Study of the boron nitrogen interaction and its influence on the catalysis of amide formation reactions by aromatic boronic acids

by

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Abstract

The synthesis of two nitrogen containing aromatic boronic acids was accomplished in the premise that the interaction between B and N would grant hydrolytic resistance to a boronic ester intermediate in the catalysis of an amide formation reaction. One of these catalysts, 2-(dimethylamino)methyl-phenylboronic acid, gave comparable yields to known boronic acids catalysts, despite lacking electron withdrawing groups and furthermore, without the need to remove water. Following NMR investigations of the boronic ester intermediate formed during the reaction, it was found that less of this intermediate was formed due to the presence of the B-N interaction when compared to other boronic acids. It is postulated that this interaction lowers the Lewis acidity of the boron atom, effectively causing lower levels of formation of the desired intermediate. Higher than expected yields are obtained, as a result of the molecule being a bifunctional catalyst and not as a result of increased hydrolytic stability.
Résumé

La synthèse de deux acides boroniques aryles, qui contiennent une interaction B-N fut accompli; étant donné que cette interaction puisse rendre l’ester de cette acide boronique, produite durant la formation d’un amide, résistant à l’hydrolyse. Une de ces catalyseurs, l’acide boronique 2-(dimethyleamino)méthylephényle, produit un bon rendement dans une de ces réactions sans que l’eau ne soit enlevée. Le rendement est comparable à ceux qui sont obtenus par des acides boroniques connus qui contiennent un groupe qui retire des électrons du système aromatique. Des analyses NMR ont déterminé que l’ester de l’acide boronique se forme moins bien lorsque la molécule contient une interaction B-N. On croit que c’est parce que cette interaction a comme résultat de réduire la capacité de l’atome de bore d’accepter des électrons, devenant ainsi un acide de Lewis moins fort. Le bon rendement lors des réactions de formation est attribué au fait que la molécule est en elle-même, un catalyseur bi fonctionnel.
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Introduction

All proteins in the human body are composed of repeated subunits, known as amino acids molecules. They are aptly named as they contain an amine and a carboxylic acid group. These subunits are linked together through a reaction where an amine moiety of an amino acid reacts with the carboxylic acid end of another. This results in the expulsion of a water molecule and the formation of an amide bond.

This condensation reaction however, is hard to reproduce without excessive heating. When mixed together without additional reagents, amines and carboxylic acids prefer to perform the faster acid base reaction which results in an exchange of protons and the formation of two charged species. The amine with a resulting positive charge is less nucleophilic and conversely the carboxylic acid anion is less electrophilic. Because of this, a low yield is obtained for the desired reaction.¹

\[
\begin{align*}
\text{Carboxylic Acid} & \quad + \quad \text{Amine} \\
\text{Amide} & \quad + \quad \text{Water}
\end{align*}
\]

Amide condensation reaction.

Formation of an amide bond is one of the most widely performed reactions in the pharmaceutical industry and is used in the synthesis of a variety of drugs.⁹
As such there are numerous methods that have been developed to circumvent the aforementioned issue. The two most popular methods involve the formation of an active carboxylic acid derivative: an acyl chloride or a carbodiimide intermediate\(^2\). While the desired amide is achieved in satisfactory yields, there are numerous disadvantages with each of the current methods. Both require the use of a stoichiometric reagent. This subsequently results in very poor atom economy as high molecular weight reagents are used to obtain the end product but they themselves are not incorporated in the molecule.\(^3\) These atoms are hence wasted. In addition, these reagents are hazardous and require special care during their synthesis, transport, and handling. All these issues result in a very high cost to pharmaceutical companies. Because of this, an alternative is highly desired. The Pharmaceutical Roundtable (PRT), a regroupment of eight of the top pharmaceutical companies in the world, have stated that in terms of reactions needing improvement, the discovery of a new “amide formation reaction avoiding poor atom economy reagent”, one which is greener and subsequently more economical, is their number one issue which they would like solved.\(^2\)

A catalytic approach is an ideal solution to this problem. It is highly efficient given that the catalyst is used in small amounts when compared to the reactants, and can sometimes be reused. It prevents waste, avoids the formation of a derivative and the use of a stoichiometric reagent; all of which are principles of Green Chemistry.\(^3\) One such approach is the use of compounds known as boronic acids. In 1996, Yamamoto et al. discovered that aromatic boronic acids
containing an electron withdrawing group (EWG) were capable of catalyzing the condensation of an amide and a carboxylic acid in satisfactory yields\textsuperscript{4}.

Boronic acids are very acceptable compounds because they are non-toxic species to the human body; in addition they are fairly inert, and hence safe, and generate no undesirable byproducts.\textsuperscript{5} Since then, Yamamoto, and other groups have developed many aromatic boronic acid derivatives that were successful in forming these compounds.\textsuperscript{13} However, despite their relative successes, one large issue remained. The reaction has to be run in the absence of water. A boronic ester intermediate that is formed during the reaction is highly susceptible to hydrolytic cleavage. Hence water, which is a side product, must be removed continuously; otherwise the yield is compromised. While achievable in a laboratory setting, this proves to be a major hindrance at larger scales.

A possible solution to this problem is investigated in this study. In the late 1960s, François et al were synthesizing polymers containing a boronic acid as well as a substituted amine.\textsuperscript{6} They discovered that the resulting polymer was highly resistant to hydrolysis and they speculated that this was a result of a B-N interaction. The nitrogen donates electron density to the boron thus lowering its Lewis acidity: its ability to accept electrons, and henceforth the rate of hydrolysis. Over the years, the B-N interaction has been well characterized. In particular X-Ray diffraction experiments have been performed on aromatic boronic acids and have confirmed the existence of this B-N interaction.\textsuperscript{7}
We believe that this could be a potential solution to issue to the hydrolysis of boronic esters during the formation of an amide. If an N moiety is allowed to interact with the boron atom, it could lower the rate of hydrolysis of the active intermediate in an amide coupling reaction. This would increase the lifetime of the boronic ester intermediate, and thus increase the likeliness that the amine will be allowed to react with the intermediate and form the product before hydrolysis can occur. If a sufficient drop in the rate of hydrolysis is achieved, then the formation of amides catalyzed by boronic acids could be performed without the need to remove water. This would be a huge improvement to this method and could lead to potential application in the pharmaceutical industry.
1. Amide Formation Reaction

An amide bond is the linkage between the carbon of a carbonyl group with a nitrogen atom adjacent to it, with variable R groups on either side.

\[ \begin{array}{c}
\text{O} \\
\text{R} \\
\text{N} \\
\text{R'} \\
\text{R''}
\end{array} \]

**Figure 1.1** An amide bond.

An amide is the most stable carbonyl functional group and this linkage is highly resistant to cleavage in most organic medium. They are prone to hydrolysis only in extremely aqueous acidic or basic media under boiling conditions. Given their stability, they form a large part of many molecules. From an analysis of the Comprehensive Medicinal Chemistry database, 25% of all drugs contained an amide functionality. The amide bond, because of this stability, is a very popular disconnection strategy during the synthesis of a complex molecule. A large number of protecting groups require acidic or basic conditions for removal; the amide bond is left unaffected by deprotecting procedures. As a result, a very large number of amide formation reaction are performed in various drug syntheses. In a recent survey of the synthesis of 128 drugs, it was found that in 65% of the cases, an amide condensation was used.
1.1 Amine-Carboxylic Acid Condensation

As its name suggests, this reaction involves the reaction of an amino group with a carboxylic acid, which produces an amide with the release of a water molecule.

\[
\begin{align*}
\text{Carboxylic Acid} & \quad + \\
\text{Amine} & \quad \rightarrow \\
\text{Amide} & \quad + \\
\text{Water} & 
\end{align*}
\]

*Figure 1.2 Amide condensation reaction.*

Amino groups can be either secondary, or tertiary. The mechanism involves the nucleophilic attack of the amino group to the carbonyl group of the acid. This results in the formation of a tetrahedral intermediate. Following a proton exchange, a water molecule is released as the amide bond is formed.
1.1.1 Limitations of this reaction

Amine carboxylic acid condensation was discovered in 1858 but has since been largely ignored in synthesis. This is due to the fact this reaction gives a poor yield. To understand why, let’s take a look at this very similar condensation reaction: an esterification.

![Figure 1.3 Mechanism of an amide formation reaction.](image)

![Figure 1.4 Esterification condensation reaction.](image)
It is a condensation reaction between a carboxylic acid and another molecule, in this case, an alcohol. The mechanism is identical. In an acidic medium and with heat, this reaction goes to completion. The yields are excellent.

However under these same conditions, swapping the alcohol for an amine results in a poor yield. This is because unlike its counterpart in the esterification reaction, the alcohol, the amino group is more basic. Its pKa is high enough that it is able to extract the hydrogen present on the carboxylic acid residue. Because this is an acid-base reaction, this will occur faster than the competing condensation reaction.¹

Figure 1.5 Acid-Base reaction resulting in formation of an inactive salt.

This results in the formation of two charged species, which form an unreactive salt. The ammonium cation is now less nucleophilic than the amine, since it possesses an overall positive charge. Conversely, the carboxylic acid anion is less likely to undergo nucleophilic attack given that the resulting negative charge is delocalized through the carbonyl bond. This lowered reactivity explains the poor yields.
1.2 Formation via Acyl Chloride

Low yielding reactions are unacceptable for pharmaceutical companies and are avoided, when possible, given the waste of resources, which are costly. Particularly in this case, since an amide formation could possibly be the unification of two separate complex molecules that have been synthesized independently through the use of multiple reagents. A poor yield at this crucial step is very expensive.

Hence an amine-carboxylic acid direct coupling cannot be used. Instead, the following reaction is a popular alternative. The carboxylic acid is converted to an acyl chloride before reacting with the amine. Not only is the acyl chloride a more reactive species than a carboxylic acid, but it also lacks hydrogens which can be extracted by the amino group.

\[
\begin{align*}
\text{R-COOH} & \rightarrow \text{R-COCl} & \text{H-N} & \rightarrow \text{N-CO-R'} \\
\text{R-COCl} & \rightarrow \text{N-CO-R'N-R''} & + & \text{HCl}
\end{align*}
\]

\textbf{Figure 1.6} Acyl chloride amidation reaction.

Known as the Schotten-Baumann reaction, this method was discovered in 1883. The amine reacts with an acyl chloride to form the desired amide, releasing
HCl. Because no competing acid base reaction is possible, this reaction goes to completion and excellent yields of the amide are obtained.

This reaction is highly relevant in the pharmaceutical field given that it was determined in a recent survey of 128 drugs that 41% of amide formation reaction were produced in such a way.\(^9\) However, despite achieving high yields, an improvement over this method is desired. There are many reasons for this and first one must look at how the acyl chloride is formed. This reactive species is typically formed through the reaction of a carboxylic acid with thionyl chloride (SOCl\(_2\)).

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

\[
\text{SOCl}_2 \quad \rightarrow \quad \text{SO}_2 \quad + \quad \text{HCl}
\]

**Figure 1.7** Formation of an acyl chloride derivative.

This results in the production of two undesirable species, HCl and SO\(_2\), which must be removed by scrubbing with a basic solution. This leads to very poor mass intensity (MI), which can be defined as the ratio weight of material used to achieve the products over the weight of the product itself.\(^3\) While other ways exist to produce acyl halides, they also have their own issues. For example, use of oxalyl chloride rather than thionyl chloride releases carbon monoxide, a very toxic gas.
1.3 Reaction via Carbodiimide

An alternative to the acyl chloride formation is to react the carboxylic acid with a carbodiimide, such as dicyclohexylcarbodiimide (DCC). The carboxylic acid derivative that is formed is also very prone to nucleophilic attack as a very stable urea molecule is formed upon release. This side product can be removed by filtration.

![Figure 1.8 Carbodiimide amidation reaction.](image)

Used in 36% of amide bond formation reaction in a recent study on the synthesis of 128 drugs\textsuperscript{9}, this method is somewhat of an improvement to the acyl method because it is not restricted to organic media. In addition, acid sensitive moieties can be present in either starting reagents. A water soluble version of this reaction can be performed by using a derivative known as EDC·HCl (1-ethyl-3-(3’-dimethylamino)carbodiimide HCl). Water is an abundant, cheap and innocuous solvent, which is considered to be very “green”.\textsuperscript{11}
However, this is still a stoichiometric procedure. As such an equivalent amount of DCC is required. Also, unlike thionyl chloride, carbodiimide coupling agents are bulky molecules with a very high molecular weight. This means this reaction is even poorer in terms of atom economy, roughly twice poorer in regards to molecular weight of this compound alone. In addition, another high molecular weight molecule, 1-Hydroxybenzotriazole (HOBt), is often used as an added nucleophile. It is a hazardous material that is a potential explosive. These are the reason why a new method is highly desirable.

1.4 Other Approaches

There are other ways to form amides, and they include modification of the carboxylic acid group to an anhydride or to other derivatives such as an azide. However, they will not be discussed in detail here, given they form part of the minority in terms of amide formation reactions actually used in industry. Regardless they still involve transformation of the carboxylic acid into derivates prior to reaction with amines and are such very poor in terms of MI and atom economy.

It should also be noted that stereochemistry will not be discussed here. Highly relevant in both peptide synthesis and during the synthesis of some drugs, the racemization of the carbon alpha to the nitrogen will not be accounted for. This project will focus on the majority of cases where the alpha carbon is achiral.
Catalysis is the ultimate solution to the problems of poor atom economy and mass intensity of previously mentioned amide coupling reactions. These are the two major improvements, which are quoted as desirable, by pharmaceutical companies in PRT. A very little amount, and hence mass, of catalyst is used when compared to stoichiometric reagents greatly improving mass intensity. Also, the catalysts can potentially be reused, leading to better atom economy compared to the use of derivatives. While catalytic enzymes, such as peptidases have been developed to perform amidation formation reactions, they are often too substrate specific. A more general catalyst is desired.

2. Boronic Acids

Boronic acids form part of a large family of molecule where a boron atom which is attached to two hydroxyl group and an alkyl group.

![Boronic Acids Diagram](image)

They are a result of a second oxidation of boranes and were first discovered in 1860 by Frankland. Boronic acids are considered to be mild Lewis acids: the boron atom contains 3 pairs of valence electrons and is one short of completion of the octet. Unlike borinic acid, the second oxidation provides atmospheric stability
to the molecule and as a result they are easily handled. In addition, boronic acids have low toxicity and they will degrade eventually into boric acid, an environmentally benign molecule. Hence they are considered to be “green” compounds. 

2.1 Catalysis in Amide Coupling Reactions

In 1996, Yamamoto et al. reported the catalysis of an amide condensation reaction using boronic acids. They tested various aryl boronic acids as catalysts, under refluxing toluene for one hour, and they obtained decent yields. Water produced during the reaction was removed via molecular sieves in a Soxhlet thimble. The catalyst, which gave the best yield, was 3,4,5-trifluorobenzeneboronic acid. Using this catalyst (5 mol%), the reflux time was increased to 18 hours and the reaction went to completion.

![Figure 2.2 Example of an amide coupling reaction catalyzed by a boronic acid.](image)

They successfully proceeded to apply this catalyst to synthesize various amides. Other effective solvents for this reaction were found to be close relatives
to toluene: xylene and mesitylene. Out of curiosity, they also tested the
effectiveness of this catalyst for esterification. The yields were lower however,
given the lower nucleophilicity of alcohols compared to amines.

They have since developed more successful aromatic boronic acid catalysts
such as pyridine based boronic acids and have successfully bound the aromatic
boronic acid residue to a polystyrene resin\textsuperscript{13}, which has made the catalyst reusable
upon filtration. Other groups have also shown that boric acid itself was capable of
catalyzing amide formation reaction\textsuperscript{14}. However, unlike boronic acids, they don’t
have a variable R group and hence improvements cannot be made on the catalyst
itself. Very recently, syntheses of real drug intermediates such as a Galanthamine
intermediate, used to treat Alzheimer’s disease, was accomplished using an aryl
boronic acid as a catalyst\textsuperscript{15}. This shows that if developed further, this method of
catalysis could be applied directly to real drug syntheses.

However, one aspect that prevents such an application is that water needs to
be removed as the reaction proceeds. If water is not removed, the yield is
compromised. The mechanism of water interference will be discussed in section
3.2.
2.1.1 Effect of various substituents

When Yamamoto et al. tested the effectiveness of various substituted phenyl boronic acids, here is the reaction that they used and their results.

![Chemical structure](image)

**Figure 2.3 Amidation formation reaction catalyzed by aryl boronic acids.**

**Table 2.1 Yields of various aryl boronic acids in the reaction shown in figure 2.3.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>Yield (%)</th>
<th>Entry</th>
<th>Ar</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3,4,5-F2C6H2</td>
<td>74</td>
<td>5</td>
<td>C6H5</td>
<td>23</td>
</tr>
<tr>
<td>2</td>
<td>3-NO2C6H4</td>
<td>60</td>
<td>6</td>
<td>2,4,6-(CF3)3C6H2</td>
<td>21</td>
</tr>
<tr>
<td>3</td>
<td>3,5-(CF2)2C6H3</td>
<td>56</td>
<td>7</td>
<td>2,3,4,5-F4C6H</td>
<td>11</td>
</tr>
<tr>
<td>4</td>
<td>4-CF3C6H4</td>
<td>54</td>
<td>8</td>
<td>No catalyst</td>
<td>2</td>
</tr>
</tbody>
</table>

The neutral phenyl boronic acid is still capable of catalysis albeit at a lower rate. Yields drastically improved when electron withdrawing group (EWG) were placed at the 3, 4 an 5 position of the benzene ring. This can be logically explained. EWG withdraw electrons from the benzene ring through an inducing effect. As a result the ring becomes electron deficient and hence will also cause
an inducing effect on the electrons of the boron atom. The boron atom is as a result, a better Lewis acid. This increases the formation of the reaction intermediate described in the next section and hence increases the yield. Ortho and para positioned EWG will have a more drastic effect on the boronic acid group based on resonance.

However, entries 6 and 7 show that lower yields are achieved when groups are present in the ortho position. It is believed that steric hindrance is the cause of this drop in yield, despite the small size of a F atom in entry 7.

The next catalyst developed by Yamamoto et al. was a pyridine based boronic acid. The N atom of the pyridine is methylated in the presence of a counteranion to create a positive charge in the ring. This positive charge follows the same logic, in that it increases the Lewis acidity of the boron atom.

![Pyridine based boronic acid catalysts. A reusable catalyst is shown on the right.](image)
2.2 Proposed Mechanism of Catalyzed Amide Formation Reaction

This is the mechanism proposed by Yamamoto et al. in their first paper on this topic.\textsuperscript{4}

\[
\begin{align*}
\text{ArB(OH)}_2 + \text{H}_2\text{O} &\rightleftharpoons \text{ArB(OH)}_2\text{H}_2\text{O} + \text{H}_2\text{O} \\
\text{R'COOH} &\rightarrow \text{R'B(OH)}_2\text{R''NH} \\
&\rightarrow \text{R'N}\text{R''} \text{Ar}
\end{align*}
\]

\textbf{Figure 2.5 Proposed pathway for the formation of the amide.}

The rate-limiting step is the formation of the boronic acetate intermediate. After its formation, the amine performs the attack, forming the desired amide and regenerating the catalyst. In figure 2.5, a boroxine is shown. Boroxines are trimers of boronic acids that are formed when the boronic acid is dried thoroughly.\textsuperscript{5} Isoelectronic to benzene, they are stable species but are vulnerable to hydrolysis back to their monomer forms. They are present in the reaction but it is generally accepted that they don’t participate directly in the mechanism and are simply broken down to boronic acids during the reaction. In this case, it is possible that the carboxylic acid may attack any present boroxine directly to form the desired intermediate and release two boronic acid molecules.
As evidence for this mechanism, Yamamoto et al. presented an experiment where the starting carboxylic acid is reacted with the boronic acid in the absence of amine.\textsuperscript{4} Subsequent NMR studies confirmed the presence of the acylated boronic species. The experiment was then repeated but without removal of water. Upon addition of the amine, 50\% conversion to the amide was achieved. They concluded that this was proof that the boronic acetate residue is the active species.

Recently, in 2006, Andrew Whiting and his group put forth that perhaps another species was the active intermediate.\textsuperscript{16} Performing soft ionization electrospray mass spectrometric techniques, they found that in addition to boroxine and the monoacyloxyboronate species, a diacyloxyboronate species was also present. Given that diacyloxyboronate systems are known acylating agents, they argue that while not conclusive, it is good evidence that this species is the active one.

![Diacyloxyboronate species.](image)

Regardless, the formation of a boronic acetate intermediate is the rate-limiting step. And the reason why water is removed during amide formation reaction is because this boronic acetate intermediate is susceptible to hydrolysis.
This leads to regeneration of the starting reagents and is a great hindrance to the formation of the desired amide, thus lowering the yield.

3. Hydrolytic Stability in B-N Compounds

In 1963, Williams et al. conducted a study of bicyclic azaboroxanes containing B and N atoms and tested their resistance towards hydrolysis. Based on molecular models, they found that the most rigid azaboroxanes have better resistance to hydrolysis when compared amongst one another.

For example, the azaboroxane on the right has a hydrolysis half-time of two minutes while the more rigid structure on the right, because of the addition of
methyl groups and the change to a small ring, has a hydrolysis half-time of 50 minutes.

A few years later, in 1967, Francois et al. reported the synthesis of a polymer containing an arylboronic acid monomer, which contained a dimethylated nitrogen side arm, which interacted with the boron atom.\textsuperscript{6}

![Figure 3.2 Polymer containing a B-N interaction](image)

Their goal was to synthesize a low molecular weight polymer soluble in multiple solvents, but sensitive to chemical reactions. They found that the polymer was very stable to hydrolysis. They concluded that the B-N interaction was responsible for this stability. However, they were not able to achieve their desired solubility, citing that the B-N interaction was probably the cause of it.

More recently, NMR studies have shown the interaction in a stand alone 2-(N,N-dimethylaminomethyl)phenylboronic ester (figure 3.2) and that in the presence of a nucleophilic solvent, the coordination bond is dissociated.\textsuperscript{7} Interested in learning about the mechanism of dissociation, Oki et al. synthesized
a boronic acid containing two dimethyl nitrogen side arms.\textsuperscript{18} He found both arms to be magnetically equivalent, an indication that there is a rapid $S_N^2$ switching of the ligand. Below is the X-ray structure of the two-arm complex.

![Figure 3.3 Crystal structure of the boronic ester showing B-N interaction](image)

Based on these studies, it is evident that B-N coordination exists in these aryl boronic esters and as a result these molecules are more stable towards hydrolysis. Therefore we conclude, that incorporation of a B-N interaction in boronic acids is a possible solution to the problem of hydrolysis encountered during amide coupling reactions.
4. Plan and objectives

To go about and answer that question, the first step is the synthesis of desirable boronic acid derivatives containing said B-N interaction. The B-N interaction that was to be the focus would be the dimethylaminobenzyl group, given that the amount of background on that particular moiety. Other B-N interactions were also of interest, as it would reinforce the idea this interaction in general would have an influence on the hydrolysis of the boronic ester bond.

The next step was to choose which boronic acid would be used as a skeleton to which the B-N side arm would be grafted. Yamamoto’s boronic acid catalysts were chosen because of their relative simplicity, which would hasten their overall synthesis. In addition, the yields for these amide condensation reactions were readily available and could be compared directly with the yields of any of our synthesized catalysts.

When the desired compounds would be synthesized, the effectiveness would be ascertained using various amide formation reactions. The latter would be reactions performed by Yamamoto, and all conditions, including catalytic load would also be identical, at first, to allow direct comparison. In contrast, water would not be removed from the reaction. The difference in yields would then be noted. We expect some of the amide to be formed because of the added hydrolytic stability.
The results of these reactions would determine the next step. If the yields were considered poor in comparison, additional electron withdrawing groups would have to be included in the boronic acid to increase yields. Furthermore, it might be wise to try and include rigidity in the molecule to force the B-N interaction to occur. In addition, quantifying the amount of boronic ester formed may give insight on whether the B-N interaction is favoring the formation of the reactive intermediate.

However, if the yields obtained are good in comparison, the next thing to do would be to generalize the results by using a variety of amide formation reactions. The reaction conditions such as temperature and catalyst load as well as reflux time would be lowered to see if a high yield could still be achieved. Finally, water would be introduced in the reaction to see the effect of its addition on the yield. Additional of electron withdrawing groups would still be of interest if the yield drops with those aforementioned changes.

In summary, the objectives of this thesis are to successfully synthesize boronic acid derivatives containing B-N interactions, compare their effectiveness with other catalysts an amide formation reaction, and perform additional experiments based on the results of the comparison. This will elucidate whether the addition of a B-N interaction in a boronic acid increases hydrolytic resistance of a reactive boronic ester intermediate in an amide formation reaction.
5. Experimental Methods

All of the starting materials, chemicals and solvents used in the experiments were purchased from Sigma Aldrich Chemical Company while the rest of the materials used like glassware and TLC plates was purchased form VWR International.

All NMR spectra were taken using a 400 MHz Varian Instrument with single z gradient, with 5 mm SW PFG $^1$H probe. The software used was VNMR 6.1C on SUN Ultra. An H$^1$-NMR experiment using D-chloroform as the solvent is assumed, unless otherwise indicated. NMR for the synthesized compounds can be found in the appendix. Additional spectroscopic data for these compounds can be found on the papers containing the reaction references.

5.1 Syntheses of B-N Aromatic Boronic Acids

None of the desired boronic acid derivatives were commercially available and had to be synthesized.

5.1.1 Pyridine derivative

The first target molecule was a pyridine based aromatic boronic acid. Modification, such as methylation of the pyridine N moiety can be done after the boronic acid is obtained.
Based on a reaction performed by Sunman et al.\textsuperscript{19}, the first step is an Eschweiler-Clarke methylation. To a solution of 8ml of 3-picolyamine (79 mmol) was added 180mL of formalin and 180mL of formic acid (excess). The reaction was heated for 25h at 90°C. Upon completion, the solvents were evaporated and excess water added followed by basification to pH9 using potassium carbonate under stirring. The solution was extracted twice with 100mL of dichloromethane (DCM) and the resulting organic layer was washed with saturated salt solution and dried over sodium sulfate. Evaporation to dryness yielded 4.73g of an oil whose structure and purity was confirmed by HNMR, a yield of 43%.

Direct lithiation of the resulting N-N-dimethyl-3-aminomethylpyridine was then attempted. Lauer and Wulff successfully achieved ortho lithiation to the dimethylamine group in the aryl version of this molecule\textsuperscript{20}, and this procedure was reproduced for this compound. To a solution of 230mg of N,N-dimethyl-3-aminomethylpyridine (1.5 mmol) in 0.22mL of TMEDA (1.5 mmol) and 2.0mL of dry ether, was added 0.70mL of a 2.15M solution of n-ButylLithium (n-BuLi)
(1.5 mmol) under stirring, at RT, in dry conditions. After vigorous stirring for 3 hours, the reaction mixture was cooled in a methanol/dry ice bath. It was then cannulated simultaneously with a solution of 0.23mL of trimethylborate (2.0 mmol) in 0.29mL of dry ether, to a precooled flask. After one hour of stirring, the reaction was allowed to warm up to room temperature (RT). The solvent was evaporated in vacuo and the resulting residue diluted with 50mL of chloroform. To this solution was added 100mL of water to promote hydrolysis. Removal of the volatile solvents in vacuo followed by azeotropic removal of water using toluene yielded very few crystals, which by NMR, seem to indicate that the starting material had been butylated.

After a bit of research, it was confirmed that pyridines are known to butylate in the presence of BuLi, often resulting in a side product. Also, direct lithiation while achieving high regioselectivity in pyridines is considered to be a challenge despite the fact that the nitrogen side arm can stabilize the resulting lithiated compound, and requires special lithiating agents which much be synthesized. Lithiumdiisopropylamide (LDA) a non nucleophilic lithiating agent was tried, under the same conditions but the starting material was recovered.

Another approach would be to perfect a lithium halogen exchange reaction to direct the boronic acid group to the right position. However, a suitable commercially available starting reagent was lacking. Due to these complications,
it was decided that the pyridine derivative would not be pursued further as there are other interesting derivatives that could be more easily synthesized.

5.1.2 Aryl derivative

Our focus shifted towards the synthesis of the aryl version of the derivative, based on the reaction performed by Lauer and Wulff.\textsuperscript{20}

\[
\begin{align*}
\text{(i) n-BuLi} & \\
\text{(ii) B(O\text{Me})\text{$_3$}} & \\
\text{(iii) H$_2$O} & \\
\end{align*}
\]

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{figure52}
\caption{Synthesis of 2-((dimethylamino)methyl)phenylboronic acid}
\end{figure}

To a solution of 1.3mL of N-N-dimethylbenzylamine (8.6 mmol), 1.3mL TMEDA (8.6 mmol) in 12mL of ether, was added 4mL of 2.15M n-BuLi, under stirring, in dry conditions. After 17h of stirring at RT, 1.4mL of B(O\text{Me})$_3$ (14.7 mmol) in 1.8mL of ether was added simultaneously with the lithium reagent in a precooled flask at −78°C, dropwise and under stirring. The solution was allowed to stand at RT for 24h under mild stirring. The solvents were evaporated in vacuo and the residue dissolved in DCM and subsequently filtered. Water was added to the filtrate and the mixture stirred to promote hydrolysis. Evaporation of the solvent followed by azeotropic removal of water yielded crude crystals in an oil, which looked like the starting material. The residue was recrystallized using
toluene to yield 760mg of the product, a yield of 45%. The NMR spectrum showed formation of the product along with presence of boroxine and some minor impurities. A second recrystallization was performed yielding 90mg of product, a yield of 5%. An additional NMR spectrum was taken using D$_2$O as solvent so as to eliminate boroxines from the spectrum. A very pure compound was obtained.

5.1.3 Azo derivative

The next target derivative was an azo compound:

![Figure 5.3 Synthesis of (E)-2-(phenyldiazenyl)phenylboronic acid](image)

This derivative was chosen because a boronic ester variant had been synthesized. Kawashima and al. were interested in the synthesis of a catecholborane Lewis acid which could be activated or deactivated by light$^{22}$ A couple of years later, they modified the boronic ester and found that the B-N interaction in the molecule as well as strong EWG made the molecule extremely fluorescent.$^{23}$
Based on a paper by Lewis et al.\textsuperscript{24}, 2.8g of nitrosobenzene (13 mmol) and 1.4g of 2-iodoaniline (13 mmol) were dissolved in 3.5mL of acetic acid. The mixture was heated at 80°C for 18 hours. The solution was extracted with light petroleum ether and the organic phase washed with water, dilute sulfuric acid, and water. The organic layer was dried over MgSO\textsubscript{4} and evaporated to dryness. Recrystallization in ethanol yielded a relatively pure (E)-2-iodoaazobenzene, which weighed 0.55g, a yield of 14%. The low yield can be attributed to the recrystallization step as 55% of crude product was recovered prior. Ethanol is probably not the ideal solvent as difficulty was encountered in recrystallization when this experiment was run at lower scale.

To a solution of 0.31g of this material in 8mL of ether was added 0.69mL of a 1.6M solution of n-BuLi, rapidly, at –112°C. The reaction was slowly allowed to warm up and then quenched with water at 0°C. The mixture was then treated with dilute sulfuric acid. The organic layer was isolated and the aqueous layer extracted with ether. The combined organic layers were treated with dilute NaOH. The resulting aqueous layer was then acidified with dilute H\textsubscript{2}SO\textsubscript{4} resulting in the precipitation of a yellow solid. After filtration, and dissolution in ether, evaporation of the solvents in vacuo yielded 0.035g of the desired product, a yield of 14%. NMR confirmed purity of the product. This experimental is based on the work of Kawashima et al.\textsuperscript{22}
An unusually low temperature of –112°C is used here to avoid butylating the azo residue. An aqueous workup here affords pure product, and is usable because the final product is insoluble in water.

5.1.4 Other Derivatives

Another aryl boronic acid that was desirable is the one with two nitrogen side arms.

![](image.png)

**Figure 5.4 Synthesis of 2,6-bis((dimethylamino)methyl)phenylboronic acid**

The above scheme is a brand new scheme for the final target molecule, which was conceived due to low reported yields in current methods. The reported synthesis of the desired final product through direct lithiation boasts a yield of 5-10% through direct lithiation of 1,1'-(1,3-phenylene)bis(N,N-dimethylmethanamine) if performed at very large scales. Because the desired position of the boronic acid is sterically hindered, lithiation often occurs in the non-hindered ortho position drastically reducing yield. It was postulated by the authors that a directed lithiation would yield better results.
The first step is a microwave reaction\textsuperscript{25} where 4.4mg of azobisisobutyronitrile (AIBN) and 495mg of N-bromosuccinimide (NBS) are added along with 250mg of the starting material, 2-bromo-m-xylene, in a test tube. The solids were dissolved in 6.6mL of methyl acetate and a stirrer was added. The test tube was then introduced in a microwave and allowed to react at 110°C, 3 bar pressure for 10 minutes. The reaction mixture was allowed to warm up to RT and then further cooled in an ice bath. The solvents were evaporated in vacuo and the residue extracted with boiling hexanes. The solution was allowed to crystallize overnight in a fridge. A total of 100mg of crystals were recovered, a yield of 30%. NMR confirmed purity of the compound.

The next step of the reaction is an SN\textsubscript{2} reaction\textsuperscript{26}. The procedure is reported in the appendix. The reaction time was 64h and 16 mole equivalents of dimethylamine, NH(Me)\textsubscript{2}, were used in order for the reaction to go to completion, and have both substitutions occur.

The final step, a lithium halogen exchange reaction unfortunately did not go according to plan. Despite numerous attempts, the quenched product, 1-3-((dimethylamino)methyl)benzene, was always recovered. It is postulated that steric hindrance prevented interaction between the trimethylborate and the lithiated intermediate.
5.2 Amide Formation Reactions

Two derivatives containing a B-N bond had been synthesized and they were to be tested in amide formation reaction. The two following amide formation reactions were chosen. The first reaction involves a tertiary amine whereas the second involves a secondary amine.

![Figure 5.5 Amide coupling reactions catalyzed by aryl boronic acids](image)

What follows is a typical experimental for one of these reactions which follows the procedure first employed by Yamamoto. To a solution of 2ml of toluene, was added 66.4mg of 4-phenylbutyric acid (0.4 mmol) and 45.2mg of 3,5-dimethylpiperidine (0.4 mmol), along with 3.5mg of 2-
(dimethylamino)methylphenylboronic acid (0.02 mmol). The reaction mixture was refluxed for one hour. The solvents were evaporated and the residue chromatographed using a 1:1 solution of EtOAc:Hexanes. Evaporation of the solvent in vacuo yielded 51.6mg of the desired amide, a yield of 50%.

The experimental for the first amidation reaction can be found in the appendix.

5.3  NMR Study of Formation of Boronic Ester

Finally, of importance is the study of the monoacyloxyboronate species during the reaction. Formation of the boronic ester is considered to be the rate-limiting step of the reaction and as such is an indication of a successful catalyst. If more of the boronic acid is converted to boronic ester, the yield will be higher.

Based on the NMR study done by Yamamoto\(^4\), here is the procedure. To 94.3mg of 4-phenylbutyric acid (0.6 mmol) and 156.9mg of 3,5-bis(trifluoromethyl)phenylboronic acid (0.54 mmol), was added 2ml of d\(_8\)-toluene. The round bottom flask was equipped with an addition funnel with a pressure equalizing side-arm, charged with 2g of molecular sieves 4A (acting as a Soxhlet). A condenser was then attached and the solution was refluxed for 2 hours. The resulting mixture was cooled to RT and then filtered. NMR was taken and revealed that the desired monoacyloxyacetate was formed, the ratio being 10:3 in favor of the free carboxylic acid
The ratio can be determined by integration because of the shift of peaks of the methylene hydrogens in the molecule. The labeled NMR below shows in details the change in shift (ppm) of the hydrogens.
Figure 4.6  NMR of the reaction displayed in figure 5.6
6. Results

After synthesis of the derivatives, we were eager to test our hypothesis. The following reaction was performed using these catalysts.

![Chemical structure](image1)

Figure 6.1 List of catalysts used in the following amide condensation reaction.

Water was not removed and since it was hypothesized that product would be obtained despite hydrolysis.

<table>
<thead>
<tr>
<th>Catalyst used</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Catalyst Added</td>
<td>37</td>
</tr>
<tr>
<td>1</td>
<td>73</td>
</tr>
<tr>
<td>2</td>
<td>46</td>
</tr>
<tr>
<td>3</td>
<td>34</td>
</tr>
<tr>
<td>4</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>93</td>
</tr>
</tbody>
</table>
The results were very surprising. First of all, 37% yield of the amide was obtained without any catalyst. Amides are known to form under heating through formation of an anhydride\textsuperscript{16}, and as such, some yield was expected. Water was not removed from the reaction mixture, and yet 4 and 5 produced relatively high yields. Catalyst 1 was mildly successful at producing the desired product while catalyst 2 and 3 had failed to improve the yield when compared to the no catalyst scenario.

Catalyst 3 was not expected to produce a good yield. This is because this catalyst lacks EWG and as such the boron atom is less Lewis acidic. Catalysts 4 and 5 were expected to give decent yields because of EWG present. Overall, catalyst 1 performed decently, given that it contained no EWG while catalyst 2 was a mild disappointment.

To confirm these finding, the second amidation reaction was performed on these catalysts. The reflux time was kept to one hour and the reaction conditions matching those attempted by Yamamoto when he was comparing aryl boronic acids.

![Figure 6.2 Amide Formation Reaction performed in refluxing toluene](image-url)
Water was not removed to see if the results differed from Yamamoto’s findings. Here are the results:

Table 6.2  Yields obtained for the reaction depicted in figure 5.2

<table>
<thead>
<tr>
<th>Catalyst used</th>
<th>Yield (%)</th>
<th>Yield with removal of water (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No catalyst added</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>1</td>
<td>54</td>
<td>Not performed</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>Not performed</td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>23</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>64</td>
<td>56</td>
</tr>
</tbody>
</table>

Results for compounds 4 and 5 with removal of water are taken from Yamamoto’s paper (Ref. 4)

Very little yield is obtained when no catalyst is added in this case, as the reaction time is only one hour. As such, thermal driven formation of the product does not occur. The first conclusion that can be determined from these two sets of data is that the azo compound, compound 2 is a poor catalyst. The reason for this is probably due to steric. There is a very large bulky group in the position ortho to the boronic acid rendering entry of other molecules difficult. Catalyst 1 also contains an ortho substituent, however it is smaller in size and other effects may be compensating for that effect. Catalysts 4 and 5 again, perform relatively well as expected due to the increased Lewis acidity of their respective boron residues.

Interestingly, the yields of compounds 3, 4 and 5 are very similar compared to Yamamoto’s results despite the fact that water was not removed
from this reaction. Water removal, which was regarded as crucial to good yields, may not be as vital as originally thought.

Overall, these results were mildly encouraging. All things considered, catalyst 1 was mildly successful. The next logical step was to test how the catalyst would perform if electron withdrawing groups were added to the molecule. If the amide is more easily formed in superior yields compared to generic boronic acids, then it can be argued that it is a result of the N side arm. However, the answer to that question was provided to us. In early 2008, Andrew Whiting released a paper using the following boronic acid catalyst as a model.27

![Bifunctional Catalyst](image)

**Figure 6.3** A bifunctional catalyst

He found that adding EWG to the ring of the above compound does indeed increase the rate of reaction as expected due to the change in Lewis acidity. The reaction conditions and substrates that he uses are optimized for this catalyst and it should be noted that water is still removed from the reaction mixture. Upon further reading, it was discovered that he also tested catalyst 1 briefly16 and found it to be less performing in those conditions. He suggested that the reason why
these molecules are decent amide formation catalyst is due to their bifunctional nature. In other word, they contain both an acidic group and a basic group. The basic group referred to here is the N atom. Primary amines are quite capable of accepting a proton and as such it is postulated that this group may have some role during the formation of the product. Though, the exact role or mechanism of this interaction has yet to be determined, this nitrogen side arm may act as a proton scavenger. As a result, it is possible that the acid is deprotonated when performing the attack on the boronic acid group and that as a result, formation of the boronic ester, which is the rate-limiting step, is favored.

This would explain why two isopropyl groups would give slightly better yields that two methyl groups. Isopropyl groups are better electron pushers than methyl groups as such the nitrogen atom is more nucleophilic and perform better as proton scavengers. However, there is one big difference between 1 and 6, in that it is known that there is no B-N interaction in compound 6. This is because of the presence of the bulkier isopropyl groups and was confirmed via X-ray diffraction experiments.  

Without a doubt, adding electron withdrawing groups would increase the yields for amidation reactions for species 1. At that time, however, we were more interested in answering the following question: what is the consequence of having a B-N interaction? Does it enhance the boronic ester formation as a result of decreased hydrolysis rates? It became clear that the NMR experiments discussed
in section 4.3, where Yamamoto’s group detected the amounts of boronic ester formed when compared to free carboxylic acid, would elucidate this matter.

The length and the substrates used were optimized carefully as boronic acids are known to cleave in acidic media. It was found that the boronic esters formed even when water was not removed from the reaction. After 24h of reflux time in d₈ toluene, without removal of water, using catalyst 5, 23% of the carboxylic acid was found to have been converted to the desired acyloxyboronic acetate. When this reaction was performed using compound 1 and 2, no acyloxyboronic acetate intermediate could be detected by NMR. The experiment was repeated with removal of water; after 4 hours, catalyst 5 had converted 60% of the carboxylic acid into the desired intermediate. Again, catalysts 1 and 2, failed to produce any conversion.

From this data it is clear that boronic ester formation is not favored without electron withdrawing groups. Also, one has to consider that because of the B-N interaction, the boron atom is less Lewis acidic due to this “donation” of the nitrogen electrons. Added to the fact, that the ortho group adds steric to the equation, these factors combine and greatly reduce boronic ester formation.

We can therefore conclude that the B-N interaction does not enhance formation of the boronic ester intermediate. While it may have some stabilization effect on the hydrolysis of boronic esters, it is negligible because other boronic acids are also capable of synthesizing these amides despite the fact that water is
not removed from the reaction. This finding, although purely coincidental, is interesting as it seems the need to remove water from the reaction is not as critical as once thought. Concerning formation of the boronic ester, a B-N interaction might also have the negative effect of lowering the Lewis acidity of the boron atom causing lower reactivity. Nitrogen has electron lone pairs which it can donate to the boron atom; as a result, the boron atom is less likely to be attacked by a carboxylic acid group. It seems that the promising yields are simply due to the bifunctional nature of these molecules: through the ability of the nitrogen side arm to participate in the reaction through proton transfer.
7. Contribution to Knowledge and Future Work

In summary, it was shown that B-N interactions did not produce the desirable effect on boronic acid catalysts through NMR experiments, which showed lower formation of the reactive intermediate. The higher than expected yields in amide condensation reactions in absence of water were probably obtained due to the bifunctional nature of the molecule itself. The lower yields in comparison to boronic acids without the B-N interaction is attributed in part to the fact that the N atom acts as an electron donor to the B atom, thus lowering the rate of attack of the carboxylic acid residue on the latter.

In regards to future work, further understanding of the exact role of the B-N interaction needs to begin with the elucidation of the exact mechanism of the boronic acid catalyst. The active intermediate needs to be found and to achieve this, the two potential active intermediates (mono- and di- acyloxyboronic ester) need to be isolated or synthesized independently and tested to see if they both results in good formation of the amide when an amine is added. It is quite possible that they could be active intermediates and that they both contribute to formation of the amide but it needs to be confirmed.

Furthermore, the exact role of the nitrogen side arm needs to be investigated further. The next logical step would be to synthesize the boronic ester intermediates directly and find the hydrolysis rate with, and without the B-N
interaction. This would confirm whether the B-N interaction reduces hydrolysis rates in those molecules.

Also, synthesis of a derivative with a more rigid structure might help improve hydrolysis rates, although increasing sterics around the B atom may cause a drop off in the rates of catalysis. Addition of electron withdrawing groups to such a compound may be necessary to counter this effect. The donation of electrons to the B atom by the N moiety resulting in lower Lewis acidity of the B and thus lower reactivity is also a concern. There isn’t really a solution to this although the effect may be reduced by additional EWGs to overcome the effect.

The most interesting finding is that regarding the need to remove water from the reaction mixture. Yields should be compared, with and without removal, for various carboxylic acid and amides, to generalize the finding. If the results are consistent, it is possible that by increasing reaction conditions, such as temperature or catalytic load might give a sufficient increase in yield such that water need not be removed at all. This would be a great step towards improving boronic acid catalysis in general.

In closing, boronic acid catalysis of amide formation reactions is an exciting new area, which is still in its infancy. Further developments in catalysts and reaction conditions will pave the way to eventual applications in the industry.
References


Appendix

Formation of 1,1'-(2-bromo-1,3-phenylene)bis(N,N-dimethylmethanamine

To a three neck round bottom flask under argon, was added 20.8mL of dimethylamine in THF solution (2M) (41.6 mmol). The reaction mixture was cooled to 0°C upon which 878mg of 2-bromo-1,3-bis(bromomethyl)benzene was added, dropwise, from an additional funnel, while stirring. The solution was allowed to warm up to RT and was left standing for 64h. The solution was then filtered, concentrated to half volume, refiltered and evaporation of the solvents in vacuo yielded an oil. This residue was dissolved in pentane and the filtered. The filtrate was dried over MgSO₄. The drying agent was filtered off and the solvents evaporated to yield 586mg of an oil, a yield of 83%. NMR confirmed purity of the product.
Formation of N-benzyl-3-phenylpropanamide

A typical experimental for the amidation reaction depicted in figure 4.5 and 5.1 is listed below. To a round bottom flask was added 50.1mg of 4-phenylbutyric acid (0.31 mmol), 36.9mg of benzylamine (0.34 mmol) and 2mL of toluene. The reaction mixture was refluxed for 18 hours. The solution was chromatographed using a 1:1 EtOAc:Hexanes solution and 69.2mg of the product was recovered, a yield of 90%. Purity was confirmed by NMR.
Two isomers: DL and meso

Aromatic

Ha, Hb, Hc, Hd

2.02 1.66 1.60 1.55 1.52 1.30 0.70 0.65 2.00 2.80 3.45 5.48