Suzuki-Miyaura Reactions Are Used to Synthesize Z-Alkenes from Cyclic Boronic Half-Acids

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Thesis title: 
Suzuki-Miyaura Reactions Are Used to Synthesize Z-Alkenes from Cyclic Boronic Half-Acids

Intended date of commencement: 
May 10, 2014

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For Honors Program use:

Level of Honors conferred: 
University: Summa Cum Laude
Departmental: Highest Honors in Chemistry
Suzuki-Miyaura Reactions Are Used to Synthesize Z-Alkenes from Cyclic Boronic Half-Acids

A Thesis
Presented to the Department of Chemistry
College of Liberal Arts and Sciences
And
The Honors Program
Of
Butler University
In Partial Fulfillment
of Requirements for Graduation Honors.

Daniel Lee French
27 April 2014
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
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<tbody>
<tr>
<td>CBHA</td>
<td>Cyclic Boronic Half-Acid</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>Batho.</td>
<td>Bathophenanthroline</td>
</tr>
<tr>
<td>KOtBu</td>
<td>Potassium Tert-butoxide</td>
</tr>
<tr>
<td>Ni(COD)$_2$</td>
<td>Bis(1,5-cyclooctadiene) nickel(0)</td>
</tr>
<tr>
<td>2-IPr</td>
<td>2-iodopropane</td>
</tr>
<tr>
<td>S-BuOH</td>
<td>s-butanol</td>
</tr>
<tr>
<td>[HP(tBu)$_2$Me]BF$_4$</td>
<td>Di-tert-butyl(methyl)phosphoniumtetrafluoroborate</td>
</tr>
<tr>
<td>Pd(OAc)$_2$</td>
<td>Palladium (II) Acetate</td>
</tr>
<tr>
<td>1-Bu-2MePr</td>
<td>1-butyl-2-methylpropane</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>6-Br-1-hexanol</td>
<td>6-bromo-1-hexanol</td>
</tr>
<tr>
<td>PdCl$_2$(DPPF)</td>
<td>Dicloro 1,1’-bis(diphenylphosphino)ferrocene palladium(II)</td>
</tr>
<tr>
<td>Pd(COD)</td>
<td>Dicloro(1,5-cyclooctadiene) palladium (II)</td>
</tr>
<tr>
<td>HWE</td>
<td>Horner-Wadsworth-Emmons Reaction</td>
</tr>
<tr>
<td>BINAP</td>
<td>racemic-2,2’-Bis(diphenylphosphino)-1,1’-binaphthyl</td>
</tr>
</tbody>
</table>
Abstract

Cis-Alkenes provide the basic structure and reactivity for a variety of compounds, from the common chemicals found in any organic laboratory to advanced drugs used to treat cancer or suppress the immune system (Littke & Fu, 2002). Synthetically, alkenes are also of use in that they serve as a site for further chemistry. Historically, Z-alkenes have been more difficult to synthesize than their E-counterparts (McNulty et al., 2010; Siau, Zhang, & Zhao, 2012). Furthermore, in many reactions, a mixture of E- and Z- conformations of the alkene is produced. Such differences may seem trivial upon first inspection, but because there can be no rotation around the alkene bond, a change in conformation can drastically change the functionality of the molecule. There have been many efforts to force the synthesis of the Z-alkene, revealing that various coupling reactions are adept at forcing a desired conformation (Siau et al., 2012). The Suzuki-Miyaura coupling is one such reaction. The Suzuki-Miyaura coupling is also desirable for the non-toxicity of the reaction conditions and ease of synthesizing the starting materials (Siau et al., 2012). To date, the efficacy of Suzuki-Miyaura couplings with alkyl halides has been demonstrated with reported good yields (Littke, Dai, & Fu, 2000; Siau et al., 2012). The feasibility of forcing the Z-conformation by using a cyclic alkene as the substrate for the reaction was investigated. To test this possibility, a cyclic boronic half-acid (CBHA) was reacted with various alkyl halides under differing conditions. HNMR was used for analysis. The reaction, though offering only the Z-conformation of the desired product, produced a mixture of other products. Finally, the mechanism of the reaction was explored.
Introduction

Many aspects of chemistry, material science, and pharmacology depend on the synthesis of new chemical compounds, or developing synthetic pathways to some natural product. One functional group that dictates much of a compound’s reactivity is the alkene, or carbon-carbon double bond. Alkenes, or olefins, contribute to a static nature in molecules, meaning that they hold the molecule in a particular arrangement around the double bond. Alkenes are crucial in certain biological molecules (Siau et al., 2012), such as fatty acids and proteins, and other natural products, including rubber. Furthermore, alkenes are useful in organic synthesis in that they are much more reactive than the alkane counterpart in many regards (Siau et al., 2012).

Figure 1. E- vs. Z- alkenes. Note that E alkenes have major substituents on opposite sides of the double bond. The reverse is true for Z-alkenes. Image courtesy of science.uvu.edu.

Two conformations of alkenes, E (trans) and Z (cis), exist: Figure 1. The conformation of the alkene dictates the chemistry that the molecule will perform. Historically, synthesis of E-alkenes has been more developed than of the Z form of the alkene (McNulty et al., 2010; Siau et al., 2012). Despite this difficulty, Z-alkenes have many uses biologically and synthetically, including in the synthesis of certain drugs (Littke & Fu, 2002). As an example, Z-alkenes are one functional component of a potent tumor inhibitor, (+)-discodermolide (Siau et al., 2012). Synthetically, Z-alkenes also hold the molecule in a conformation that is conducive to ring formation, as seen below.
1.1 Methods for Alkene synthesis

The focus of this work was to develop new methods that efficiently force the Z-conformation of an alkene. There are a variety of modern reactions known that are commonly used to synthesize alkenes, each with their own advantages and disadvantages. Provided below is a brief introduction into some of these methods, along with an explanation as to why the Suzuki-Miyaura reaction was ultimately chosen to explore the selective synthesis of Z-alkenes.

1.1.1 Lindlar Reduction

The Lindlar reduction reduces an alkyne (carbon-carbon triple bond) to an alkene using a heterogeneous catalyst composed of metals and salts (Siau et al., 2012). Typically, an alkyne is added for new carbon-carbon bond formation. Once in place, the new bond is reduced to produce the desired alkene. Though this method produces Z-alkenes exclusively in good yield, the heterogeneous nature of the catalyst is such that it is difficult to control the reaction (Siau et al., 2012). If too little catalyst is added, the reaction does not run to completion. Conversely, if too much is added, there is over-reduction of the triple bond and an alkane is produced rather than an alkene. Furthermore, this reaction requires a toxic catalyst containing lead, which is less desirable for use in the manufacture of drugs (Siau et al., 2012).
1.1.2 Wittig Reaction

The Wittig reaction involves the reaction between a carbonyl with a phosphorous ylide to produce an alkene. Though the Z-alkene can be produced, there have been a limited number of substrates that are able to produce the Z-conformation exclusively. The E-alkene has been found to be the predominant product in those cases. Furthermore, the reaction produces extensive waste (Siau et al., 2012). Because we desire to study the effectiveness of the CBHA in alkene synthesis, and because the Wittig has historically been sub-optimal for the synthesis of Z-alkenes, other methods are required.

1.1.3 Horner-Wadsworth-Emmons Reaction (HWE)

The Horner-Wadsworth-Emmons Reaction was developed as a modification of the Wittig reaction that is easier to conduct and allows for a greater variety of substrates. However, as it is a modification of the Wittig, the E-conformation of the produced alkene is still favored under normal conditions (Siau et al., 2012). Alternative conditions have been developed, however, that allow for the stereoselectivity desired of our reaction (Ando, 1998). Furthermore, even when the Z-conformation is favored, it is not forced, and the reaction therefore produces a mixture of the E- and Z-conformations.

1.1.4 Still-Gennari Reaction
Further modification of the HWE was undertaken by Still and Gennari (Siau et al., 2012). The modifications allowed for the synthesis of Z-alkenes using organo-tin reagents (Littke & Fu, 2002). The reaction proceeds under even more mild conditions than the HWE, as the process is stable to air and moisture. This process was used to produce rapamycin, an immunosuppressant, and dynemicin, a tumor suppressant (Littke & Fu, 2002). Though upon first inspection the reaction appears favorable, organo-tin reagents are toxic (Littke & Fu, 2002).

1.1.5 Negishi Coupling

Because a majority of the previous reactions produce both isomers, coupling reactions were explored to produce Z-alkenes exclusively. Coupling reactions have been typically identified by the attachment of two hydrocarbon compounds using a metal catalyst (JACS). Coupling reactions preserve existing stereochemistry, which can be established before the metal mediated coupling (McNulty et al., 2010; Siau et al., 2012). One example of a coupling reaction is the Negishi coupling, which uses organo-zinc compounds and a palladium catalyst to assist the formation of the Z-alkenes (Littke & Fu, 2002). In alkenyl Negishi coupling, a trans-alkenylhalide is required. As such, there can still be significant difficulty of synthesizing the required alkene.

1.1.6 Suzuki-Miyaura Coupling

The Suzuki-Miyaura coupling was developed in the mid-1970’s and has been used extensively throughout the past 40 years. The reaction proceeds by reacting “highly electrophilic boronic compounds with alkyl halides” (Miyaura & Suzuki, 1995). Double bond geometry has been found to be conserved throughout the reaction, which will lead to the Z-conformation of the
alkene, provided the desired conformation was in place prior to the coupling. The process is catalyzed by a homogeneous palladium catalyst in the following steps: oxidative addition, transmetalation, reductive elimination (see figure 3). Oxidative addition, the addition of the alkyl halide to the Pd⁰ species, is commonly the rate-limiting step of the process with iodides being more reactive than triflates, which in turn are more reactive than bromides, which are much more reactive than chlorides (Littke et al., 2000; Miyaura & Suzuki, 1995). Modifications of the process have been expanded upon in recent years to extend this reaction to aryl chlorides, which previously have been unreactive (Fu, 2008; Littke & Fu, 2002). Fu further developed this work and described in depth the relationship between substrate, ligand, and catalyst to provide the most reactive conditions, some of which were further explored in this work (Littke & Fu, 2002).

As mentioned before, the Suzuki-Miyaura catalytic cycle can be separated into three steps: oxidative addition, transmetallation, and reductive elimination. In the oxidative addition, the alkyl halide, R₂X, is added to the metal, forming a halide and alkyl ligand on the catalyst and oxidizing the metal center from a Pd⁰ species to a Pd²⁺ species. The complex then undergoes
transmetallation, in which ligands on different metal centers are exchanged. In this case, the R-group on the boron complex is exchanged with the halide ligand on the palladium catalyst. In the final step, reductive elimination, a bond is created between the R-groups to form the final product and the Pd° catalyst is reformed (Cross Coupling Reactions).

The Suzuki-Miyaura coupling is convenient for a number of reasons. All of the reagents are easy to synthesize or purchase, compared to some of the reactions discussed previously. Organoboronic compounds are also stable in the presence oxygen and water, are temperature stable, yet still react under mild conditions, and yield non-toxic byproducts (Littke et al., 2000; Littke & Fu, 2002; Miyaura & Suzuki, 1995). Extensive research had been done on the reaction, illustrating that under a variety of conditions, the reaction produces good yields with a variety of substrates.

1.2 Project Focus

Though extensive research has been done on the Suzuki-Miyaura reaction in general, no reports were found investigating the ability of the reaction to force isolated Z-alkenes using cyclic boronic half-acids. Boronic half-acids are relatively easy to synthesize and the final product contains a hydroxyl group on the homoallylic carbon, which is not only common to natural products, but allows for further chemistry to be done at that site (McNulty et al., 2010). Optimization of conditions for the starting material catalyst with CBHA would allow for the use of a new, powerful tool in synthetic chemistry.

*Suzuki-Miyaura reactions of cyclic boronic half-acids can be utilized to force the production of Z-alkenes, producing a new compound with an alcohol on the homoallylic carbon. The optimization of reaction conditions will provide a powerful tool for organic chemists for the synthesis of Z-alkenes.*
Results and Discussion

A series of experiments was performed demonstrating the ability to form the desired Z-alkenes with the Suzuki-Miyaura reaction.

2.1 Suzuki Coupling

A variety of conditions were used to evaluate the efficacy of the Suzuki-Miyaura reaction. Work was divided into three sub-categories based on the over-all goal of each section. To begin, literature-published reaction conditions were tried to see if the reaction would work with our modified starting material (Reports in the literature call for a true boronic acid, whereas we utilized a cyclic boronic half-acid, Figure 4). Secondly, the reaction was performed in a microwave, both for convenience and to show that the reaction could be accelerated, which may be of benefit in various industrial applications. Finally, an extended reaction was performed to provide information on the mechanism by which this reaction may occur.

![Figure 4. Boronic half acid (left) vs. True Boronic Acid (Right).](image)

2.2.1 Original Reaction Conditions
Literature conditions were first tried with the new electrophile (CBHA) in order to determine whether or not this substrate would participate in the Suzuki-Miyaura reaction. Six trials were run, Table 1.

Table 1. Reaction conditions as adopted from Fu, et al. Ratios of desired alkene to proteo-product also given. Some reactions were found to have starting material remaining (*) and some produced a substituted dihydrofuran (').

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Ligand</th>
<th>Base</th>
<th>Catalyst</th>
<th>CBHA</th>
<th>Allyl Halide</th>
<th>Solvent</th>
<th>Pre-Stir</th>
<th>Temperature</th>
<th>Reaction Time</th>
<th>Product:Proteo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Barho.</td>
<td>KOtBu</td>
<td>Ni(COD)2</td>
<td>1 eq</td>
<td>2-Br</td>
<td>S-BuOH</td>
<td>overnight</td>
<td>60C</td>
<td>overnight</td>
<td>1:2</td>
</tr>
<tr>
<td>2</td>
<td>Barho.</td>
<td>KOtBu</td>
<td>Ni(COD)2</td>
<td>1 eq</td>
<td>2-Bromo</td>
<td>S-BuOH</td>
<td>75C</td>
<td>overnight</td>
<td>1:2</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>(HP(tBu)2Me)BF4</td>
<td>KOtBu</td>
<td>Pd(OAc)2</td>
<td>1.5 eq</td>
<td>1-Br-2-MePr</td>
<td>S-BuOH</td>
<td>Room</td>
<td>overnight</td>
<td>*1:2</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>(HP(tBu)2Me)BF4</td>
<td>KOtBu</td>
<td>Pd(OAc)2</td>
<td>1.5 eq</td>
<td>2-Br</td>
<td>S-BuOH</td>
<td>Room</td>
<td>24 Hr</td>
<td>*1:1.5</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>(HP(tBu)2Me)BF4</td>
<td>KOtBu</td>
<td>Pd(OAc)2</td>
<td>1.5 eq</td>
<td>2-Bromo</td>
<td>S-BuOH</td>
<td>Room</td>
<td>24 Hr</td>
<td>*1:1.5</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>(HP(tBu)2Me)BF4</td>
<td>KOtBu</td>
<td>Pd(OAc)2</td>
<td>1.5 eq</td>
<td>1-Br-2-MePr</td>
<td>S-BuOH</td>
<td>Room</td>
<td>over weekend</td>
<td>1:0.75</td>
<td></td>
</tr>
</tbody>
</table>

In all cases, a mixture of products was observed. The mixture included the desired coupling product and a product here referred to as proteo-product. The proteo-product is the same chemical as that which was used as the alcohol starting material used to synthesize the CBHA. In many cases, however, a third product, a substituted dihydrofuran, was observed in the reaction mixture. The CBHA starting material was also present in some reactions.
Reactions 1 through 3 generated a mixture of desired Z-alkene and proteo species in a 1:2 ratio, favoring the proteo-product. Starting material was also present in these three reactions.

Reaction 4 generated the same mixture, but the ratio was slightly improved to favor the Z-alkene 1:1.5. Reactions 5 and 6 yielded more of the desired product, as they produced ratios of 1:1 and 1:0.75, respectively. However, the dihydrofuran product was also observed in reaction 5.

As can be seen from Figure 5 the desired product and proteo were similar in structure, and therefore in chemical properties. As such, it was nearly impossible to separate the two from each other. Separation was attempted using various conditions using chromatography. Two solid phases were tested, silica and alumina. It was found that alumina was particularly well suited to removing excess starting material and the dihydrofuran product. However, alumina did not affect the separation between the product of interest and the proteo-product. Various elution conditions were tested with both solid phases, and a solution of 1% methanol in dichloromethane was found to be optimal. With the correct drip rate, it was sometimes
possible to get a “pure” product. However, this required the formation of extremely small partitions, was not reproducible, and did not yield enough product to successfully quantify. In lieu of true yields, NMR integrations were used to approximate the yield ratios. This method of quantization may not be entirely accurate, however, as some of the principle regions for detection overlap.

2.2.2 Microwave Series

Table 2. Reaction conditions of those reactions run in the microwave. In some reactions starting material remained (*) and in some, dihydrofuran product was formed (†).

<table>
<thead>
<tr>
<th>Reaction #</th>
<th>Ligand</th>
<th>Base</th>
<th>Catalyst</th>
<th>CBHA</th>
<th>Alkyl Halide</th>
<th>Solvent</th>
<th>Pre-Stir</th>
<th>Temperature</th>
<th>Reaction Time</th>
<th>Product: Proteo</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>[HP(tBu)2Me]BF4</td>
<td>KOtBu</td>
<td>Pd(OAc)2</td>
<td>1.5 eq</td>
<td>1-Bu-2-MePr</td>
<td>S-BuOH</td>
<td></td>
<td>35C</td>
<td>30 min</td>
<td>NA</td>
</tr>
<tr>
<td>8</td>
<td>[HP(tBu)2Me]BF4</td>
<td>KOtBu</td>
<td>Pd(OAc)2</td>
<td>1.5 eq</td>
<td>1-Bu-2-MePr</td>
<td>S-BuOH</td>
<td>overnight</td>
<td>35C</td>
<td>30 min</td>
<td>*1:1:2</td>
</tr>
<tr>
<td>9</td>
<td>[HP(tBu)2Me]BF4</td>
<td>KOtBu</td>
<td>Pd(OAc)2</td>
<td>1.5 eq</td>
<td>1-Bu-2-MePr</td>
<td>S-BuOH</td>
<td></td>
<td>45C</td>
<td>45 min</td>
<td>*1:0:75</td>
</tr>
<tr>
<td>10</td>
<td>[HP(tBu)2Me]BF4</td>
<td>KOtBu</td>
<td>Pd(OAc)2</td>
<td>1.5 eq</td>
<td>1-Bu-2-MePr</td>
<td>S-BuOH</td>
<td></td>
<td>35C</td>
<td>30 min</td>
<td>*1:1</td>
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<tr>
<td>11</td>
<td>[HP(tBu)2Me]BF4</td>
<td>KOtBu</td>
<td>Pd(OAc)2</td>
<td>1.5 eq</td>
<td>1-Bu-2-MePr</td>
<td>S-BuOH</td>
<td></td>
<td>35C</td>
<td>90 min</td>
<td>NA</td>
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<td>KOtBu</td>
<td>Pd(OAc)2</td>
<td>1.5 eq</td>
<td>1-Bu-2-MePr</td>
<td>S-BuOH</td>
<td></td>
<td>35C</td>
<td>15 min</td>
<td>*1:3</td>
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<td>KOtBu</td>
<td>Pd(OAc)2</td>
<td>1.5 eq</td>
<td>1-Bu-2-MePr</td>
<td>6-Br-1-hexanol</td>
<td>S-BuOH</td>
<td>35C</td>
<td>30 min</td>
<td>*1:1</td>
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<td>Pd(OAc)2</td>
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<td>1-Bu-2-MePr</td>
<td>S-BuOH</td>
<td></td>
<td>35C</td>
<td>30 min</td>
<td>*1:1:16</td>
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<tr>
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<td>1-Bu-2-MePr</td>
<td>THF</td>
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<td>35C</td>
<td>30 min</td>
<td>NA</td>
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<td>16</td>
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<td>1-Bu-2-MePr</td>
<td>THF</td>
<td></td>
<td>30 min</td>
<td>35C</td>
<td>30 min</td>
<td>NA</td>
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<tr>
<td>17</td>
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<td>1-Bu-2-MePr</td>
<td>THF</td>
<td></td>
<td>30 min</td>
<td>35C</td>
<td>45 min</td>
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<tr>
<td>18</td>
<td>BINAP</td>
<td>KOtBu</td>
<td>Pd(COD)</td>
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<td>THF</td>
<td></td>
<td>30 min</td>
<td>35C</td>
<td>30 min</td>
</tr>
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<td>Pd(OAc)2</td>
<td>1.5 eq</td>
<td>1-bu</td>
<td>THF</td>
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<td>35C</td>
<td>30 min</td>
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<td>1.5 eq</td>
<td>1-bu</td>
<td>THF</td>
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<td>30 min</td>
<td>35C</td>
<td>30 min</td>
<td>*1:1</td>
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<tr>
<td>21</td>
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<td>35C</td>
<td>30 min</td>
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<tr>
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<td>1-Bu-2-MePr</td>
<td>THF</td>
<td></td>
<td>35C</td>
<td>30 min</td>
<td>*1:1:5</td>
<td></td>
</tr>
<tr>
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<td>PdC2(DPPF)</td>
<td>1.5 eq</td>
<td>1-Bu-2-MePr</td>
<td>Toluene</td>
<td></td>
<td>35C</td>
<td>30 min</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>24</td>
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<td>PdC2(DPPF)</td>
<td>1.5 eq</td>
<td>2-Br</td>
<td>Toluene</td>
<td></td>
<td>35C</td>
<td>30 min</td>
<td>NA</td>
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</tr>
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<td>25, 29-32</td>
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<td>PdC2(DPPF)</td>
<td>1.5 eq</td>
<td>1-bu</td>
<td>THF</td>
<td></td>
<td>100C</td>
<td>30 min</td>
<td>NA</td>
<td></td>
</tr>
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<td>26</td>
<td>Cs2CO3</td>
<td>Pd(PPh3)3</td>
<td>1.5 eq</td>
<td>1-bu</td>
<td>THF</td>
<td></td>
<td>85C</td>
<td>35 min</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>CsF</td>
<td>Pd(PPh3)3</td>
<td>1.5 eq</td>
<td>1-bu</td>
<td>THF</td>
<td></td>
<td>85C</td>
<td>35 min</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>[HP(tBu)2Me]BF4</td>
<td>Cs2CO3</td>
<td>Pd(OAc)2</td>
<td>1.5 eq</td>
<td>1-Bu-2-MePr</td>
<td>THF</td>
<td></td>
<td>35C</td>
<td>30 min</td>
<td>NA</td>
</tr>
</tbody>
</table>
In general, it was determined that the reaction was sufficiently able to produce desired product that it was worthwhile to examine a broader set of reaction conditions. To do so, the reaction was moved to the microwave reactor in both an effort to save time and to demonstrate the ability to accelerate the reaction using this method, which may be of benefit in certain industrial situations. Reaction conditions for this class of reaction can be seen in Table 2.

As before, a mixture of products was generally observed. No ratio data was available for reactions 7, 11, 15-19, 21, or 23-32 due to in vast quantity of starting material observed in the final product. Because of the structure commonalities between the starting material and the products, some of the regions overlapped in the NMR spectra, making yield based on integration unreliable. Furthermore, reactions 8, 9, 12, 13, and 22 generated ratios at or above 1:2 Z-alkene to proteo-product, marking them as no better than as observed in the non-microwaved reactions. Reactions 10, 14, and 20, however, yielded ratios of around 1:1.

Upon inspection of the reactions that yielded ratios of 1:1, there appeared to be little correlation. A variety of alkyl halides and catalyst systems were used – leaving the relationship between these reactions and the improved yield of the Z-alkenes in mystery.

In many of the reactions, there remained starting material, indicating that the reaction had not gone to completion. However, upon further examination, it seems that the excess CBHA may be an artifact of the method by which the samples were prepared for analysis. Typically, an aliquot would be removed from a reaction mixture, solvent would be removed via rotary evaporation and the remaining material would be dissolved in deuterated chloroform for NMR. In one instance, it was noted that when the NMR were performed in deuterated benzene, there appeared to be no CBHA remaining. Another sample from the same source was processed as previously described and NMR analysis revealed the presence of CBHA. As of now, it is not
known whether the drying vessel was contaminated with CBHA or whether the act of heating the reaction mixture re-formed the CBHA. If this is the case, however, yields may be higher than initially observed.

In addition to the desired Z-alkene and the proteo-product, a third byproduct of the reaction was observed. Through analysis via HNMR and CNMR, it was determined that this byproduct was a substituted cyclical alkenylether, previously described as the dihydrofuran-like product. If oxidative addition is the rate limiting step, it is possible for the CBHA to undergo the transmetallation process before the oxidative addition of the alkyl halide. The alkenylether product may be generated from this alternative catalytic process.

2.2.3 Extended Reaction
To elucidate the mechanism by which this reaction proceeds, and therefore identify a method by which it may be improved, a reaction was run without heating over the course of one or two days. The reaction was prepared as with the original conditions described by Fu. Reaction samples were collected every one to two hours. Deuterated benzene was added to the crude reaction sample and NMR's were obtained.

The mechanistic experiment yielded little to no Z-alkene while forming the proteo-product and the dihydrofuran product. No starting material remained. The lack of desired product formed under these conditions was interesting in that it may reveal that under the current conditions, we may fail to generate the active Pd\(^0\) catalyst. As described above, this may be the result of the sluggishness of the oxidative addition step. If the transmetallation step is possible before the addition of the alkyl halide to the Pd\(^0\) through oxidative addition, then it may be possible for the side reaction to occur and the oxidative addition of the alkyl halide does not occur. This effect, however, is not thought to contribute to the generation of the proteo-product, as the
synthesis of proteo-product occurs without the generation of the dihydrofuran product in some cases.

Experimental

3.1 Production of Cyclic Boronic Half-Acid (CBHA)


To a round-bottom flask charged with 100 mL tetrahydrofuran (THF) was added 5 g (47.11 mmol) benzaldehyde under nitrogen. Allyl-magnesium bromide (51.81 mmol, 51.81 mL 1 M solution) was slowly added to the flask. The reaction was stirred at 0°C for one hour, then allowed to warm to room temperature. The reaction was stirred for one week, following which diethyl ether was added to dilute the product. Hydrochloric acid (10%, 70.0 mL) was added to quench the reaction. Product was extracted with 4 portions of 50 mL diethyl Ether. The alcohol product was separated, dried, concentrated, and subjected to NMR to verify the product before continuing to the next step.

To a round-bottom flask charged with dichloromethane was added 2 g (13.5 mmol) of the alcohol and 1.16 g (13.5 mmol) cis-1-propen-1-yl boronic acid. The flask was degassed and the vessel was stirred for one hour, after which was added Grubbs catalyst (1st generation). The contents were degassed a second time. The reaction was heated to reflux and stirred for one day. After refluxing, the solution was cooled to room temperature, concentrated via rotary evaporation and purified using flash column chromatography, yielding the cyclic boronic half-acid.
3.2 Suzuki Coupling

3.2.1 Original Reaction Conditions

Original procedures adopted from Fu (Kirchhoff, Netherton, Hills, & Fu, 2002).

To a schlenk vial was added a stir bar and ligand (100 m.eq), Base (4/3 eq.), and Catalyst (50 m.eq), were added to the vessel, capping and evacuating the flask between each addition. Following the final addition of the catalyst, the flask was evacuated and filled with argon twice. In a separate, flame-dried rbf was added anhydrous solvent and the cyclic-boronic half acid (1.5 eq). This solution was added to the schlenk vial. After pre-stirring (when applicable), the alkyl halide (1 eq) was added. The contents were vigorously stirred.

3.2.2 Microwave Series

To a dry microwave vial was added a stir-bar and CBHA in ether solution. The vial was capped and evacuated to remove ether. Base, catalyst, and ligand (if separate from the catalyst) were added to the vessel according to table 2. The vial was then subjected to three repetitions of evacuation and flushing with argon. Solvent was added via syringe. After a period of pre-stirring (when applicable), the alkyl halide was added. The vial was subjected to heating using a CEM Discover Labmate.

2.2.3 Extended Reaction

A schlenk vial was prepared in the same manner as the microwave vials of the previous sub-category. The reaction was stirred vigorously for an extended period of time. Aliquots (0.5 mL) were removed throughout the course of the reaction. Samples were filtered through cotton and added to 0.2 mL benzene d-6 in an NMR tube. Samples were centrifuged for 45 seconds and frozen at -80°C until subjected to NMR analysis, before which each sample was thawed.
Conclusion

The application of the Suzuki-Miyaura reaction was shown to be capable of producing the Z-conformation of an alkene. In spite of this accomplishment, however, the product was not pure. A proteo-alkene and a dihydrofuran product were frequently observed in the reaction mixture. It is thought that these products are the result of an inability of the system to generate the active catalyst $\text{Pd}^0$, either through bypassing the oxidative addition phase of the reaction or by some other means.

There is still much to be done towards the optimization of this reaction to give high yields. First needs to be developed a system capable of purifying the desired product from the proteo-product in order to record accurate yields. The optimization of the reaction with respect to our desired starting material will be minimal. Provided that a purification method can be produced, reaction conditions must be optimized to be able to maximally produce the desired product. A mechanistic understanding of the reaction may aid in this endeavor.
Reference


Figure 6. Z-alkene
Figure 7. Substituted Dihydrofuran
Figure 8. Proteo-Product.
Figure 9. Extended Reaction
Figure 10. Extended Reaction Samples 5-8