.23 (s, 6H), 1.33 (m, 6H), 1.47 – 1.51 (m, 2H), 1.73 – 1.79 (m, 3H), 1.94 – 2.01 (m, 1H), 2.22 – 2.40 (m, 2H), 3.514 (t, J = 6.6 Hz, 2H), 5.04 (dd, J = 5.9, 7.7, 1H), 6.37 (t, J = 7.3 Hz, 1H), 6.88 (dt, J = 2.7, 10.5 Hz, 2H), 8.13 (dt, J = 2.7, 10.5 Hz, 2H). 

$^{13}$C NMR (150 MHz, CDCl$_3$): δ 163.8, 148.9, 141.1, 125.8, 115.5, 83.7, 78.1, 44.8, 35.6, 32.4, 31.7, 29.3, 26.4, 25.8, 24.9, 24.7, 22.7, 14.1. (the vinyl carbon attached to the boron is not observed) IR (neat, cm$^{-1}$): 2978, 2929, 2855, 2238, 1691, 1580, 1507, 1495, 1450, 1360, 1306, 1263, 1258, 1158, 115.5, 83.6, 78.1, 35.6, 31.7, 30.1, 29.7, 28.6, 26.3, 25.8, 24.9, 24.7, 22.7, 22.6, 14.1. IR (neat, cm$^{-1}$): 2978, 2929, 2855, 2238, 1691, 1580, 1507, 1495, 1450, 1360, 1339, 1294, 1254, 1164, 1135, 1106. HRMS (ESI+): Calcd for C$_{24}$H$_{38}$O$_5$NBCl 466.25315, found : 466.25274.

(Z)-tert-Butyl (7-(4-nitrophenoxy)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)dodec-5-en-1-yl)carbamate, 22e

Isolated in 84% yield as a yellow oil (α:β = 98:2). Rf = 0.43 (9:1 Hexanes:EtOAc). 

$^1$H NMR (600 MHz, CDCl$_3$): δ 0.90 (t, J = 7.2 Hz, 3H), 1.20 (s, 6H), 1.23 (s, 6H), 1.22 – 1.25 (m, 3H), 1.45 (s, 9H), 1.46 – 1.51 (m, 5H), 1.52 – 1.59 (m, 1H), 1.61 – 1.66 (m, 1H), 1.69 – 1.74 (m, 1H), 1.94 – 2.00 (m, 1H), 2.20 – 2.27 (m, 1H), 2.30 – 2.40 (m, 1H), 3.08 – 3.14 (m, 2H), 4.51 (br s, 1H), 5.03 (dd, J = 5.9, 7.7 Hz, 1H), 6.36 (t, J = 7.2 Hz, 1H), 6.88 (dt, J = 2.7, 10.5 Hz, 2H), 8.13 (dt, J = 2.7, 10.5 Hz, 2H). 

$^{13}$C NMR (150 MHz, CDCl$_3$): δ 163.8, 149.2, 141.1, 126.3, 125.8, 115.8, 115.5, 83.6, 78.1, 35.6, 31.7, 30.1, 29.7, 28.6, 26.3, 25.8, 24.9, 24.7, 22.7, 22.6, 14.1. IR (neat, cm$^{-1}$): 2978, 2929, 2855, 2238, 1691, 1580, 1507, 1495, 1450, 1360, 1339, 1294, 1254, 1164, 1135, 1106. HRMS (ESI+): Calcd for C$_{29}$H$_{47}$BN$_2$O$_7$ 569.33740, found : 569.33804.

(Z)-Triisopropyl((7-(4-nitrophenoxy)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)dodec-5-en-1-yl)oxy)silane, 22f
Isolated in 82% yield as a light yellow oil (α:β = 96:4). Rf = 0.62 (9:1 Hexanes:EtOAc). 

$^1$H NMR (600 MHz, CDCl$_3$): δ 0.90 (t, J = 6.8 Hz, 3H), 1.05 (s, 6H), 1.05 (s, 12H), 1.19 (s, 6H), 1.22 (s, 6H), 1.31 – 1.34 (m, 6H), 1.41 – 1.45 (m, 1H), 1.47 – 1.50 (m, 2H), 1.51 – 1.55 (m, 2H), 1.68 – 1.76 (m, 1H), 1.95 – 2.01 (m, 1H), 2.20 – 2.27 (m, 1H), 2.33 – 2.39 (m, 1H), 3.66 (t, J = 6.3 Hz, 2H), 5.04 (dd, J = 5.9, 7.7 Hz, 1H), 6.40 (t, J = 7.3 Hz, 1H), 6.88 (dt, J = 2.8, 10.5 Hz, 2H), 8.12 (dt, J = 2.8, 10.5 Hz). 

$^{13}$C NMR (150 MHz, CDCl$_3$): δ 163.9, 150.0, 141.0, 125.8, 115.6, 83.6, 78.1, 63.3, 35.6, 33.1, 31.8, 30.0, 25.8, 25.4, 24.9, 24.7, 22.7, 18.2, 14.2, 12.1.(the vinyl carbon attached to the boron is not observed) IR (neat, cm$^{-1}$): 2937, 2855, 2353, 2316, 1667, 1625, 1593, 1511, 1486, 1450, 1376, 1335, 1307, 1254, 1172, 1139, 1106, 1066, 1004. LRMS (Cl$^{-}$) [M -H$^{-}$] 602.6.

(Z)-2-(1,7-Bis(4-nitrophenoxy)dodec-5-en-6-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, 22g

Isolated in 94% yield as a yellow oil (α:β = 98:2). Rf = 0.54 (9:1 Hexanes:EtOAc). 

$^1$H NMR (600 MHz, CDCl$_3$): δ 0.88 (t, J = 6.5 Hz, 3H), 1.21 (s, 6H), 1.24 (s, 6H), 1.31 – 1.35 (m, 5H), 1.48 – 1.65 (m, 4H), 1.71 – 1.77 (m, 2H), 1.79 – 1.84 (m, 2H), 1.95 – 2.01 (m, 1H), 2.28 – 2.35 (m, 1H), 2.39 – 2.46 (m, 1H), 4.02 (t, J = 6.4 Hz, 2H), 5.06 (dd, J = 6.0, 7.6 Hz, 1H), 6.39 (t, J = 7.3 Hz, 1H), 6.89 (dt, J = 2.7, 10.5 Hz, 2H), 6.92 (dt, J = 2.8, 10.5 Hz, 2H), 8.12 (dt, J = 2.8, 10.6 Hz, 2H), 8.20 (dt, J = 2.7, 10.4 Hz, 2H). 

$^{13}$C NMR (150 MHz, CDCl$_3$): δ 164.1, 163.8, 148.9, 141.1, 126.1, 125.8, 115.5, 114.5, 83.7, 78.1, 68.6, 35.6, 31.7, 31.1, 29.8, 29.0, 25.8, 25.5, 24.9, 24.7, 22.7, 14.1.(the vinyl carbon attached to the boron is not observed) IR (neat, cm$^{-1}$): 2973, 2931, 2852, 1705, 1591, 1512, 1496, 1469, 1365, 1339, 1259, 1171, 1142, 1110. HRMS (Cl$^+$): Calcd for C$_{30}$H$_{41}$BN$_2$O$_8$ 591.28537 found : 591.28508.
(Z)-4,4,5,5-Tetramethyl-2-(3-(4-nitrophenoxy)-1-phenyloct-1-en-2-yl)-1,3,2-
dioxaborolane, 22h

Isolated in 98% yield as a yellow oil (α:β = 94:6). R<sub>f</sub> = 0.31 (9:1 Hexanes:EtOAc). <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ 0.92 (t, J = 7.1 Hz, 3H), 1.22 (s, 6H), 1.23 (s, 6H), 1.35 – 1.39 (m, 5H), 1.42 – 1.47 (m, 1H), 1.59 – 1.66 (m, 1H), 1.83 – 1.89 (m, 1H), 2.31 – 2.37 (m, 1H), 5.20 (dd, J = 3.4, 9.4 Hz, 1H), 6.52 (dt, J = 2.8, 10.5 Hz, 2H), 7.26 – 7.28 (m, 2H), 7.40 – 7.44 (m, 3H), 7.99 (dt, J = 2.8, 10.5 Hz, 2H). <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ 163.8, 145.1, 141.0, 136.8, 129.1, 128.6, 128.4, 125.7, 115.7, 83.7, 35.1, 31.7, 26.0, 25.1, 24.7, 24.5, 22.8, 14.2. (the vinyl carbon attached to the boron is not observed). IR (neat, cm<sup>-1</sup>): 2977, 2954, 2927, 2851, 2362, 1625, 1605, 1591, 1496, 1481, 1463, 1448, 1369, 1305, 1259, 1228, 1169, 1143, 1110, 1059. HRMS (Cl+): Calcd for C<sub>26</sub>H<sub>35</sub>O<sub>5</sub>NB 452.26083 found : 452.26115.

(Z)-2-(1-Cyclohexyl-4,4-dimethyl-3-(4-nitrophenoxy)pent-1-en-2-yl)-4,4,5,5-
tetramethyl-1,3,2-dioxaborolane, 22i

Isolated in 27% yield as a light yellow oil (α:β = >98:2). R<sub>f</sub> = 0.43 (9:1 Hexanes:EtOAc). <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ 0.74 (br s, 1H), 1.02 (s, 9H), 1.04 – 1.14 (m, 3H), 1.25 (s, 6H), 1.27 (s, 6H), 1.48 (br s, 1H), 1.57 (s, 2H), 1.60 – 1.72 (m, 3H), 2.57 – 2.63 (m, 1H), 4.82 (s, 1H), 6.14 (d, J = 11.0 Hz, 1H), 6.91 (dt, J = 2.7, 10.6 Hz, 2H), 8.13 (dt, J = 2.7, 10.6 Hz, 2H). <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ 164.3, 155.3, 140.9, 125.8, 115.3, 83.7, 36.6, 32.5, 31.9, 26.5, 26.1, 25.8, 25.6, 24.8, 24.7.(the vinyl carbon attached to the boron is not observed) IR (neat, cm<sup>-1</sup>): 2973, 2954, 2927, 2851, 2362, 1625, 1605, 1591, 1514, 1496, 1481, 1463, 1448, 1369, 1305, 1259, 1228, 1169, 1143, 1110, 1059. HRMS (Cl+): Calcd for C<sub>25</sub>H<sub>39</sub>O<sub>5</sub>NB 444.29213 found : 444.29308.
C.1.5 Synthesis of Propargylic Alcohols

Representative Procedure: To a flame-dried 50 mL round-bottom flask was added a 0.3 M solution of terminal alkyne (3 equiv) in dry THF at 0 °C. To this solution, n-BuLi (2.0 M in hexanes, 1.3 equiv) was added cautiously. This solution was stirred for 10 minutes at 0 °C before aldehyde (redistilled, 1 equiv) was added, then the reaction mixture was warmed to room temperature and stirred for 4 hours. The reaction was quenched with saturated ammonium chloride solution, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed once with saturated sodium bicarbonate solution and once with brine, then dried over MgSO$_4$ and concentrated under reduced pressure. The crude material was purified by flash chromatography (gradient from 100% hexanes to 9:1 Hexanes:EtOAc) to yield the desired alcohols in 60 – 99% yield.

Dodec-7-yn-6-ol, 23b

98% yield as a light yellow oil. R$_f$ = 0.43 (8:2 Hexanes:EtOAc). $^1$H NMR (600 MHz, CDCl$_3$): δ 0.90 (q, J = 7.4 Hz, 6H), 1.29 – 1.34 (m, 4H), 1.38 – 1.51 (m, 6H), 1.60 – 1.71 (m, 3H), 2.21 (t, J = 7.1 Hz, 2H), 4.35 (m, 1H). $^{13}$C NMR (150 MHz, CDCl$_3$): δ 85.6, 81.5, 63.0, 38.4, 31.6, 30.9, 25.0, 22.7, 22.1, 18.5, 14.1, 13.7. IR (neat, cm$^{-1}$): 3331, 2957, 2933, 2661, 2215, 1674, 1466, 1379, 1328, 1148, 1109, 1026. LRMS (Cl+) [M+H]$^+$ 183.2.

1-Phenylhept-2-yn-1-ol, 23c

92% yield as a yellow oil. R$_f$ = 0.24 (8:2 Hexanes:EtOAc). $^1$H NMR (600 MHz, CDCl$_3$): δ 0.92 (t, J = 7.4 Hz, 3H), 1.41 – 1.44 (m, 2H), 1.51 – 1.55 (m, 2H), 1.89 (br s, 1H), 2.28 (dt, J = 2.1, 7.1 Hz, 2H), 5.45 (s, 1H), 7.31 – 7.33 (m, 1H), 7.36 – 7.39 (m, 2H), 7.53 – 7.55 (m, 2H). $^{13}$C NMR (150 MHz, CDCl$_3$): δ 141.4, 128.7, 128.3, 126.8, 87.8, 80.0, 65.0, 31.9, 30.8, 22.1, 18.6,
13.7. IR (neat, cm$^{-1}$): 3385, 2957, 2932, 2872, 2226, 1493, 1454, 1135, 1002. HRMS (Cl+): Calcd for C_{13}H_{16}O 188.1201 found : 188.1185.

**12-Chlorododec-7-yn-6-ol, 23d**

88% yield as a light yellow oil. $R_f = 0.15$ (9:1 Hexanes:EtOAc). $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 0.92 (t, $J = 6.8$ Hz, 3H), 1.34 (m, 4H), 1.45 (m, 2H), 1.66 – 1.74 (m, 5H), 1.91 (p, $J = 7.1$ Hz, 2H), 2.29 (dt, $J = 1.5$, 3.5 Hz, 2H), 3.59 (t, $J = 6.6$ Hz, 2H), 4.37 (t, $J = 6.4$ Hz, 1H). $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 84.6, 82.2, 62.9, 44.6, 38.3, 31.7, 31.6, 25.9, 25.0, 22.7, 18.2, 14.1. IR (neat, cm$^{-1}$): 3373, 2954, 2932, 2860, 2226, 1455, 1434, 1378, 1332, 1301, 1139, 1102, 1023. LRMS (Cl-) [M-H] $^-$ 215.1.

**12-((Triisopropylsilyl)oxy)dodec-7-yn-6-ol, 23f**

95% yield as a yellow oil. $R_f = 0.30$ (9:1 Hexanes:EtOAc). $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 0.90 (t, $J = 7.0$ Hz, 3H), 1.05 (s, 6H), 1.06 (s, 12H), 1.29 – 1.33 (m, 5H), 1.41 – 1.45 (m, 2H), 1.57 – 1.70 (m, 9H), 2.25 (dt, $J = 1.9$, 3.4 Hz, 2H), 3.70 (t, $J = 6.1$ Hz, 2H), 4.34 (tt, $J = 1.9$, 3.4 Hz). $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 85.5, 81.7, 63.0, 63.0, 38.3, 32.2, 31.6, 25.0, 22.7, 18.7, 18.2, 14.1, 12.1. IR (neat, cm$^{-1}$): 3396, 2941, 2889, 2865, 2213, 1673, 1463, 1382, 1325, 1247, 1108, 1068, 1013. LRMS (Cl-) [M-H] $^-$ 353.3.

**12-(4-Nitrophenoxy)dodec-7-yn-6-ol, 23g**

95% yield as a dark yellow oil with minor impurities, used without further purification. $R_f = 0.22$ (8:2 Hexanes:EtOAc). $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 0.89 (t, $J = 6.9$ Hz, 3H), 1.30 (m, 4H), 1.41 – 1.45 (m, 2H), 1.62 – 1.74 (m, 5H), 1.92 – 1.97 (m, 2H), 2.32 (dt, $J = 1.9$, 3.5 Hz, 2H), 4.08 (t, $J = 6.3$ Hz, 2H), 4.35 (tt, $J = 1.8$, 3.3 Hz, 1H), 6.94 (dt, $J = 2.7$, 10.5 Hz, 2H), 8.20
(dt, J = 2.7, 10.5 Hz, 2H). $^{13}$C NMR (150 MHz, CDCl$_3$): δ 164.2, 141.6, 126.1, 114.5, 84.6, 82.3, 68.4, 62.9, 38.3, 31.6, 28.2, 25.2, 25.0, 22.7, 18.5, 14.1. IR (neat, cm$^{-1}$): 3390, 2952, 2933, 2854, 2374, 1607, 1593, 1512, 1498, 1468, 1340, 1261, 1173, 1110, 1016. HRMS (CI-): Calcd for C$_{18}$H$_{25}$O$_4$N 319.17836 found : 319.17833.

1-Phenyloct-1-yn-3-ol, 23h

84% yield as a bright yellow oil. R$_f$ = 0.63 (8:2 Hexanes:EtOAc). $^1$H NMR (600 MHz, CDCl$_3$): δ 0.91 (t, J = 7.1 Hz, 3H), 1.35 (m, 4H), 1.52 (m, 2H), 1.79 (m, 2H), 1.93 (s, 1H), 4.60 (t, J = 6.6 Hz, 1H), 7.30 (m, 3H), 7.43 (m, 2H). $^{13}$C NMR (150 MHz, CDCl$_3$): δ 131.8, 128.5, 128.4, 122.9, 90.4, 85.0, 63.2, 38.0, 31.6, 25.0, 22.7, 14.1. IR (neat, cm$^{-1}$): 3313, 2955, 2930, 2659, 2215, 1596, 1469, 1464, 1443, 1377, 1335, 1117, 1071, 1052, 1026. HRMS (CI+): Calcd for C$_{14}$H$_{18}$O 202.1358 found : 202.1371.

1-Cyclohexyl-4,4-dimethylpent-1-yn-3-ol, 23i

95% yield as a clear, colorless oil. R$_f$ = 0.3 (9:1 Hexanes:EtOAc). $^1$H NMR (600 MHz, CDCl$_3$): δ 0.98 (s, 9H), 1.27 – 1.36 (m, 3H), 1.42 – 1.52 (m, 3H), 1.66 – 1.72 (m, 3H), 1.74 – 1.81 (m, 2H), 2.42 (br s, 1H), 4.00 (d, J = 1.8 Hz, 1H). $^{13}$C NMR (150 MHz, CDCl$_3$): δ 90.5, 80.0, 71.7, 36.0, 32.8, 29.1, 26.3, 26.1, 25.4, 24.9. IR (neat, cm$^{-1}$): 3431, 2930, 2855, 2207, 1671, 1479, 1449, 1392, 1363, 1317, 1297, 1234, 1147, 1129, 1064, 1042, 1004. LRMS (CI+) [M+H]$^+$ 195.2.

C.1.5.1 Synthesis of tert-Butyl-(7-hydroxydodec-5-yn-1-yl)carbamate, 23e
**Figure C.2** Reaction scheme followed to yield desired carbamate derivative 23e

12-Iodododec-7-yn-6-ol:

A 100 mL round-bottom flask was charged with 12-clorododec-7-yn-6-ol (500 mg, 2.3 mmol, 1 equiv) and sodium iodide (1.38 g, 9.2 mmol, 4 equiv) in acetone (11 mL, 0.2 M) and heated to reflux for 16 hours with stirring. The reaction was filtered to remove solid precipitates and purified by flash chromatography (9:1 Hexanes:EtOAc) to yield the desired product with ~5% starting material impurity, which was used in the next reaction without further purification. The reaction resulted in the desired product as a dark yellow solid in 96% yield (683.3 mg). $R_f = 0.55$ (7:3 Hexanes:EtOAc). $^1$H NMR (600 MHz, CDCl$_3$): δ 0.90 (t, $J = 6.7$ Hz, 3H), 1.32 (m, 4H), 1.43 (m, 2H), 1.60 – 1.71 (m, 6H), 1.94 (p, $J = 7.1$ Hz, 2H), 2.26 (t, $J = 6.5$ Hz, 2H), 3.21 (t, $J = 6.1$ Hz, 2H), 4.35 (t, $J = 6.4$ Hz, 1H). $^{13}$C NMR (150 MHz, CDCl$_3$): δ 84.5, 82.2, 62.9, 38.2, 32.5, 31.6, 29.4, 25.0, 22.7, 17.8, 14.1, 6.2. δ IR (neat, cm$^{-1}$): 3357, 2954, 2930, 2858, 2230, 1708, 1455, 1429, 1360, 1288, 1212, 1165, 1146, 1106, 1025. HRMS (Cl+): Caled for C$_{12}$H$_{20}$OI 307.05592 found : 307.05469.

12-Azidododec-7-yn-6-ol:
A 100 mL round-bottom flask was charged with 12-iodododec-7-yn-6-ol (200 mg, 0.64 mmol, 1 equiv) and sodium azide (63 mg, 0.97 mmol, 1.5 equiv) in DMAC (3 mL, 0.3 M), then stirred at 60 °C. After 3 hours, the reaction was judged to be complete by crude $^1$H NMR analysis. The crude reaction mixture was diluted with DCM, then washed with ice-cold water (x5) to remove DMAC. The combined organic layers were washed with brine, then dried over MgSO$_4$ and concentrated to ¼ volume. This material was not fully concentrated, and used in the next reaction without further purification.

*tert*-Butyl (7-hydroxydodec-5-yn-1-yl)carbamate, 23e

A 50 mL round-bottom flask was charged with 12-Azidododec-7-yn-6-ol (145 mg, 0.64 mmol, 1 equiv), triphenylphosphine (204 mg, 0.78 mmol, 1.2 equiv), water (0.5 mL) and diethyl ether (4 mL, 0.2 M) and stirred at room temperature for 12 hours. The reaction was then charged with di-tert-butyl dicarbonate (1.19 mL, 5.1 mmol, 8 equiv) and stirred for 4 hours, after which time the crude reaction mixture was diluted with water. The aqueous layer was extracted with Et$_2$O three times, and the combined organic layers were washed with brine, then dried over MgSO$_4$ and concentrated. The crude residue was chromatographed to purify (7:3 Hexanes:EtOAc, $R_f$ = 0.32), yielding 132.5 mg of desired product as a light yellow oil (69% yield). $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 0.90 (t, $J = 7.0$ Hz, 3H), 1.27 – 1.35 (m, 4H), 1.40 – 1.48 (m, 2H), 1.44 (s, 9H), 1.51 – 1.56 (m, 2H), 1.58 – 1.62 (m, 2H), 1.63 – 1.71 (m, 2H), 2.13 (br s, 1H), 2.25 (dt, $J = 1.9$, 3.4 Hz, 2H), 3.16 (q, $J = 6.8$ Hz, 2H), 4.34 (br q, $J = 5.8$ Hz, 1H), 4.58 (br s, 1H). $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 156.0, 84.7, 82.1, 79.2, 62.7, 40.1, 38.1, 31.5, 29.2, 28.4, 25.6, 24.9, 22.6, 18.4, 14.0. IR (neat, cm$^{-1}$): 3354, 2925, 2864, 2336, 1687, 1519, 1450, 1393, 1356, 1274, 1241, 1164, 1029. HRMS (ESI+): Calcd for C$_{17}$H$_{31}$O$_3$N 320.22016 found : 320.21934.
C.1.6 Procedure for the Deprotection of $p$-Nitrophenyl Ether

(Z)-4,4,5,5-Tetramethyl-2-((7-(4-nitrophenoxy)dodec-5-en-6-yl)-1,3,2-dioxaborolane

Acetic acid (250 µL, 4.0 mmol) was added to a mixture of indium powder (69 mg, 0.60 mmol), nitroarene, 22b (65 mg, 0.15 mmol) and acetic anhydride (284 µL, 3.0 mmol) in MeOH (0.5 mL). The reaction mixture was stirred overnight. After the reaction was complete, the reaction mixture was centrifuged to remove white solid. The recovered solution was concentrated under high vac. And re-dissolved in acetonitrile/water (10/1, 2 mL). CAN (131 mg, 0.24 mmol) was added to the reaction mixture at 0 °C. After 5 min, the reaction mixture was diluted with water and extracted with EtOAc. The combined organic extracts were dried over MgSO4, filtered, and concentrated. This crude material was purified by flash chromatography to yield the desired compound. Obtained in 71% yield as a yellow oil. Rf = 0.61 (9:1 Hexanes:EtOAc). $^1$H NMR (600 MHz, CDCl3): δ 0.87 – 0.91 (m, 6H), 1.27 (s, 6H), 1.28 (s, 6H), 1.26 – 1.46 (m, 11H), 1.56 – 1.67 (m, 1H), 2.05 (sx, J = 7.2 Hz, 1H), 2.19 (sx, J = 7.5 Hz, 1H), 4.38-4.45 (m, 1H), 6.30 (t, J = 7.4 Hz, 1H). $^{13}$C NMR (150 MHz, CDCl3): δ 146.3, 83.4, 70.8, 38.7, 31.9, 31.2, 28.5, 25.5, 24.9, 24.5, 22.7, 22.5, 14.0, 13.9. (the vinyl carbon attached to the boron is not observed) IR (neat, cm$^{-1}$): 3561, 2957, 2929, 2859, 1628, 1467, 1410, 1379, 1306, 1142, 1020, 969. HRMS (Cl+): Calcd for C$_{20}$H$_{37}$O$_4$B 352.27850 found : 352.27998.

C.1.7 Hydroboration of Substituted Propargyl Alcohols

Representative Procedure: Propargylic alcohol (30 mg, 1 equiv, 23a - i) in diethyl ether (0.2 M, dry) was charged to an oven-dried Schlenk tube and sealed under nitrogen flow. Bis(pinacolato)diboron (1.2 equiv) and sodium $t$-butoxide (0.3 equiv) were each separately charged to the reaction vessel by removing the septum and dumping the solid material in one
portion under light nitrogen flow. The reaction vessel was then cooled to 0 °C after washing the sides of the vessel with additional diethyl ether through the septum. Methanol (anhydrous, 2 equiv) was injected into the system, and then the 5-NHC Cu(I) catalyst 2 was added (1 mol%). The reaction was stirred for 30 minutes before the addition of triethanolamine (2 equiv), after which the reaction was stirred for 30 minutes while warming to room temperature. The reaction was then filtered and the filtrate was washed three times with water and once with brine, then dried and concentrated. This crude material was redissolved into dichloromethane (0.2 M, dry) in a 50 mL round bottom, and the vessel was charged with acetic anhydride (2 equiv) and DMAP (10 mol%). After stirring for 3 hours, this solution was filtered through a plug of silica gel, and purified by flash chromatography to yield the desired compounds in 65 − 88% yield.

(Z)-8-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)dodec-7-en-6-yl acetate, 24b

Isolated in 65% yield as a light yellow oil (α:β = 2:98). R_f = 0.42 (9:1 Hexanes:EtOAc). ^1H NMR (600 MHz, CDCl_3): δ 0.88 (t, J = 6.0 Hz, 3H), 0.90 (t, J = 6.4 Hz, 3H), 1.26 (s, 12H), 1.27 – 1.33 (m, 9H), 1.34 – 1.40 (m, 1H), 1.47 – 1.51 (m, 1H), 1.63 – 1.68 (m, 1H), 2.02 (s, 3H), 2.13 – 2.24 (m, 2H), 5.60 – 5.64 (m, 1H), 6.07 (d, J = 8.7 Hz, 1H). ^13C NMR (150 MHz, CDCl_3): δ 170.5, 141.8, 83.5, 70.8, 31.7, 32.5, 31.8, 31.0, 29.2, 24.9, 24.9, 22.9, 22.6, 21.5, 14.2, 14.1. (the vinyl carbon attached to the boron is not observed) IR (neat, cm\(^{-1}\)): 2956, 2932, 2860, 2350, 1734, 1716, 1633, 1460, 1408, 1371, 1310, 1240, 1142, 1018. LRMS (CI+) [M]+ 352.3.

(Z)-1-Phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hept-2-en-1-yl acetate, 24a

Isolated in 84% yield as a dark yellow oil (α:β = 2:98). R_f = 0.36 (9:1 Hexanes:EtOAc). ^1H NMR (600 MHz, CDCl_3): δ 0.88 (t, J = 7.1 Hz, 3H), 1.24 (d, J = 2.7 Hz, 12H), 1.27 – 1.43 (m, 4H), 2.06 (s, 3H), 2.23 – 2.31 (m, 2H), 6.39 (d, J = 8.6 Hz, 1H), 6.62 (d, J = 8.7 Hz, 1H),
7.26 – 7.29 (m, 1H), 7.32 – 7.35 (m, 2H), 7.37 – 7.40 (m, 2H). $^1^3$C NMR (150 MHz, CDCl$_3$): δ 170.1, 140.7, 140.1, 128.7, 128.0, 127.2, 83.6, 72.3, 32.1, 29.4, 24.9, 24.9, 22.9, 21.5, 14.2. (the vinyl carbon attached to the boron is not observed) IR (neat, cm$^{-1}$): 2959, 2929, 2664, 2247, 1732, 1372, 1311, 1237, 1136, 1019. LRMS (CI+) [M]$^+$ 358.3.

$(Z)$-12-(4-Nitrophenoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)dodec-7-en-6-yl acetate, 24g

Isolated in 80% yield as a dark yellow oil ($\alpha;\beta = 10:90$). $R_f = 0.45$ (9:1 Hexanes:EtOAc).

$^1$H NMR (600 MHz, CDCl$_3$): δ 0.87 (t, J = 6.9 Hz, 3H), 1.25 (s, 12H), 1.27 – 1.32 (m, 5H), 1.46 – 1.52 (m, 1H), 1.53 – 1.59 (m, 3H), 1.63 – 1.68 (m, 1H), 1.83 (p, J = 7.2 Hz, 2H), 2.02 (s, 3H), 2.23 – 2.32 (m, 2H), 4.03 – 4.10 (m, 2H), 5.59 – 5.63 (m, 1H), 6.12 (d, J = 8.9 Hz, 1H), 6.94 (dt, J = 2.8, 10.5 Hz, 2H), 8.19 (dt, J = 2.8, 10.5 Hz, 2H). $^1^3$C NMR (150 MHz, CDCl$_3$): δ 170.6, 164.5, 142.7, 141.4, 126.0, 114.6, 83.6, 70.7, 68.9, 34.7, 31.8, 28.9, 28.8, 26.3, 25.0, 24.9, 24.8, 22.7, 21.5, 14.1. (the vinyl carbon attached to the boron is not observed) IR (neat, cm$^{-1}$): 2976, 2952, 2933, 2862, 1733, 1607, 1593, 1514, 1496, 1468, 1408, 1372, 1340, 1311, 1260, 1242, 1174. HRMS (CI+): Calcd for C$_{26}$H$_{40}$O$_7$NB 489.28978 found : 489.29119.

$(Z)$-12-Chloro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)dodec-7-en-6-yl acetate, 24d

Isolated in 88% yield as a yellow oil ($\alpha;\beta = 5:95$). $R_f = 0.29$ (9:1 Hexanes:EtOAc). $^1$H NMR (600 MHz, CDCl$_3$): δ 0.88 (t, J = 6.9 Hz, 3H), 1.26 (s, 12H), 1.27 – 1.32 (m, 6H), 1.46 – 1.56 (m, 3H), 1.63 – 1.68 (m, 1H), 1.74 – 1.82 (m, 2H), 2.02 (s, 3H), 2.18 – 2.28 (m, 2H), 3.51 – 3.57 (m, 2H), 5.57 – 5.60 (m, 1H), 6.11 (d, J = 9.0 Hz, 1H). $^1^3$C NMR (150 MHz, CDCl$_3$): δ 170.5, 142.6, 83.6, 70.7, 45.2, 34.7, 32.6, 31.8, 28.5, 27.4, 25.0, 24.9, 24.9, 22.7, 21.5, 14.1. (the
vinyl carbon attached to the boron is not observed) IR (neat, cm$^{-1}$): 2978, 2953, 2929, 2864, 2247, 1724, 1625, 1458, 1405, 1372, 1307, 1245, 1135, 1106, 1008. LRMS (CI+) [M]$^+$ 386.3.

(Z)-12-((tert-Butoxycarbonyl)amino)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)dodec-7-en-6-yl acetate, 24e

Isolated in 75% yield as a light yellow oil ($\alpha$:$\beta$ = >2:98). $R_f = 0.35$ (9:1 Hexanes:EtOAc). $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 0.88 (t, J = 6.9 Hz, 3H), 1.26 (s, 12H), 1.27 – 1.31 (m, 5H), 1.44 (s, 9H), 1.46 – 1.51 (m, 4H), 1.64 (br s, 3H), 2.02 (s, 3H), 2.19 (t, J = 7.7 Hz, 2H), 3.10 – 3.17 (m, 2H), 4.80 (br s, 1H), 5.57 – 5.60 (m, 1H), 6.08 (d, J = 8.8 Hz, 1H). $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 170.6, 156.1, 142.2, 83.6, 78.9, 70.7, 40.1, 34.7, 31.7, 31.0, 29.5, 28.6, 26.9, 24.9, 24.8, 22.6, 21.4, 14.1. (the vinyl carbon attached to the boron is not observed) IR (neat, cm$^{-1}$): 3391, 2978, 2929, 2855, 2247, 1703, 1630, 1503, 1454, 1405, 1364, 1311, 1241, 1160, 1135, 1008. LRMS (CI+) [M + H]$^+$ 468.4.

(Z)-8-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-12-((triisopropylsilyl)oxy)dodec-7-en-6-yl acetate, 24f

Isolated in 77% yield ($\alpha$:$\beta$ = 9:91). $R_f = 0.48$ (9:1 Hexanes:EtOAc). $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 0.87 (t, J = 6.9 Hz, 3H), 1.04 (s, 6H), 1.05 (s, 12H), 1.25 (s, 12H), 1.26 (s, 2H), 1.27 – 1.32 (m, 5H), 1.37 – 1.45 (m, 2H), 1.46 – 1.51 (m, 1H), 1.52 – 1.57 (m, 2H), 1.36 – 1.67 (m, 1H), 2.02 (s, 3H), 2.15 – 2.28 (m, 2H), 3.64 – 3.70 (m, 2H), 5.59 – 5.63 (m, 1H), 6.09 (d, J = 8.7 Hz, 1H). $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 170.3, 141.8, 83.3, 70.7, 63.5, 34.6, 33.2, 31.6, 29.3, 26.5, 25.1, 24.8, 24.7, 22.5, 31.3, 18.1, 14.0, 12.0. (the vinyl carbon attached to the boron is not observed) IR (neat, cm$^{-1}$): 2940, 2865, 2356, 1739, 1696, 1463, 1408, 1371, 1310, 1239. HRMS (CI+): Calcd for C$_{29}$H$_{58}$O$_5$BSi 525.41466 found : 525.41534.
C.2 Spectral Data

Figure C.3 $^1$H NMR and $^{13}$C NMR of compound 20g
**Figure C.4** $^1$H NMR and $^{13}$C NMR of compound 20f
Figure C.5 $^1$H NMR and $^{13}$C NMR of compound 20d
Figure C.6 $^1$H NMR and $^{13}$C NMR of compound 20b
Figure C.7 $^1$H NMR and $^{13}$C NMR of compound 20e
Figure C.8 $^1$H NMR and $^{13}$C NMR of compound 20c
Figure C.9 $^1$H NMR and $^{13}$C NMR of compound 21a
Figure C.10 $^1$H NMR and $^{13}$C NMR of compound 21b
Figure C.11 $^1$H NMR and $^{13}$C NMR of compound 21c
Figure C.12 $^1$H NMR and $^{13}$C NMR of compound 21d
Figure C.13 $^1$H NMR and $^{13}$C NMR of compound 21f
Figure C.14 $^1$H NMR and $^{13}$C NMR of compound 21g
Figure C.16 $^1$H NMR and $^{13}$C NMR of compound 21i
Figure C.17 $^1$H NMR and $^{13}$C NMR of iodo-compound toward 21e
Figure C.18 $^1$H NMR and $^{13}$C NMR of compound 21e
Figure C.19 $^1$H NMR and $^{13}$C NMR of compound 22a
Figure C.20 $^1$H NMR and $^{13}$C NMR of compound 22b
Figure C.21 $^1$H NMR and $^{13}$C NMR of compound 22d
Figure C.22 $^1$H NMR and $^{13}$C NMR of compound 22e
Figure C.23 $^1$H NMR and $^{13}$C NMR of compound 22f
Figure C.24 $^1$H NMR and $^{13}$C NMR of compound 22g
Figure C.25 $^1$H NMR and $^{13}$C NMR of compound 22h
Figure C.26 $^1$H NMR and $^{13}$C NMR of compound 22i
Figure C.27 $^1$H NMR and $^{13}$C NMR of compound 23b
Figure C.28 \(^1\)H NMR and \(^{13}\)C NMR of compound 23c
Figure C.29 $^1$H NMR and $^{13}$C NMR of compound 23d
Figure C.30 $^1$H NMR and $^{13}$C NMR of compound 23f
Figure C.31 $^1$H NMR and $^{13}$C NMR of compound 23g
Figure C.32 $^1$H NMR and $^{13}$C NMR of compound 23h
Figure C.33 $^1$H NMR and $^{13}$C NMR of compound 23i
Figure C.34 $^1$H NMR and $^{13}$C NMR of iodo-compound toward 23e
Figure C.35 $^1$H NMR and $^{13}$C NMR of compound 23e
Figure C.36 $^1$H NMR and $^{13}$C NMR of deprotected aryl ether
Figure C.37 $^1$H NMR and $^{13}$C NMR of compound 24b
Figure C.38 $^1$H NMR and $^{13}$C NMR of compound 24c
Figure C.39 $^1$H NMR and $^{13}$C NMR of compound 24g
Figure C.40 $^1$H NMR and $^{13}$C NMR of compound 24d

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Figure C.41 $^1$H NMR and $^{13}$C NMR of compound 24e
Figure C.42 $^1$H NMR and $^{13}$C NMR of compound 24f
APPENDIX D

SUPPORTING INFORMATION FOR CHAPTER 5

D.1 Characterization Data

D.1.1 General Procedures and Instrumentation

Proton (\(^1\)H) NMR spectra were recorded on a Bruker. Chemical shifts were reported in ppm as downfield from the standard tetramethylsilane peak at 0 ppm. Peaks are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sx = sextet, hp = heptet, br = broad, m = multiplet), coupling constants (reported in Hz), and integration. Carbon (\(^{13}\)C) NMR spectra were recorded on the same instrument using the residual solvent signal as an internal standard (typically CDCl\(_3\) = 77.16 ppm, unless otherwise noted). Infrared (IR) spectra were recorded on a Thermo Scientific Nicolet 380 FT-IR spectrometer. High-resolution mass spectrometry was performed by Dr. Umesh Goli at FSU. All reactions were conducted in oven- or flame-dried glassware under a nitrogen atmosphere. Diethyl ether, dichloromethane (DCM), toluene and tetrahydrofuran (THF) solvents were collected from a dry solvent system, and used as they were. Commercially available Grignard reagents were titrated prior to use using 1-pyreneacetic acid,\(^1\) which was purchased from Aldrich and stored in a nitrogen-filled glove box upon receipt. Prepared Grignard reagents were prepared with magnesium turnings which were activated by crushing with a mortar and pestle, then washed successively with 1 M HCl, water, methanol and diethyl ether. The washed magnesium was then dried under reduced pressure overnight and stored in a glove box under nitrogen atmosphere until use. Bis(pinacolato)diboron was purchased through Combiphos Catalysts, Inc. and used as received. All other chemicals were purchased through Sigma-Aldrich and used as received,
except anhydrous methanol, which was transferred to a Schlenk pot upon receipt, and all aldehydes were purified by washing with dilute sodium bicarbonate and fractional distillation prior to their use.

**D.1.2 Synthesis of Propargyl Alcohols**

Representative Procedure: Terminal alkyne (2 equiv.) in dry THF (0.2 M), was charged to a flame-dried round bottom flask and cooled to 0 °C in an ice water bath. Slowly, n-butyllithium (1.3 equiv., 2.5 M in hexanes) was added, causing the solution to turn a deep yellow color. The solution was stirred for 30 minutes at 0 °C before adding the corresponding aldehyde (1 equiv.), which had been purified before use by washing with sodium bicarbonate and distillation. The solution was then removed from the ice bath and stirred for 4 hours while warming to room temperature. The reaction was quenched with a saturated ammonium chloride solution and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with saturated sodium bicarbonate, brine, then dried over MgSO₄ and concentrated. The crude mixture was purified using flash chromatography to yield the desired products in 65 – 92 % yield.

**Non-4-yn-3-ol**, 86 % yield as a yellow oil. R<sub>f</sub> = 0.19 (9:1 Hexanes:EtOAc). <sup>1</sup>H NMR (600 MHz, CDCl₃): δ = 0.91 (t, J = 7.3 Hz, 3H), 1.00 (t, J = 7.5 Hz, 3H), 1.38 – 1.44 (m, 2H), 1.47 – 1.52 (m, 2H), 1.64 – 1.75 (m, 2H), 1.84 (br s, 1H), 2.21 (dt, J = 2.0, 3.6 Hz, 2H), 4.30 (br t, 1H). <sup>13</sup>C NMR (150 MHz, CDCl₃): δ 85.7, 81.2, 64.1, 31.4, 30.9, 22.0, 18.5, 13.7, 9.6. IR (neat, cm⁻¹): 3399, 2962, 2925, 2864, 2365, 1707, 1458, 1372, 1319, 1266, 1225, 1151, 1094, 1029, 1004. LRMS (CI-) [M]⁻ 140.1.
1-Phenylnon-2-yn-4-ol.

Isolated as a light yellow oil in 65 % yield with minor impurities. The NMR spectra were compared with known values\(^2\) and used without further purification. \(R_f = 0.43\) (8:2 Hexanes:EtOAc). \(^1H\) NMR (600 MHz, CDCl\(_3\)): \(\delta 0.90\) (t, \(J = 7.0\) Hz, 3H), 1.30 – 1.34 (m, 4H), 1.44 (m, 2H), 1.68 – 1.75 (m, 2H), 3.64 (d, \(J = 1.8\) Hz, 2H), 4.42 (tt, \(J = 2.0, 3.3\) Hz, 1H), 7.22 – 7.25 (m, 1H), 7.29 – 7.34 (m, 4H). \(^{13}C\) NMR (150 MHz, CDCl\(_3\)): \(\delta\) LRMS:

1-((tert-Butyldimethylsilyl)oxy)dec-5-yn-4-ol.

The aldehyde (4-((tert-butyldimethylsilyl)oxy)butanal) was prepared according to known literature procedures,\(^2\) and used in accordance with the general method above to yield the desired product in 76% yield. \(R_f = 0.34\) (9:1 Hexanes:EtOAc). \(^1H\) NMR (600 MHz, CDCl\(_3\)): \(\delta 0.07\) (d, \(J = 1.7\) Hz, 6H), 0.91 (s, 9H), 0.91 (t, 3H, obscured by TBDMS peak), 1.37 – 1.43 (m, 2H), 1.46 – 1.51 (m, 2H), 1.64 – 1.69 (m, 1H), 1.75 – 1.82 (m, 3H), 2.20 (dt, \(J = 1.9, 7.1\) Hz, 2H), 2.97 (br s, 1H), 3.63 – 3.71 (m, 2H), 4.41 (br t, 1H). \(^{13}C\) NMR (150 MHz, CDCl\(_3\)): \(\delta 85.4, 81.3, 63.4, 62.5, 35.8, 30.9, 28.7, 26.1, 22.1, 18.5, 18.5, 13.7, -5.2. IR (neat, cm\(^{-1}\)): 3342, 2949, 2917, 2230, 1458, 1384, 1249, 1098, 1021. LRMS (CI-) [M - H]\(^-\) 283.2.

6-((tert-Butyldimethylsilyl)oxy)hex-3-yn-2-ol.

This product was prepared according to the general procedure outlined above, except that it was purified by Kügelrohr distillation (95 °C at 250 mTorr) to yield the pure product in 92 % yield. \(R_f = 0.13\) (9:1 Hexanes:EtOAc). \(^1H\) NMR (600 MHz, CDCl\(_3\)) = \(\delta 0.08\) (s, 6H), 0.90 (s, 9H), 1.43 (d, \(J = 6.5\) Hz, 3H), 2.42 (dt, \(J = 1.9, 3.6\) Hz, 2H), 3.71 (t, \(J = 7.1\) Hz, 2H), 4.51 (m, 1H). \(^{13}C\) NMR (150 MHz, CDCl\(_3\)) = \(\delta 83.5, 81.7, 62.0, 58.7, 26.0, 24.8, 23.2, 18.5, -5.1. IR
(neat, cm\(^{-1}\)) = 3356, 2958, 2930, 2864, 2242, 1472, 1388, 1361, 1333, 1254, 1154, 1105, 1005. LRMS (Cl-) [M – H\(^-\)] 227.2

**D.1.3 Hydroboration of Propargyl Alcohols**

Representative Procedure: An oven-dried Schlenk tube with stir bar, under nitrogen flow, was charged with propargyl alcohol (1 equiv.) in diethyl ether (0.2 M). Bis(pinocolato)diboron (1.2 equiv.), then sodium \(t\)-butoxide (0.3 equiv.) were added in one portion by removing the septum and adding under nitrogen flow. The reaction vessel was then cooled to 0 °C in an ice bath before adding methanol (2 equiv.) in one portion directly through the septum. The 5-NHC CuCl complex (0.01 equiv.) was then added in one portion by removing the septum under nitrogen flow. The reaction was removed from the ice bath and allowed to stir for 20 minutes while warming to room temperature. After 20 minutes, triethanolamine (2 equiv. of a 1.3 M solution in ethyl acetate) was added to the solution at room temperature, and the reaction was again stirred for 30 minutes at room temperature. After 30 minutes, the reaction had developed dark precipitate, which was removed by simple filtration through a frit, eluting with additional diethyl ether. The filtrate was washed 5 times with water, and once with brine before being dried over MgSO\(_4\) and concentrated. The desired allylic alcohol products were difficult to isolate by column, so the alcohol was protected by dissolving the crude product in dichloromethane (0.2 M), and adding acetic anhydride (2 equiv.) and DMAP (0.1 equiv.) and stirring for 3 hours. The resulting solution was filtered through silica gel, and then purified by flash chromatography to yield the desired vinylboronates with yields ranging from 80 – 84 % yield.

\((Z)-3-(4,4,5,5\text{-Tetramethyl-1,3,2-dioxaborolan-2-yl})\text{hept-2-en-1-yl acetate, 33}\)
84 % yield as a pale yellow oil. \( R_f = 0.42 \) (9:1 Hexanes:EtOAc). \(^1\)H NMR (600 MHz, CDCl\(_3\)): \( \delta \) 0.89 (t, \( J = 7.1 \) Hz, 3H), 1.26 (s, 12H), 1.28 – 1.33 (m, 4H), 2.07 (s, 3H), 2.16 (t, \( J = 7.1 \) Hz, 2H), 4.71 (d, \( J = 6.1 \) Hz, 2H), 6.30 (t, \( J = 6.2 \) Hz, 1H). \(^1\)C NMR (150 MHz, CDCl\(_3\)): \( \delta \) 171.1, 137.8, 83.6, 61.4, 32.3, 29.0, 24.9, 22.7, 21.1, 14.2 (the vinyl carbon attached to boron is not observed). IR (neat, cm\(^{-1}\)): 2978, 2958, 2931, 2263, 1744, 1638, 1473, 1410, 1379, 1359, 1312, 1266, 1230, 1139, 1025. LRMS (Cl+) [M+H]^+ 283.2.

(Z)-5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)non-4-en-3-yl acetate, \( \text{26} \)

Isolated in 80 % yield as a light yellow oil. \( R_f = 0.46 \) (9:1 Hexanes:EtOAc). \(^1\)H NMR (600 MHz, CDCl\(_3\)): \( \delta \) 0.89 (t, \( J = 7.4 \) Hz, 3H), 0.90 (t, \( J = 7.1 \) Hz, 3H), 1.26 (s, 12H), 1.29 – 1.38 (m, 5H), 1.52 – 1.60 (m, 1H), 1.60 – 1.72 (m, 1H), 2.03 (s, 3H), 2.15 – 2.24 (m, 2H), 5.54 – 5.58 (m, 1H), 6.08 (d, \( J = 8.8 \) Hz, 1H). \(^1\)C NMR (150 MHz, CDCl\(_3\)): \( \delta \) 170.5, 141.4, 83.5, 72.0, 32.5, 29.2, 27.8, 24.9, 24.9, 22.9, 21.4, 14.2, 9.7 (the vinyl carbon attached to boron is not observed). IR (neat, cm\(^{-1}\)): 2974, 2925, 2872, 2361, 1736, 1630, 1462, 1405, 1368, 1307, 1237, 1139, 1070, 1012. LRMS (Cl+) [M]^+ 310.3.

(Z)-1-Phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)non-2-en-4-yl acetate, \( \text{31} \)

Isolated in 81 % yield as a dark yellow oil (\( \alpha: \beta = 2:98 \)). \( R_f = 0.56 \) (9:1 Hexanes:EtOAc). \(^1\)H NMR (600 MHz, CDCl\(_3\)): \( \delta \) 0.84 (t, \( J = 7.0 \) Hz, 3H), 1.17 (d, \( J = 8.3 \) Hz, 12H), 1.90 – 1.25 (m, 6H), 1.39 – 1.44 (m, 1H), 1.59 – 1.64 (m, 1H, partially obscured by water peak), 2.01 (s, 3H), 3.60 (q, \( J = 13.9 \) Hz, 2H), 5.67 – 5.70 (m, 1H), 6.20 (d, \( J = 8.7 \) Hz, 1H), 7.11 – 7.14 (m, 1H), 7.19 – 7.23 (m, 4H). \(^1\)C NMR (150 MHz, CDCl\(_3\)): \( \delta \) 170.5, 142.8, 141.4, 128.9, 128.2, 125.7, 83.7, 71.0, 35.0, 34.4, 31.7, 24.9, 24.7, 22.6, 21.4, 14.1. IR (neat, cm\(^{-1}\)): 2978, 2953,
2929, 2855, 2251, 1736, 1630, 1470, 1413, 1372, 1307, 1254, 1135, 1098, 1021. LRMS (Cl+) [M+H]$^+$ 387.3.

(Z)-1-((tert-Butyldimethylsilyl)oxy)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)dec-5-en-4-yl acetate, 28

Product was obtained in 90% yield as a colorless oil. $R_f = 0.45$ (9:1 Hexanes:EtOAc). $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 0.04 (s, 6H), 0.88 (s, 9H), 0.89 (t, 3H, obscured by TBDMS peak), 1.25 (s, 12H), 1.29 – 1.34 (m, 3H), 1.35 – 1.38 (m, 1H), 1.48 – 1.56 (m, 2H), 1.57 – 1.63 (m, 1H), 1.66 – 1.72 (m, 1H), 2.02 (s, 3H), 2.14 – 2.24 (m, 2H), 3.59 – 3.62 (m, 2H), 5.62 – 5.65 (m, 1H), 6.08 (d, $J = 8.7$ Hz, 1H). $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 170.5, 141.6, 83.5, 70.7, 62.9, 32.4, 31.2, 29.2, 28.6, 26.0, 24.9, 24.9, 22.9, 21.4, 18.5, 14.2, -5.2. (the vinyl carbon attached to the boron is not observed) IR (neat, cm$^{-1}$): 2966, 2921, 2851, 1736, 1474, 1405, 1372, 1307, 1237, 1135, 1094, 1017. HRMS (Cl+): Calcd for C$_{24}$H$_{46}$O$_5$BSi 453.32076 found : 453.32205.

(Z)-6-((tert-Butyldimethylsilyl)oxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-3-en-2-yl acetate.

Product was obtained in 85% yield as a very light yellow oil. $R_f = 0.41$ (9:1 Hexanes:EtOAc). $^1$H NMR (600 MHz, CDCl$_3$) = $\delta$ 0.05 (s, 6H), 0.88 (s, 9H), 1.25 (s, 12H), 1.30 (d, $J = 6.4$ Hz, 3H), 2.01 (s, 3H), 2.38 (m, 1H), 2.50 (m, 1H), 3.57 (m, 1H), 3.67 (m, 1H), 5.71 (m, 1H), 6.25 (d, $J = 4.7$ Hz, 1H). $^{13}$C NMR (150 MHz, CDCl$_3$) = 170.4, 145.3, 83.6, 67.9, 62.9, 33.1, 26.2, 25.0, 24.9, 21.5, 20.8, 18.6, -5.1, -5.1 (The sp$^2$ carbon attached to boron is not observed). $\delta$ IR (neat, cm$^{-1}$) = 2978, 2954, 2884, 2858, 1741, 1638, 1472, 1409, 1371, 1311, 1239, 1142, 1095, 1045. HRMS (Cl+): Calcd for C$_{20}$H$_{40}$O$_5$BSi 399.27381 found : 399.27322.
D.1.4 Grignard Addition Experiments to Produce Allylboronates

Representative Procedure: A flame-dried and nitrogen-purged Schlenk tube was equipped with a stirbar and sealed with a rubber septum. Vinylboronate (1 equiv.) in dry diethyl ether (0.2 M) was charged to the reaction vessel, with additional ether used to wash the sides of the tube. This reaction mixture was cooled to 0 °C in an ice-water bath before slowly adding the desired Grignard reagent (1.5 equiv.), after which the reaction vessel was stirred for 30 minutes while warming to room temperature. After 30 minutes, the reaction mixture was filtered quickly through silica and the filtrate was concentrated. Flash chromatography of the crude compound yielded the desired tertiary allylboronates in 97 – 66 % yield.

\((E)-4,4,5,5\text{-Tetramethyl}-2-(5\text{-phenylnon}-3\text{-en-5-yl})-1,3,2\text{-dioxaborolane}, 27a\)

Isolated in 93 % yield as a yellow oil. \(R_f = 0.83\) (9:1 Hexanes:EtOAc). \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 0.83 (t, J = 7.7 Hz, 3H), 1.00 (t, J = 7.4 Hz, 3H), 1.05 – 1.11 (m, 2H), 1.21 (d, J = 4.9 Hz, 12H), 1.21 – 1.26 (m, 2H), 1.78 – 1.87 (m, 2H), 2.08 – 2.13 (m, 2H), 5.54 (dt, J = 6.4, 15.8 Hz, 1H), 5.66 (dt, J = 1.3, 15.8 Hz, 1H), 7.12 – 7.14 (m, 1H), 7.24 – 7.27 (m, 4H). \(^{13}\)C NMR (150 MHz, CDCl\(_3\)) \(\delta\) 146.2, 133.5, 132.1, 128.6, 128.0, 125.3, 83.4, 37.0, 28.2, 26.4, 24.6, 24.6, 23.5, 14.4, 14.3 (the sp\(^3\) carbon attached to boron is not observed). IR (neat, cm\(^{-1}\)): 2962, 2929, 2872, 2361, 2324, 1656, 1450, 1366, 1348, 1311, 1266, 1213, 1139, 1102, 1025. LRMS (Cl+) [M+H]\(^+\) 329.3.

\((E)-2-(5\text{-}(2\text{-Methoxyphenyl)non}-3\text{-en-5-yl})-4,4,5,5\text{-tetramethyl}-1,3,2\text{-dioxaborolane}, 27b\)

Isolated in 97 % yield as a light yellow oil. \(R_f = 0.39\) (9:1 Hexanes:EtOAc). \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 0.77 (t, J = 7.1 Hz, 3H), 1.01 (t, J = 7.4 Hz, 3H), 1.11 – 1.21 (m, 4H), 1.19 (s, 6H), 1.22 (s, 6H), 1.80 – 1.85 (m, 1H), 1.90 – 1.94 (m, 1H), 2.13 (dp, J = 1.2, 7.4 Hz, 2H),
3.79 (s, 3H), 5.50 (dt, J = 6.4, 15.9 Hz, 1H), 5.64 (dt, J = 1.5, 15.8 Hz, 1H), 6.79 – 6.81 (m, 1H), 6.89 – 6.91 (m, 1H), 7.12 – 7.15 (m, 2H). $^{13}$C NMR (150 MHz, CDCl$_3$): δ 156.7, 134.8, 131.8, 131.6, 129.6, 126.6, 120.6, 110.0, 82.8, 55.0, 32.2, 26.7, 26.5, 24.8, 24.8, 23.5, 14.4, 14.3 (the sp$^3$ carbon attached to boron is not observed). IR (neat, cm$^{-1}$): 2959, 2932, 2870, 1683, 1597, 1583, 1487, 1461, 1436, 1387, 1377, 1369, 1342, 1314, 1269, 1240, 1145, 1107, 1052, 1031. LRMS (CI+) [M+H]$^+$ 359.3.

*(E)*-4,4,5,5-Tetramethyl-2-(5-(thiophen-2-yl)non-3-en-5-yl)-1,3,2-dioxaborolane, 27c

Isolated in 94 % yield as a dark yellow oil. $R_f$ = 0.75 (9:1 Hexanes:EtOAc). $^1$H NMR (600 MHz, CDCl$_3$): δ 0.85 (t, J = 7.γ Hz, γH), 0.98 (t, J = 7.4 Hz, 3H), 1.23 (d, J = 2.6 Hz, 12H), 1.25 – 1.33 (m, 4H), 1.80 – 1.91 (m, 2H), 2.05 – 2.10 (m, 2H), 5.56 (dt, J = 6.4, 15.6 Hz), 5.67 – 5.70 (m, 1H), 6.91 – 6.92 (m, 2H), 7.11 – 7.12 (m, 1H). $^{13}$C NMR (150 MHz, CDCl$_3$): δ 151.5, 133.9, 132.1, 126.4, 124.5, 123.0, 83.7, 39.1, 28.7, 26.2, 24.7, 23.4, 14.2, 14.1 (the sp$^3$ carbon attached to boron is not observed). IR (neat, cm$^{-1}$): 2962, 2929, 2868, 2361, 2324, 1634, 1529, 1454, 1368, 1339, 1307, 1270, 1229, 1209, 1164, 1139, 1102. LRMS (CI+) [M+H]$^+$ 335.2.

*(E)*-4,4,5,5-Tetramethyl-2-(5-vinylnon-3-en-5-yl)-1,3,2-dioxaborolane, 27d

Isolated in 81 % yield as a very light yellow oil. $R_f$ = 0.72 (9:1 Hexanes:EtOAc). $^1$H NMR (600 MHz, CDCl$_3$): δ 0.88 (t, J = 7.0 Hz, 3H), 0.97 (t, J = 7.4 Hz, 3H), 1.23 (s, 12H), 1.25 – 1.33 (m, 4H), 1.54 – 1.58 (m, 2H), 2.03 – 2.08 (m, 2H), 5.01 – 5.06 (m, 2H), 5.41 – 5.49 (m, 2H), 5.85 – 5.90 (m, 1H). $^{13}$C NMR (150 MHz, CDCl$_3$): δ 143.3, 132.7, 131.7, 113.0, 83.3, 36.1, 28.2, 26.3, 24.7, 24.7, 23.36, 14.3, 14.2 (the sp$^3$ carbon attached to boron is not observed). IR (neat, cm$^{-1}$): 3080, 2974, 2960, 2931, 2872, 1629, 1458, 1370, 1309, 1271, 1215, 1139, 1111. LRMS (CI+) [M+H]$^+$ 279.2
\((E)-4,4,5,5\)-Tetramethyl-2-(5-methylnon-3-en-5-yl)-1,3,2-dioxaborolane, \(27e\)

Isolated in 98 % yield as a light yellow oil. R<sub>f</sub> = 0.68 (9:1 Hexanes:EtOAc). \(^1\)H NMR (600 MHz, CDCl<sub>3</sub>): δ 0.88 (t, J = 7.3 Hz, 3H), 0.95 (t, J = 7.4 Hz, 3H), 1.01 (s, 3H), 1.21 (d, J = 3.4 Hz, 12H), 1.21 - 1.30 (m, 5H), 1.47 - 1.52 (m, 1H), 1.99 - 2.04 (m, 2H), 5.35 (dt, J = 6.2, 15.7 Hz, 1H), 5.43 (dt, J = 1.1, 15.8 Hz, 1H). \(^1^3\)C NMR (150 MHz, CDCl<sub>3</sub>): δ 136.5, 128.9, 83.1, 38.8, 28.2, 26.2, 24.8, 24.7, 23.7, 20.6, 14.5, 14.3 (the sp<sup>3</sup> carbon attached to boron is not observed). IR (neat, cm<sup>-1</sup>): 2958, 2929, 2872, 2365, 2324, 1654, 1450, 1368, 1344, 1303, 1270, 1213, 1135, 1066. LRMS (CI+) [M+H]<sup>+</sup> 267.3.

\((E)-2-(5-(sec-Butyl)non-3-en-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, \(27f\)

Isolated in 76 % yield as a light yellow oil. R<sub>f</sub> = 0.76 (9:1 Hexanes:EtOAc). \(^1\)H NMR (600 MHz, CDCl<sub>3</sub>): δ 0.78 (d, J = 6.8 Hz, 2H), 0.84 – 0.89 (m, 6H), 0.97 (t, J = 7.4 Hz, 4H), 1.13 – 1.19 (m, 1H), 1.24 (s, 12H), 1.25 – 1.29 (m, 3H), 1.38 – 1.55 (m, 5H), 2.02 – 2.07 (m, 2H), 5.30 (dd, J = 6.8, 15.9 Hz, 1H), 5.43 (dq, J = 6.6, 15.7 Hz, 1H). \(^1^3\)C NMR (150 MHz, CDCl<sub>3</sub>): δ 132.3, 131.3, 83.0, 41.3, 34.3, 28.7, 27.4, 26.4, 25.1, 25.0, 24.0, 15.9, 14.7, 14.3, 13.8, 13.0. IR (neat, cm<sup>-1</sup>): 2960, 2931, 2872, 1723, 1638, 1462, 1378, 1371, 1305, 1271, 1213, 1164, 1142. HRMS (CI+): Calcd for C<sub>19</sub>H<sub>38</sub>O<sub>2</sub>B 309.29649 found : 309.29561.

\((E)-2-(5-Benzynon-3-en-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, \(27g\)

Isolated in 68 % yield as a yellow oil. R<sub>f</sub> = 0.72 (9:1 Hexanes:EtOAc). \(^1\)H NMR (600 MHz, CDCl<sub>3</sub>): δ 0.87 (t, J = 7.1 Hz, 3H), 0.95 (t, J = 7.4 Hz, 3H), 1.21 (d, J = 4.1 Hz, 12H), 1.24 – 1.33 (m, 4H), 1.38 – 1.42 (m, 2H), 2.01 – 2.06 (m, 2H), 2.81 (q, J = 10.9 Hz, 2H), 5.34 – 5.42 (m, 2H), 7.12 – 7.16 (m, 1H), 7.19 - 7.21 (m, 4H). \(^1^3\)C NMR (150 MHz, CDCl<sub>3</sub>): δ 140.1, 134.5,
(E)-2-(5-Cyclopropylnon-3-en-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, 27h

Isolated in 86 % yield as a colorless oil. Rf = 0.76 (9:1 Hexanes:EtOAc). 1H NMR (600 MHz, CDCl3): δ 0.23 – 0.34 (m, 4H), 0.72 – 0.75 (m, 1H), 0.89 (t, J = 7.0 Hz, 3H), 0.95 (t, J = 7.5 Hz, 3H), 1.21 (d, J = 1.1 Hz, 12H), 1.27 – 1.35 (m, 4H), 1.44 – 1.55 (m, 2H), 2.02 (dp, J = 1.4, 7.5 Hz, 2H), 5.25 (dt, J = 1.4, 15.8 Hz, 1H), 5.49 (dt, J = 6.4, 15.8 Hz, 1H). 13C NMR (150 MHz, CDCl3): δ 132.7, 131.1, 83.0, 37.4, 28.6, 26.4, 24.9, 24.8, 23.8, 17.4, 14.5, 14.3, 1.7, 0.6 (the sp3 carbon attached to boron is not observed). IR (neat, cm⁻¹): 3076, 2978, 2958, 2929, 2868, 2851, 1736, 1462, 1376, 1339, 1303, 1270, 1213, 1160, 1139, 1111, 1066, 1017. LRMS (Cl+) [M+H]+ 293.3.

(E)-2-(5-Isopropylnon-3-en-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, 27i and 27j

Isolated in 89 % yield (from iPrMgBr, ) as a colorless oil. Rf = 0.71 (9:1 Hexanes:EtOAc). 1H NMR (600 MHz, CDCl3): δ 0.80 (d, J = 6.8 Hz, 3H), 0.88 (m, 6H), 0.97 (t, J = 7.3 Hz, 3H), 1.24 (s, 12H), 1.26 – 1.30 (m, 4H), 1.35 – 1.50 (m, 2H), 1.74 (hp, 6.9 Hz, 1H), 2.06 (m, 2H), 5.30 (dt, J = 1.4, 16.0 Hz, 1H), 5.45 (dt, J = 6.4, 16.0 Hz, 1H). 13C NMR (150 MHz, CDCl3): δ 132.2, 131.7, 83.0, 34.6, 33.8, 26.7, 25.1, 23.9, 20.1, 17.9, 14.6, 14.3 (the sp3 carbon attached to boron was not observed). IR (neat, cm⁻¹): 2974, 2958, 2929, 2868, 2238, 1462, 1388, 1376, 1298, 1262, 1209, 1143, 1102, 1066, 1004. LRMS (Cl+) [M+H]+ 295.3.

(E)-4,4,5,5-Tetramethyl-2-(5-propylnon-3-en-5-yl)-1,3,2-dioxaborolane, 27k
Isolated in 88 % yield as a colorless oil. $R_f = 0.84$ (9:1 Hexanes:EtOAc). $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 0.88 (t, $J = 7.3$ Hz, 3H), 0.95 (t, $J = 7.5$ Hz, 3H), 1.11 – 1.23 (m, 3H), 1.22 (s, 12H), 1.24 – 1.31 (m, 3H), 1.39 – 1.46 (m, 4H), 2.01 (dq, $J = 1.2$, 7.5 Hz, 2H), 5.30 (dt, $J = 1.3$, 15.8 Hz, 1H), 5.40 (dt, $J = 6.4$, 15.8 Hz, 1H). $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 135.0, 130.2, 83.0, 37.5, 34.9, 27.6, 26.4, 24.8, 23.7, 18.5, 15.2, 14.5, 14.3 (The carbon attached to boron was not observed). IR (neat, cm$^{-1}$): 2974, 2958, 2925, 2868, 1466, 1388, 1368, 1343, 1307, 1270, 1233, 1209, 1143, 1106, 1004. LRMS (Cl+) [M+H]$^+$ 295.3.

(E)-tert-Butyldimethyl((6-phenyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)dec-4-en-1-yl)oxy)silane, 29

Isolated in 91 % yield as a light yellow oil. $R_f = 0.66$ (9:1 Hexanes:EtOAc). $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 0.05 (s, 6H), 0.83 (t, $J = 7.4$ Hz, 3H), 0.90 (s, 9H), 1.06 – 1.12 (m, 2H), 1.21 (d, $J = 5.0$ Hz, 12H), 1.23 – 1.27 (m, 2H), 1.62 (p, $J = 7.1$ Hz, 2H), 1.81 – 1.84 (m, 2H), 2.12 – 2.17 (m, 2H), 3.62 – 3.64 (t, $J = 6.7$ Hz, 2H), 5.50 (dt, $J = 6.8$, 15.8 Hz, 1H), 5.67 (dt, $J = 1.4$, 16.0 Hz, 1H), 7.12 – 7.14 (m, 1H), 7.23 – 7.27 (m, 4H). $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 146.1, 134.9, 129.9, 128.5, 128.0, 125.3, 83.4, 62.9, 36.9, 33.1, 31.1, 29.6, 28.3, 26.1, 24.6, 24.6, 23.5, 18.5, 14.2, -5.1 (the sp$^3$ carbon attached to boron is not observed). IR (neat, cm$^{-1}$): 2976, 2949, 2929, 2851, 2369, 2236, 1491, 1462, 1442, 1366, 1339, 1307, 1249, 1209, 1139, 1094. LRMS (Cl+) [M+H]$^+$ 473.3.

(E)-tert-Butyl((6-(2-methoxyphenyl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)dec-4-en-1-yl)oxy)dimethylsilane, 30

Isolated as a light yellow oil in 91 % yield. $R_f = 0.46$ (9:1 Hexanes:EtOAc). $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 0.06 (s, 6H), 0.77 (t, $J = 7.1$ Hz, 3H), 0.90 (s, 9H), 1.11 – 1.17 (m, 3H),
1.19 (s, 6H), 1.22 (s, 6H), 1.59 – 1.65 (m, 3H), 1.80 – 1.85 (m, 1H), 1.89 – 1.94 (m, 1H), 2.14 – 2.16 (m, 2H), 3.64 (t, J = 6.7 Hz, 2H), 3.78 (s, 3H), 5.45 (dt, J = 6.8, 15.8 Hz, 1H), 5.67 (d, J = 15.9 Hz, 1H), 6.80 (dd, J = 0.9, 8.1 Hz, 1H), 6.89 (dt, J = 1.0, 3.7 Hz, 1H), 7.12 – 7.15 (m, 2H).

13C NMR (150 MHz, CDCl3): δ 156.6, 134.7, 133.2, 129.5, 129.4, 126.6, 120.6, 110.0, 82.8, 63.0, 55.0, 33.2, 32.2, 31.1, 29.7, 26.8, 26.1, 24.8, 23.5, 18.5, 14.3, -5.1 (the sp3 carbon attached to boron is not observed). IR (neat, cm⁻¹): 2953, 2925, 2855, 2353, 1711, 1597, 1572, 1486, 1458, 1429, 1364, 1315, 1254, 1249, 1213, 1139, 1098, 1029. LRMS (Cl+) [M+H]+ 503.4.

(E)-2-(1,2-Diphenylnon-3-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, 32

Isolated in 73 % yield as a yellow oil. Rf = 0.51 (9:1 Hexanes:EtOAc). 1H NMR (600 MHz, CDCl3): δ 0.89 (t, J = 6.7 Hz, 3H), 1.21 (s, 12H), 1.26 – 1.32 (m, 5H), 1.34 – 1.38 (m, 2H), 2.07 – 2.10 (m, 2H), 2.17 (s, 1H), 2.99 (d, J = 12.9 Hz, 1H), 3.31 (d, J = 12.9 Hz, 1H), 5.59 (dt, J = 6.8, 15.5 Hz, 1H), 5.70 (d, J = 15.8Hz, 1H), 6.86 – 6.87 (m, 2H), 7.05 – 7.12 (m, 6H), 7.16 – 7.19 (m, 2H). 13C NMR (150 MHz, CDCl3): δ 145.2, 140.0, 134.2, 131.7, 130.8, 129.2, 127.8, 127.3, 125.6, 125.6, 83.7, 44.0, 33.3, 31.6, 29.4, 24.7, 24.7, 22.7, 14.2 (the sp3 carbon attached to boron is not observed). IR (neat, cm⁻¹): 3092, 3065, 3030, 2976, 2956, 2926, 2855, 1607, 1495, 1455, 1378, 1371, 1350, 1317, 1277, 1214, 1143, 1085, 1036. LRMS (Cl+) [M+H]+ 405.3

4,4,5,5-Tetramethyl-2-(3-phenylhept-1-en-3-yl)-1,3,2-dioxaborolane, 34

Isolated in 69 % yield as a colorless oil. Rf = 0.52 (9:1 Hexanes:EtOAc). 1H NMR (600 MHz, CDCl3): δ 0.84 (t, J = 7.3 Hz, 3H), 1.11 – 1.16 (m, 2H), 1.22 (d, J = 4.5 Hz, 12H), 1.25 – 1.29 (m,3H), 1.85 – 1.88 (m, 2H), 5.07 (dd, J = 1.5, 17.6 Hz, 1H), 5.18 (dd, J = 1.5, 10.7 Hz, 1H), 6.08 – 6.13 (m, 2H), 7.13 – 7.16 (m, 1H), 7.24 – 7.28 (m, 4H). 13C NMR (150 MHz, CDCl3): δ 145.1, 143.1, 128.5, 128.1, 125.5, 114.1, 83.6, 36.0, 28.1, 24.7, 24.6, 23.6, 14.2 (the
sp³ carbon attached to boron is not observed. IR (neat, cm⁻¹): 3088, 3056, 2977, 2957, 2932, 2874, 1638, 1598, 1495, 1464, 1451, 1378, 1371, 1358, 1317, 1272, 1223, 1143, 1112, 1009. LRMS (CI+) [M+H]+ 301.3.

**D.1.6 Rationale for E-Selectivity of Allylboronates**

![Mechanistic rationale](image)

**Figure D.1** Mechanistic rationale for the observed E-selectivity of the AMAS reaction

We hypothesize that the observed E-selectivity of our allylic substitution reaction is the result of the necessary anti-periplanar arrangement of the acetate leaving group relative to the carbon nucleophile being transferred from the ate complex. Upon formation of the ate-complex, the C-B bond will rotate into such a position that the “R²-group” approaches.
Figure D.2 $^1$H NMR and $^{13}$C NMR of compound 33
Figure D.3 $^1$H NMR and $^{13}$C NMR of compound 26
Figure D.4 $^1$H NMR and $^{13}$C NMR of compound 31
Figure D.5 $^1$H NMR and $^{13}$C NMR of compound 28
Figure D.6 $^1$H NMR and $^{13}$C NMR of compound 27a
Figure D.7 $^1$H NMR and $^{13}$C NMR of compound 27b
Figure D.8 $^1$H NMR and $^{13}$C NMR of compound 27c
Figure D.9 $^1$H NMR and $^{13}$C NMR of compound 27d
Figure D.10 $^1$H NMR and $^{13}$C NMR of compound 27e
Figure D.11 $^1$H NMR and $^{13}$C NMR of compound 27f
Figure D.12 $^1$H NMR and $^{13}$C NMR of compound 27g
Figure D.13 $^1$H NMR and $^{13}$C NMR of compound 27h
Figure D.14 $^1$H NMR and $^{13}$C NMR of compounds 27i and 27j
Figure D.15 $^1$H NMR and $^{13}$C NMR of compound 27k
Figure D.16 $^1$H NMR and $^{13}$C NMR of compound 29
Figure D.17 $^1$H NMR and $^{13}$C NMR of compound 30
Figure D.18 $^1$H NMR and $^{13}$C NMR of compound 32
Figure D.19 $^1$H NMR and $^{13}$C NMR of compound 34
APPENDIX E

SUPPORTING INFORMATION FOR CHAPTER 6

E.1 Characterization Data

E.1.1 General Procedures and Instrumentation

All reactions were conducted in oven- or flame-dried glassware under a nitrogen atmosphere. Dichloromethane (DCM), diethyl ether, and tetrahydrofuran (THF) were collected from a dry solvent system under argon and used as collected. All commercially available reagents were purchased from Aldrich and used as received, except where otherwise stated. Bis(pinocolato)diboron was purchased from Combiphos Catalysis, Inc. and used as received. All aldehydes were purified before use by washing with dilute sodium bicarbonate and fractional distillation. All organolithium reagents were titrated prior to use using 1-pyreneacetic acid or diphenylacetic acid. Grignard reagents were titrated prior to use using menthol and 1,10-phenanthroline. Proton ($^1$H) and carbon ($^{13}$C) NMR spectra were recorded on a Bruker Avance spectrometer. Chemical shifts were reported in ppm as downfield from tetramethylsilane peak at 0 ppm, or with respect to the residual solvent peak. Peaks are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sx = sextet, hp = heptet, br = broad, m = multiplet), coupling constants (reported in Hz), and integration. Carbon ($^{13}$C) NMR spectra were recorded on the same instrument using the residual solvent signal as an internal standard (typically CDCl$_3$ = 77.16 ppm, unless otherwise noted). Infrared (IR) spectra were recorded on a Thermo Scientific Nicolet 380 FT–IR spectrometer. High-resolution mass spectrometry was performed by Dr. Umesh Goli at FSU. Thin-layer chromatography was performed using glass silica gel 60 F$_{254}$ plates.
E.1.2 Synthesis of Methyl Axenoside

6-((tert-Butyldimethylsilyloxy)hex-3-yn-2-ol, 44

A flame-dried and nitrogen-purged 250 mL Schlenk flask with stir-bar and rubber septum was charged with a solution of 4-(t-butyldimethylsilyloxy)-1-butyne (5 mL, 4.47 g, 24.22 mmol, 1 equiv.) in anhydrous THF (25 mL, 0.2 M). This solution was cooled to -78 °C in a dry ice/acetone bath. n-Butyllithium (12.59 mL, 2.5 M in hexanes, 31.5 mmol, 1.3 equiv.) was added to this solution dropwise via syringe pump over the course of 1 hour, and the reaction was stirred for 45 minutes at -78 °C after addition had completed. At this point, acetaldehyde (2.74 mL, 48.4 mmol, 2 equiv.) in THF (5 mL) was charged to the reaction via syringe pump over the course of 20 minutes. The solution was then stirred while warming to room temperature and the reaction was monitored by TLC. After 2 hours, the reaction was quenched by the careful addition of water. The layers were separated, and the aqueous later was extracted with diethyl ether (x3). The combined organic layers were washed with a saturated solution of ammonium chloride, dried over MgSO₄, and concentrated. The crude product was purified by Kugelrohr distillation (85 °C at 200 mTorr), yielding 5.06 grams (92 % yield) of the desired material as a light yellow oil. Rf = 0.13 (9:1 Hexanes:EtOAc, KMnO₄ stain). ¹H NMR (600 MHz, CDCl₃) = δ 0.08 (s, 6H), 0.90 (s, 9H), 1.43 (d, J = 6.5 Hz, 3H), 2.42 (dt, J = 1.9, 3.6 Hz, 2H), 3.71 (t, J = 7.1 Hz, 2H), 4.51 (m, 1H). ¹³C NMR (150 MHz, CDCl₃) = δ 83.5, 81.7, 62.0, 58.7, 26.0, 24.8, 23.2, 18.5, -5.1. IR (neat, cm⁻¹) = 3356, 2958, 2930, 2864, 2857, 2242, 1472, 1388, 1361, 1333, 1254, 1154, 1105, 1005. LRMS (CI-) [M]⁻ 227.2

(Z)-6-((tert-Butyldimethylsilyloxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-3-en-2-yl acetate, 45
A flame-dried, nitrogen-purged 250 mL Schlenk flask equipped with a stir-bar and rubber septum was charged with 44 (5 g, 21.89 mmol, 1 equiv.) in anhydrous diethyl ether (54 mL, 0.4 M). The reaction vessel was then charged with Bis(pinacolato)diboron (6.67 g, 26.3 mmol, 1.2 equiv.) and sodium t-butoxide (631 mg, 6.57 mmol, 30 mol %) sequentially, by removing the rubber septum and adding the reagents under light nitrogen flow. At this point the reaction was cooled to 0 °C in an ice water bath, and the sides of the reaction vessel were washed with a few mL of dry ether. Once cooled, the reaction was charged with anhydrous methanol (1.77 mL, 43.8 mmol, 2 equiv.), causing the suspension to become clear. 5-NHC-CuCl catalyst (89 mg, 0.219 mmol, 1 mol %) was then added to the reaction by removing the rubber septum and adding under light nitrogen flow (CAUTION: The reaction may rapidly exotherm if not carefully monitored at this point. The flask was kept open (with light nitrogen flow) and in the ice bath for a few minutes until it had begun to turn brown and the reaction was clearly under control, at which point the septum was replaced and the vessel warmed to room temperature and stirred for 30 minutes). After 30 minutes, a pre-mixed, 1.3 M solution (5 mL EtOAc per 1 gram N(EtOH)₃) of triethanolamine (33.7 mL, 43.8 mmol, 2 equiv.) was then added to the vessel at room temperature, which immediately caused a gray precipitate. This was stirred for a further 30 minutes before being filtered through a frit. The ethereal filtrate was washed repeatedly with small aliquots of water, then once with brine, dried over MgSO₄ and concentrated. The crude product was redissolved in dichloromethane (54 mL) in a 250 mL round-bottom flask with stir-bar and rubber septum. This flask was charged with acetic anhydride (4.13 mL, 43.8 mmol, 2 equiv.) and DMAP (267 mg, 2.189 mmol, 10 mol %) and stirred at room temperature for about 2 hours, until the reaction was complete by TLC. The reaction was then filtered through a pad of silica, and concentrated. The pure product was obtained by flash chromatography (20:1
Hexanes:EtOAc), yielding 7.43 g (85 % yield) of the desired product as a light yellow oil. $R_f = 0.41$ (9:1 Hexanes:EtOAc, KMnO$_4$ stain). $^1$H NMR (600 MHz, CDCl$_3$) = $\delta$ 0.05 (s, 6H), 0.88 (s, 9H), 1.25 (s, 12H), 1.30 (d, $J = 6.4$ Hz, 3H), 2.01 (s, 3H), 2.38 (m, 1H), 2.50 (m, 1H), 3.57 (m, 1H), 3.67 (m, 1H), 5.71 (m, 1H), 6.25 (d, $J = 4.7$ Hz, 1H). $^{13}$C NMR (150 MHz, CDCl$_3$) = 170.4, 145.3, 83.6, 67.9, 62.9, 33.1, 26.2, 25.0, 24.9, 21.5, 20.8, 18.6, -5.1, -5.1 (The sp$^2$ carbon attached to boron is not observed). IR (neat, cm$^{-1}$) = 2978, 2954, 2884, 2858, 1741, 1638, 1472, 1409, 1371, 1311, 1239, 1142, 1095, 1045. HRMS (Cl+): Calcd for C$_{20}$H$_{40}$O$_5$BSi = 399.27381, found 399.27322.

$(E)$-tert-Butyldimethyl((3-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-4-en-1-yl)oxy)silane, 46

A flame-dried, nitrogen purged 250 mL round-bottom flask was charged with 45 (5 g, 12.55 mmol, 1 equiv.) in anhydrous diethyl ether (62 mL, 0.2 M) and cooled to 0 °C in an ice water bath and stirred vigorously. Methylmagnesium bromide (15.56 mL, 18.82 mmol, 1.5 equiv., 1.21 M in THF:toluene (1:3)) was added to the solution which immediately produced a precipitate, and the reaction was stirred while warming to room temperature. (NOTE: For best results the Grignard reagent should be added fairly quickly via syringe below the level of the solvent to avoid lumping together of the precipitate, and the reaction should only be allowed to stir for a few minutes before filtration.) After only 2 – 3 minutes, the reaction mixture was filtered through a pad of silica. The ethereal filtrate was concentrated and carried on without further purification. For characterization, an aliquot of the crude product was purified by flash chromatography (100 % Hexanes to 20:1 Hexanes:EtOAc) to yield 3.02 grams (67 % yield) of the desired product as a light yellow oil. $R_f = 0.66$ (9:1 Hexanes:EtOAc, KMnO$_4$ stain). $^1$H NMR (600 MHz, CDCl$_3$) = $\delta$ 0.05 (s, 6H), 0.89 (s, 9H), 1.03 (s, 3H), 1.21 (d, $J = 1.1$ Hz, 12H), 1.58 –
1.62 (m, 1H), 1.65 (dd, J = 1.5, 6.4 Hz, 3H), 1.71 – 1.76 (m, 1H), 3.59 – 3.66 (m, 2H), 5.35 (dq, J = 6.3, 15.5 Hz, 1H), 5.45 (dq, J = 1.5, 15.8 Hz, 1H). $^{13}$C NMR (150 MHz, CDCl₃) = δ 137.9, 121.9, 83.2, 61.4, 41.7, 26.2, 24.8, 21.4, 18.5, -5.0 (The sp³ carbon attached to boron, as well as the quaternary carbon in TBS were not observed). IR (neat, cm⁻¹) = 2974, 2956, 2930, 2880, 1461, 1378, 1371, 1312, 1254, 11139, 1090, 1037, 1005. LRMS (CI-) [M] - 353.3.

$(E)$-1-((tert-Butyldimethylsilyl)oxy)-3-methylhex-4-en-3-ol, 47

A 250 mL round-bottom flask equipped with stir-bar and rubber septum was charged with 46 (2.9 g, 8.18 mmol, 1 equiv.) in ethyl acetate (16 mL, 0.5 M) and cooled to 0 °C in an ice water bath. Hydrogen peroxide (5.01 mL of 30 % solution in water, 49.1 mmol, 6 equiv.) was added and the reaction was stirred for 20 minutes at 0 °C, before charging with sodium hydroxide (24.55 mL of a 2 M solution in water, 49.1 mmol, 6 equiv.) and warming to room temperature, with stirring for 3 hours or until the reaction was complete by TLC. The layers were separated, and the aqueous layer was extracted with ethyl acetate (x3). The combined aqueous layers were washed with three aliquots of water, then dried over MgSO₄ and concentrated. When purification was necessary it was accomplished by flash column chromatography (20:1 Hexanes:EtOAc) to yield 1.98 g (99 % yield) of the desired material as a near-colorless oil. $R_f$ = 0.36 (9:1 Hexanes:EtOAc, KMnO₄ stain). $^1$H NMR (600 MHz, CDCl₃) = δ 0.07 (d, J = 1.5 Hz, 6H), 0.90 (s, 9H), 1.25 (s, 3H), 1.59 – 1.63 (m, 1H), 1.71 (dd, J = 1.6, 6.5 Hz, 3H), 1.82 – 1.86 (m, 1H), 3.78 – 3.87 (m, 2H), 4.11 (s, 1H), 5.48 (dq, J = 1.6, 15.4 Hz, 1H), 5.73 (dq, J = 6.5, 15.3 Hz, 1H). $^{13}$C NMR (150 MHz, CDCl₃) = δ 137.5, 123.0, 73.3, 61.3, 42.3, 29.0, 25.9, 18.2, 17.8, -5.5, -5.5 (The quaternary carbon of the silyl ether is not observed. IR (neat, cm⁻¹) = 3509, 2956, 2929, 2884, 2857, 1724, 1662, 1471, 1369, 1360, 1255, 1164, 1065, 1027, 1005. HRMS (ESI+): Calcd for C₁₃H₂₈NaO₂Si = 267.17563, found 267.17527.

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A 100 mL round-bottom flask with stir-bar was charged with potassium hexacyanoferrate(III) (4.04 g, 12.27 mmol, 3 equiv.), potassium osmate dehydrate (7.54 mg, 0.020 mmol, 0.5 mol %), (DHQ)$_2$PHAL (159 mg, 0.205 mmol, 5 mol %), methanesulfonamide (778 mg, 8.18 mmol, 2 equiv.) and potassium carbonate (1.69 g, 12.27 mmol, 3 equiv.). These reagents were dissolved in water and $t$-butanol (20 mL of each, 0.2 M in each), and stirred at room temperature for about 10 minutes until the solution became clear. The allylic alcohol 47 (1 g, 4.09 mmol, 1 equiv.) in a small amount of $t$-butanol was added in one portion and the reaction was stirred for about 20 hours at room temperature until the reaction was complete by TLC. The reaction was quenched by the addition of 4.5 mL saturated sodium sulfite and stirred for 1 hour at room temperature. The crude reaction mixture was concentrated under reduced pressure to remove excess $t$-BuOH, then transferred to a separatory funnel and extracted several times with ethyl acetate. The combined organic layers were dried over magnesium sulfate and concentrated. The crude product was purified by flash column chromatography (100 % hexanes to 1:1 Hexanes:EtOAc) to yield 884 mg (78 % yield, 74 % ee) of the desired product as a lightly colored mixture of diastereomers, which were inseparable in their current form. $R_f = 0.37$ (1:1 Hexanes:EtOAc, ceric ammonium molybdate stain). $^1$H NMR (600 MHz, $d_6$-DMSO) = $\delta$ 0.02 (d, $J = 2.3$ Hz, 6H), 0.85 (s, 9H), 1.04 (s, 1.5H), 1.08 (d, $J = 6.4$ Hz, 3H), 1.11 (s, 1.5 H), 1.65 – 1.74 (m, 2H), 2.88 – 2.91 (m, 1H), 3.65 – 3.74 (m, 2H), 3.89 – 3.95 (m, 1H), 4.19 (dd, $J = 7.5$, 11.6 Hz, 1H), 4.27 – 4.29 (m, 1H), 4.34 – 4.35 (m, 1H). $^{13}$C NMR (150 MHz, $d_6$-DMSO) = $\delta$ 77.7, 77.7, 73.6, 73.4, 65.3, 65.0, 59.3, 42.3, 40.7, 25.8, 25.8, 24.6, 22.8, 21.9, 21.5, 17.9, 17.9, -5.3. (mixture of diastereomers present). IR (neat, cm$^{-1}$) = 3399, 2953, 2930, 2864, 2858, 1471, 1366,
(R)-4-((tert-butyldimethylsilyl)oxy)-2-((4R,5S)-2,2,5-trimethyl-1,3-dioxolan-4-yl)butan-2-ol, 51

A 100 mL round-bottom flask equipped with stir-bar and rubber septum under nitrogen was charged with 48 and 49 (1.3 g, 4.67 mmol, 1 equiv.) in DCM (39 mL, 0.12 M). The vessel was then charged with 2,2-dimethoxypropane (976 µL, 7.94 mmol, 1.7 equiv.) and pyridinium p-toluenesulfonate (PPTS, 352 mg, 1.40 mmol, 30 mol %), and stirred at room temperature for 4 hours until the reaction was complete by TLC. The reaction was quenched by the addition of a saturated sodium bicarbonate solution and the layers were separated. The aqueous layer was extracted with EtOAc (x3). The combined organic layers were washed with brine, dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (8:2 Hexanes:EtOAc) to yield 1.125 g (76 % combined yield) of the desired product as a light yellow oil. At this point it became possible to separate the diastereomers from each other, and this was accomplished very carefully by flash column chromatography (40:1 Hexanes:EtOAc). Characterization for the desired diastereomer (bottom spot, leads toward methyl axenoside): A light yellow oil isolated in 38% yield. Rᵣ = 0.63 (7:3 Hexanes:EtOAc, anisaldehyde dip). ¹H NMR (600 MHz, d₆-DMSO) = δ 0.03 (s, 6H), 0.85 (s, 9H), 1.06 (s, 3H), 1.22 (d, J = 6.0 Hz, 3H), 1.28 (d, J = 1.7 Hz, 6H), 1.65 (m, 2H), 3.71 (m, 2H), 4.00 (m, 1H), 4.34 (s, 1H). ¹³C NMR (150 MHz, d₆-DMSO) = δ 107.0, 88.0, 72.1, 69.9, 59.1, 40.6, 27.5, 26.9, 25.9, 24.2, 20.6, 17.9, -5.3 (Methyl peaks of the acetonide moiety are not equivalent). IR (neat, cm⁻¹): 3493, 2976, 2956, 2933, 2880, 2859, 1470, 1380, 1249, 1213, 1172, 1082, 1057, 1004. LRMS (ESI) [M+Na]⁺ 341.1.

HRMS (ESI+): Calcd for C₁₃H₃₀NaO₄Si = 301.18110, found 301.18085.
An oven-dried 7 mL screw-top vial with stir bar was charged with 51 (50 mg, 0.157 mmol, 1 equiv.) in THF (0.2 M). The reaction vessel was then charged with TBAF (314 µL of a 1M soln. in THF, 0.314 mmol, 2 equiv.) and the reaction was stirred at room temperature for 3 hours, until the completion of the reaction was verified by TLC. The reaction was quenched with saturated ammonium chloride solution, and the layers separated. The aqueous layer was extracted with EtOAc three times. The combined organic layers were then dried with magnesium sulfate and concentrated under reduced pressure. The crude reaction product was purified by flash chromatography (7:3 Hexanes:EtOAc to 1:1 Hexanes:EtOAc) to yield 26 mg of the desired product as a dark yellow oil (81 % yield). $R_f = 0.12$ (7:3 Hexanes:EtOAc, Ceric Ammonium Molybdate dip). $^1$H NMR (600 MHz, $d_6$-DMSO) = δ 1.07 (s, γH), 1.2γ (d, $J = 6.1$ Hz, γH), 1.27 (s, 3H), 1.29 (s, 3H), 1.59 (m, 2H), 3.38 (d, $J = 7.9$ Hz, 1H), 3.57 (m, 2H), 4.00 (m, 1H), 4.40 (t, $J = 5.1$ Hz, 1H), 4.44 (s, 1H). $^{13}$C NMR (150 MHz, $d_6$-DMSO) = δ 107.0, 87.0, 72.4, 70.7, 56.8, 42.4, 27.4, 27.0, 22.1, 20.4. IR (neat, cm$^{-1}$): 3407, 2978, 2933, 2880, 1732, 1650, 1454, 1372, 1245, 1221, 1168, 1078, 1045, 1017. LRMS (ESI) [M+Na]$^+$ 227.1.

(R)-3-Hydroxy-3-((4R,5S)-2,2,5-trimethyl-1,3-dioxolan-4-yl)butanal, 53

A 100 mL round-bottom flask with stir bar and rubber septum was charged with 52 (420 mg, 2.06 mmol, 1 equiv.) in DCM (0.08M) and pyridine (1.66 mL, 20.56 mmol, 10 equiv.) and stirred at room temperature. This solution was then charged with Dess-Martin Periodinane (959 mg, 2.26 mmol, 1.1 equiv.) in one portion by dumping the solid into the flask and quickly replacing the rubber septum. The reaction was allowed to stir for 20 minutes before it was quickly filtered through a pad of Celite, eluting with additional DCM and then concentrated. This
crude product was quickly purified by column chromatography (7:3 Hexanes:EtOAc to 1:1 Hex:EtOAc) to yield 362 mg of the desired product as a yellow oil (87 % yield), with minor impurities of pyridine and the corresponding α,β-unsaturated carbonyl compound, which was used immediately in the following reaction due to its instability if left to sit overnight. \( R_f = 0.55 \) (1:1 Hexanes:EtOAc, Ceric Ammonium Molybdate dip). \(^1\)H NMR (400 MHz, \( d_6\)-DMSO) = δ 1.28 (s, 3H), 1.36 (d, \( J = 6.1 \text{ Hz} \), 3H), 1.41 (s, 6H), 2.54 (dd, \( J = 2.7, 15.5 \text{ Hz} \), 1H), 2.75 (dd, \( J = 2.7, 15.5 \text{ Hz} \), 1H), 3.53 (d, \( J = 7.9 \text{ Hz} \), 1H), 4.16 (m, 1H), 9.88 (t, \( J = 2.4 \text{ Hz} \), 1H). \(^{13}\)C NMR (100 MHz, \( d_6\)-DMSO) = δ 203.0, 107.5, 87.7, 72.2, 70.2, 51.5, 27.5, 26.7, 25.5, 20.4. IR (neat, cm\(^{-1}\)) = 3448, 2978, 2929, 2868, 1715, 1454, 1380, 1249, 1209, 1168, 1078, 1049. LRMS (ESI+) [M+Na]\(^+\) 225.0.

**Methyl 2,6-dideoxy-3-C-methyl-L-xylo-hexopyranoside (Methyl axenoside), 54**

An oven-dried 7 mL screw-top vial was equipped with a stir bar and charged with a solution of 53 (30 mg, 0.148 mmol, 1 equiv.) in 2,2,2-trifluoroethanol (0.064 M) and cooled to -40 °C with stirring. To this solution was added trifluoromethanesulfonic acid (13 µL of a 5 % solution of triflic acid in 2,2,2-trifluoroethanol, 7.42 µmol, 5 mol %) and the reaction was stirred for 45 minutes at – 40 °C. Reaction progress was monitored by TLC, and more acid was added if necessary before the reaction was quenched with triethylamine (21 µL, 0.148 mmol, 1 equiv.) which was injected through the vial cap at – 40 °C. The reaction vessel was brought to room temperature before the crude reaction mixture was concentrated under reduced pressure. The crude reaction material was immediately redissolved in anhydrous methanol (0.2 M) and stirred at room temperature before adding acetyl chloride (105 µL, 1.483 mmol, 10 equiv.) and stirring at room temperature for 25 minutes. After 25 minutes had passed, the reaction was quenched by the addition of silver carbonate (491 mg, 1.780 mmol, 12 equiv.) and stirred for 15 minutes,
causing the reaction to turn slightly yellow with brown suspension. This crude reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure. Proton NMR (600 MHz) revealed this crude product to be a 1 : 1.8 mixture of alpha : beta anomers of methyl axenoside. The anomers were separated by flash chromatography (8:2 to 6:4 Hexanes:EtOAc), and the white solid product was washed with a minimum of petroleum ether to remove any remaining impurities, resulting in a combined yield of 90 %. \textbf{\( \alpha \)-anomer:} \( R_f = 0.34 \) (1:1 Hexanes:EtOAc, Ceric Ammonium Molybdate dip). \( ^1 \)H NMR (400 MHz, CDCl\(_3\)) = \( \delta \) 1.25 (s, 3H), 1.26 (d, \( J = 6.6 \) Hz, 3H), 1.66 – 1.74 (m, 2H), 1.92 (dd, \( J = 3.9, 14.6 \) Hz, 1H), 3.15 (d, \( J = 8.0 \) Hz, 1H), 3.39 (s, 3H), 4.03 (s, 1H), 4.31 (q, \( J = 6.6 \) Hz, 1H), 4.80 (d, \( J = 3.7 \) Hz, 1H). \( ^{13} \)C NMR (100 MHz, CDCl\(_3\)) = \( \delta \) 99.2, 74.7, 70.3, 62.7, 55.3, 35.6, 26.2, 16.8. \textbf{\( \beta \)-anomer:} \( R_f = 0.25 \) (1:1 Hexanes:EtOAc, Ceric Ammonium Molybdate dip). \( ^1 \)H NMR (400 MHz, CDCl\(_3\)) = \( \delta \) 1.28 (d, \( J = 6.7 \) Hz, 3H), 1.35 (s, 3H), 1.47 (s, 1H), 1.58 – 1.69 (m, 2H), 2.10 (d, \( J = 10.0 \) Hz, 1H), 2.98 (d, \( J = 10.0 \) Hz, 1H), 3.50 (s, 3H), 4.13 (q, \( J = 6.6 \) Hz, 1H), 4.62 (dd, \( J = 2.5, 9.7 \) Hz, 1H). \( ^{13} \)C NMR (100 MHz, CDCl\(_3\)) = \( \delta \) 100.5, 74.5, 72.7, 69.1, 56.6, 39.2, 28.0, 16.7. IR (neat, cm\(^{-1}\)): 3458, 2970, 2934, 2827, 1447, 1406, 1377, 1343, 1193, 1158, 1119. LRMS (ESI) [M+Na]+ 199.0.

\textbf{E.1.3 Synthesis of Methyl 3-epi-Axenoside}

\( \text{(S)-4-((tert-butyldimethylsilyl)oxy)-2-((4R,5S)-2,2,5-trimethyl-1,3-dioxolan-4-yl)butan-2-ol, 55} \)

Prepared as a diastereomeric mixture from 48 and 49, according to the procedure described above. Separation was achieved using flash column chromatography (40:1 Hexanes:EtOAc to 20:1 Hexanes:EtOAc). Isolated as a light yellow oil in 34 % yield.
Characterization for the desired diastereomer (top spot, leads toward methyl 3-epi-axenoside): R_f = 0.67 (7:3 Hexanes:EtOAc, Anisaldehyde dip). ^1_H NMR (600 MHz, d_6-DMSO) = δ 0.03 (s, 6H), 0.85 (s, 9H), 1.07 (s, 3H), 1.22 (d, J = 5.9 Hz, 3H), 1.26 (s, 3H), 1.28 (s, 3H), 1.61 (m, 2H), 3.75 (dt, J = 1.9, 7.3 Hz, 2H), 3.99 (m, 1H), 4.43 (s, 1H). ^13_C NMR (150 MHz, d_6-DMSO) = δ 107.0, 86.9, 72.5, 70.5, 58.8, 42.6, 27.5, 27.0, 25.8, 22.1, 20.5, 17.9, -5.3 (Methyl peaks of the acetonide moiety are not equivalent). IR (neat, cm⁻¹): 3496, 2966, 2956, 2932, 2864, 2858, 1463, 1377, 1253, 1213, 1174, 1082, 1053, 1025, 1006. LRMS (ESI) [M+Na]^+ 341.1.

(S)-3-((4R,5S)-2,2,5-trimethyl-1,3-dioxolan-4-yl)butane-1,3-diol, 56

Compound 55 was subjected to the same TBAF-deprotection procedure as was used as above. Flash chromatography resulted in the desired product as a dark yellow oil in 78 % yield. R_f = 0.10 (7:3 Hexanes:EtOAc, ceric ammonium molybdate dip). ^1_H NMR (600 MHz, d_6-DMSO) = δ 1.07 (s, 3H), 1.23 (d, J = 6.0 Hz, 3H), 1.26 (s, 3H), 1.29 (s, 3H), 1.59 (m, 2H), 3.39 (s, 1H), 3.56 (m, 2H), 4.00 (m, 1H), 4.41 (t, J = 5.0 Hz, 1H), 4.45 (s, 1H). ^13_C NMR (150 MHz, d_6-DMSO) = δ 107.0, 87.0, 72.5, 70.8, 56.8, 42.3, 27.5, 27.0, 22.1, 20.5. IR (neat, cm⁻¹): 3395, 2982, 2933, 2888, 1658, 1450, 1376, 1241, 1221, 11742, 1127, 1070, 1012. LRMS (ESI) [M+Na]^+ 227.1.

(S)-3-hydroxy-3-((4R,5S)-2,2,5-trimethyl-1,3-dioxolan-4-yl)butanal, 57

The same procedure for the Dess-Martin Periodinane oxidation of primary alcohol 56 was followed as above. The product contained a small amount of pyridine after purification, but was used in the following reaction without further purification. R_f = 0.51 (1:1 Hexanes:EtOAc, Ceric Ammonium Molybdate dip). ^1_H NMR (400 MHz, d_6-DMSO) = δ 1.28 (s, 3H), 1.36 (d, J = 6.1 Hz, 3H), 1.41 (s, 6H), 2.54 (dd, J = 2.7, 15.5 Hz, 1H), 2.75 (dd, J = 2.7, 15.5 Hz, 1H), 3.53
(d, J = 7.9 Hz, 1H), 4.16 (m, 1H), 9.88 (t, J = 2.4 Hz, 1H). $^{13}$C NMR (100 MHz, $d_6$-DMSO) = δ 203.1, 107.5, 87.3, 72.6, 70.8, 52.8, 27.4, 26.8, 22.9, 20.3. IR (neat, cm$^{-1}$) = 3456, 2982, 2937, 2876, 1715, 1454, 1376, 1241, 1217, 1168, 1074, 1049. LRMS (ESI+) [M+Na]$^+$ 225.0.

(2S,3R,4S)-6-methoxy-2,4-dimethyltetrahydro-2H-pyran-3,4-diol (Methyl 3-epi-Axenoside), 58

The same procedure for the acid-catalyzed deprotection/cyclization and subsequent methylation of compound 57 was used as above. The product was isolated (and anomers separated) by flash column chromatography (8:2 to 6:4 Hexanes:EtOAc) in 90 % yield. This product was not crystalline like its epimer 54, instead isolated as a light yellow oil. Clear characterization for this compound was unable to be obtained due to the inseparability of the alpha and beta anomers, thus the product was carried on for the sake of characterization.

Methyl 3-epi-Trioxacarcinoside A, 59

Methyl axenoside (95 mg, 0.54 mmol, 1 equiv.) was dissolved in dichloromethane (0.2 M) in a 7 mL screw-top vial with stir bar, and the reaction was charged with acetic anhydride (102 µL, 1.08 mmol, 2 equiv.) and DMAP (7 mg, 0.054 mmol, 10 mol %) and stirred for 20 hours. After checking the reaction progress with TLC, the reaction was charged with an additional equivalent of acetic anhydride and stirred for a further 90 minutes, at which point TLC showed the reaction to be complete. The crude reaction mixture was concentrated under reduced pressure and purified by flash column chromatography (8:2 to 6:4 Hexanes:EtOAc) to yield separately the alpha and beta anomers of methyl 3-epi-trioxacarcinoside A quantitatively. $\alpha$-anomer: $R_f = 0.54$ (1:1 Hexanes:EtOAc, ceric ammonium molybdate dip). $^1$H NMR (600 MHz, CDCl$_3$): δ = 1.14 (d, J = 6.5 Hz, 3H), 1.46 (s, 3H), 1.73 (d, J = 13.6 Hz, 1H), 1.92 (dd, J = 4.3,
13.6 Hz, 1H), 2.15 (s, 3H), 3.30 (s, 3H), 3.49 (s, 1H), 4.00 (q, 6.4 Hz, 1H), 4.79 (d, J = 3.8 Hz, 1H). $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta = 171.8, 98.7, 76.5, 68.7, 64.0, 55.1, 38.0, 27.2, 21.0, 17.3$. IR (neat, cm$^{-1}$): 3464, 2970, 2933, 2864, 1744, 1654, 1548, 1442, 1372, 1321, 1127, 1066, 1045. LRMS (ESI+) [2M+MeOH+H$^+$] 469.2. $\beta$-anomer: $R_f = 0.36$ (1:1 Hexanes:EtOAc, ceric ammonium molybdate dip). $^1$H NMR (600 MHz, CDCl$_3$): $\delta = 1.21$ (d, 6.4 Hz, 3H), 1.37 (s, 3H), 1.76 – 1.81 (m, 2H), 2.17 (s, 3H), 3.31 (s, 1H), 3.50 (s, 3H), 3.74 (dq, J = 1.2, 2.1 Hz, 1H), 4.39 (dd, J = 2.7, 9.4 Hz, 1H). $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta = 171.7, 100.9, 75.7, 70.4, 69.0, 56.7, 40.6, 25.4, 21.1, 17.3$.

### E.1.4 Determination of AD Enantioselectivity

An NMR sample containing 5 mg (0.018 mmol) of AD-products 48 and 49 dissolved in 0.4 mL deuterated acetonitrile and a spectrum was taken (400 MHz). This NMR vial was then charged with 23.6 mg (0.0198 mmol, 1.1 equiv.) europium(III) tris[3-heptafluoropropylhydroxymethylene-$d$-camphorate] (Eu(hfc)$_3$). The vial was shaken vigorously until all shift reagent had dissolved, then the proton NMR spectrum was retaken.

This procedure was repeated for the products resulting from a racemic dihydroxylation reaction (same procedure as for above, omitting chiral ligand) and the opposite-configuration asymmetric dihydroxylation (same procedure as for above, substituting (DHQ)$_2$PHAL for (DHQD)$_2$PHAL). The spectra were compared by overlay and comparison to the product spectrum pre-addition of Eu(hfc)$_3$. Integration of the peaks showed that the reaction with (DHQ)$_2$PHAL occurred in 74 % er, and the reaction with (DHQD)$_2$PHAL occurred in 79 % er.
E.2 Spectral Data

Figure E.1 $^1$H NMR and $^{13}$C NMR of compound 45
Figure E.2 $^1$H NMR and $^{13}$C NMR of compound 46
Figure E.3 $^1$H NMR and $^{13}$C NMR of compound 47
Figure E.4 $^1$H NMR and $^{13}$C NMR of compounds 48 and 49
Figure E.5 $^1$H NMR and $^{13}$C NMR of compound 51
Figure E.6 $^1$H NMR and $^{13}$C NMR of compound 52
Figure E.7 $^1$H NMR and $^{13}$C NMR of compound 53
Figure E.8 $^1$H NMR and $^{13}$C NMR of compound $\beta$-54
Figure E.9 $^1$H NMR and $^{13}$C NMR of compound 59
REFERENCES


BIOGRAPHICAL SKETCH

Brian was born in Pittsburgh, Pennsylvania on June 15th, 1984. His love for chemistry began in high school under the guidance of Steve Witowich, who was always willing to try a dangerous demonstration for the amusement of his students. In the fall of 2003, Brian began attending the College of Wooster, where he was introduced to his future advisor, Dr. Paul Bonvallet. After completing his Senior Independent Study project involving electroluminescent organic polymers, Brian graduated from the College of Wooster in May of 2007 with a degree in Chemistry and a minor in Biology. After working in the Quality Control department of the Valspar Corporation in Rochester, Pennsylvania for the next two years, Brian began pursuing his Ph. D. at Florida State University in August of 2009. Soon thereafter, Brian began working under the guidance of Dr. Tyler McQuade, and has been extremely fortunate to be able to learn from all of the great scientists in the Chemistry department.