Synthesis and Application of Boronic Acid Derivatives

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Abstract

Boronic acids are attractive synthetic intermediates and have been shown to be effective as inhibitors of various enzymes. In this project, the overarching goal is the selective inhibition of a protease present in the mitochondria known as human ClpXP. To study the potential selective inhibition of Human ClpXP using N-terminal peptidic boronic acid, we have designed a synthetic scheme that includes β-borylation of α, β-unsaturated carbonyl compounds using Cu(I) as catalyst, α-alkylation, saponification/hydrogenation, amidation, and oxidative removal of pinacolyl group with sodium periodate. A simple amidoboronic acid was also synthesized for stability studies. This compound, synthesized in 44% overall yield, could be used as a surrogate for N-terminal peptidic boronic acid to provide basic understanding of the stability of more elaborate N-terminal peptidic boronic acids. During the synthesis of this compound, published deprotection methods were not suitable to deprotect the pinacol group. A two-step protocol for pinacolyl boronic ester deprotection via a diethanolamine protected intermediate was successfully developed with the advantages of mild reaction conditions, tolerance to various functional groups, short reaction time and ease of product isolation. The current results will be useful for the deprotection of other boronic esters, such as pinanediol protected compounds, which are being used extensively in stereoselective synthesis.

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Abbreviations

Ac	acetyl
Bn	benzyl
Boc	tert-butoxycarbonyl
DCM	dichloromethane
DEA	diethanolamine
DMSO	dimethyl sulfoxide
DPEphos	bis(2-diphenylphosphinophenyl)ether
EtOAc	ethyl acetate
GC	gas chromatography
HOAt	1-hydroxy-7-azabenzotriazole
HRMS	high-resolution mass spectrometry
KHMDS	potassium hexamethyldisilazide
LDA	lithium diisopropylamine
LiHMDS	lithium hexamethyldisilazide
MeOH	methanol
MIDA	N-methyliminodiacetic acid
NaHMDS	sodium hexamethyldisilazide
NMR	nuclear magnetic resonance
Pd/C 10%	palladium on activated carbon (Pd 10%)
THF	tetrahydrofuran
TMSCl	chlorotrimethylsilane
TLC	thin layer chromatography

Chapter 1 . Introduction to Boronic Acids

1.1. Overview of Boronic Acids

Boronic acids are trisubstituted organoboron compounds with one alkyl, alkenyl or aryl group, and two hydroxyl groups covalently attached to boron. They are the second oxidation products of boranes. Figure 1.1 shows the structure of organoboron compounds. Borinic acids are the first oxidation products of boranes, which have one hydroxyl group and two alkyl or aryl groups. Further oxidation of boronic acids will give the product of third oxidation of boranes, boric acid, which has three hydroxyl groups. Other commonly seen organoboron species also include boronic esters, and boron-ate complex. Boron-ate complex is the structure in which boron has four substituents on it and bears a negative formal charge.

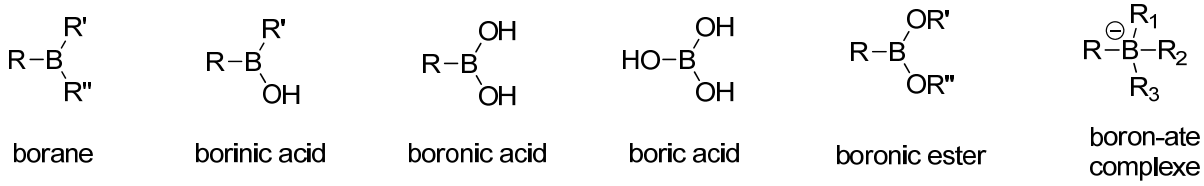


Figure 1.1 Structure of organoboron compounds.

In boronic acids, there are only six valence electrons on boron, which leaves boron with an empty *p* orbital. In this case, boron is sp^2 hybridized, and therefore boronic acids will adopt a trigonal planar geometry. The vacant *p* orbital is orthogonal to the three substituents and can easily accept electrons from Lewis bases.

Boronic acids are not found in nature. Usually they are synthesized and their primary source is boric acid (Figure 1.2). Boric acid found in nature mainly comes from the product of acidification of borax with carbon dioxide. Borax is a white-powder like mineral, which has a molecular formula $Na_2B_4O_7 \cdot 10H_2O$ or $Na_2[B_4O_5(OH)_4] \cdot 8H_2O$. Once boric acid is formed, it can undergo dehydration with alcohols to give borate esters, which are the main precursors for boronic acid derivatives used in organic synthesis. The first preparation and isolation of a boronic acid was performed by Frankland in 1860.[1] In their report, they treated triethylborate with diethylzinc to obtain triethylborane, which is highly sensitive. After slow oxidation in air, ethylboronic acid was formed.

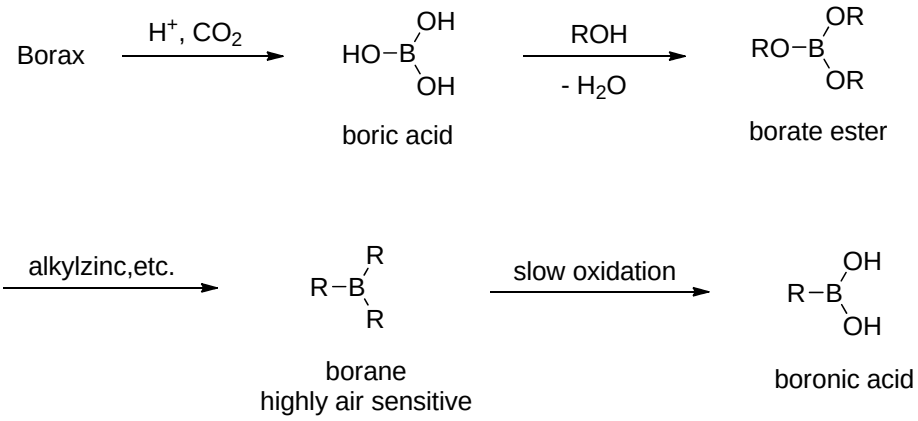


Figure 1.2 Primary sources for boronic acids preparation.

Boronic acids have been proven to have low toxicity and are less sensitive to oxygen than borinic acids.[2] Therefore, they are easier to handle. Their further oxidation product, boric acid, is also very stable and considered to be relatively benign in the human body. All these properties combined with their unique mild Lewis acidity makes boronic acids very attractive synthetic intermediates. As seen in Figure 1.3, the number of publications focused on boronic acid derivatives has increased dramatically, especially in the 1980's.[3] The most remarkable discovery

is their application in palladium-catalyzed cross-coupling reaction with carbon halides by Suzuki and Miyaura in 1979.[4] They have also found use in biology and medicinal chemistry, which culminated in the first FDA approved boronic acid anti-cancer drug, Velcade®.[5] Boronic acid derivatives are finding profound usefulness in a variety of areas.

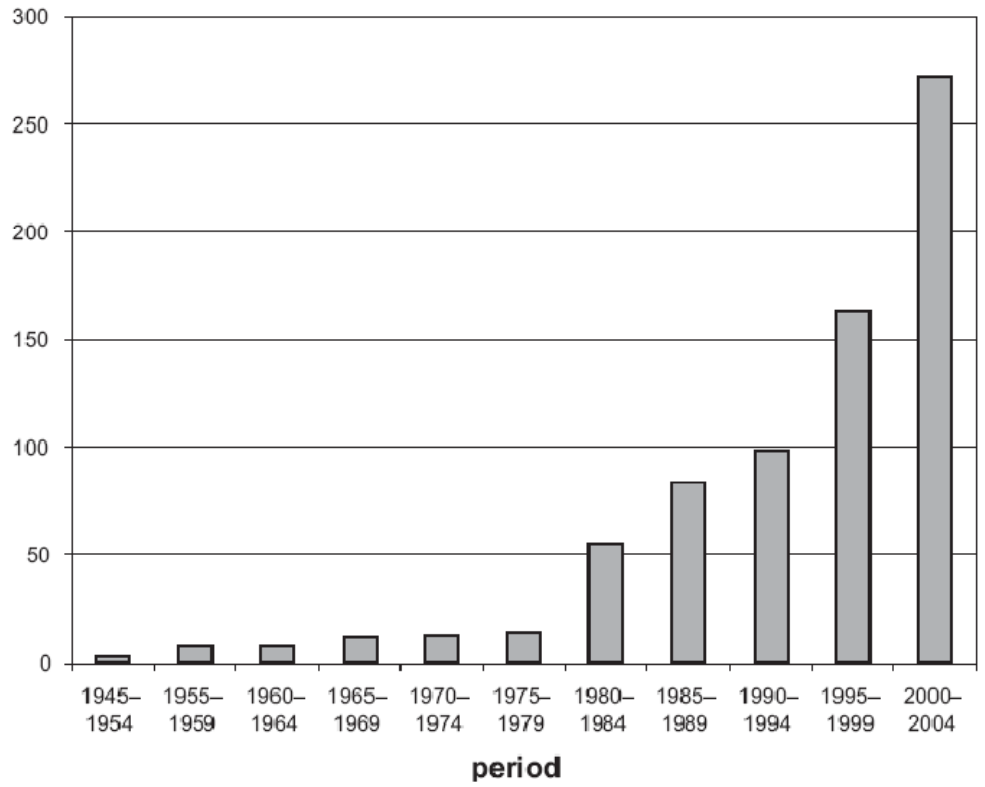


Figure 1.3 Number of publications focused on boronic acids over time (Note that only those publications including the word "boronic" in their title were included). [3]

1.2. Structure and Properties of Boronic Acid Derivatives

In this section, the structural and physicochemical properties of boronic acids and their several derivatives will be generally described.

1.2.1. Boronic Acids

1.2.1.1. Structure Characters: Bond Length and Bond Energy

In Dennis Hall's book, he gives several examples of the relationship between the structures and bond lengths of different boronic acids and their derivatives.[6,7,8] In Figure 1.4, compounds **1.1** to **1.3** are aryl boronic acids with different substituents on the phenyl ring. As shown in Table 1.1, their B-C bond lengths are within the range from 1.57 to 1.59 Å, while the B-O bond lengths are in the range of 1.35-1.38 Å.[6,7,8] Their X-ray crystallographic analysis shows that each single asymmetric unit actually contains two molecules, which are linked to each other through hydrogen bonds (Figure 1.5 A). Then each dimer is attached to other four similar units through the same binding pattern (Figure 1.5 B). In compounds **1.1** and **1.3**, the CBO_2 portions are almost coplanar with the benzene rings, while in compound **1.2**, it is nearly perpendicular to the ring, which might be caused by the steric hindrance of the nearby nitro group and the possible interaction between one oxygen from the nitro group and the trigonal boron atom.

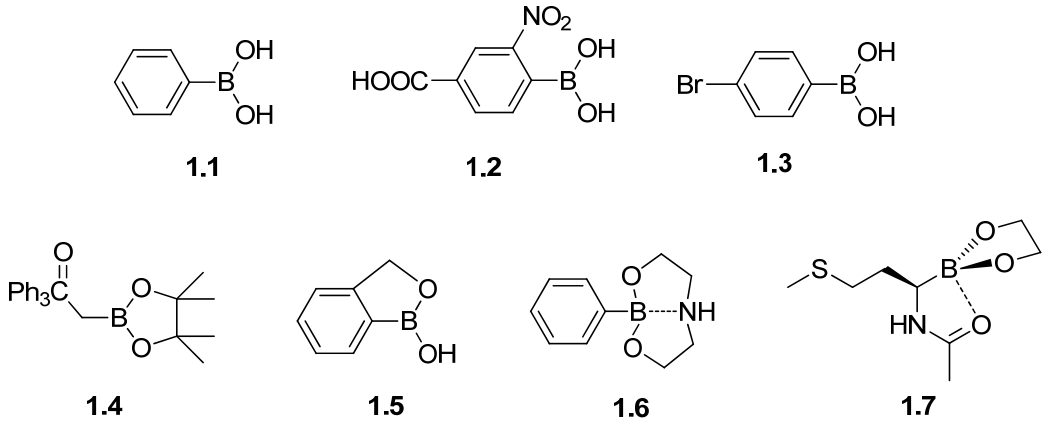


Figure 1.4 Boronic acids and derivatives analyzed by X-ray crystallography.

Table 1.1 Bond lengths from X-ray crystallography for compounds **1.1**-**1.7**.[3]

Compound	B-C (Å)	B-O^1 (Å)	B-O^2 (Å)	B-X (Å)
1.1[6]	1.568	1.378	1.362	-
1.2[7]	1.588	1.365	1.346	-
1.3[8]	1.573	1.363	1.357	-
1.4[9]	1.560	1.316	1.314	-
1.5[10]	1.494	1.408	1.372	-
1.6[11]	1.613	1.474	1.460	1.666
1.7[12]	1.613	1.438	1.431	1.641

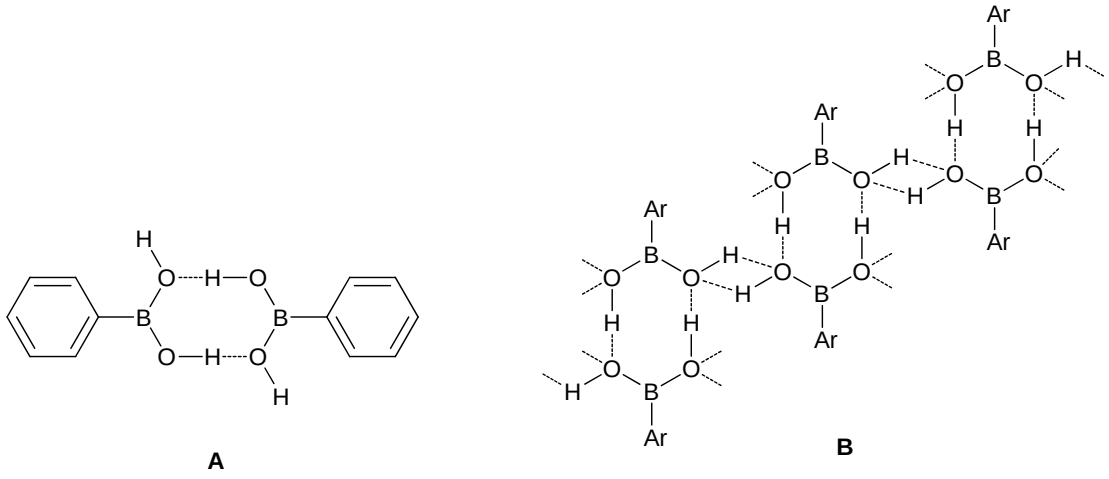


Figure 1.5 (A) Dimeric unit showing hydrogen bonds. (B) Extended hydrogen-bonded network.[3]

Compound **1.4** is a pinacolboronic ester, which has a shorter B-C and B-O bond distance compared to boronic acids (Table 1.1).[9] In the cyclic hemiester **1.5**, these numbers are even smaller.[10] The X-ray crystallographic analysis of **1.5** shows that its B-O bond is slightly longer than the B-OH bond due to the ring constraint, which prevents effective lone-pair-electron

conjugation of the oxygen and the boron empty orbital. The crystallographic structure also shows that instead of extended network as shown in Figure 1.5, the cyclic hemiester only exists in a dimeric pattern because of the absence of a second hydroxyl group.

Because the boron atom has an empty p orbital, to fulfill its octet, it can accept electrons from a Lewis base to form a tetracoordinated complex. In this case, boron will bear a formal negative charge and this structure is named as "ate complex" (Figure 1.1). Ate complexes are usually in a tetrahedral geometry. For example, compounds **1.6** and **1.7** are both ate complexes. **1.6** was formed from the coordination between phenylboronic acid and diethanolamine. Nitrogen from the amine would donate its lone pair electrons to the empty orbital of tricoordinated boron atom to form a tetracoordinate complex. The distance of B-O in this case will be about 0.1 Å longer than in the corresponding tricoordinated boron compounds, which is consistent with the estimation that the bond energy of B-O in tricoordinated boron compounds will be a little stronger than that in tetracoordinated boron ate complexes (about 12 kcal/mol).[13]

Generally B-C bond energy is slightly less than that of C-C single bond (77 vs. 86 kcal/mol).[14] B-O bonds in tricoordinated boronic acids on average are much stronger than C-O bonds of ethers (124 vs. 92 kcal/mol).

1.2.1.2. Physical Properties

Most boronic acids are known to be white solids and are relatively stable under ambient temperature. They can be handled in air without special precautions and usually have long shelf lives. However, when they are dehydrated, boronic acids tend to form oligomeric anhydrides, which can complicate their characterization. The anhydrides will then perform as the initiators

for further decomposition of boronic acids upon exposure to air.[15] Therefore, in order to avoid or minimize oxidation, it is better to store boronic acids under inert environment or in a slightly moist state. Because of the potential formation of anhydrides, the melting points of boronic acids are not reliable. Due to the inconveniences mentioned above, the corresponding boronic esters are used instead.

Because most small boronic acids dissolve in both polar organic solvents and aqueous solutions, their purification and isolation process may be complicated.

1.2.1.3. Chemical Properties

The most characteristic feature of boronic acids is their Lewis acidity. Because of the empty p orbital on boron, boronic acids can accept electrons from Lewis bases to form reversible covalent tetrahedral complexes with amino acids, sugars, etc. The pKa values of boronic acids could vary depending on the alkyl or aryl substituents, but are generally about 9. While complexing in aqueous solution, the pKa value of the tetrahedral boronate complexes will decrease to about 7. The boronic acid-diol equilibrium in water was first studied by Lorand and Edwards.[16] They confirmed that the structure of a borate ion in aqueous media should be a tetrahedral Lewis acid-base adduct (Figure 1.6, A), instead of a trigonal Brönsted base form (B).

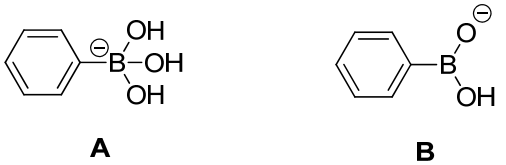


Figure 1.6 Structures of phenyl borate ions: (A) tetrahedral Lewis acid-base adduct. (B) trigonal Brönsted base form.

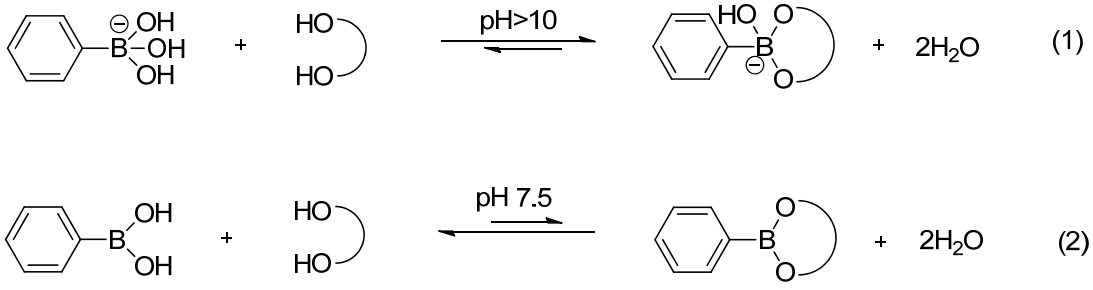


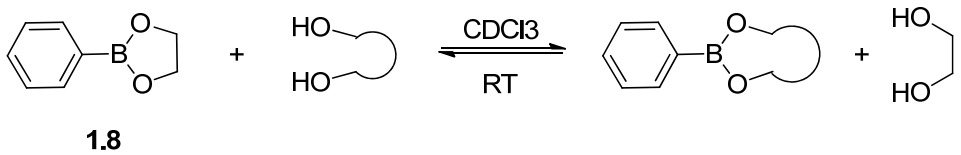
Figure 1.7 Equilibrium formation of boronic esters under high (1) and neutral (2) pH in water.

A lot of studies have been done on the equilibrium between boronic acids and their ester forms with different diols.[17,18,19,20] The ester formation was shown to be more favored under a high pH condition (Figure 1.7, Equation. 1), while the acid was the major form under neutral condition (Figure 1.7, Equation. 2). The existence of the tetrahedral boron ate complex under basic conditions confirms the Lewis acidity of boronic acids. The fact that acid form is more favored than the corresponding ester under neutral condition shows that the ester is more acidic than the starting boronic acid. For example, phenylboronic acid has a pKa value of 8.8, while the ester forms with glucose and fructose are 6.8 and 4.5 respectively (which is consistent with the known order of sugar-boronate complex stabilities because boronic acids prefer to complex with compounds containing vicinal *cis*-diols).[19,21] This trend is only general. When comes to a specific boronic acid, the measurement of equilibrium could be effected by several factors, such as the pronounced effect of the solvent, pH, buffer compounents, temperature and the concentration of these species on the equilibrium.[20]

1.2.2. Boronic Acid Derivatives: Boronic Esters

As mentioned earlier, the handling of boronic acids are not very convenient in terms of purification and characterization. They tend to undergo autoxidation process and do not have a long shelf life when they are in an anhydrous condition. Therefore, the ester derivatives, in which the two hydroxyl groups are protected, are used instead.

Boronic esters are less polar than the original boronic acids. Usually they exist as a liquid and can be purified by distillation or chromatography on silica gel. Boronic esters can be formed as in the equilibrium shown in Figure 1.7 (Equation. 2), in which the diol can be cyclic or acyclic. The equilibrium will favor the right side when the ester product is not soluble in the reaction solvent. In this case the product can be isolated by filtration and usually does not need further purification. Otherwise, ester formation can be favored by azeotropic distillation of the water produced using a Dean-Stark apparatus or by removing the byproduct water using dehydrating reagents, such as anhydrous $MgSO_4$. Transesterification is also one way to synthesize boronic esters, which utilizes relatively less stable boronic esters reacting with diols to form more stable ester products. H. C. Brown and his coworkers studied the structure effects on the relative rate of transesterification of 2-(phenyl)-1,3,2-dioxaborolane (**1.8**).[22] They used a wide variety of cyclic and acyclic diols (Figure 1.9) to compare electronic and steric effects on transesterification.



1.8

Figure 1.8 General scheme for the transesterification of 2-(phenyl)-1,3,2-dioxaborolane (**1.8**) with various diols.[22]

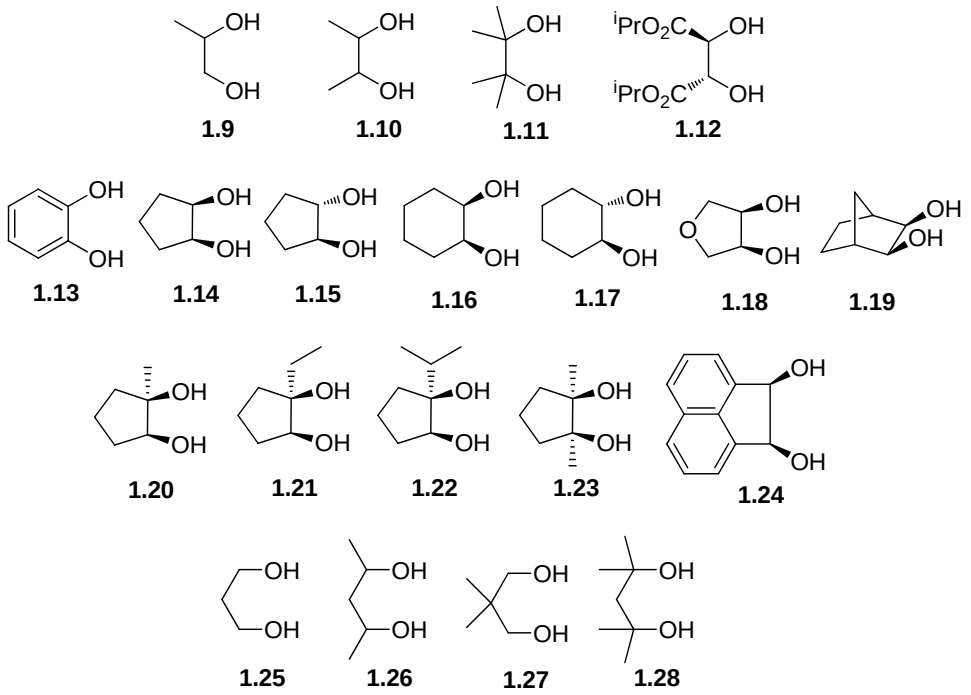


Figure 1.9 Diols of diverse structure types.[22]

The reactions were carried out in $CDCl_3$ at room temperature in NMR tubes and monitored by ^{1}H NMR.[22] The results showed that alkyl groups on the α position of diols will slow down the reaction, but form thermodynamically more stable products (among **1.9**-**1.12, 1.9** reacts faster than the others while **1.12** forms the most stable complex with boronic acid). The introduction of alkyl group on the diol will slow down the reaction but yields thermodynamically more stable substituted cyclopentanediol boronic esters (**1.23** is the most stable among **1.20**-**1.24**, however, the reaction takes 285 hours to get 99% yield). Six-membered boronic esters are thermodynamically more stable than their corresponding five-membered boronic esters (boronate complexes with **1.25**-**1.28** are more stable than the ones with **1.9**-**1.12**). Only *cis*-diols will undergo transesterification (**1.14** vs. **1.15**).

1.3. Major Reactions of Boronic Acid Derivatives

1.3.1. Suzuki Coupling Reaction

In 1979 Miyaura and Suzuki published a paper in *Chemical Communications.* They reported the palladium-catalyzed cross coupling between organoboronic acid and halides, which is called Suzuki coupling or more appropriately Suzuki-Miyaura coupling (Figure 1.10).[4] This method has several advantages, such as using boronic acids which are environmentally safer and much less toxic than the organostannanes used in Stille coupling, mild reaction conditions, commercial availability of many boronic acids, easy removal of inorganic by-products, the tolerance of starting materials to a wide variety of functional groups and even water, stereo- and regioselectivity.[23]

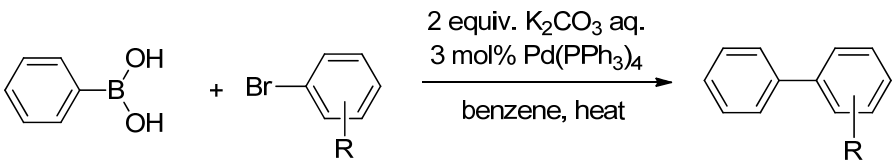


Figure 1.10 First published Suzuki coupling.

Recent developments of catalysts and methods have broadened the application of the Suzuki coupling reaction dramatically, so the scope of the reactants is not restricted to aryls, but has been expanded to alkyls (Figure 1.11), alkenyls and alkynyls.[24]

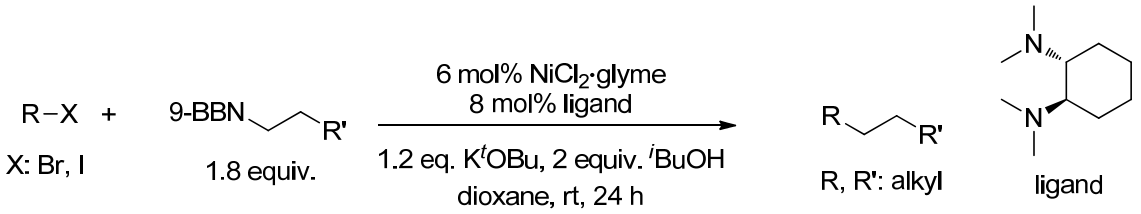


Figure 1.11 Alkyl-alkyl Suzuki cross-couplings of unactivated secondary alkyl halides at room temperature.[24]

Instead of boronic acids, potassium trifluoroborates (Figure 1.12) and boronate esters can also be used.[25,26] Some pseudohalides such as triflates may also be used as coupling partners (Figure 1.13).[27] Due to the stability, ease of preparation and low toxicity of boronic acid compounds and the versatility of Suzuki coupling, these compounds have become one of the most useful intermediates to synthesize a broad range of compounds as pharmaceutical intermediates, with new development and improvement being reported constantly.

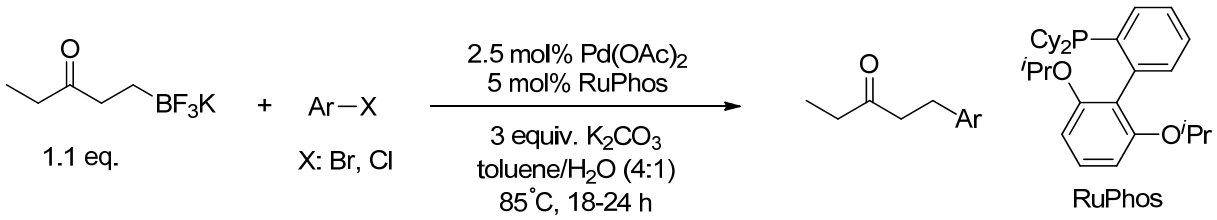


Figure 1.12 Suzuki-Miyaura cross-coupling of potassium trifluoroboratohomoenolates.[25]

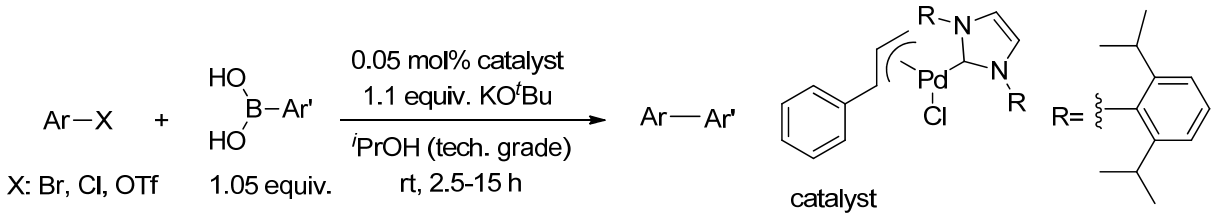


Figure 1.13 Modified (NHC)Pd(allyl)Cl Complexes for RT Suzuki-Miyaura coupling.[26]

1.3.2. Allylation of Carbonyl Compounds

The first reaction between aldehyde and allyboronate was reported in 1979. This reaction is important in the stereoselective carbon-carbon bond formation, especially the synthesis of acetate and propionate containing compounds.[28] Recently, with the addition of Lewis acids, for example $Sc(OTf)_3$, the reaction could be accelerated, and the reaction temperature decreased, leading to increased diastereo- and enantioselectivity (Figure 1.14).[29]

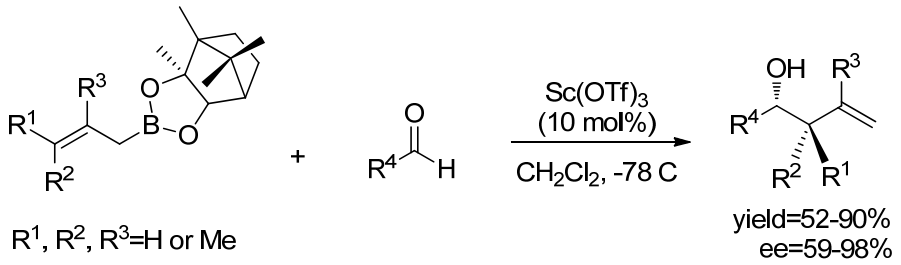


Figure 1.14 $Sc(OTf)_3$-catalyzed enantioselective addition of allylboronates with model aldehydes.[29]

1.3.3. Other Reactions and Applications

There are many other useful reactions which can be performed with boronic acid derivatives, such as metal-catalyzed protodeboronation, carbon-heteroatom bond forming processes, nucleophilic addition reactions of aryl and alkenylboronic acids, cycloadditions to alkenyl-, alkynyl- and dienyl boronic esters, etc.[30] Boronic acid derivatives can also be used as supports for derivatization and affinity purification of diols, sugars and glycosylated proteins; or be used as receptors and sensors for carbohydrates and other small molecules.[31,32] Since these are not the emphasis of this thesis, they will not be discussed here.

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Chapter 2 Designing N-terminal Peptidic Boronic Acids as Protease Inhibitors

2.1. Biological and Medicinal Applications of Boronic Acids

Boronic acids have unique properties as follows: ready inter-convertibility between the sp^2- and sp^3- forms, strong interaction with diol-containing compounds and Lewis acidity. All these properties make boronic acid compounds useful in both biological and medicinal applications.

2.1.1. Boronic Acid Derivatives as Neutron Capture Therapy Agents

Boron neutron capture therapy (BNCT) is a radiation therapy that was first proposed for potential application in the field of medicine by Locher in 1936.[1] As the name suggests, this therapy has two key aspects. The first aspect is the use of a stable ^{10}B-containing compound that will selectively bind to tumor cells and is usually given to patients by intravenous injection. The second is a beam of low energy neutrons. When these two parts are kept separate, there will be only minor effects on cells. After a high concentration of a ^{10}B-containing compound around target tumor

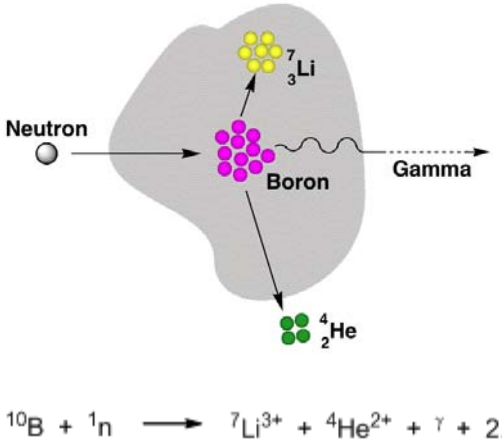
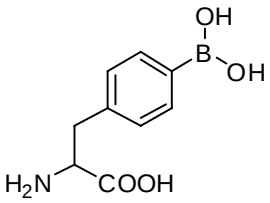


Figure 2.1 BNCT cell graphic and BNCT reaction.[2]

cells is accumulated, a neutron beam is used to interact with it. The ^{10}B adjacent to the tumor cells will disintegrate once a neutron is captured, and the resulting high energy heavy particles generated will destroy the cells close to it (Figure 2.1).[2]

One of the most important developments of this therapy is the synthesis of boron-containing compounds that are selective to tumor cells. Many reports of BNCT have been published including compounds like boronic acids, boronated benzamide and boron clusters.[3,4,5,6]

4-Dihydroxyborylphenylalanine (BPA, compound **2.1**) was first synthesized by Snyder and his coworkers and evaluated biologically.[7,8] Its potential in BNCT was not recognized until two decades later when Mishima et al. showed its potential in treating melanomas. It was finally used as a BNCT agent in treating malignant brain tumors by Coderre.[9,10] The driving force behind their interest is that BPA is an amino acid and could be viewed as an analogue of phenylalanine or tyrosine. Clinical trials as a BNCT agent using this compound are currently ongoing and so far no negative effects have been observed.[6]



2.1

2.1.2. Boronic Acid Compounds as Transmembrane Transport Agents

Boronic acids easily form cyclic esters with diols in water and some of the boronate esters can be stable. However, when the pH changes, most of these boronate esters can be converted to the starting boronic acids. These boronate esters have a trigonal planar structure and can form tetrahedral "ate" complexes with Lewis bases, for example, hydroxyl groups, or alkoxide anions. The transformation between trigonal and tetrahedral configurations of boron compounds is an equilibrium which can be affected by pH, pKa of boronate esters, the original

diols, etc. If the counter ion is lipophilic, the boron-ate anion-cation pair could have very different solubility than the original diols. Because of this property, boronic acids have been studied extensively in molecular transport across lipophilic membranes. One important application of boronic acid carriers is the selective transport of fructose across lipophilic membranes (Figure 2.2).[11] When the pH is higher than the pKa value of boronic acid, this mechanism dominates. The sugar molecule is transported from the aqueous departure phase to the receiving phase along with hydroxide. Therefore a pH gradient can be used as the driving force.

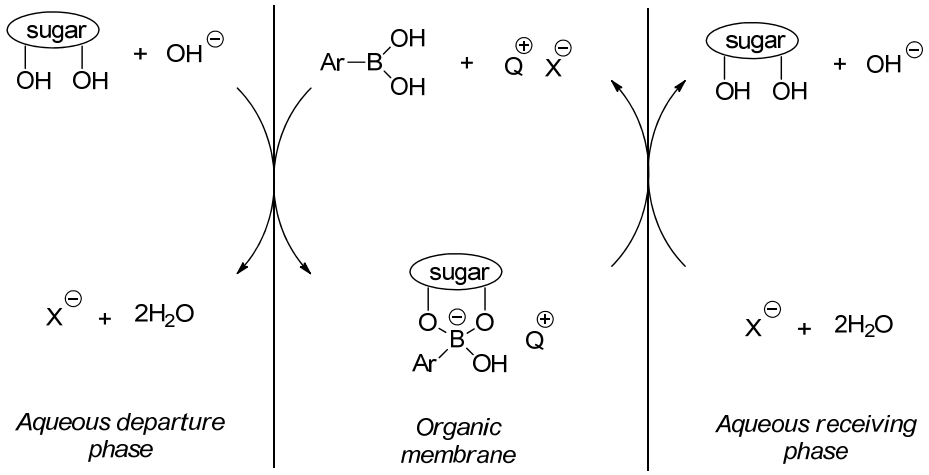


Figure 2.2 Conjugation of arylboronic acids with lipophilic salts (Q^+X^-) assists in the passage of sugars through a lipophilic organic membrane.[11]

2.1.3. Boronic Acids as Protease Inhibitors

Boronic acids have been shown to be effective as inhibitors of various enzymes, in particular of serine proteases (Figure 2.3).[12,13] Boron contains three valence shell electrons and an orthogonal empty p-orbital, making it a mild Lewis acid. Boron can readily convert from

trigonal planar to a tetrahedral geometry to adopt a carbon-like configuration. Formation of a reversible covalent bond between a serine residue and boron can significantly boost the binding affinity because the B-O bond of the substrate-protein adduct is strong. The B-C bond is also believed to be more stable to hydrolysis than the C-N bond of the tetrahedral intermediate during peptide hydrolysis (energy difference between B-C and C-N bonds is about 11 kcal/mol). All of the above properties make boronic acid a good carboxyl group mimetic of α-amino acids.

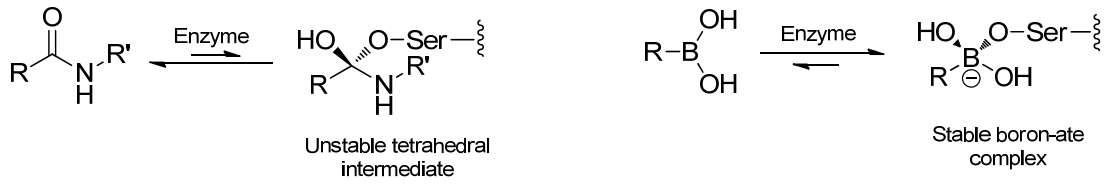


Figure 2.3 Boronic acids as mimetics for hydrolysis intermediate of targeted peptide substrates.

2.2. Designing Peptidic Boronic Acids as Lead Compounds

2.2.1. Synthetic Rationale

During peptide hydrolysis, the scissile amide bond is first attacked by an activated water molecule that produces a tetrahedral intermediate containing a geminal diol (Figure 2.4). These hydroxyl groups are well organized and are recognized by the residues on the protein active site. The enzyme catalyzes the formation of this tetrahedral intermediate. When the intermediate collapses, two peptidic fragments are generated (N-terminal fragment **2.2** and C-terminal fragment **2.3**). By replacing the scissile amide functional group with a boronic acid we could mimic the tetrahedral intermediate formed during the transition state. *C*-terminal boronic acid inhibitors **2.4** will take advantage of the left side (P sites) of the scissile amide bond. It is expected that the residues on the right side (P′) should also contribute to substrate selectivity and

affinity. In the design of N-terminal peptidic boronic acids, the nitrogen derived from the scissile amide bond is changed to carbon (due to the poor stability of carbamic acid **2.6**) and the carboxyl group is replaced with a boronic acid moiety. Compound **2.5** would be the actual N-terminal peptide analogue synthetic target.

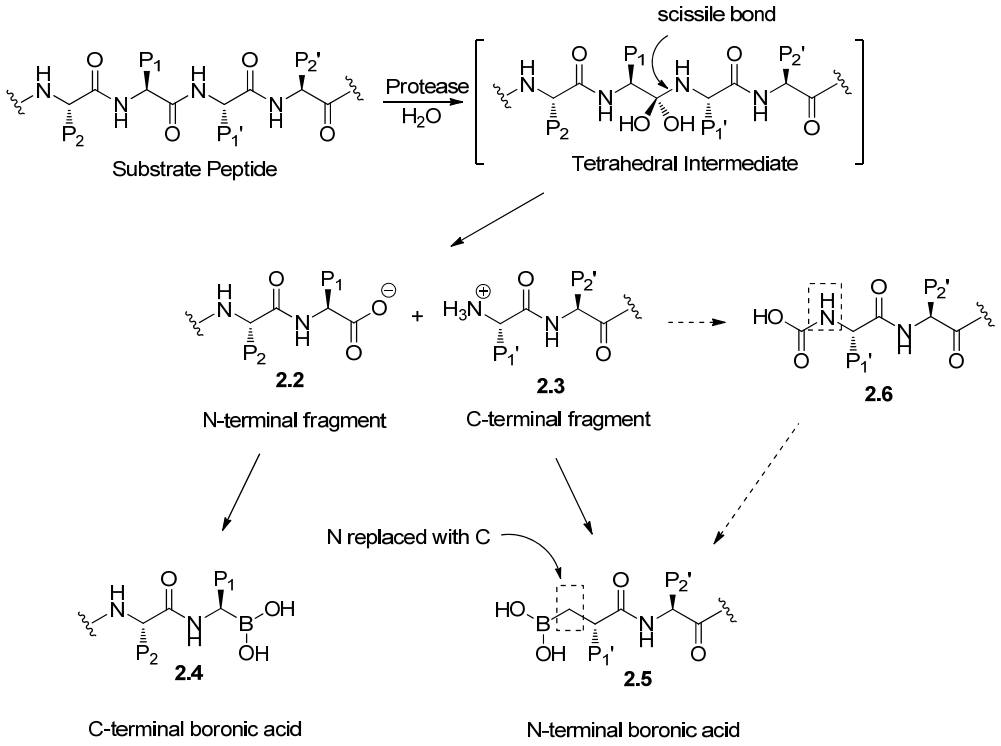
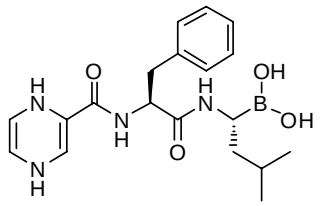


Figure 2.4 Enzyme catalyzed peptide hydrolysis and the boronic acid mimetics of hydrolysis fragments.

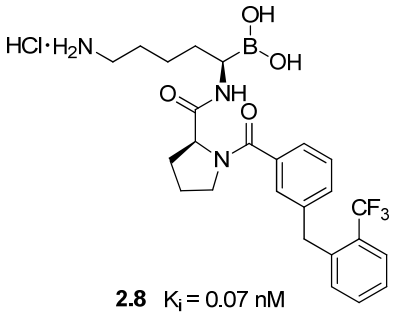
2.2.2. *C*-terminal and *N*-terminal Peptidic Boronic Acid Mimetics

To our knowledge, all published peptidic boronic acid derivatives to date are C-terminal boronic acids, which suggest that the substrate P site interactions with the binding pocket dominate the selectivity and binding affinity. The design of these inhibitors takes into

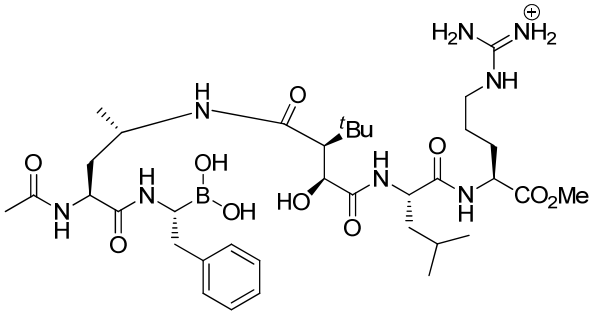
consideration the binding pocket to the left of the scissile amide bond only (Figure 2.4). One of the most successful C-terminal boronic acids so far is bortezomib (Velcade; PS_341, compound **2.7**), which was approved by the US Food and Drug Administration in early 2003. It was the first FDA approved boronic acid agent for clinical use and have been applied in the treatment of mantel cell lymphoma and multiple myeloma, a bone marrow cancer that affects two to three people per 100, 000.[14] It is a dipeptide, therefore has low molecular weight and was easy to synthesize.[15] The most important advantage is its high selectivity for the proteasome over common serine proteases. Currently it's being evaluated for the treatment of other cancers, eg. lung cancer, and in combination therapies.



2.7 bortezomib (Velcade, PS_341)



2.8 K_i = 0.07 nM



2.9 K_i = 26 nM

Other examples of C-terminal boronic acids are a thrombin inhibitor (compound **2.8**), a potential chymotrypsin inhibitor (compound **2.9**), etc.[16,17] Thrombin, as the final serine protease in the blood coagulation cascade, has been considered as a promising target for the development

of antithrombotic agents. Compound **2.8** is an extremely potent thrombin inhibitor, with K_i value (0.07 nM) much more potent than its precursor.[16] Cacciola et al.'s work shows that inhibitors with these P3 residues have a unique binding mode which allows for the direct interaction of the P1 amino side chain with the Asp189 side chain in the S1 pocket. [16]

In order to explore the possibility of forming a peptide boronate adduct which could mimic the first tetrahedral intermediate during the peptide hydrolysis in the serine protease active site, compound **2.9** was designed and synthesized.[17] However, the results showed that the affinity of **2.9** is neither time- nor pH-dependent and it only shows a moderate increase in affinity compared to compounds that cannot form a diester adduct, which might either be because the boronate ester did not form, or that the occupancy of the S1'-S3' subsites and formation of the boronate diester do not offer enough additional binding affinity to overcome the flexibility or binding characteristics of the linking group. Although there have not been any positive results achieved on this kind of inhibitors, compound **2.9** did offer a good starting point for further study in this approach, especially in the design of appropriate linking unit.[17]

Theoretically, the residues to the right-hand side of the scissile amide bond should also contribute to substrate selectivity and affinity. However, N-terminal peptidic boronic acids have not been reported to date. This might due to the synthetic methodology used to make N-terminal boronic acids is not available and is unexplored. Thus, we propose to develop routes for synthesizing N-terminal boronic acids, which could provide insight into the importance of the P' residues on binding affinity and selectivity, especially when they are compared with their C-terminal boronic acid counterparts.

2.3. Target Protease: Human Lon and ClpXP

Lon and ClpXP are two soluble ATP-dependent serine proteases, which could be found in the matrix of mammalian mitochondria.

Lon protease, also known as protease La, is a homo-oligomeric complex which is responsible for the selective degradation of abnormal proteins and certain short-lived regulatory proteins in various organisms.[18] Lon is important for protein quality control and metabolic regulation in both bacteria and mitochondria.[19,20] Although Lon is a homo-oligomer, each subunit of Lon contains both an ATPase and a protease active site, which makes Lon attractive as the simplest model for studying the mechanism of ATP-dependent proteolysis.[21]

ClpXP forms hetero-oligomeric complexes and shares some similar properties with Lon: (1) they both need energy (ATP) for degradation of protein substrates; (2) their domains encoding the ATPase and proteolytic acitive sites are separated, with the ATPase active site responsible for substrates recognition; and (3) they both form short peptide products of 10-15 amino acids.[22] Figure 2.5 shows the proteolytic cycle of ClpXP (A) and the schematic of Clp protease function (B).[22] The top portion (A) shows three EM images of ClpXP degrading lambda O protein. In Image **1**, complexes with ClpX ATPase on either or both sides of ClpP are active for proteolysis. In Image **2**, density associated with binding of a substrate (lambda O protein) can be seen at the surface of the ATPase. In Image **3**, after treatment with ATP, in an inactive ClpP derivative, lambda O disappears from the surface and density can be seen inside of ClpP, consistent with translocation. In the lower portion (B), the substrate tags (yellow) are recognized by ATPase, leading to substrate binding in the presence of nucleotides. ATP hydrolysis is accompanied by substrate unfolding in the ATPase, followed by translocation to the proteolytic

core. Degradation yields short peptides. However, it is not known how these peptides escape the proteolytic chamber.[22]

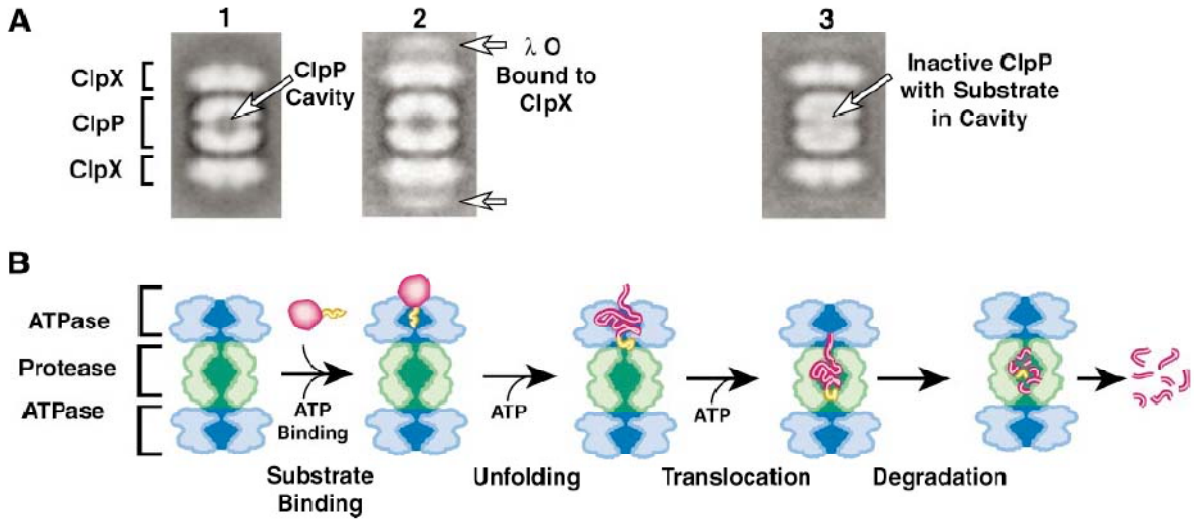


Figure 2.5 Proteolytic cycle of ClpXP (A) and schematic of Clp protease function (B).[22]

Currently the functions of ClpXP are not fully understood.[23,24] Lon can be found in yeast and it is the only ATP-dependent protease found in mitochondrial matrix while ClpXP proteases are absent in lower eukaryotes. The physiological roles of mitochondrial Lon proteases are better defined than ClpXP. So far the functions of mitochondrial ClpXP proteases could only be estimated based on the known functions of the bacterial homologs. However, mammalian and bacterial ClpXP have different substrate specificity therefore human enzyme complexes fail to recognize the protein substrates of *E. coli* ClpXP.[25] If we could find a selective inhibitor for hClpXP, it will help to understand its role in biology. To date, there are no known selective inhibitors published for ClpXP.

2.4. Designing *N*-terminal Boronic Acid Mimetics for Human ClpXP

In our effort to understand the function of human ClpXP proteases, we decided to design N-terminal peptidic boronic acids and study their selectivity in inhibiting ClpXP in mitochondrial extracts. In Figure 2.6, at the top of the scheme is the optimal sequence achieved by Lee's group.[26] **2.10** is the tetrahedral intermediate during peptide hydrolysis. After the scissile amide bond is broken, two fragments are formed. As described earlier, N-terminal peptidic boronic acid **2.11** will be our target as an entry into hLon/ClpXp peptide inhibitors. Once a lead is discovered, we will modify the substituents on the α position, and study the selectivity and binding affinity for Human ClpXP proteases with different substituents or stereochemistry at that position.

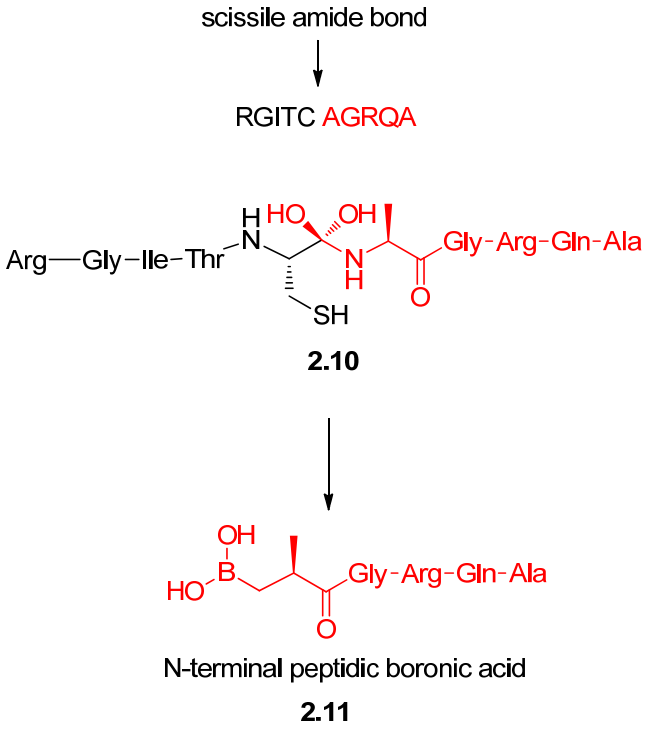


Figure 2.6 N-terminal boronic acid mimetic for human ClpXP

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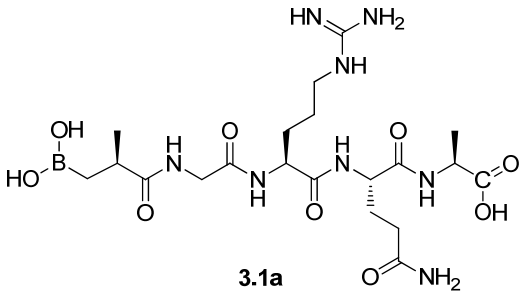
Chapter 3. Synthesis of *N*-terminal Peptidic Boronic Acids and Boronic Acid Derivatives

3.1. Synthetic Plan

As mentioned at the end of Chapter 2, in order to study the potential selective inhibition of human ClpXP proteases using N-terminal boronic acids, compound **3.1a** will be our ultimate synthetic target. A combinatorial library of peptides has indicated that AGRQA is the optimal P' substrate sequence.[1] If the synthesized peptide mirrors the activity of the substrate during the screening, then we predict that compound **3.1a** will have good binding or inhibitory activity. In order to synthesize **3.1a** we will develop the synthesis of N-terminal boronic acid monomers **3.2** which can be incorporated into a longer peptide sequence through solid phase peptide synthesis (Figure 3.1). Because the structure-activity relationship in ClpXP is not well defined, substituents other than a methyl group may confer selectivity. Therefore we will synthesize compounds **3.1b-e**, where the P_1' residues are benzyl, allyl, propyl, *tert*-butyl acetate, respectively, and study their inhibitory activity against hClpXP. Further modifications to the P_2'-P_5' residues will not be considered in this thesis due to their distance from the scissile amide bind.



3.1a

Synthesis target: N-terminal peptidic boronic acid

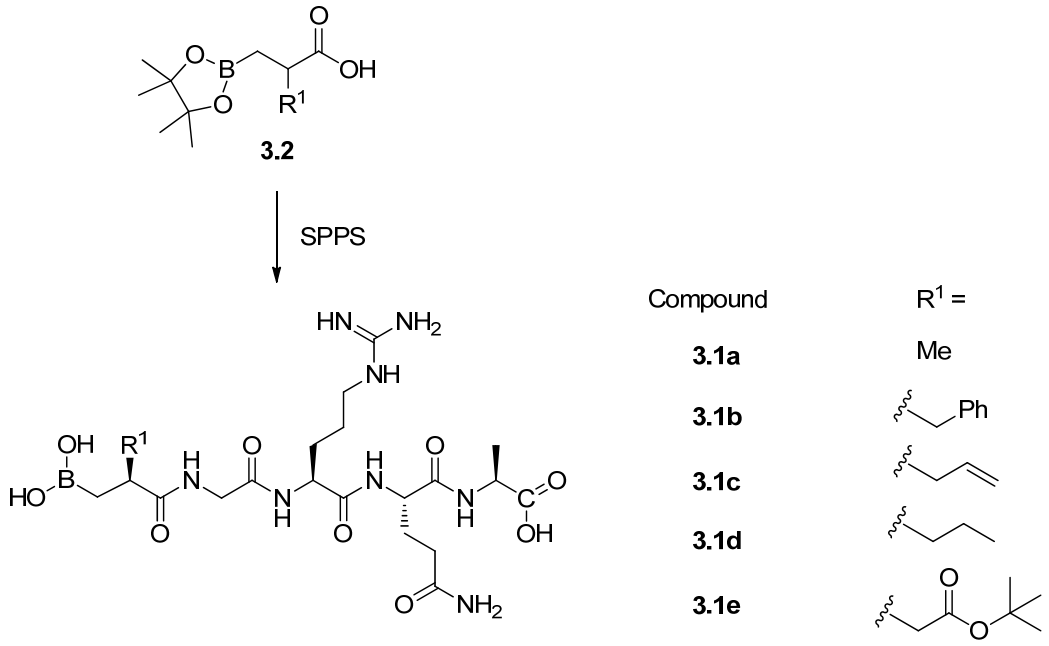


Figure 3.1 Target N-terminal peptidic boronic acids.

3.2. Synthesis of Racemic β-(Pinacolato)borolanylpropanoic Acids (**3.2**)

The synthesis outline described in Figure 3.2 was performed by following the procedure developed by Ken Knott from our group.

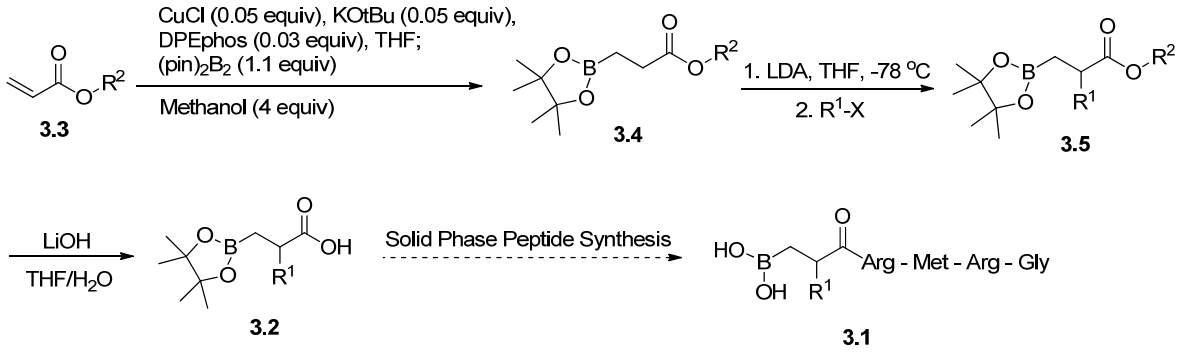


Figure 3.2 Synthesis of *N*-terminal boronic acids.

3.2.1. β-Borylation of α, β-Unsaturated Esters

The copper-catalyzed conjugation addition reactions of bis(pinacolato)diboron to α, β-unsaturated enones were initially reported independently in the laboratories of Hosomi and Miyaura.[2,3] Further improvement on the reactivity and scope of the β-borylation of unsaturated carbonyl compounds with a copper-diphosphine catalyst was reported by Yun.[4] Applying this procedure, the pinacol boronic ester was introduced at the β-position of unsaturated esters **3.3a-b**. This reaction uses copper (I) as the metal catalyst and sodium *tert*-butoxide as base, followed by an addition of chelating ligand bis(2-diphenylphosphinophenyl)ether (DPEphos). Bis(pinacolato)diboron and the additive methanol were then added to achieve boronic esters **3.4a-b** as colorless oil with good yield (Figure 3.3).

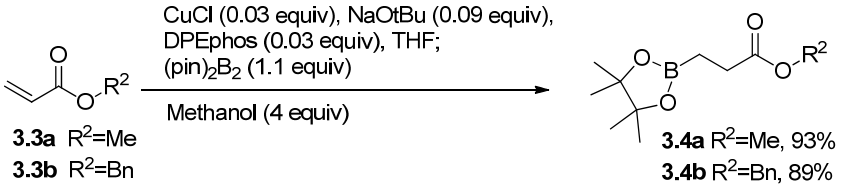


Figure 3.3 β-borylation of α, β-unsaturated esters.

The proposed catalytic cycle for β-boration is shown in Figure 3.4.[4] Ligand exchange of copper (I) chloride with *tert*-butoxide generates THF soluble copper (I) salt that coordinates with DPEphos.[5] Transmetallation with bis(pinacolato)diboron provides nucleophilic boron-cuprate species **3.5**, as proposed from preliminary mechanistic studies reported by Miyaura and co-workers.[3] The formation of this nucleophilic borylcuprate intermediate is supported by NMR studies as well as X-ray crystal structures of related borylcuprate species by Sadighi.[3,6,7] Conjugate addition with **3.6** produces carbon-bound **3.7** or oxygen-bound **3.8** copper enolate that subsequently reacts with methanol to generate a copper alkoxide. The copper alkoxide continues

the catalytic cycle. In 2008, using density functional theory calculations, Marder and co-workers proved that the catalyzed borylation occurs through C=C insertion into Cu-B to give a β-borylalkyl C-bound Cu(I) enolate intermediate.[8] In the borylation of methylacrylate, the keto-to-enol isomerization does not occur due to the inertness of the ester group unless a proton source is added.

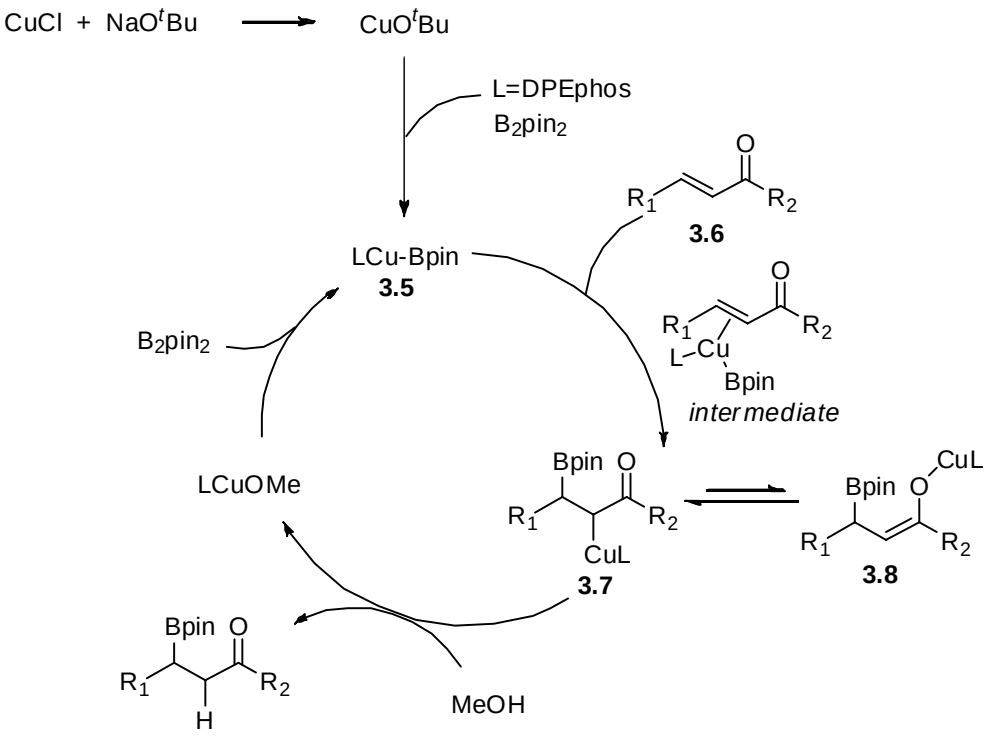
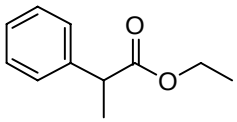


Figure 3.4 β-boration catalytic cycle of α, β-unsaturated esters.[4,8]

3.2.2. α-Alkylation of β-(Pinacolato)borolanylpropanoates

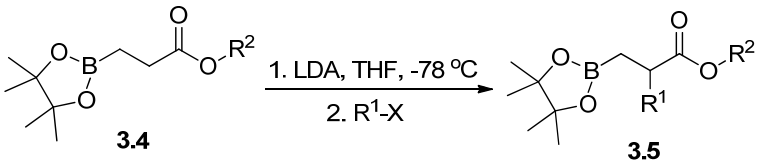
The borylated products **3.4a-b** were treated with 1.1 equivalents of lithium diisopropylamide followed by six different alkylating reagents at -78 °C in THF to afford α-alkylated boronic esters **3.5a-i** as colorless oil in 26-62% yield (Table 3.1). In comparison to

alkylation procedures of substrates that do not contain boron, the yields of these reactions are poor to moderate. For example, the highest was 62% (**3.5b**) while for 3 of them the reaction failed (**3.5c**, **h**, **i**). In order to rule out the possibility of technical manipulation issue, methylation of ethyl 2-phenylacetate using the same procedure was performed (**3.5j**). The reaction provided a 97% yield which indicated the problem was not technical manipulation or the LDA reagent.

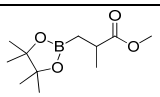
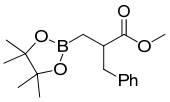
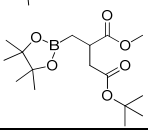
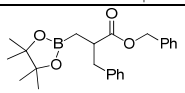
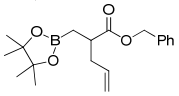
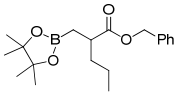
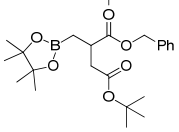
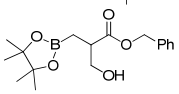
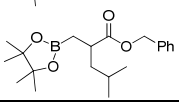


3.5j

Table 3.1 Yields for alkylation of boronic esters.

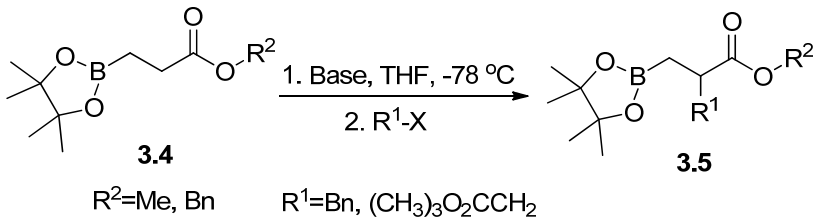


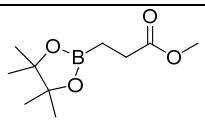
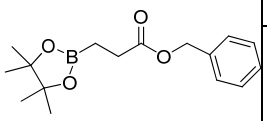
3.4 **3.5**

Entry	Substrate	R^2	R^1-X	3.5	Yield (%)
1	**a**	**Me**	MeI		60
2	**b**		BnBr		62
3	**c**		^{t}BuO$_2$CCH$_2$Br		0
4	**d**	**Bn**	BnBr		31
5	**e**		AllylBr		26
6	**f**		PrI		26
7	**g**		^{t}BuO$_2$CCH$_2$Br		27
8	**h**		HCHO		0
9	**i**		*i*BuI		0

Control experiments using different amounts of LDA, slightly different reaction temperatures and durations, and other bases did not result in improvement (Table 3.2). After work up, TLC and ^{1}H NMR of the crude product revealed the presence of unreacted starting material. However, even if this portion was accounted into the recovered yield, it would still be less than 100%, which indicates the possibility of product decomposition.

Table 3.2 Optimization of alkylation (*using GC/MS).



Substrate	Alkylation Reagent (AR)	Base	Temperature and Reaction Time		Reaction Scale (mmol)	Molarity	Yield (%)
			Before add AR	After			
 **3.4a**	BnBr 2 equiv	LDA 1.1 equiv	-78, 1h	-78, 20min; 0, 20min; rt, 30min	1.401	0.234	62
 **3.4b**	BnBr 2 equiv	LDA 2 equiv	-78, 1.5h	-78, 10min; -45, 4h	0.689	0.230	31
	BnBr 2 equiv	*sec*-BuLi 1.1 equiv	-78, 1.5h	-78, 10min; -45, 4h	0.689	0.230	0*
	$(CH_3)_3$ O_2CCH_2Br 2equiv	LDA 2 equiv	-78, 1.5h	-78, 10min; -45, 4h	0.689	0.230	7

3.2.3. Hydrolysis of β-(Pinacolato)borolanylpropanoates: Saponification and Hydrogenation

Saponification of the esters (**3.5a**-**b**, **d**-**f**) with an excess of LiOH (10 equivalents) in THF/H_2O biphasic condition provided the corresponding carboxylic acids within 8 hours. Since the *t*-butyl acetate group is sensitive to basic condition, catalytic heterogeneous hydrogenation with 10% Pd/C and hydrogen gas was applied to compound **3.5g** (Figure 3.5). All carboxylic acid products were colorless oil. Saponification of **3.5b** and **d** provided the same carboxylic acid. However, methyl ester **3.5b** gave a slightly higher yield than the benzyl ester **3.5d**.

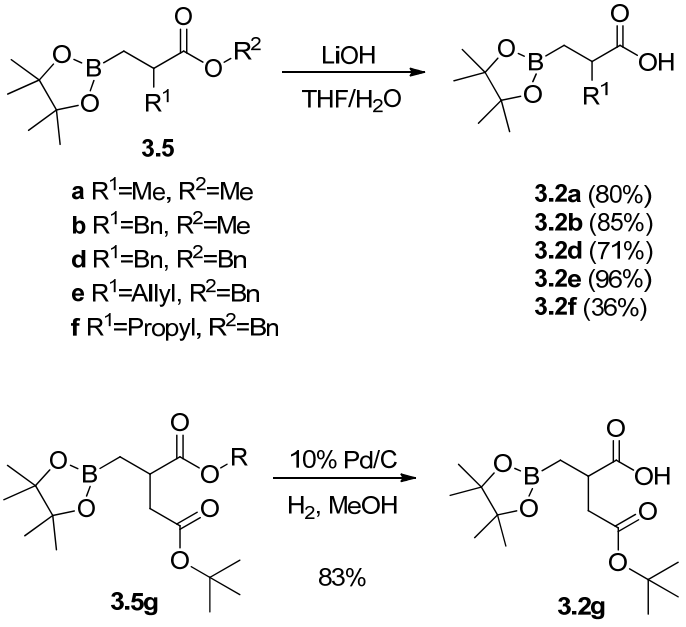


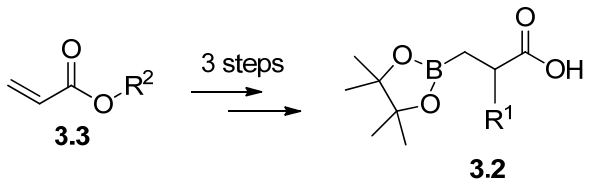
Figure 3.5 Saponification/hydrogenation of **3.5.**

3.2.4. Conclusion

The author's contribution on this project stops before the solid phase peptide synthesis, in which a series of β-(pinacolato)borolanylpropanoic acids containing pinacol protected boron on

one side (β position) and a carboxylic acid on the other side, were synthesized. These compounds were then easily applied toward peptide coupling reactions and the pinacol group was removed to unmask a boronic acid for use in inhibition studies. Starting with α, β-unsaturated esters **3.3**, compounds **3.2** were synthesized in three steps with 8-49% yield (Table 3.3).

Table 3.3 Overall yields for compounds **3.2a-g.**



3.3 **3.2**

Entry	3.2	R^1	Overall Yield (%)
1	a	Me	45
2	b	Bn	49
3	d	Bn	20
4	e	Allyl	22
5	f	Pr	8
6	g	$CH_2CO_2{}^tBu$	20

The main reason for low yields of compound **3.2** is the alkylation step. In the current synthetic methodology, no chiral auxiliaries/ligands are involved and thus all products are racemic. In the inhibition studies of boron containing compounds with specific stereochemistry, different inhibition activities are expected. We will have to separate the diastereomers after solid phase peptide synthesis to test their inhibitory activities. Therefore, chiral HPLC will be needed, which is time consuming and laborious. In order to solve this problem, a chiral auxiliary approach to stereoselectively synthesize boron compounds was attempted.

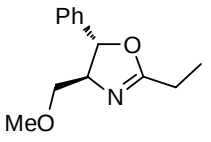
3.3. Attempt at Asymmetric Synthesis of β-Boronic Esters

In this section I will talk about the work I have done in the synthesis of chiral β-boronic esters by using oxazolidinone as the chiral auxiliary.

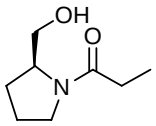
3.3.1. Oxazolidinones as Chiral Auxiliaries in Asymmetric Alkylation

Oxazolidinones, also called Evans' reagents, were reported as chiral auxiliaries by Evans and coworkers in 1980's.[9] They turned out to be better than either oxazolines (**3.9**) or prolinol amides (**3.10**) because they are synthetically much easier to cleave. The 4-isopropyl (**3.11**) and 4-benzyl (**3.12**) derivatives, and the *cis*-4-methyl-5-phenyl (**3.13**) derivatives are readily available from commercial vendors. Another useful auxiliary is the 4-phenyl derivative (**3.14**).[10]

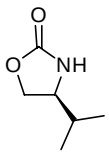
The synthesis of oxazolidinone **3.12** is shown in Figure 3.6. L-Phenylalanine **3.15** is first treated with $NaBH_4$ and I_2 to achieve the corresponding L-phenylalaninol **3.16**.[11] Then **3.16** is treated with diethyl carbonate and K_2CO_3 to achieve chiral auxiliary 4-benzyl oxazolidinone **3.12.**[12]



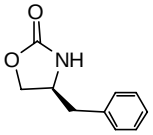
3.9 2-ethyloxazoline



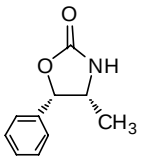
3.10 prolinol amide



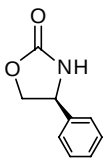
3.11



3.12



3.13



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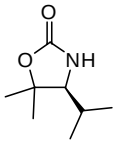
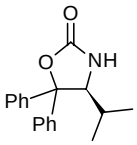


3.17



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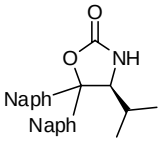


3.19

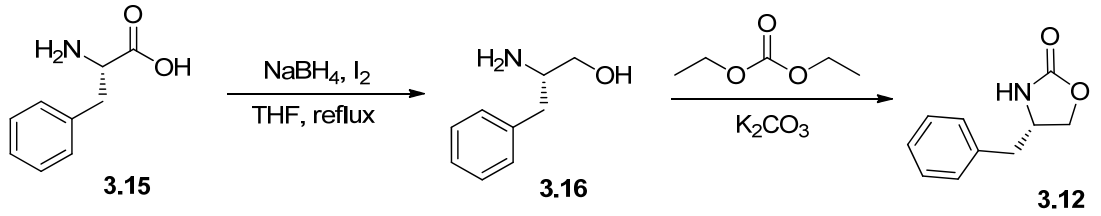


Figure 3.6 Evans' reagents and synthesis of 4-benzyl oxazolidinon.[12,]**Error! Bookmark not defined.**

Further structural modifications on oxazolidinones revealed that the 4-isopropyl-5,5-dimethyl derivative (**3.17**) and 5,5-diaryl derivatives **3.18** and **3.19** provided good enantioselectivity.[13, 14, 15, 16, 17]

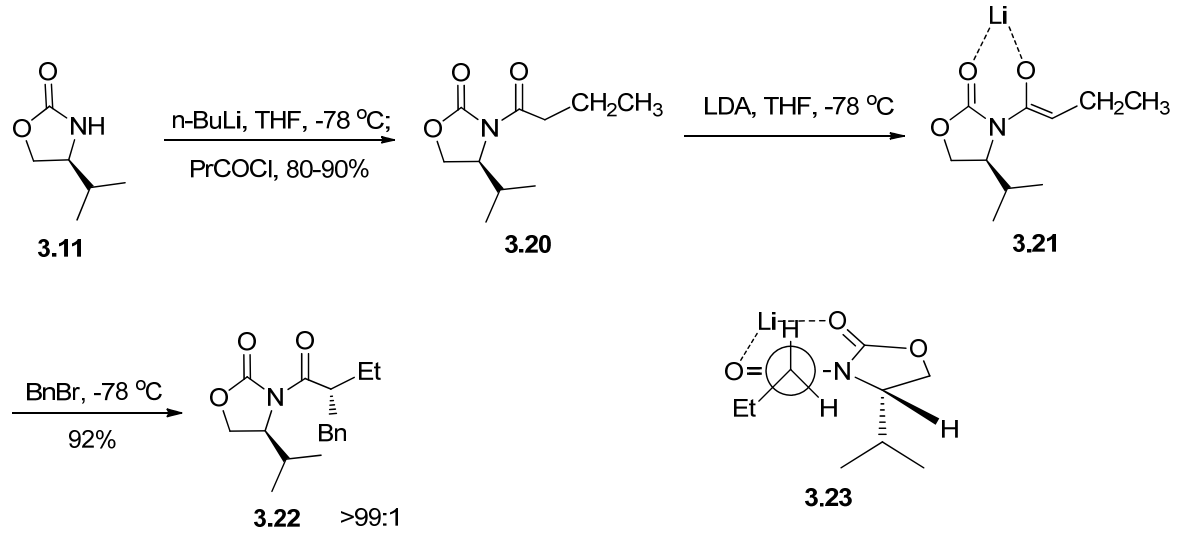


Figure 3.7 Alkylation using oxazolidinone as chiral auxiliary and more favored transition state from **3.20** to **3.21**.[9]

By using Evans' reagent, reactants are typically coupled to the chiral auxiliary as *N*-acyl derivatives.[18] Acylation provides imides with acidic α-carbons which are closer to esters than amides in terms of acidity, enolate nucleophilicity and cleavage chemistry. (*Z)*-Enolates are

formed with very high selectivity (transition state **3.23** in Figure 3.7) through minimization of steric hindrance between the isopropyl group and the ethyl group. A chelated geometry is presumed in ground and transition states, which locks the six membered ring and prohibits C-N bond rotation.[9] In **3.21**, alkylating reagents prefer to attack at the α-carbon from the α-face as the β-face of the enolate is shielded by the isopropyl group. The major and minor products are diastereomers, which can be separated by crystallization or chromatography on SiO_2.

Less reactive electrophiles (non-allylic/non-benzylic) require the use of sodium enolates (Figure 3.8) or triflate leaving groups (Figure 3.9).[9, 19, 20] In Figure 3.8, ethyl iodide is the alkylating reagent. In the alkylation of **3.24** to **3.25**, sodium enolate gives better diastereoselectivity than lithium enolate due to the size of metal ion and the stability of the enolate.

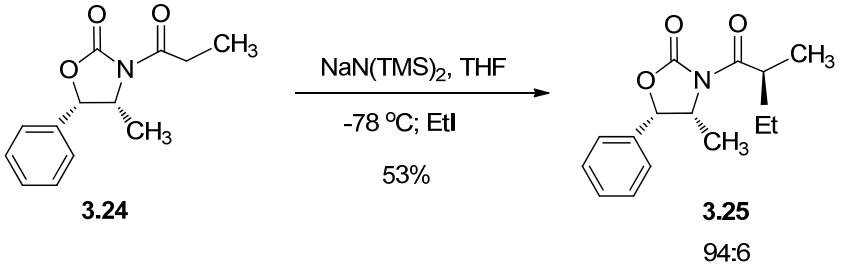


Figure 3.8 Alkylation with ethyl iodide through sodium enolate.[9]

In Figure 3.9, a branched alkylating reagent is involved. In order to minimize the elimination side product and maximize alkylation product **3.27**, *N*-acyl derivative **3.26** is treated with LDA and the leaving group of the alkylating reagent is replaced with triflate.

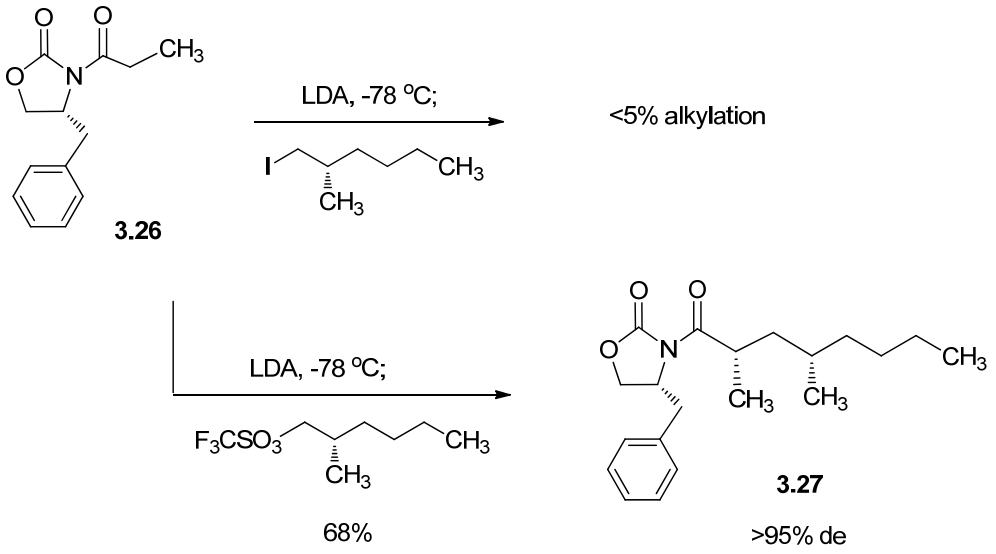


Figure 3.9 Alkylation with branched alkylating reagent with triflate as leaving group.[19,20]

Figure 3.10 shows that a recyclable polymer-supported Evans' reagent was used to optimize enolate alkylation reaction.[21] A cleavable linker strategy was involved using this Scheme.

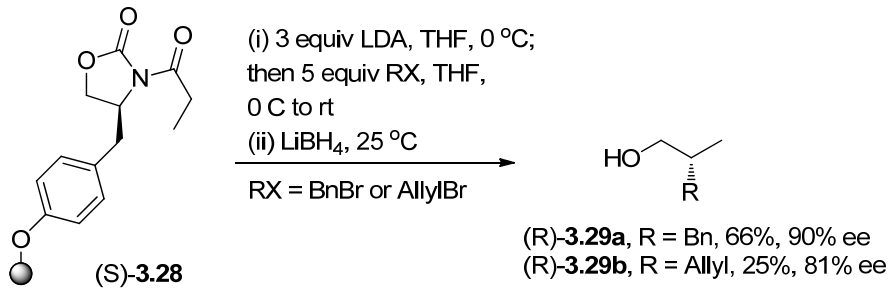


Figure 3.10 Enolate alkylation reactions of L-tyrosine derived polymer (*S*)-**3.28**.[21]

The most common cleavage of acyl oxazolidinone auxiliaries is performed by basic hydrolysis (Figure 3.11). The reformed oxazolidinone can be recycled, making the auxiliary very attractive.

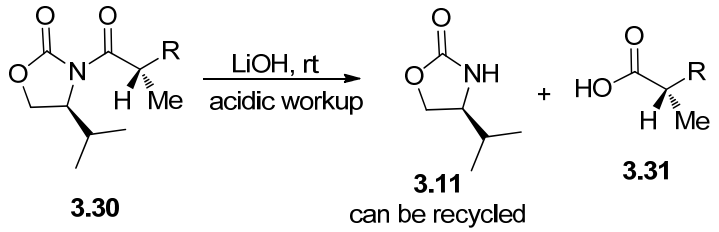


Figure 3.11 Using basic hydrolysis to cleave Evans' reagent.

As shown in Figure 3.12, there are several other ways to remove the oxazolidinone auxiliaries. The products are compounds with a wide range of functional groups: carboxylic acids, alcohols, aldehydes, esters, amides, Weinreb amides and thioate.[22] All these compounds could be used as synthetic intermediates and easily undergo further modifications. As with the Evans' reagents, each of the systems permits hydrolytic removal and recovery of the chiral auxiliary.

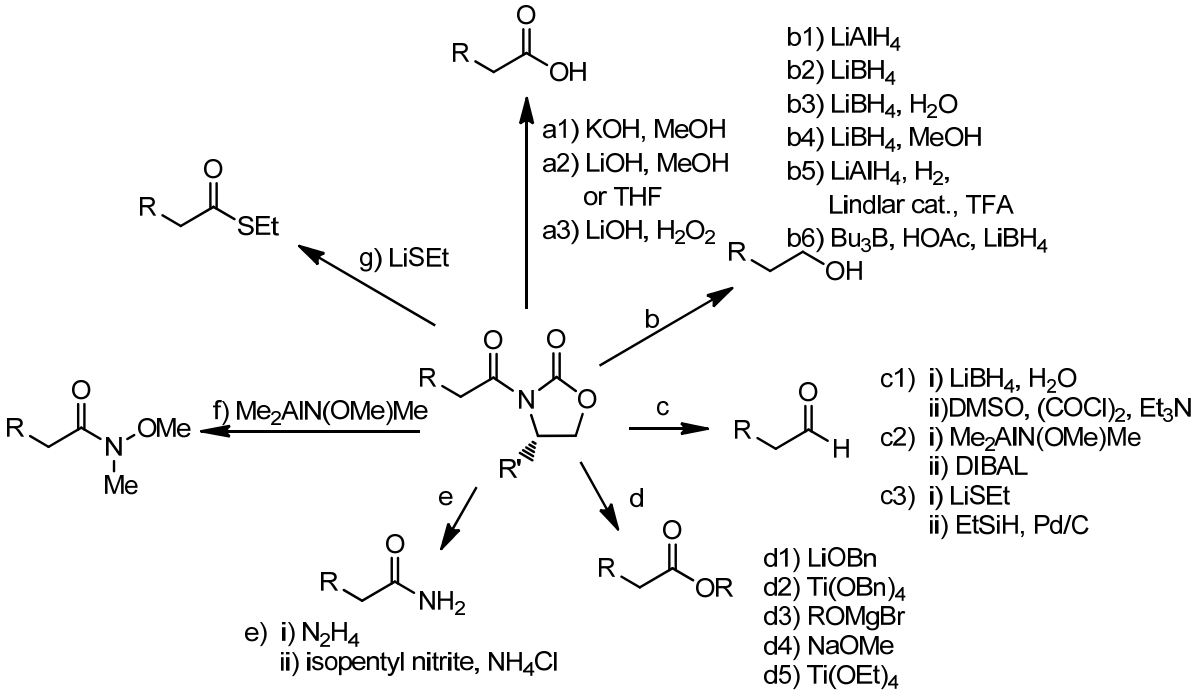
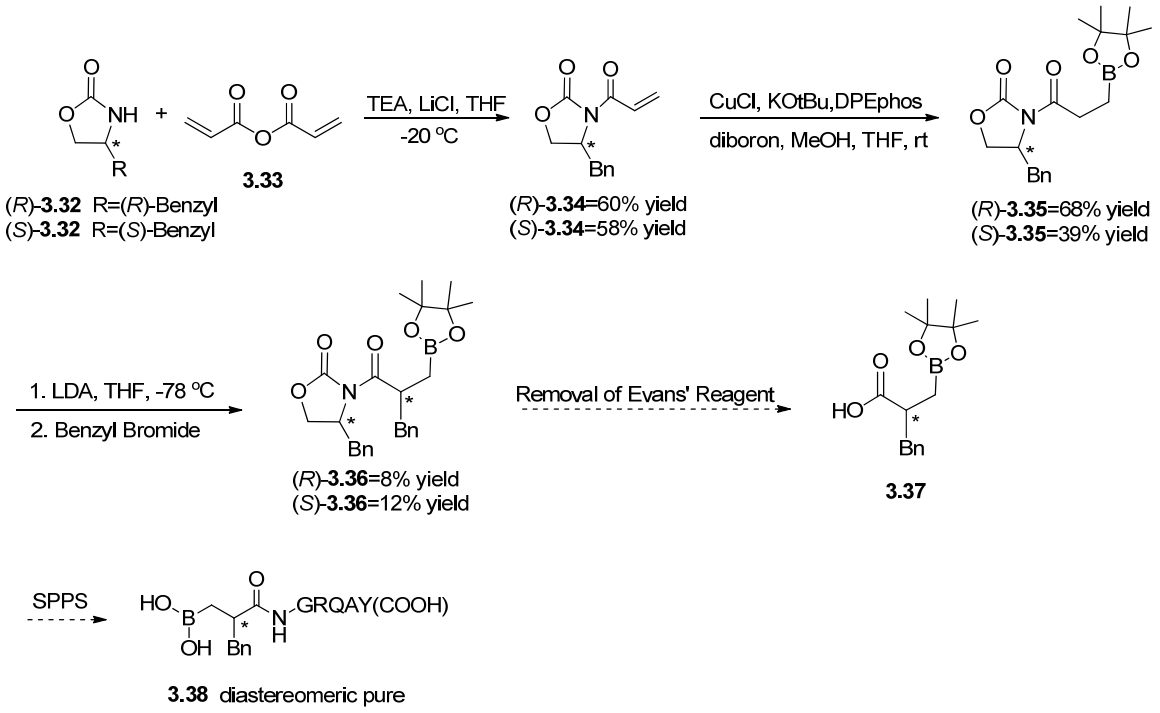


Figure 3.12 Cleavages of Evans' Reagents.[22]

3.3.2. Asymmetric Synthesis of β-Boronic Esters using Oxazolidinone

It is clear that the products **3.2** will be racemic because of the absence of a chiral directing moiety. However, use of Evans' chiral auxiliaries could introduce stereochemical selectivity. The goal in this project is to use Evans' reagent to produce diastereomerically pure boronic acids (**3.38**).



(*R*)-**3.32** R=(*R*)-Benzyl
(*S*)-**3.32** R=(*S*)-Benzyl

3.33

(*R*)-**3.34**=60% yield
(*S*)-**3.34**=58% yield

(*R*)-**3.35**=68% yield
(*S*)-**3.35**=39% yield

(*R*)-**3.36**=8% yield
(*S*)-**3.36**=12% yield

3.37

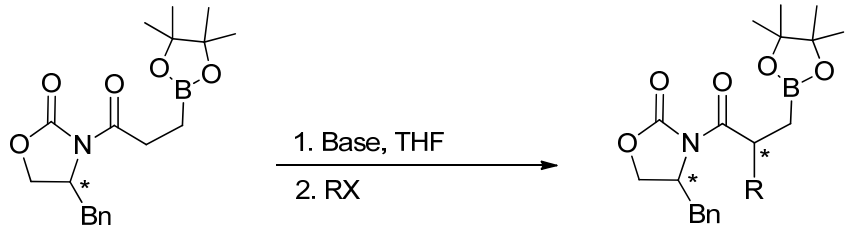
3.38 diastereomeric pure

Figure 3.13 Diastereoselective syntheses of *N*-termianl boronic acids.

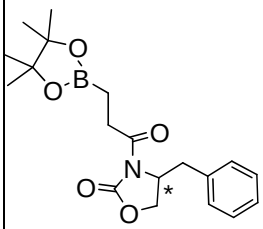
The synthetic route to diastereoselective boronic ester **3.37** is shown in Figure 3.13. Acrylic anhydride **3.33** was formed in situ, using acrylic acid, acrylic chloride, LiCl and triethylamine. Addition of 4-benzyl oxazolidinone **3.32** provided chiral compound **3.34**.[23] Subsequent treatment of **3.34** following Yun's method with a catalytic amount of CuCl, KO^{t}Bu and 1.1 equivalent bis(pinacolato)diboron generated compound **3.35**.[4] The subsequent alkylation using benzyl bromide provided low yields. Clean ^{1}H and ^{13}C NMR spectrum were measured for

compounds **3.36**. No additional peaks as impurity or contaminating diastereomers were detected, suggesting that a single diastereomer was formed.

Table 3.4 Yields of asymmetric alkylation using Evans' reagent under different conditions.



3.35 **3.36**

Substrate	RX	Base	Temperature and Reaction Time		Reaction Scale (mmol)	Molarity of Substrate	Yield (%)
			Before add AR	After			
	$PhCH_2Br$ 2 equiv	LDA 1.1 equiv	-78, 1h	-78, 2h; 0, 3h; rt, 0.5h	0.223	0.074	5 (*S*)
					0.557	0.139	12 (*S*)
				-78, 6h	0.418	0.139	SM (*S*)
		LDA 1.5 equiv	-78, 1h	-78, 10min; -45, 3h	0.139	0.070	8 (*R*)
	$PhCH_2I$ 2 equiv	LDA 1.1 equiv	-78, 1h	-78, 2h; 0, 3h; rt, 0.5h	2.000	0.200	0 (*R*)
					0.835	0.167	0 (*R*)
	$PhCH_2Br$ 1.2 equiv	LiHMDS 1.2 equiv	-78, 1h	-78, 30min; 0, 1h; rt 8h	0.278	0.093	0 (*R*)
	$CH_2=CHCH_2Br$ 5 equiv	KHMDS 1.5 equiv	-78, 1h	-78, 10min; -45, 3h	0.139	0.070	0 (*R*)
	MeI 5 equiv	NaHMDS 2 equiv	-78, 1h	-78, 10min; -45, 3h	0.209	0.104	0 (*R*)

Optimization of the reaction by starting with replacing benzyl bromide with iodide was attempted. Benzyl iodide, a better leaving group, was formed in situ and used immediately.

However, no product was observed. Changing the base to LiHMDS or KHMDS were also tried without success. Alkylating reagents also included methyl iodide and allyl bromide in different amounts. Higher temperatures and longer reaction times were also tried in order to increase the percentage yield. However, no significant improvement was observed in all of these cases and no starting material could be recovered. We postulate that the empty p orbital of boron and its resulting Lewis acidity interfere with the enolate formation. Table 3.4 shows the optimization of asymmetric alkylation.

3.3.3. Alkylation of MIDA and DEA Protected-Boronates

We hypothesized that boron on the beta carbon interferes with enolization/alkylation synthetic sequence and thus, we decided to investigate whether conversion of the sp^2 boron to an sp^3 by a coordinating ligand can circumvent this problem. Simple aminoalcohol, diethanolamine (DEA), and a known protecting group for boron, N-methyliminodiacetic acid (MIDA), were used.

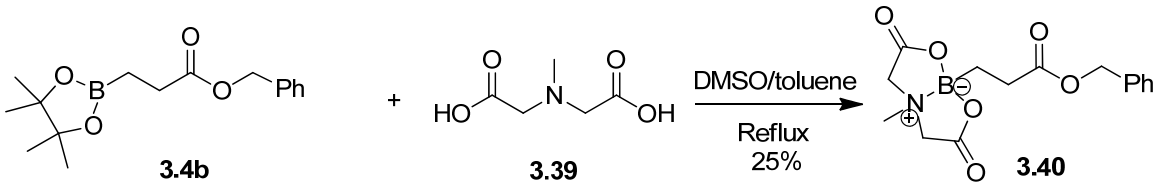


Figure 3.14 Synthesis of MIDA protected-boronate **3.40.**

In order to sythnesize boronate **3.40**, (pinacolato)boronic ester **3.4b** was treated with N-methyliminodiacetic acid (MIDA) in a mixture of DMSO/toluene at reflux with a Dean-Stark apparatus overnight. This provided the product **3.40** in 25% yield (Figure 3.14).[24] The

characterization with ^{1}H and ^{13}C NMR confirmed the product and the sp^3 boron was confirmed by ^{11}B NMR. Alkylations of compound **3.40** were attempted with BnBr and MeI with LDA as the base. However, no product was formed.

The synthesis of DEA protected boronate was also performed (Figure 3.15). By treating (pinacolato)boronic ester **3.4b** with 1.1 equivalents of ethanolamine derivatives (**3.41**) in ethyl acetate for 2 hours, **3.42** was expected to be generated. However, for N-methyldiethanolamine (**3.41a**), no product was isolated after stirring over 24 hours. For diethanolamine (**3.41b**), compound **3.42b** was successfully performed in 85% yield. Thus, the alkylation of **3.42b** was performed (with 2.2 equiv base and 5 equiv MeI) and based on TLC, there was no product formed.

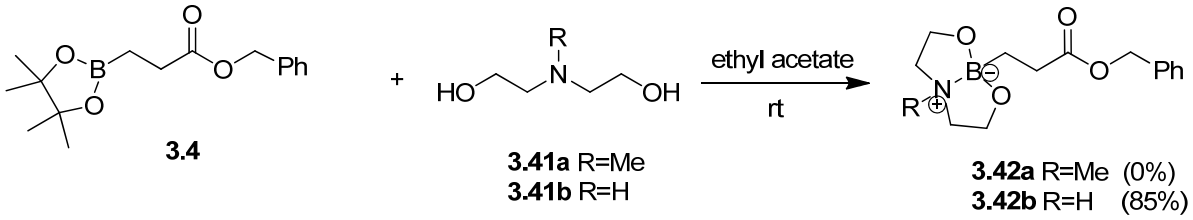


Figure 3.15 Synthesis of DEA/MDEA protected-boronates **3.42a-b**.

3.3.4. Conclusion

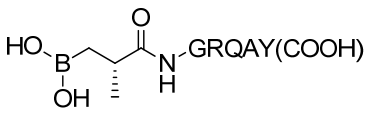
Here we attempted the diastereoselective synthesis of boronic esters using chiral Evans' oxazolidinone. The yields are relatively low (~3% overall) for the 3-step synthesis. The main problem is the low yield of the alkylation step. Several optimizations were performed but no obvious improvements resulted. The possible formation of a stable "ate" complex between boronic ester boron and the negatively charged enolate carbonyl oxygen may cause the low

reactivity of compounds **3.35** towards alkylation. Therefore I synthesized a diol protected-boronate **3.42b** which contains a sp^3 boron with no empty orbital to interact with enolate oxygen. The alkylation of that compound was attempted but has been unsuccessful thus far. Further optimization on alkylation involving boron containing compounds is under way and the removal of Evans' reagent will not be performed until the problem is solved.

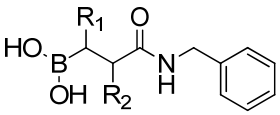
3.4. Synthesis of Simple *N*-terminal Peptidic Boronic Acids

3.4.1. Rationale and Synthetic Scheme

Due to the repeated issues with the alkylation step during the synthesis of N-terminal peptidic boronic acids, and since Ken Knott from our group had already successfully synthesized diastereomerically pure peptide **3.43** using chiral HPLC, the diastereomeric synthesis of N-terminal peptidic boronic acids using chiral auxiliary is no longer a priority. However, it would be important and useful to have information about the stability of compounds like **3.43** under different conditions, for example, acidic, basic, and oxidative, etc.

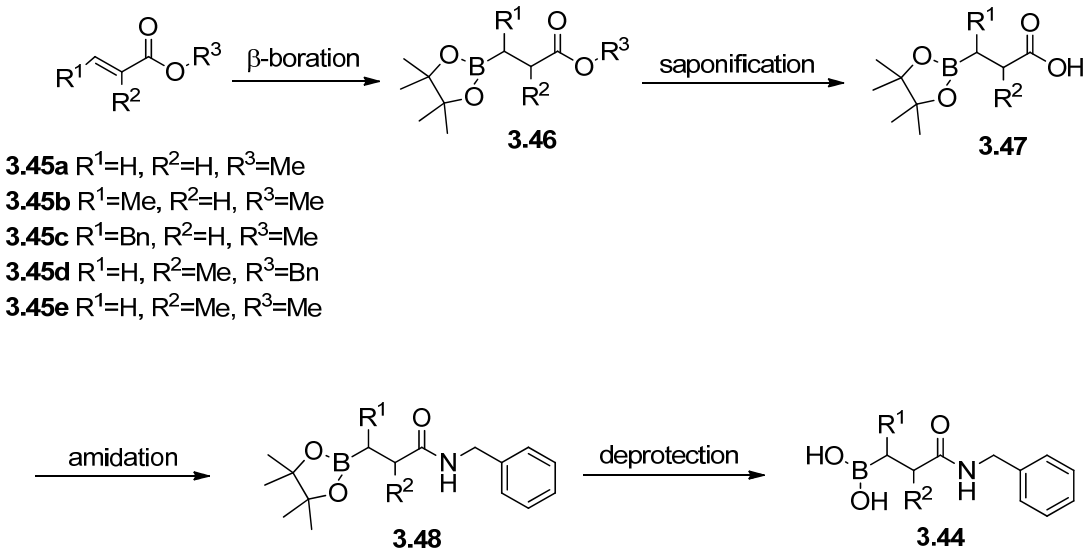


3.43



3.44

In this part of the research, the synthesis of N-terminal boronic acids **3.44** (Figure 3.16) was performed. These compounds have simple structures (benzyl amide with a boronic acid group on the β position). We expect to readily synthesize and purify these as they are still good surrogates for peptides. By changing the substituents at the α and β position, we could study their effect on the stability of the molecule. With this data in hand, we will relate the results to the



3.45a R^1=H, R^2=H, R^3=Me
3.45b R^1=Me, R^2=H, R^3=Me
3.45c R^1=Bn, R^2=H, R^3=Me
3.45d R^1=H, R^2=Me, R^3=Bn
3.45e R^1=H, R^2=Me, R^3=Me

Figure 3.16 Synthetic schemes for compound **3.44.**

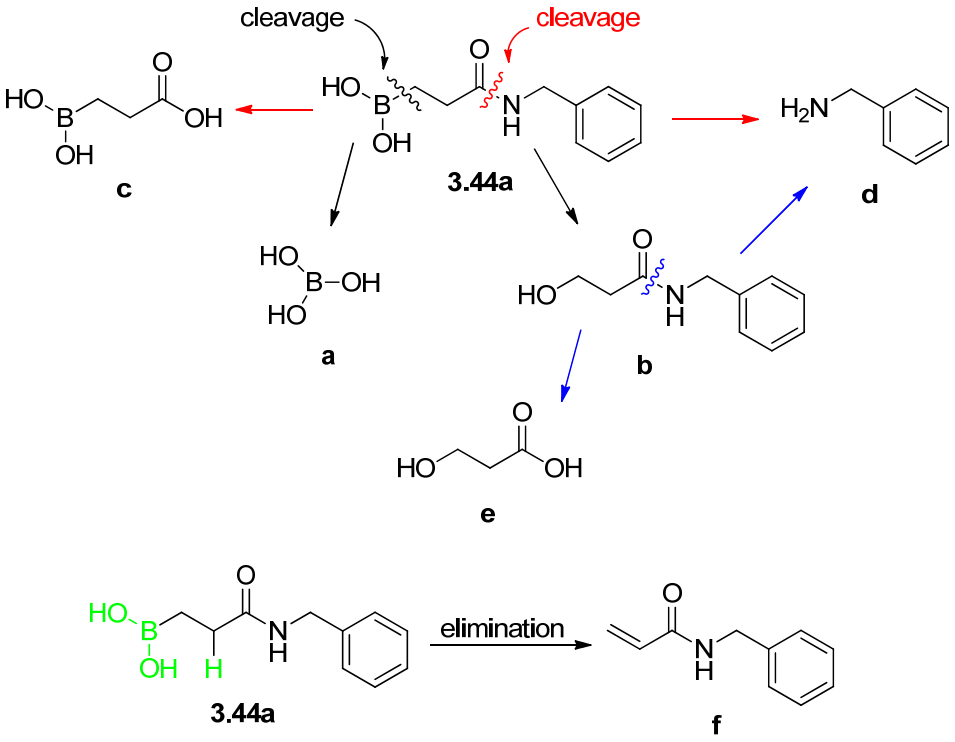


Figure 3.17 Possible degradation fragments for compound **3.44a.**

stability of more complicated molecules such as **3.43**. Some possible degradation fragments for compound **3.44a** are listed in Figure 3.17. Fragments **a** and **b** are derived from oxidation of **3.44a** while **c** and **d** are derived from hydrolysis of the amide bond in **3.44a**. Fragment **e** is the product of hydrolysis of **b**. The elimination of **3.44a** will form compound **f** as α, β-unsaturated amide.

3.4.2. β-Borylation and Saponification

β-borylation of unsaturated esters **3.45** was performed using Yun's method to afford compounds **3.46** in 36-96% yield (Figure 3.18). Then the carboxylic acids **3.47a-c** were obtained by saponification with LiOH to generate the desired products with 94-97% yield (Figure 3.19). However, using the same method with **3.46e** no product was formed. The desired product was alternatively obtained using catalytic heterogeneous hydrogenation (98% yield).

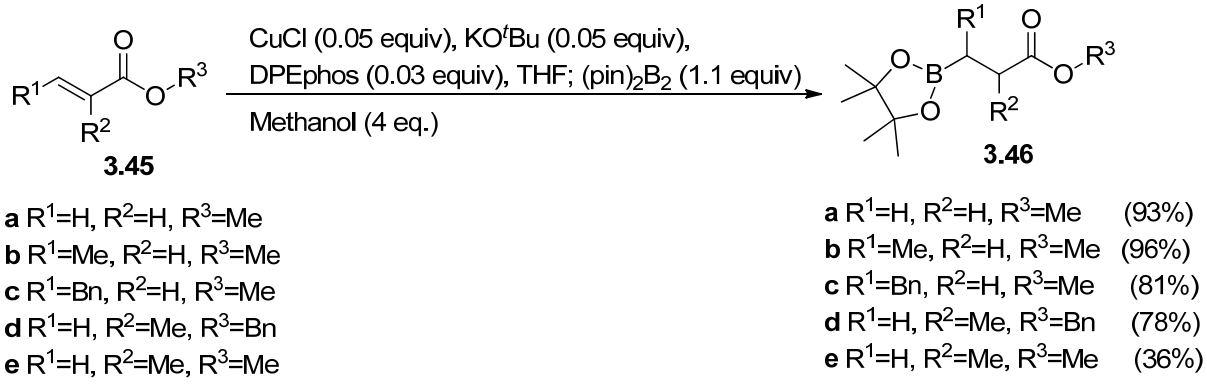
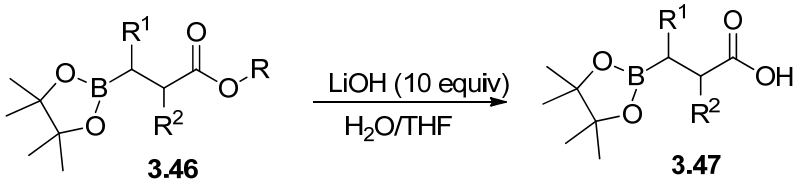


Figure 3.18 β-Borylation of compound **3.45.**



3.46

a R^1=H, R^2=H, R^3=Me
b R^1=Me, R^2=H, R^3=Me
c R^1=Bn, R^2=H, R^3=Me
d R^1=H, R^2=Me, R^3=Bn
e R^1=H, R^2=Me, R^3=Me

3.47

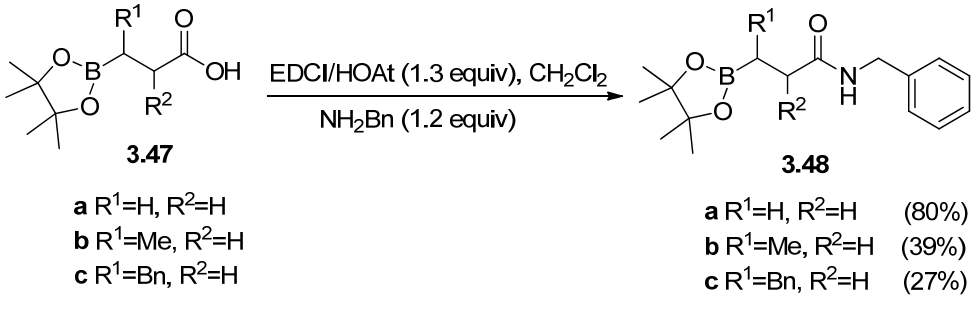
a R^1=H, R^2=H, R^3=Me (94%)
b R^1=Me, R^2=H, R^3=Me (94%)
c R^1=Bn, R^2=H, R^3=Me (97%)
d R^1=H, R^2=Me, R^3=Bn (98%)*
e R^1=H, R^2=Me, R^3=Me -

Figure 3.19 Saponification of compound **3.46.**

*product was obtained using hydrogenation method

3.4.3. Amidation

Coupling reagents, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) and 1-hydroxy-7-azabenzotriazole (HOAt), were used to form the benzyl amide product **3.48** with 27-80% yield after recrystallization (Figure 3.20).[25] Amide product **3.49** was also formed with pyrrolidine using the same method but with a lower yield (10%).

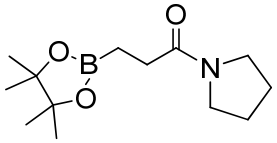


3.47

a R^1=H, R^2=H
b R^1=Me, R^2=H
c R^1=Bn, R^2=H

3.48

a R^1=H, R^2=H (80%)
b R^1=Me, R^2=H (39%)
c R^1=Bn, R^2=H (27%)



3.49

Figure 3.20 Amidation of **3.47**.

3.4.4. Deprotection of Pinacol-protected Boronic Acids

There are many published papers dealing with the deprotection of boronic acids. This deprotection, however, is not straight forward. For example, treatment of **3.48** with phenylboronic acid and diethylether/water solution was unsuccessful (Figure 3.21).[26]

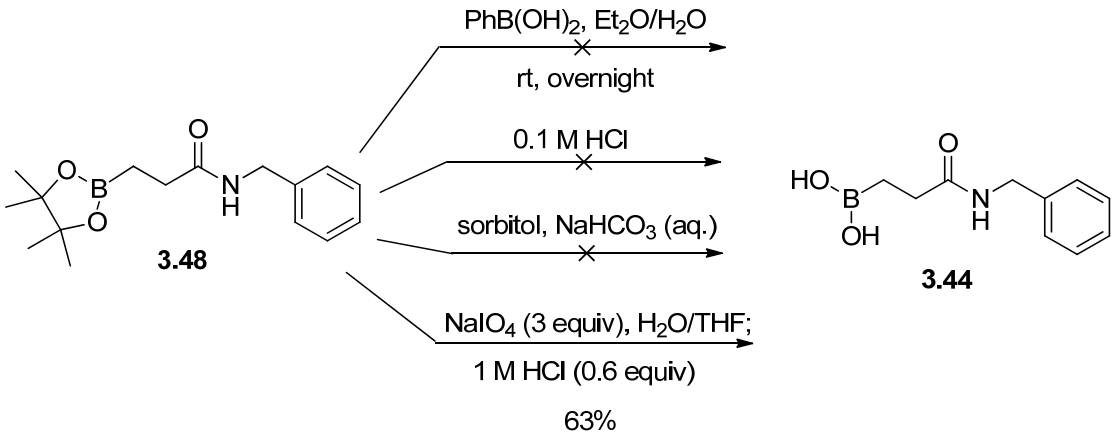


Figure 3.21 Deprotection of boronic acid **3.44a.**[26,2827,28]

By using a deprotection method with HCl was also unsuccessful.[27] Additional methods such as using sorbitol with $NaHCO_3$ did not provide the desired product.

Finally, sodium periodate (3 equiv) was used to react with compound **3.48a** followed by the addition of 1 M HCl (0.6 equiv) after 30 minutes.[28] The mixture was stirred overnight then product **3.44a** was isolated by filtration as a white solid with 63% yield (Figure 3.21). However, this method was only effective with compound **3.48a**, when the α and β positions were not substituted.

3.4.5. Conclusion

(3-(benzylamino)-3-oxopropyl)boronic acid (**3.44a**) was successfully synthesized in 44% overall yield in 4 steps. This compound could be used as a simple N-terminal boronic acid model in stability studies. This compound could offer basic understanding of more complicated N-terminal peptidic boronic acids. During the synthesis of this compound, published deprotection methods were not suitable to deprotect the pinacol group. Therefore, a more general deprotection methodology is needed in order to make further progress, which will be discussed in the next chapter.

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Chapter 4. Protecting Groups for Boronic Acids and Methods of Deprotection

4.1. Protecting Groups for Boronic Acids

Boronic acids are very polar and have short shelf lives.[1] During synthesis, they are usually protected and exist as boronic esters, which can be converted back to boronic acids at the final step. Low molecular weight boronic esters are generally liquid at room temperature and can be purified by distillation or silica gel chromatography. They can be synthesized by the treatment of the corresponding boronic acid with diols using azeotropic distillation of water produced (with a Dean-Stark apparatus or dehydrating agent, e.g., anhydrous sodium sulfate, molecular sieves). Boronic esters could also be formed by transesterification, when the by-product alcohol is volatile and could be removed with distillation. The conversion of a boronic acid to a boronic ester and transesterification are both reversible reactions.[2,3] The forward reaction is favored when the ester product is not soluble in the system. Otherwise, removal of the by-product (water

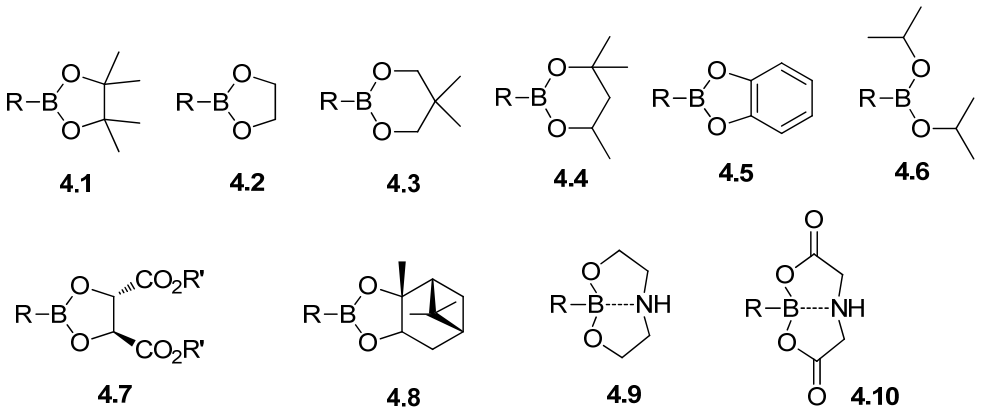


Figure 4.1 Commonly used boronic esters.[4]

or alcohol) can be used to drive the reaction forward. Figure 4.1 gives some commonly used boronic esters including some chiral ones (**4.7**, **4.8**), which have been used in stereoselective reactions.[4]

4.2. Deprotection of Boronic Esters

The hydrolysis of acyclic boronic esters such as **4.6** and small unhindered cyclic ones like those made from ethylene glycol (**4.2**), and tartrate derivatives (**4.7**) is rapid.[5, 6] However, some hindered cyclic aliphatic esters such as pinacol (**4.1**) and pinanediol (**4.8**) are notorious for being difficult to remove due to their bulkiness and stability.[7, 8] It has been our experience that these traditional boronic acid protecting groups require harsh deprotection conditions, especially in organic solvents (biphasic conditions are a little better, but not quantitative). In order to remove a pinanediolyl ester, either transborylation with boron trichloride or reduction using lithium aluminum hydride is used to achieve the corresponding boronic acid after hydrolysis (Figure 4.2).[8,9,10,11]

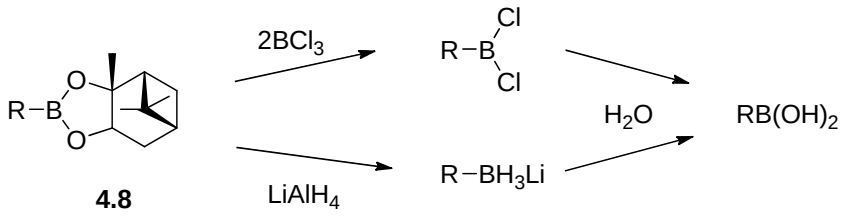


Figure 4.2 Cleavage of pinanediol boronic esters.[10,11]

In 1994, Coutts and coworkers published an efficient method for the cleavage of pinanediol boronic esters under mild conditions.[12] They were synthesizing dipeptides of proline boronic acids. Their synthetic intermediate contained a Boc protecting group, which is sensitive

to published pinanediol cleavage methods. Therefore they were looking for appropriate methods that could be applied to Boc protected dipeptide (Figure 4.3). An oxidative cleavage of **4.11** using sodium periodate allowed the recovery of free boronic acid **4.12** in a good yield without affecting the Boc group, although it destroyed the pinanediol group. The second method was using a biphasic transesterification with phenylboronic acid, which successfully recovered the chiral auxiliary from the phenylboronic ester **4.14**.

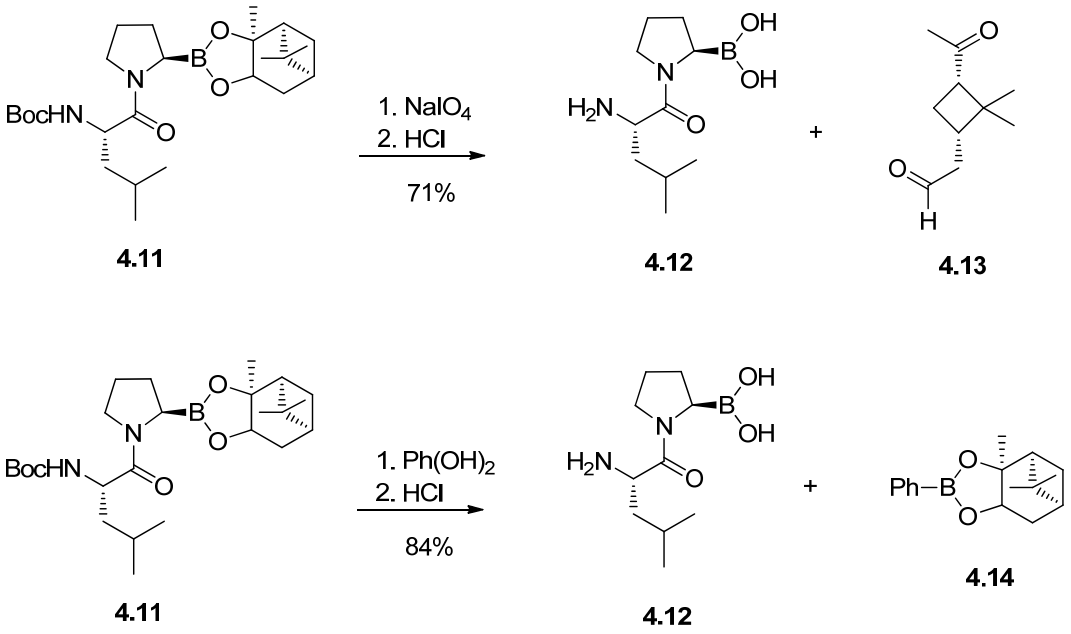


Figure 4.3 Cleavage of pinanediol boronic esters.[12]

In 1986, Kinder and Ames reported the synthesis of a boronic acid analogue of aspartic acid.[13] A transesterification with diethanolamine was involved in order to remove the pinacol ester (Figure 4.4). The boron-ate complex **4.16** was isolated with 83% yield followed by an alkaline hydrolysis and then acidification using anion exchange resin. After hydrogenation, the final deprotected boronic acid **4.17** was obtained. In this deprotection process, resin as a solid support was used. This deprotection was only applied on the synthesis of one amino acid.

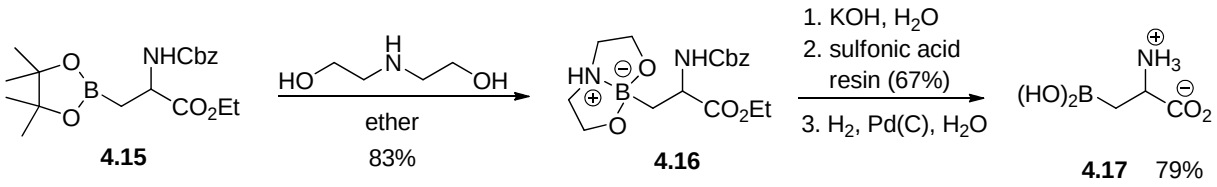


Figure 4.4 Removal of protecting groups in the synthesis of the boronic acid analogue of aspartic acid.[13]

Another example using diethanolamine to remove protected boronic ester was Song and Morin's work in 2001, wherein a boronated nucleoside analogue was synthesized (Figure 4.5).[14] The 2-step procedure, transesterification followed by acid treatment, gave the free boronic acid **4.20** with the nucleoside linkage intact. Nucleoside **4.20** was the first boronated indole nucleoside to be prepared. This procedure was compatible with functionalized aryl iodides, which exploits the synthetic potential of borylating agent **4.21** (Table 4.1).

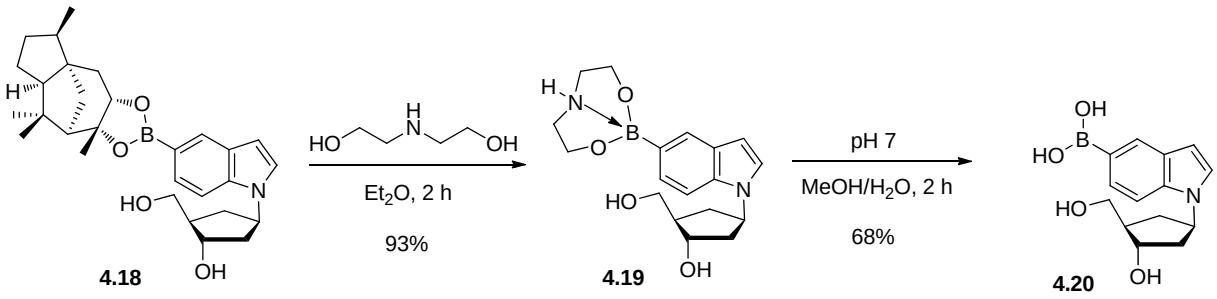
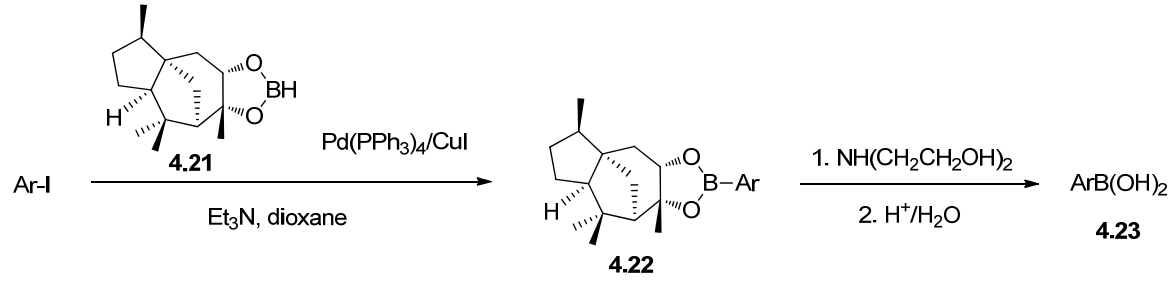
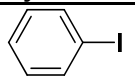
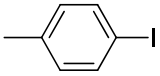
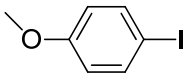
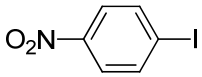
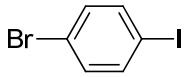
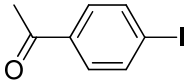
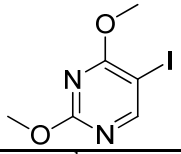


Figure 4.5 Deprotection of cedranediol boronic ester.[14]

Table 4.1 Reaction with representative aryl iodides and deprotection of the resulting boronates.[14]



entry	aryl iodide	yield of 4.22 (%)	yield of 4.23 (%)[a]
1		81[b]	71
2		86	70
3		87	64
4		79	72
5		89	63
6		69	58
7		-	83 [c]

[a]overall yields from aryl iodides. [b]previously obtained by esterification of phenylboronic acid. [c]converted to the boronic acid without isolation.

Previous methods suffer from the disadvantages such as incomplete transesterification or problems in isolating the final boronic acid product from the excess of transesterification partner. To improve this procedure, the Hutton group developed a mild deprotection procedure which applies polystyrene-linked boronic acid to convert arylboronic pinacolyl esters with sensitive functional groups (Figure 4.6, **4.24**) into their corresponding boronic acids (**4.25**).[15] This transesterification procedure gave good to excellent yields. With the ease of purification and the

regeneration of the solid-supported reagent, however, it still suffers from one limitation, the availability of polymer-supported boronic acid.

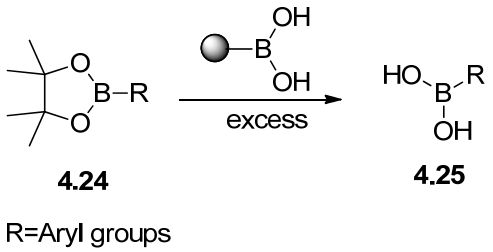


Figure 4.6 Deprotection of arylboronic pinacolyl esters with polymer-supported boronic acid.[15]

One year later, the same group reported an alternative method for deprotection of pinacolyl boronate esters via the hydrolysis of potassium trifluoroborate intermediates (Figure 4.7).[16] This two step protocol first converts the pinacolyl arylboronate **4.26** into readily isolable trifluoroborate **4.27** using potassium hydrogen fluoride, followed by subsequent fluoride removal with trimethylsilyl chloride or alkali metal base. They successfully applied this method to a range of pinacolyl arylboronates with different functional groups such as free phenol, *ortho* electron-donating substituents, however, at that time it was only applied to the deprotection of arylboronates.

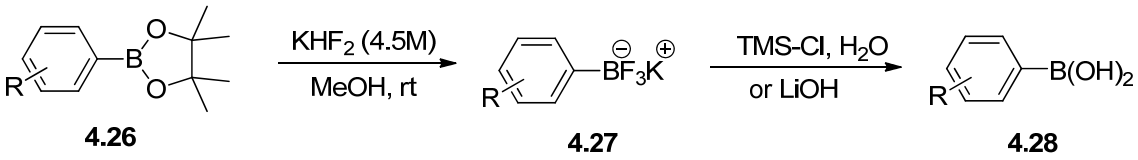


Figure 4.7 Conversion of pinacolyl esters to boronic acids via the corresponding trifuoroborates.[16]

Earlier this year, another paper was published describing the deprotection of pinanediol and pinacol boronate esters via fluorinated intermediates (Figure 4.8).[17] Via trifluoroborate or

difluoroborane intermediates, both α-amino alkyl pinanediolboronates and *o*-amino pinacol phenylboronates can be deprotected to their corresponding free boronic acids by using aqueous or nonaqueous workup.

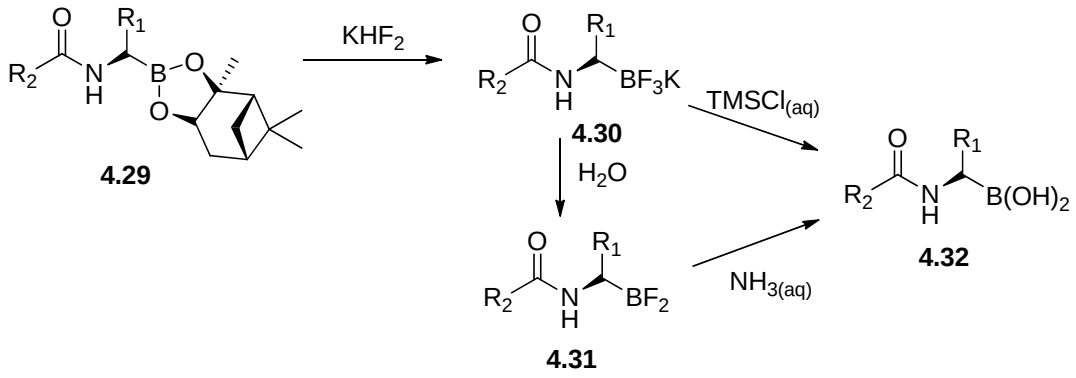


Figure 4.8 Conversion of α-amino alkyl pinanediolboronates to boronic acids via trifuoroborate or difluoroborane intermediates.[17]

4.3. Synthesis of Boronic Acids by using DEA as Protecting Group and Their Deprotection

The protecting groups for boron such as pinacol, pinanediol have found extensive use in organic transformations because of their compatibility with numerous reaction conditions. However, these protecting groups are notorious for being difficult to remove. [8,18] It has also been our experience that traditional boron protecting groups require harsh deprotection conditions especially in organic solvents. Among the deprotection protocols discussed in section 4.2, some of them give good to excellent yields. However, the methods are not general. Morin or Hutton's work can only be applied to the deprotection of arylboronic esters while Schofield's method was only used in the deprotection of α-amino alkyl pinanediolboronates and *o*-amino pinacol phenylboronates.[14,15,1616] Some of the procedures require the presence of resin or polymer-

supported boronic acids, which are not always commercially available and will increase the synthesis cost.[13,1515]

With the synthesis of N-terminal boronic acids in mind, we developed a protocol for pinacolyl boronic ester deprotection that offers several advantages (Figure 4.9). First, the reactions could be carried out under a mild deprotection condition (1M HCl) to produce boronic acids. Second, the functional group in boron compounds could not only be amide, but also ester, ketone and even nitrile, making them attractive for further functionalization into more elaborate chemical structures. The third advantage of using these procedures is the short reaction time. The transesterification using diethanolamine could be done in 30 minutes while the deprotection would only take about 20 minutes with moderate to excellent yields. Finally, there's no resin or solid-supported compounds involved which lowers the overall cost of the deprotection process. Both the boronic acid products (**4.35**) and the DEA protected compounds (**4.34**) can be isolated easily by filtration or extraction as the conversions are quantitative, with no silica gel chromatography needed. After deprotection the diethanolamine can be recovered and used again.

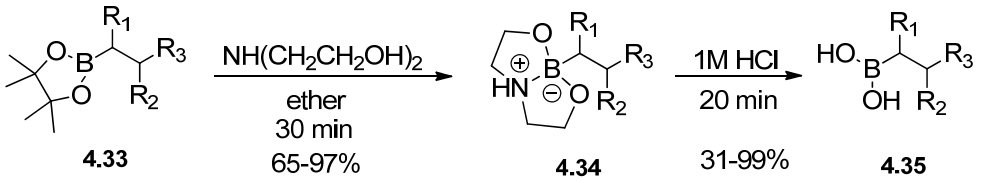
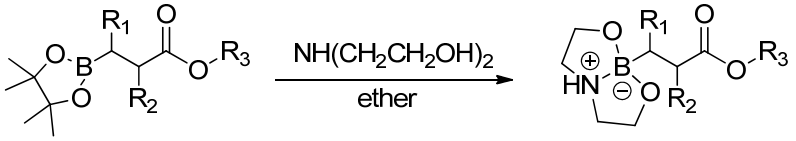


Figure 4.9 Deprotection of pinacolyl boronic esters.

4.3.1. Transesterification with DEA

First the transesterification of pinacolyl boronic esters with diethanolamine was carried out with compounds with ester groups (Table 4.2). The procedure works with methyl, benzyl and *tert*-butyl esters (**4.33**, R_3) and also works with β-phenyl esters (**4.33**, R_1) with a 72-88% yield. In this reaction, the tetracoordinate boronate precipitates within minutes. Simple filtration and washing provides analytically pure products.

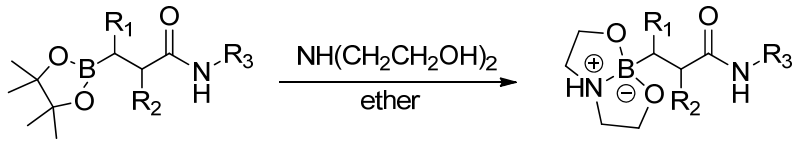
Table 4.2 Transesterification with esters. [a]Yields from Michael Perfetti.



4.33a-e **4.34a-e**

4.34	R_1	R_2	R_3	Yield (%)
a	H	H	Bn	85
b	H	H	Me	72
c	Ph	H	Me	88
d	Ph	H	^{t}Bu	75[a]
e	Ph	H	Bn	84[a]

The success of this protocol with esters provided the impetus to determine the generality of this procedure. To our delight, amides **4.34f-g** were produced in 65 and 68% yield, respectively (Figure 4.10).

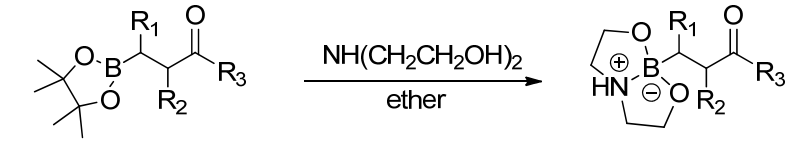


4.33f R_1=Me, R_2=H, R_3=Bn
4.33g R_1=Ph, R_2=H, R_3=Bn

4.34f 65%
4.34g 68%

Figure 4.10 Transesterification with amides.

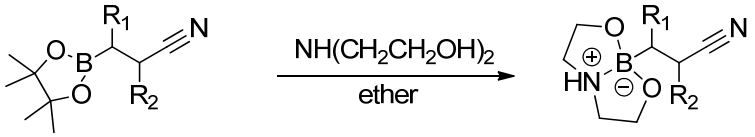
In order to explore the generality of this protocol, we also applied it to compounds such as ketones (Figure 4.11), nitriles (Figure 4.12) and phenylboronic ester (Figure 4.13). The corresponding tetracoordinate boron compounds were achieved with moderate to excellent yields. All these compounds **4.34a-l** are white solids, stable to atmosphere condition, and have long shelf lives.



4.33h R_1=H, R_2-R_3=CH_2CH_2
4.33i R_1=H, R_2=Ph, R_3=Ph

4.34h 79%[a]
4.34i 80%[a]

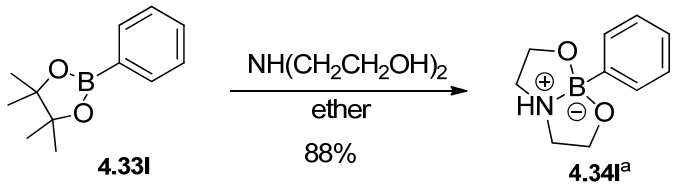
Figure 4.11 Transesterification with ketones. [a]Yield from Michael Perfetti.



4.33j R_1=H, R_2=H
4.33k R_1=Ph, R_2=H

4.34j 76%[a]
4.34k 97%[a]

Figure 4.12 Transesterification with nitriles. [a]Yield from Michael Perfetti.



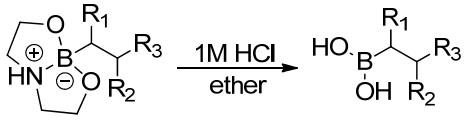
4.33l **4.34l**[a]

Figure 4.13 Transesterification of pinacoloyl phenylboronic ester.[a]Yield from Michael Perfetti.

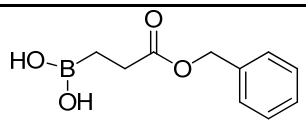
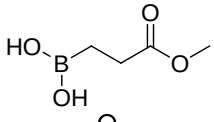
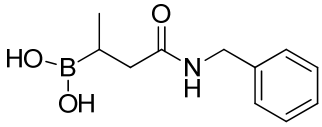
4.3.2. Hydrolytic Deprotection of Diethanolamine

The following deprotection step was performed under a slightly acidic biphasic condition with an extraction workup. For compound **4.34a**, **b**, **f**, **g**, **j**, **l**, the deprotection successfully gives the corresponding boronic acids as white solid (Table 4.3). However, the attempt of deprotection of **4.34c**, **d**, **e**, **h**, **i**, **k** failed, which is probably due to the poor stability of the corresponding boronic acids of these compounds. In order to circumvent this problem, compounds **4.34c**, **d**, **e**, **h**, **i** and **k** were reacted with 2 equivalents pinacol in a biphasic condition of hexane/H_2O (Table 4.4). The tetracoordinate boron compound is in H_2O and the pinacolylboronic ester is in hexane. Upon deprotection, a boronic acid is produced and immediately protected with pinacol that is stable and goes in the hexane layer. The successful isolation of the corresponding pinacolyl boronic esters suggests that the boronic acids were formed but could not be isolated since they are unstable.

Table 4.3 Yields of boronic acids.



4.34 **4.35**

4.35	Structure	Yield (%)
a		95
b		90
f		98

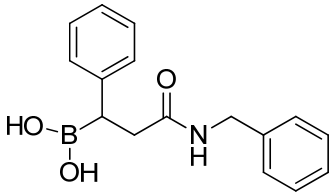
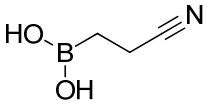
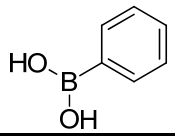
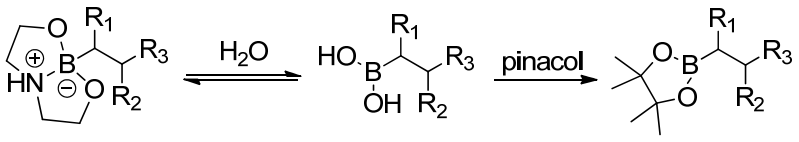
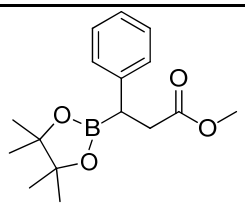
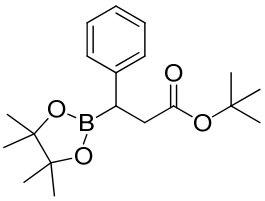
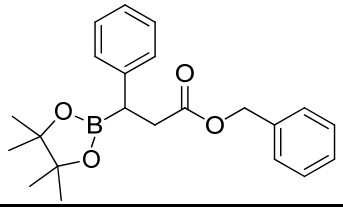
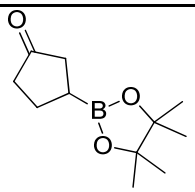
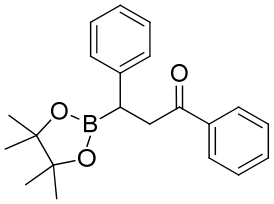
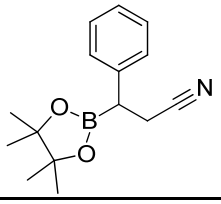
g		69
j		31
l		99

Table 4.4 Conversion from **4.34** to **4.33**.



4.34 **4.35** **4.33**

4.33	**Structure**	**Yield (%)**
c		92
d		96
e		90

h		79
i		82
k		89

4.3.3. Conclusions

A two-step protocol for pinacolyl boronic ester deprotection via diethanolamine protected intermediate was successfully developed with the advantages of mild reaction conditions, tolerance to various functional groups, short reaction time and ease of product isolation. Moderate to excellent yield was achieved for stable boronic acid products. The current results will be useful to study the deprotection of other boronic esters, such as pinanediol protected compounds, which are being used in chiral synthesis extensively. Similar compounds other than diethanolamine could also be candidates in this kind of deprotection protocol.

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Chapter 5. Experimental

5.1. General Information and Instrumentation

Chemicals for syntheses including anhydrous solvents were purchased from Aldrich Chemical Company (Milwaukee, WI), Sigma Chemicals (St. Louis, MO) and were used without further purification unless specified otherwise.

All reactions were carried out under an inert atmosphere of nitrogen unless otherwise stated. Thin layer chromatography (TLC) was performed on EMD silica gel 60 F_{254} aluminum backed TLC plates and spots were visualized with ultraviolet light and $KMnO_{4(aq)}$ or aqueous phosphomolybdic acid (PMA) stain.

^{1}H, ^{13}C, and ^{11}B NMR spectra were recorded on either a JEOL 500 or a Varian Inova 400 MHz NMR spectrometer. Chemical shifts (δ) are reported in parts per million with residual solvent protons (^{1}H: $CDCl_3$, s, 7.26; CD_3CN, s, 1.94; CD_3OD, s, 3.31) or the solvent carbons (^{13}C: $CDCl_3$, 77.16 ± 0.016; CD_3CN, 1.32 ± 0.02, 118.26 ± 0.02; CD_3OD, 49.00 ± 0.01) as internal standards. Boron NMR spectra were referenced to external $BF_3{\cdot}OEt_2$ (no solvent, 0.00). ^{1}H-NMR data are presented as follows: chemical shift in ppm downfield from Me_4Si (multiplicity, coupling constant, integration). The following abbreviation are used in reporting NMR data: s, singlet; br s, broad singlet; d, doublet; t, triplet; dd, doublet of doublets; dt, doublet of triplets; q, quartet; m, multiplet. High resolution mass spectroscopy (HRMS) was performed on an Agilent 6220 LC/MS time-of-flight mass spectrometer using electrospray ionization (ESI). Melting Points were measured on BÜCHI Melting Point B-540.

5.2. Experimental Procedures and Characterization Data

General Procedure A: β-Borylation of α, β-Unsaturated Carbonyl Compounds.

A flame-dried, N_2 flushed round bottom flask was charged with copper(I) chloride (0.03 equiv), DPEphos (0.03 equiv), and sodium *tert*-butoxide or potassium *tert*-butoxide (0.09 equiv) in dry THF (1 mL). After 0.5 h, bis(pinacolato)diboron (1.1 equiv) dissolved in dry THF was added dropwise to provide a dark red solution. After 0.5 h, the α,β-unsaturated ester (1 equiv) and methanol (4 equiv) were added simultaneously. This reaction was stirred until all starting material was consumed as followed by TLC (~2-5 h). The reaction mixture was passed through a plug of Celite, concentrated under reduced pressure, and purified by flash column chromatography on silica gel to provide the product.

General Procedure B: α-Alkylation.

To a solution of LDA (1.1 equiv) in THF was added β-borylated carbonyl compound at -78 °C. The mixture was allowed to stir for 0.5 hour before the addition of alkyl/aryl halide (2 equiv). After 20 minutes at -78 °C, the mixture was warmed to 0 °C. After 1-2 hour as followed by TLC, the reaction was quenched by the addition of saturated ammonium chloride solution. The mixture was extracted with ethyl acetate (3x), brine (1x), dried with sodium sulfate and the organic solvent was removed under reduced pressure. Flash column chromatography provided the product.

General Procedure C: Saponification.

To a solution of β-borylated ester in THF was added lithium hydroxide (10 equiv) aqueous solution at 0 °C. The turbid white mixture was stirred for 2-8 hours until the reaction was

finished as judged by TLC. The reaction was quenched by the addition of 3M HCl until the pH reaches 3-4 and the mixture was allowed to warm to room temperature. Following the addition of saturated aqueous sodium chloride solution, the mixture was extracted with ethyl acetate (4x), dried with sodium sulfate and the organic solvent was removed under reduced pressure. Flash chromatography provided the product.

General Procedure D: Hydrogenation.

To a solution of benzyl ester in methanol was added 10% Pd/C. The reaction mixture was placed under hydrogen atmosphere by capping the flask with a hydrogen balloon. After about 30 minutes as judged by TLC, the mixture was filtered through Celite and solvent was removed under reduced pressure to provide the product sufficiently pure for use in the next reaction.

General Procedure E: Amidation.

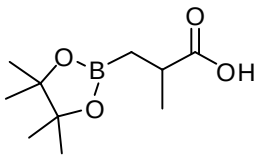
To a solution of carboxylic acid in CH_2Cl_2 was added 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDCI, 1.3 equiv), 1-hydroxy-7-azabenzotriazole (HOAt, 1.3 equiv) and amine (1.2 equiv) at room temperature. After 6-10 hours as judged by TLC, the reaction was diluted with CH_2Cl_2 and washed with 5% $NaHCO_3$ solution (1x), brine (1x), dried with sodium sulfate and the organic solvent was removed under reduced pressure. Recrystalization provided the product.

General Procedure F: Transesterification.

To a solution of pinacolyl boronic ester in ethyl acetate was added diethanolamine (1.1 equiv). The reaction was stirred until a white precipitate was observed (~1-10 min). The reaction was then filtered, washed with ethyl acetate, and dried to obtain the product as white solid.

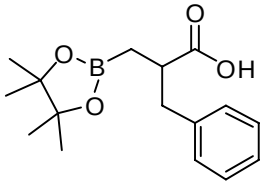
General Procedure G: Deprotection of DEA-Boronates.

To a solution of diethanolamine-boronate in ether was added 1 M HCl until the pH reaches 3-4. After about 20 minutes as judged by TLC, the reaction was extracted with ether (3x), brine (1x), dried with sodium sulfate and the organic solvent was removed under reduced pressure. The white solid was filtered and washed with ether to provide pure product. Due to their facile dehydration, boronic acids tend to provide somewhat unreliable melting points. Therefore the melting points for boronic acids were not taken.



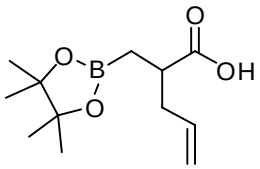
2-Methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoic acid (3.2a)

This product was prepared as described in General Procedure C. Clear oil, 80% yield; R_f (SiO_2, 50% ethyl acetate in hexane) 0.3; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.67 (dd, *J* = 7.2 Hz, 14.4, 1H), 1.20 (d, *J* = 3.2 Hz, 12H), 1.18 (s, 3H), 1.08 (dd, *J* = 7.6, 15.8 Hz, 1H), 0.91 (dd, *J* = 7.3, 15.8 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.58, 83.24, 35.43, 24.76, 19.20, 16.18. ^{11}B NMR (160 MHz, $CDCl_3$) δ 31.63.



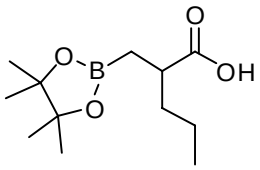
2-Benzyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoic acid (3.2b/d)

This product was prepared as described in General Procedure C. Clear oil, 85% (**b**)/ 71% (**d**) yield; R_f (SiO_2, 50% ethyl acetate in hexane) 0.3; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (dt, *J* = 12.8, 7.9 Hz, 5H), 3.08 (dd, *J* = 13.4, 6.4 Hz, 1H), 2.97 – 2.86 (m, 1H), 2.76 (dd, *J* = 13.4, 7.8 Hz, 1H), 1.21 (d, *J* = 7.4 Hz, 12H), 1.03 (dd, *J* = 16.0, 8.8 Hz, 1H), 0.93 (dd, *J* = 16.0, 6.1 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.98, 139.51, 129.20, 128.34, 126.35, 83.35, 42.94, 39.71, 24.65, 24.49, 13.38. HRMS (ESI+) Calculated for $C_{16}H_{22}BO_4$ [M-H]: 289.1617, found: 289.1617.



2-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)pent-4-enoic acid (**3.2e**)

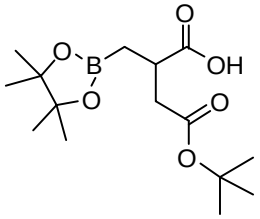
This product was prepared as described in General Procedure C. Clear oil, 96% yield; R_f (SiO_2, 50% ethyl acetate in hexane) 0.3; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.76 (td, *J* = 17.2, 7.1 Hz, 1H), 5.12 – 4.95 (m, 2H), 2.71 (dq, *J* = 13.3, 6.7 Hz, 1H), 2.36 (ddt, *J* = 85.6, 14.2, 6.9 Hz, 2H), 1.22 (d, *J* = 6.2 Hz, 12H), 1.02 (ddd, *J* = 22.4, 16.0, 7.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.28, 135.42, 117.35, 83.41, 40.49, 37.99, 24.86, 24.75.



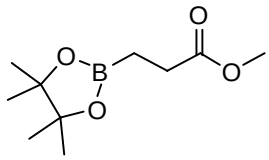
2-((4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)pentanoic acid (**3.2f**)

This product was prepared as described in General Procedure C. Clear oil, 36% yield; R_f (SiO_2, 50% ethyl acetate in hexane) 0.3; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.37 (dq, *J* = 8.6, 6.5 Hz, 1H), 1.34 (dddd, *J* = 27.4, 14.2, 10.3, 6.2 Hz, 2H), 1.09 (ddd, *J* = 9.4, 8.0, 4.9 Hz, 2H), 0.96 (d, *J* = 5.6

Hz, 12H), 0.76 (ddd, *J* = 22.4, 16.0, 7.5 Hz, 2H), 0.64 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.54, 83.14, 40.19, 35.98, 30.14, 24.58, 24.48, 20.10, 13.77.

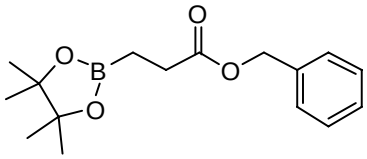


4-(*tert*-Butoxy)-4-oxo-2-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)butanoic acid (**3.2g**) This product was prepared as described in General Procedure D. Clear oil, 83% yield; R_f (SiO_2, 50% ethyl acetate in hexane) 0.3; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.02 – 2.91 (m, 1H), 2.64 – 2.43 (m, 2H), 1.41 (s, 9H), 1.21 (d, *J* = 3.5 Hz, 12H), 1.12 – 0.91 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.40, 171.57, 83.25, 80.99, 39.02, 37.45, 28.09, 24.80, 24.76, 14.19. HRMS (ESI+) Calculated for $C_{15}H_{26}BO_6$ [M-H]: 313.1901, found: 313.1812.



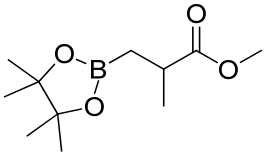
Methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoate (**3.4a**)

This product was prepared as described in General Procedure A. Clear oil, 93% yield; R_f (SiO_2, 10% ethyl acetate in hexane) 0.3; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.61 (s, 3H), 2.39 (t, *J* = 7.5 Hz, 2H), 1.19 (s, 12H), 0.97 (t, *J* = 7.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.10, 83.26, 51.52, 28.62, 24.78. ^{11}B NMR (160 MHz, $CDCl_3$) δ 32.65. HRMS (ESI+) Calculated for $C_{10}H_{20}BO_4$ [M+H]: 215.1449, found: 215.1448.



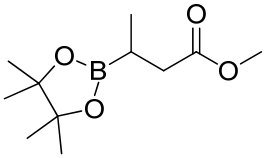
Benzyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoate (3.4b)

This product was prepared as described in General Procedure A. Clear oil, 89% yield; R_f (SiO_2, 10% ethyl acetate in hexane) 0.3; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.08 (m, 5H), 5.08 (s, 2H), 2.48 (t, *J* = 7.5 Hz, 2H), 1.19 (s, 12H), 1.03 (t, *J* = 7.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.55, 136.32, 128.56, 128.16, 83.32, 66.15, 28.91, 24.83. ^{11}B NMR (160 MHz, $CDCl_3$) δ 32.72. HRMS (ESI+) Calculated for $C_{16}H_{24}BO_4$ [M+H]: 291.1762, found: 291.1747.



Methyl 2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoate (3.4c)

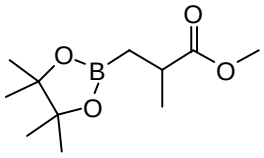
This product was prepared as described in General Procedure A except **3.43** was used instead of DPEphos (clear oil, 96% yield). This product had the same structure and spectroscopic properties as **3.5a**.



Methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoate (3.4d)

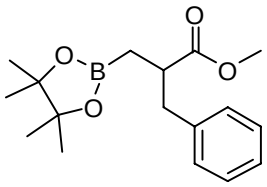
This product was prepared as described in General Procedure A except **3.43** was used instead of DPEPhos. Clear oil, 91% yield; R_f (SiO_2, 10% ethyl acetate in hexane) 0.3; ^{1}H NMR (500 MHz, CD_3Cl) δ 3.58 (d, *J* = 2.1 Hz, 3H), 2.34 (qd, *J* = 7.2, 16.4 Hz, 2H), 1.30 (dd, *J* = 7.4, 14.5 Hz,

1H), 1.17 (d, *J* = 2.1 Hz, 12H), 0.93 (d, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, CD_3Cl) δ 174.08, 83.01, 51.15, 37.33, 24.62, 24.54, 14.97. ^{11}B NMR (160 MHz, CD_3Cl) δ 31.95. HRMS (ESI+) Calculated for $C_{11}H_{21}BO_4Na$ [M+Na]: 251.14306, found: 251.14319.



Methyl 2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoate (3.5a)

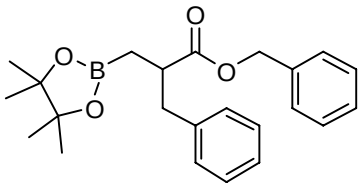
This product was prepared as described in General Procedure B. Clear oil, 60% yield; R_f (SiO_2, 10% ethyl acetate in hexane) 0.3; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.59 (d, *J* = 4.4 Hz, 3H), 2.62 (dd, *J* = 4.2, 7.2 Hz, 1H), 1.17 (t, *J* = 4.1 Hz, 12H), 1.13 (dd, *J* = 4.4, 7.1 Hz, 3H), 1.05 (ddd, *J* = 4.6, 7.6, 15.7 Hz, 1H), 0.87 (ddd, *J* = 4.4, 7.2, 15.8 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.39, 82.97, 51.30, 35.20, 35.18, 24.66, 24.63, 19.26. ^{11}B NMR (160 MHz, $CDCl_3$) δ 32.35. HRMS (ESI+) Calculated for $C_{11}H_{21}BO_4Na$ [M+Na]: 251.14360, found: 251.14305.



Methyl 2-benzyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoate (3.5b)

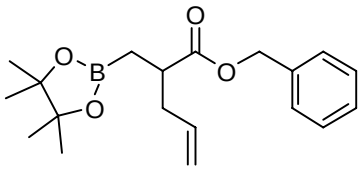
This product was prepared as described in General Procedure B. Clear oil, 62% yield; R_f (SiO_2, 10% ethyl acetate in hexane) 0.3; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.31 – 7.09 (m, 5H), 3.58 (s, 3H), 2.98 (dd, *J* = 13.1, 6.8 Hz, 1H), 2.84 – 2.76 (m, 1H), 2.72 (dd, *J* = 13.1, 7.3 Hz, 1H), 1.19 (d, *J* = 6.7 Hz, 12H), 0.93 (ddd, *J* = 22.0, 15.9, 7.4 Hz, 2H). ^{13}C NMR (125 MHz, CD_2Cl_2) δ 176.30,

139.81, 129.14, 128.26, 126.23, 83.20, 51.32, 43.08, 40.14, 24.69, 24.51. HRMS (ESI+) Calculated for $C_{17}H_{26}BO_4$ $[M+H]^+$: 305.1922, found: 305.1910.



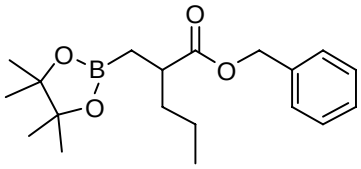
Benzyl 2-benzyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoate (3.5d)

This product was prepared as described in General Procedure B. Clear oil, 31% yield; R_f (SiO_2, 10% ethyl acetate in hexane) 0.3; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.11 (m, 10H), 5.09 – 5.00 (m, 2H), 3.02 (dd, *J* = 13.1, 7.3 Hz, 1H), 2.93 (dt, *J* = 13.7, 7.0 Hz, 1H), 2.78 (dd, *J* = 11.4, 7.5 Hz, 1H), 1.18 (d, *J* = 8.2 Hz, 12H), 1.10 (dd, *J* = 15.9, 8.6 Hz, 1H), 0.96 (dd, *J* = 16.0, 6.4 Hz, 1H).



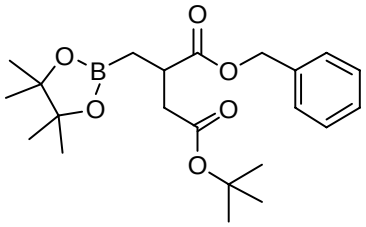
Benzyl 2-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)pent-4-enoate (3.5e)

This product was prepared as described in General Procedure B. Clear oil, 26% yield; R_f (SiO_2, 10% ethyl acetate in hexane) 0.3; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.34 – 6.27 (m, 5H), 4.77 – 4.64 (m, 1H), 4.08 (q, *J* = 12.5 Hz, 2H), 4.00 (dd, *J* = 6.0, 23.1 Hz, 2H), 1.72 (dd, *J* = 6.7, 8.5 Hz, 1H), 1.46 – 1.22 (m, 2H), 0.17 (d, *J* = 9.0 Hz, 12H), 0.03 (ddd, *J* = 7.5, 16.0, 22.6 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.90, 135.36, 134.60, 127.50, 127.14, 127.04, 116.10, 82.46, 65.26, 39.67, 37.38, 23.66. HRMS (ESI+) Calculated for $C_{19}H_{28}BO_4$ [M+H]: 331.20807, found: 331.20802.



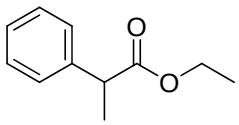
Benzyl 2-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)pentanoate (3.5f)

This product was prepared as described in General Procedure B. Clear oil, 26% yield; R_f (SiO_2, 10% ethyl acetate in hexane) 0.3; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 – 7.19 (m, 5H), 5.01 (q, *J* = 12.5 Hz, 2H), 2.63 – 2.49 (m, 1H), 1.65 – 1.50 (m, 2H), 1.37 (dt, *J* = 13.5, 7.2 Hz, 1H), 1.25 – 1.17 (m, 2H), 1.10 (d, *J* = 8.6 Hz, 12H), 1.02 (dd, *J* = 15.8, 8.6 Hz, 1H), 0.87 (dd, *J* = 15.9, 6.6 Hz, 1H), 0.79 (t, *J* = 7.3 Hz, 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ 175.87, 135.48, 127.50, 127.05, 125.52, 82.24, 64.95, 39.78, 35.58, 23.84, 19.43, 13.05. HRMS (ESI+) Calculated for $C_{19}H_{30}BO_4$ [M+H]: 333.22371, found: 333.22352.



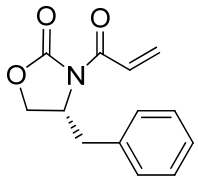
1-Benzyl 4-tert-butyl 2-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)succinate (3.5g)

This product was prepared as described in General Procedure B. Clear oil, 26% yield; R_f (SiO_2, 10% ethyl acetate in hexane) 0.3; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.27 (m, 5H), 5.11 (q, *J* = 12.5 Hz, 2H), 3.04 (td, *J* = 13.4, 7.7 Hz, 1H), 2.64 (dd, *J* = 16.2, 8.1 Hz, 1H), 2.47 (dd, *J* = 11.9, 4.3 Hz, 1H), 1.39 (s, 9H), 1.18 (d, *J* = 5.2 Hz, 12H), 1.15 (dd, *J* = 7.7 Hz, 1H), 0.99 (dd, *J* = 16.0, 7.1 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.32, 171.14, 130.95, 128.93, 128.50, 128.10, 104.45, 83.40, 80.62, 66.43, 66.35, 39.22, 37.48, 28.11, 24.84, 24.78. HRMS (ESI+) Calculated for $C_{22}H_{33}BO_6Na$ [M+Na]: 427.22679, found: 427.22536.



Ethyl 2-phenylpropanoate (**3.5j**)

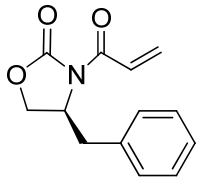
This product was prepared as described in General Procedure B. Clear oil, 97% yield; R_f (SiO_2, 10% ethyl acetate in hexane) 0.3; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 – 6.92 (m, 5H), 4.24 – 4.01 (m, 2H), 3.73 (q, *J* = 7.2 Hz, 1H), 1.52 (d, *J* = 7.9 Hz, 3H), 1.21 (t, *J* = 7.1 Hz, 3H).



(4*R*)-3-Acryloyl-4-benzyloxazolidin-2-one (**(*R*)-3.34**)

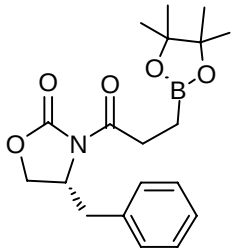
To a solution of acrylic acid (1.269 ml, 18.49 mmol) in 50 ml of THF at -20 °C was added triethylamine (5.570 ml, 39.60 mmol) followed by acryloyl chloride (1.395 ml, 17.17 mmol) and slightly yellow precipitate showed up immediately. The mixture was stirred at that temperature for 2 hours. LiCl (0.672 g, 15.85 mmol) was added followed by oxazolidinone (*R*)-**3.32** (2,340 g, 13.21 mmol). The mixture was allowed to warm to room temperature and stirred for 8 hours. The reaction was quenched by addition of 0.2 N HCl. The residue was partitioned between ethyl acetate and 0.2 N HCl. The organic layer was washed with half-saturated $NaHCO_3$ and brine, dried over sodium sulfate and concentrated in vacuo. Column chromatography using 0-15% ethylacetate/hexane yielded the title compound as white crystal (1.845 g, 60%). mp 72.9-73.4 °C; R_f (SiO_2, 10% ethyl acetate in hexane) 0.3; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 17.0, 10.5 Hz, 1H), 7.28 (ddd, *J* = 32.3, 18.4, 7.0 Hz, 5H), 6.60 (d, *J* = 17.0 Hz, 1H), 5.93 (d, *J* = 10.5

Hz, 1H), 4.78 – 4.69 (m, 1H), 4.28 – 4.13 (m, 2H), 3.07 (ddd, *J* = 23.0, 13.4, 6.4 Hz, 2H).[13]C NMR (125 MHz, $CDCl_3$) δ 177.05, 153.24, 139.39, 135.44, 129.64, 129.54, 128.96, 128.34, 127.31, 126.40, 65.86, 55.18, 37.99.

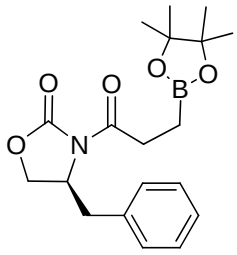


(4*S*)-3-Acryloyl-4-benzyloxazolidin-2-one (**(*S*)-3.34**)

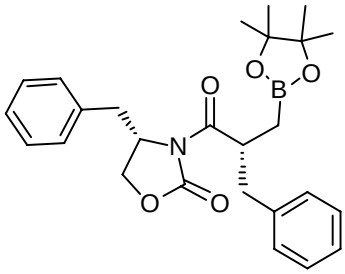
This product had similar spectroscopic properties as its enantiomer **(*R*)-3.34**.



(4*R*)-Benzyl-3-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoyl)oxazolidin-2-one (**(*R*)-3.35**) This product was prepared as described in General Procedure A. White solid, 68% yield; R_f (SiO_2, 20% ethyl acetate in hexane) 0.3; [1]H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.26 (m, 3H), 7.22 (dd, *J* = 5.2, 3.3 Hz, 2H), 4.66 (ddt, *J* = 11.0, 7.9, 3.1 Hz, 1H), 4.24 – 4.12 (m, 2H), 3.26 – 3.19 (m, 1H), 3.18 – 2.97 (m, 2H), 2.82 (dd, *J* = 13.5, 9.2 Hz, 1H), 1.25 (d, *J* = 5.8 Hz, 12H), 1.13 – 0.97 (m, 2H). [13]C NMR (125 MHz, $CDCl_3$) δ 174.39, 153.58, 135.36, 129.61, 129.02, 127.42, 83.29, 66.16, 55.09, 37.79, 31.06, 24.94, 24.82.

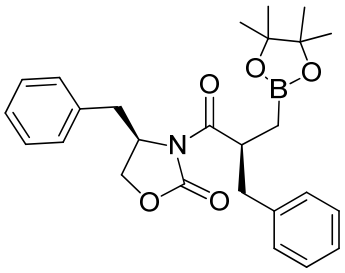


(4*S*)-Benzyl-3-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoyl)oxazolidin-2-one (**(*S*)-3.35**) This product had similar spectroscopic properties as its enantiomer **(*R*)-3.35**.



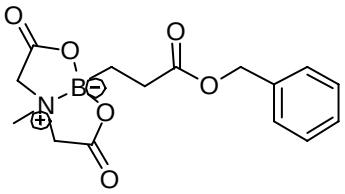
(4*S*)-Benzyl-3-((2*R*)-benzyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoyl)oxazolidin-2-one (**(*S*)-3.36**)

This product was prepared as described in General Procedure B. White solid, 12 % yield; R_f (SiO_2, 25% ethyl acetate in hexane) 0.3; mp 85.1-86.1 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.06 (m, 10H), 4.70 – 4.17 (m, 2H), 4.13 (t, *J* = 8.4 Hz, 1H), 4.09 (dd, *J* = 9.0, 3.0 Hz, 1H), 3.09 (ddd, *J* = 16.7, 13.2, 5.1 Hz, 2H), 2.65 (ddd, *J* = 22.8, 13.2, 8.6 Hz, 1H), 1.19 (d, *J* = 7.0 Hz, 12H), 1.05 (ddd, *J* = 21.6, 16.0, 7.4 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.05, 153.24, 139.39, 135.44, 129.64, 129.54, 128.96, 128.34, 127.31, 126.40, 83.30, 65.86, 55.18, 40.83, 40.68, 37.99, 24.96, 24.83.



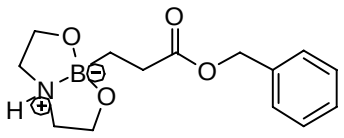
(4*R*)-Benzyl-3-((2*S*)-benzyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoyl)oxazolidin-2-one (**(*R*)-3.36**)

This product had similar spectroscopic properties as its enantiomer **(*S*)-3.36**.

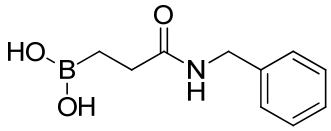


8-(3-(Benzyloxy)-3-oxopropyl)-4-methyl-2,6-dioxohexahydro-[1,3,2]oxazaborolo[2,3-b][1,3,2]oxazaborol-4-ium-8-uide (**3.40**)

To a 25 mL roundbottom flask was added compound **3.4b** (0.246 g, 0.848 mmol), N-methyliminodiacetic acid (0.137 g, 0.933 mmol), DMSO (1 mL) and toluene (4 mL). The flask was fitted with a Dean-Stark apparatus filled with toluene. The Dean-Stark apparatus was fitted with a water-cooled reflux condenser vented to ambient atmosphere. The stirred mixture was refluxed with azeotropic removal of diol overnight. The mixture was cooled to room temperature. To the flask was added water (10 mL) which caused the crystallization of a colorless solid. The mixture was filtered and provided the product as a white solid (0.068 g, 25%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.02 – 6.77 (m, 5H), 4.67 (s, 2H), 3.49 (d, J = 71.2 Hz, 4H), 2.49 (s, 3H), 2.09 – 1.96 (m, 2H), 0.56 – 0.45 (m, 2H).



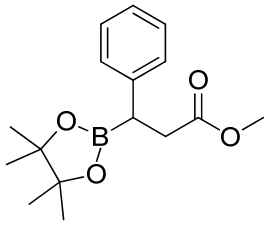
8-(3-(Benzyloxy)-3-oxopropyl)hexahydro-[1,3,2]oxazaborolo[2,3-b][1,3,2]oxazaborol-4-ium-8-uide (**3.42b**) This product was prepared as described in General Procedure F. White solid, 85 % yield; mp 159.7-161.6 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.27 (m, 5H), 6.16 (s, 1H), 5.18 – 4.97 (m, 2H), 3.95 (td, *J* = 5.3, 9.5 Hz, 2H), 3.81 (ddd, *J* = 3.2, 6.6, 9.9 Hz, 2H), 3.15 – 3.00 (m, 2H), 2.76 – 2.65 (m, 2H), 2.60 – 2.48 (m, 2H), 0.81 – 0.56 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.31, 136.09, 128.66, 128.32, 128.03, 66.34, 63.27, 51.25, 29.77. ^{11}B NMR (160 MHz, $CDCl_3$) δ 11.26. HRMS (ESI+) Calculated for $C_{14}H_{21}BO_4$ [M+H]: 278.1558, found: 278.1532.



(3-(Benzylamino)-3-oxopropyl)boronic acid (**3.44**)

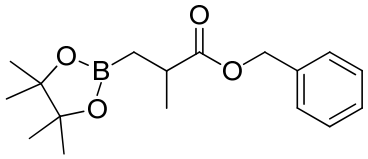
To a solution of **3.48a** (250 mg, 0.865 mmol) in 4:1 THF/water was added sodium periodate (555 mg, 2.59 mmol) and stirred for 30 min, at which time aqueous hydrochloric acid (1N, 0.519 ml, 0.519 mmol) was added to the suspension. The reaction mixture was stirred at ambient temperature overnight or until GC analysis showed complete consumption of the boronic ester **3.48**. The reaction mixture was diluted with water and extracted with ethyl acetate (4x). The combined extracts were washed with water (2x) and brine (1x), dried over sodium sulfate, filtered, and concentrated to dryness by rotary evaporation. The residue was washed with small portions of hexane to give a white solid product (113 mg, 63%). ^{1}H NMR (500 MHz, DMSO-D_6)

δ 8.25 (t, *J* = 6.0 Hz, 1H), 7.58 (s, 2H), 7.34 – 7.16 (m, 5H), 4.24 (d, *J* = 6.0 Hz, 2H), 2.18 (t, *J* = 7.8 Hz, 2H), 0.79 (t, *J* = 7.8 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-D_6) δ 174.64, 140.21, 128.79, 127.69, 127.03, 42.49, 30.91. ^{11}B NMR (160 MHz, DMSO-D_6) δ 31.02. HRMS (ESI+) Calculated for $C_{10}H_{15}BNO_3$ [M+H]: 208.114, found: 208.114.



Methyl 3-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoate (3.46c)

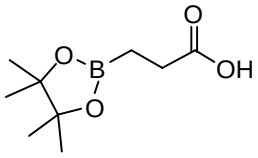
This product was prepared as described in General Procedure A. Clear oil, 81% yield; R_f (SiO_2, 10% ethyl acetate in hexane) 0.3; mp 71.7-72.2 °C ^{1}H NMR (500 MHz, CD_3Cl) δ 7.44 – 6.89 (m, 5H), 3.64 (s, 3H), 2.89 (dd, *J* = 10.1, 16.2 Hz, 1H), 2.73 (dd, *J* = 6.0, 10.1 Hz, 1H), 2.66 (dd, *J* = 6.0, 16.2 Hz, 1H), 1.19 (d, *J* = 22.5 Hz, 12H). ^{13}C NMR (125 MHz, CD_3Cl) δ 173.89, 141.39, 128.57, 128.26, 125.78, 83.65, 83.64, 51.63, 37.20, 24.64, 24.55, 0.07. ^{11}B NMR (160 MHz, CD_3Cl) δ 31.98. HRMS (ESI+) Calculated for $C_{16}H_{24}BO_4$ [M+H]: 291.1762, found: 291.1766.



Benzyl 2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoate (3.46d)

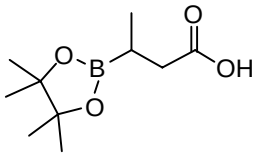
This product was prepared as described in General Procedure A. Clear oil, 78% yield; R_f (SiO_2, 10% ethyl acetate in hexane) 0.3; ^{1}H NMR (500 MHz, CD_3Cl) δ 7.44 – 7.17 (m, 5H), 5.09 (q, *J* = 12.5 Hz, 2H), 2.73 (dd, *J* = 7.2, 14.4 Hz, 1H), 1.22 (d, *J* = 7.1 Hz, 3H), 1.19 (d, *J* = 5.7 Hz, 12H), 1.18 – 1.12 (m, 1H), 0.95 (dd, *J* = 7.4, 15.9 Hz, 1H). ^{13}C NMR (125 MHz, CD_3Cl) δ

177.11, 136.49, 128.53, 128.04, 127.99, 83.24, 66.04, 35.52, 24.82, 19.44, 16.25. ^{11}B NMR (160 MHz, CD_3Cl) δ 32.43. HRMS (ESI+) Calculated for $C_{17}H_{26}BO_4$ [M+H]: 305.1919, found: 305.1934.



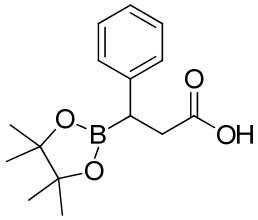
3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)propanoic acid (3.47a)

This product was prepared as described in General Procedure C. Clear oil, 94% yield; R_f (SiO_2, 50% ethyl acetate in hexane) 0.3; ^{1}H NMR (500 MHz, CD_3Cl) δ 2.46 (t, *J* = 7.4 Hz, 2H), 1.20 (d, *J* = 0.6 Hz, 12H), 0.98 (t, *J* = 7.4 Hz, 2H). ^{13}C NMR (125 MHz, CD_3Cl) δ 180.95, 83.40, 28.70, 24.77. ^{11}B NMR (160 MHz, CD_3Cl) δ 32.71. HRMS (ESI+) Calculated for $C_{10}H_{20}BO_4$ [M+H]: 215.1449, found: 215.1451.



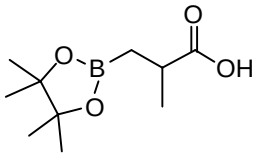
3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)butanoic acid (3.47b)

This product was prepared as described in General Procedure C. Clear oil, 94% yield; R_f (SiO_2, 50% ethyl acetate in hexane) 0.3; ^{1}H NMR (500 MHz, CD_3Cl) δ 2.55 – 2.35 (m, 2H), 1.35 (dd, *J* = 7.1, 14.6 Hz, 1H), 1.22 (t, *J* = 2.1 Hz, 12H), 1.01 (dd, *J* = 2.5, 7.5 Hz, 3H). ^{13}C NMR (125 MHz, CD_3Cl) δ 179.80, 83.35, 37.38, 24.73, 24.65, 15.05. ^{11}B NMR (160 MHz, CD_3Cl) δ 32.93. HRMS (ESI+) Calculated for $C_{11}H_{22}BO_4$ [M+H]: 229.1606, found: 229.1595.



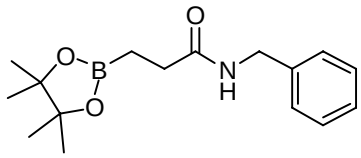
4-Phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoic acid (3.47c)

This product was prepared as described in General Procedure C. Clear oil, 97% yield; R_f (SiO_2, 50% ethyl acetate in hexane) 0.3; mp 93.4-95.1 °C; ^{1}H NMR (500 MHz, CD_3Cl) δ 7.21 (dq, *J* = 7.8, 15.0 Hz, 5H), 2.95 (dd, *J* = 12.0, 18.7 Hz, 1H), 2.80 – 2.60 (m, 2H), 1.18 (d, *J* = 21.8 Hz, 12H). ^{13}C NMR (125 MHz, CD_3Cl) δ 178.75, 141.00, 128.64, 128.23, 125.89, 83.75, 36.96, 24.58, 24.50. ^{11}B NMR (160 MHz, CD_3Cl) δ 31.95. HRMS (ESI+) Calculated for $C_{15}H_{22}BO_4$ [M+H]: 277.1606, found: 277.1612.



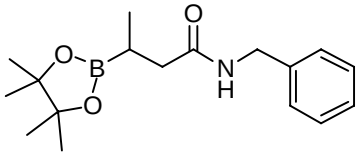
2-Methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoic acid (3.47d)

This product was prepared as described in General Procedure D (clear oil, 98% yield) and had the same structure and spectroscopic properties as **3.2a**.



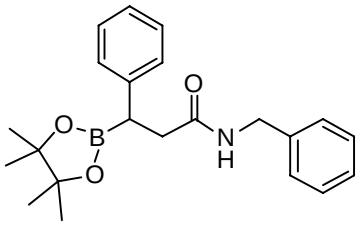
N-Benzyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanamide (3.48a)

This product was prepared as described in General Procedure E. White solid, 80% yield; ^{1}H NMR (500 MHz, CD_3Cl) δ 7.30 (m, 5H), 4.42 (d, *J* = 5.6 Hz, 2H), 2.35 (t, *J* = 7.4 Hz, 2H), 1.20 (d, *J* = 0.4 Hz, 12H), 1.08 (t, *J* = 7.4 Hz, 2H). ^{13}C NMR (125 MHz, CD_3Cl) δ 173.81, 138.63, 128.72, 127.92, 127.49, 83.41, 43.71, 31.06, 24.84. HRMS (ESI+) Calculated for $C_{16}H_{25}BNO_3$ [M+H]: 290.1922, found: 290.1927.



N-Benzyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanamide (3.48b)

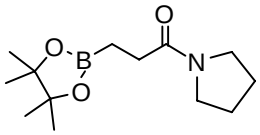
This product was prepared as described in General Procedure E. White solid, 39% yield; mp 99.7-100.2 °C ^{1}H NMR (500 MHz, CD_3Cl) δ 7.61 – 6.98 (m, 5H), 5.98 (s, 1H), 4.41 (d, *J* = 5.6 Hz, 1H), 2.30 (ddd, *J* = 7.1, 14.7, 20.7 Hz, 2H), 1.41 (d, *J* = 7.2 Hz, 1H), 1.19 (d, *J* = 3.4 Hz, 12H), 1.01 (d, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, CD_3Cl) δ 173.08, 138.61, 128.71, 127.96, 127.48, 83.31, 43.68, 40.15, 24.78, 24.74, 15.47. ^{11}B NMR (160 MHz, CD_3Cl) δ 33.06. HRMS (ESI+) Calculated for $C_{17}H_{27}BNO_3$ [M+H]: 304.2079, found: 304.2093.



N-benzyl-4-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanamide (3.48c)

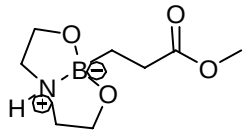
This product was prepared as described in General Procedure E. White solid, 27% yield; mp 108.8-110.0 °C; ^{1}H NMR (500 MHz, CD_3Cl) δ 7.37 – 7.06 (m, 11H), 5.68 (s, 1H), 4.38 (d, *J* =

5.7 Hz, 2H), 2.80 (p, *J* = 9.6 Hz, 2H), 2.60 – 2.45 (m, 1H), 1.17 (d, *J* = 20.5 Hz, 12H). ^{13}C NMR (125 MHz, CD_3Cl) δ 172.44, 141.88, 138.37, 128.70, 128.69, 128.68, 128.63, 128.38, 127.82, 127.46, 125.76, 83.63, 43.65, 39.92, 24.66, 24.63. ^{11}B NMR (160 MHz, CD_3Cl) δ 31.67. HRMS (ESI+) Calculated for $C_{22}H_{29}BNO_3$ [M+H]: 366.2235, found: 366.2219.

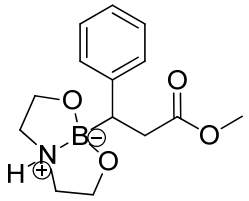


1-(pyrrolidin-1-yl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-one (**3.49**)

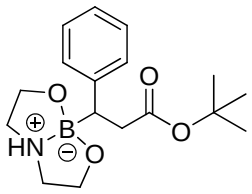
This product was prepared as described in General Procedure E. White solid, 10% yield; mp 81.5-81.9 °C; ^{1}H NMR (500 MHz, CD_3Cl) δ 3.38 (dt, *J* = 6.9, 25.4, 4H), 2.35 (t, *J* = 7.4, 2H), 1.94 – 1.70 (m, 4H), 1.20 (s, 12H), 0.93 (t, *J* = 7.4, 2H).^{13}C NMR (125 MHz, CD_3Cl) δ 172.73, 82.75, 46.48, 45.81, 45.56, 29.54, 26.10, 24.89, 24.48. ^{11}B NMR (160 MHz, CD_3Cl) δ 31.53. HRMS (ESI+) Calculated for $C_{13}H_{25}BNO_3$ [M+H]: 254.1922, found: 254.1919.



8-(3-Methoxy-3-oxopropyl)hexahydro-[1,3,2]oxazaborolo[2,3-b][1,3,2]oxazaborol-4-ium-8-uide (**4.34b**) This product was prepared as described in General Procedure F. White solid, 72% yield; mp 147.3-148.4 °C; ^{1}H NMR (500 MHz, CD_3Cl) δ 6.39 (s, 1H), 4.00 (td, *J* = 5.3, 9.6, 2H), 3.87 (ddd, *J* = 3.3, 6.6, 9.8, 2H), 3.65 (s, 3H), 3.21 (ddt, *J* = 7.0, 9.3, 11.7, 2H), 2.80 (dtd, *J* = 3.0, 5.5, 8.1, 2H), 2.53 – 2.45 (m, 2H), 0.77 – 0.60 (m, 2H).^{13}C NMR (125 MHz, CD_3Cl) δ 180.13, 63.27, 51.71, 51.30, 29.40. ^{11}B NMR (160 MHz, CD_3Cl) δ 11.25. HRMS (ESI+) Calculated for $C_8H_{17}BNO_4$ [M+H]: 202.1245, found: 202.1243.

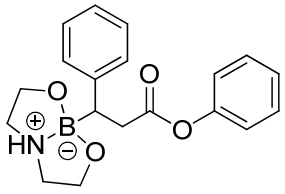


8-(3-Methoxy-3-oxo-1-phenylpropyl)hexahydro-[1,3,2]oxazaborolo[2,3-b][1,3,2]oxazaborol-4-ium-8-uide (**4.34c**) This product was prepared as described in General Procedure F. White solid, 88% yield; mp 188.7-189.9 °C; ^{1}H NMR (500 MHz, CD_3Cl) δ 7.29 – 6.98 (m, 5H), 5.65 (s, 1H), 3.95 (dtd, *J* = 5.4, 9.4, 14.7 Hz, 2H), 3.83 (qd, *J* = 3.4, 9.7 Hz, 2H), 3.62 (s, 3H), 3.12 – 3.01 (m, 1H), 3.00 – 2.89 (m, 2H), 2.76 – 2.64 (m, 3H), 2.32 (dd, *J* = 5.5, 8.1 Hz, 1H). ^{13}C NMR (125 MHz, CD_3Cl) δ 177.92, 147.34, 128.23, 127.78, 124.54, 63.37, 63.22, 51.68, 51.48, 51.40, 36.97. ^{11}B NMR (160 MHz, CD_3Cl) δ 11.25. HRMS (ESI+) Calculated for $C_{14}H_{21}BNO_4$ [M+H]: 278.1558, found: 278.1543.

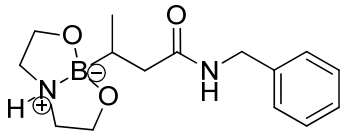


8-(3-(tert-Butoxy)-3-oxo-1-phenylpropyl)hexahydro-[1,3,2]oxazaborolo[2,3-b][1,3,2]oxazaborol-4-ium-8-uide (4.34d) This product was prepared as described in General Procedure F. White solid, 75% yield; mp 186.5-187.7 °C; ^{1}H NMR (500 MHz, CD_3Cl) δ 6.01 (s, 1H), 3.96 (dtd, *J* = 5.4, 9.4, 14.4 Hz, 2H), 3.89 – 3.81 (m, 2H), 3.22 – 3.11 (m, 1H), 3.02 – 2.94 (m, 1H), 2.94 – 2.84 (m, 1H), 2.79 – 2.68 (m, 2H), 2.61 (dd, *J* = 4.8, 17.2 Hz, 1H), 2.27 (dd, *J* = 4.6, 8.9 Hz, 1H), 1.39 (s, 9H). ^{13}C NMR (125 MHz, CD_3Cl) δ 155.70, 131.75, 127.99, 127.76, 124.23, 80.31, 77.30, 76.99, 76.67, 63.38, 63.18, 51.31, 51.20, 38.47, 28.00. ^{11}B NMR (160

MHz, CD_3Cl) δ 10.38. HRMS (ESI+) Calculated for $C_{17}H_{27}BNO_4$ [M+H]: 320.2028, found: 320.2006.

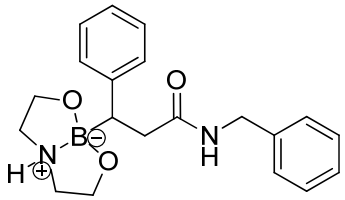


8-(3-Oxo-3-phenoxy-1-phenylpropyl)hexahydro-[1,3,2]oxazaborolo[2,3-b][1,3,2]oxazaborol-4-ium-8-uide (4.34e) This product was prepared as described in General Procedure F. White solid, 84% yield; mp 173.9-174.8 °C; ^{1}H NMR (400 MHz, CD_3CN) δ 7.41 – 6.99 (m, 9H), 4.96 (s, 3H), 3.76 (qd, *J* = 5.5, 9.2 Hz, 2H), 3.67 – 3.49 (m, 2H), 3.01 – 2.85 (m, 1H), 2.82 – 2.60 (m, 6H), 2.34 (dd, *J* = 5.8, 9.8 Hz, 1H). ^{13}C NMR (100 MHz, CD_3CN) δ 174.73, 128.34, 127.99, 127.70, 127.58, 123.99, 117.32, 104.98, 65.17, 62.47, 62.38, 51.17, 51.03, 36.69, 0.95, 0.75, 0.54, 0.34, 0.13, -0.08, -0.28. ^{11}B NMR (160 MHz, CD_3Cl) δ 10.86. HRMS (ESI+) Calculated for $C_{20}H_{25}BNO_4$ [M+H]: 354.1871, found: 354.1878.

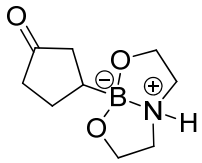


8-(4-(Benzylamino)-4-oxobutan-2-yl)hexahydro-[1,3,2]oxazaborolo[2,3-b][1,3,2]oxazaborol-4-ium-8-uide (**4.34f**) This product was prepared as described in General Procedure F. White solid, 65% yield; mp 127.5-128.6 °C; ^{1}H NMR (500 MHz, CD_3Cl) δ 7.77 (s, 1H), 7.41 – 7.10 (m, 5H), 6.00 (s, 1H), 4.39 (d, *J* = 5.7 Hz, 2H), 4.04 – 3.77 (m, 4H), 3.35 – 3.01 (m, 2H), 2.82 – 2.68 (m, 2H), 2.49 – 2.10 (m, 2H), 0.99 (d, *J* = 6.1 Hz, 3H), 0.94 (dd, *J* = 9.1, 17.7 Hz, 1H). ^{13}C NMR (125 MHz, CD_3Cl) δ 177.33, 137.99, 128.83, 127.64, 127.61, 63.52, 63.40, 51.49, 51.25, 43.69,

40.75, 17.31. ^{11}B NMR (160 MHz, CD_3Cl) δ 11.37. HRMS (ESI+) Calculated for $C_{15}H_{24}BN_2O_3$ [M+H]: 291.1874, found: 291.1890.

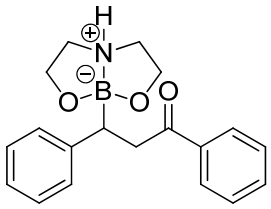


8-(3-(Benzylamino)-3-oxo-1-phenylpropyl)hexahydro-[1,3,2]oxazaborolo[2,3-b][1,3,2]oxazaborol-4-ium-8-uide (4.34g) This product was prepared as described in General Procedure F. White solid, 68% yield; mp 197.3-198.2 °C; ^{1}H NMR (500 MHz, CD_3Cl) δ 7.34 – 7.19 (m, 10H), 7.08 – 7.01 (m, 1H), 6.04 (s, 1H), 4.39 (d, *J* = 5.7 Hz, 2H), 4.02 – 3.76 (m, 4H), 3.25 (dt, *J* = 15.4, 7.0 Hz, 1H), 3.10 – 2.62 (m, 2H), 2.53 – 2.19 (m, 2H). ^{13}C NMR (125 MHz, CD_3Cl) δ 176.65, 148.07, 137.85, 128.84, 128.18, 127.89, 127.59, 124.38, 63.57, 63.50, 51.36, 43.81, 40.20. ^{11}B NMR (160 MHz, CD_3Cl) δ 11.03. HRMS (ESI+) Calculated for $C_{20}H_{26}BN_2O_3$ [M+H]: 353.2031, found: 353.2034.

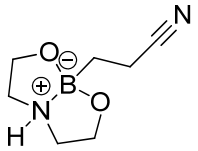


8-(3-Oxocyclopentyl)hexahydro-[1,3,2]oxazaborolo[2,3-b][1,3,2]oxazaborol-4-ium-8-uide (4.34h) This product was prepared as described in General Procedure F. White solid, 79% yield; mp 201.4-202.1 °C; ^{1}H NMR (500 MHz, CD_3CN) δ 5.13 (s, 1H), 3.82 (dd, *J* = 9.3, 14.6 Hz, 3H), 3.73 – 3.63 (m, 3H), 3.16 – 3.03 (m, 3H), 2.82 – 2.73 (m, 3H), 2.13 – 2.07 (m, 1H), 2.01 (dd, *J* = 8.5, 18.9 Hz, 2H), 1.82 (dd, *J* = 11.5, 18.0 Hz, 3H), 1.67 – 1.55 (m, 1H), 1.24 – 1.11 (m, 1H). ^{13}C NMR (125 MHz, CD_3Cl) δ 171.17, 63.41, 63.27, 52.27, 42.19, 39.85, 31.09, 26.21. ^{11}B NMR

(160 MHz, CD_3Cl) δ 11.56. HRMS (ESI+) Calculated for $C_9H_{17}BNO_3$ [M+H]: 198.1296, found: 198.1308.

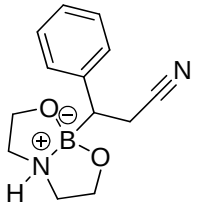


8-(3-Oxo-1,3-diphenylpropyl)hexahydro-[1,3,2]oxazaborolo[2,3-b][1,3,2]oxazaborol-4-ium-8-uide (4.34i) This product was prepared as described in General Procedure F. White solid, 72% yield; mp 170.0-171.4 °C; ^{1}H NMR (400 MHz, CD_3CN) δ 7.98 – 6.96 (m, 8H), 3.78 (ddd, *J* = 17.6, 8.8, 5.6 Hz, 2H), 3.67 – 3.52 (m, 2H), 3.46 – 3.28 (m, 2H), 3.03 – 2.89 (m, 1H), 2.88 – 2.74 (m, 1H), 2.75 – 2.64 (m, 2H), 2.56 – 2.45 (m, 1H). ^{13}C NMR (125 MHz, CD_3Cl) δ 199.37, 148.02, 137.20, 133.29, 128.62, 128.30, 128.27, 128.14, 124.48, 63.49, 63.30, 51.48, 51.33, 43.31, 24.82. ^{11}B NMR (160 MHz, CD_3Cl) δ 11.32. HRMS (ESI+) Calculated for $C_{19}H_{23}BNO_3$ [M+H]: 324.1766, found: 324.1777.

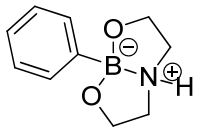


8-(2-Cyanoethyl)hexahydro-[1,3,2]oxazaborolo[2,3-b][1,3,2]oxazaborol-4-ium-8-uide (4.34j) This product was prepared as described in General Procedure F. White solid, 76% yield; mp 218.6-220.4 °C; ^{1}H NMR (400 MHz, CD_3CN) δ 3.81 (td, *J* = 9.3, 5.4 Hz, 1H), 3.74 – 3.63 (m, 1H), 3.14 (ddt, *J* = 11.8, 9.0, 6.9 Hz, 1H), 2.84 – 2.69 (m, 1H), 2.20 (dd, *J* = 16.1, 7.8 Hz, 1H), 0.75 – 0.61 (m, 1H). ^{13}C NMR (100 MHz, CD_3CN) δ 117.32, 62.50, 51.24, 12.45. ^{11}B NMR

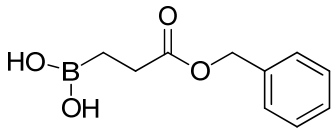
(160 MHz, CD_3Cl) δ 11.28. HRMS (ESI+) Calculated for $C_7H_{14}BN_2O_2$ [M+H]: 169.1148, found: 169.1165.



8-(2-Cyano-1-phenylethyl)hexahydro-[1,3,2]oxazaborolo[2,3-b][1,3,2]oxazaborol-4-ium-8-uide (4.34k) This product was prepared as described in General Procedure F. White solid, 97% yield; mp 147.5-148.9 °C; ^{1}H NMR (500 MHz, CD_3CN) δ 7.34 – 7.07 (m, 6H), 4.86 (s, 1H), 3.82 – 3.71 (m, 3H), 3.67 – 3.61 (m, 1H), 3.56 (dt, *J* = 4.8, 9.9 Hz, 1H), 3.04 – 2.94 (m, 1H), 2.74 – 2.61 (m, 7H), 2.18 (t, *J* = 8.3 Hz, 1H), 2.14 (s, 1H). ^{13}C NMR (125 MHz, CD_3CN) δ 145.33, 128.05, 127.99, 124.91, 117.41, 62.60, 62.54, 51.31, 51.20, 19.56. ^{11}B NMR (160 MHz, CD_3CN) δ 10.47. HRMS (ESI+) Calculated for $C_{13}H_{16}BN_2O_2$ [M-H]: 243.1310, found: 243.1335.

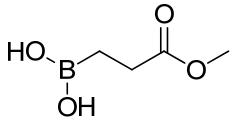


8-Phenylhexahydro-[1,3,2]oxazaborolo[2,3-b][1,3,2]oxazaborol-4-ium-8-uide (4.34l) This product was prepared as described in General Procedure F. White solid, 88% yield; mp 215.1-217.5 °C; ^{1}H NMR (400 MHz, CD_3CN) δ 7.55 – 7.15 (m, 2H), 3.97 (td, *J* = 9.3, 5.4 Hz, 1H), 3.93 – 3.81 (m, 1H), 3.28 – 3.14 (m, 1H), 2.90 – 2.78 (m, 1H). ^{13}C NMR (100 MHz, CD_3CN) δ 132.54, 126.91, 126.65, 63.09, 51.10. ^{11}B NMR (160 MHz, CD_3CN) δ 10.55. HRMS (ESI+) Calculated for $C_{10}H_{15}BNO_2$ [M+H]: 192.1196, found: 192.1204.



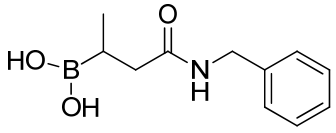
(3-(Benzyloxy)-3-oxopropyl)boronic acid (4.35a)

This product was prepared as described in General Procedure G. White solid, 95% yield; ^{1}H NMR (500 MHz, CD_3Cl) δ 7.45 – 7.22 (m, 5H), 5.13 (s, 2H), 2.53 (t, *J* = 7.2 Hz, 2H), 1.12 (t, *J* = 7.0 Hz, 2H). ^{13}C NMR (125 MHz, CD_3Cl) δ 175.15, 136.02, 128.68, 128.35, 66.58, 28.69, 24.84. ^{11}B NMR (160 MHz, CD_3Cl) δ 31.59. HRMS (ESI+) Calculated for $C_{10}H_{13}BO_4Cl$ [M+Cl]: 243.0601, found: 243.0619.



(3-Methoxy-3-oxopropyl)boronic acid (4.35b)

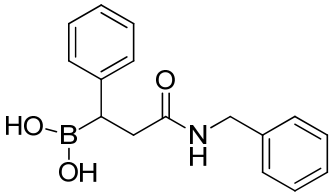
This product was prepared as described in General Procedure G. White solid, 90% yield; ^{1}H NMR (500 MHz, CD_3Cl) δ 3.66 (s, 3H), 2.48 (t, *J* = 7.2 Hz, 2H), 1.11 (t, *J* = 7.2 Hz, 2H). ^{13}C NMR (125 MHz, CD_3Cl) δ 175.87, 51.85, 28.41, 10.43. ^{11}B NMR (160 MHz, CD_3Cl) δ 31.49. HRMS (ESI+) Calculated for $C_4H_{10}BO_4$[M+H]: 133.0672, found: 133.0665.



(4-(Benzylamino)-4-oxobutan-2-yl)boronic acid (4.35f)

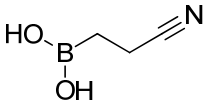
This product was prepared as described in General Procedure G. White solid, 98% yield; ^{1}H NMR (500 MHz, CD_3OD) δ 7.39 – 7.16 (m, 5H), 4.37 (q, *J* = 14.9 Hz, 2H), 2.32 (d, *J* = 8.3 Hz,

2H), 1.51 – 1.34 (m, 1H), 0.92 (d, J = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, CD_3OD) δ 176.32, 138.39, 128.22, 127.28, 126.96, 43.15, 39.55, 14.30. ^{11}B NMR (160 MHz, CD_3OD) δ 26.96. HRMS (ESI+) Calculated for $C_{11}H_{20}BN_2O_3$[M+NH_4]: 239.1561, found: 239.1568.



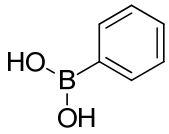
(3-(Benzylamino)-3-oxo-1-phenylpropyl)boronic acid (4.35g)

This product was prepared as described in General Procedure G. White solid, 69% yield; ^{1}H NMR (500 MHz, CD_3OD) δ 7.29 – 6.97 (m, 10H), 4.50 – 4.22 (m, 2H), 2.77 (dd, J = 16.9, 7.4 Hz, 1H), 2.72 – 2.43 (m, 2H). ^{13}C NMR (125 MHz, CD_3OD) δ 176.65, 148.07, 137.85, 128.84, 128.18, 127.89, 127.67, 127.59, 124.38, 43.81, 40.20. ^{11}B NMR (160 MHz, CD_3OD) δ 25.39. HRMS (ESI+) Calculated for $C_{16}H_{19}BNO_3$[M+H]: 284.1453, found: 284.1478.



(2-Cyanoethyl)boronic acid (4.35j)

This product was prepared as described in General Procedure G. White solid, 31% yield; ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 2.42 (t, 2H), 1.08 (t, 2H). ^{13}C NMR (125 MHz, CD_3Cl) δ 120.75, 11.34. ^{11}B NMR (160 MHz, $(CD_3)_2CO$) δ 18.89. HRMS (ESI+) Calculated for $C_3H_6BNO_2Cl$[M+Cl]: 134.0186, found: 134.0180.



Phenylboronic acid (4.35l)

This product was prepared as described in General Procedure G. White solid, 99% yield; ^{1}H NMR (500 MHz, CD_3Cl) δ 8.25 (dd, *J* = 7.9, 1.3 Hz, 2H), 7.69 – 7.57 (m, 1H), 7.56 – 7.46 (m, 2H). ^{13}C NMR (125 MHz, CD_3Cl) δ 135.75, 132.80, 128.09. ^{11}B NMR (160 MHz, CD_3Cl) δ 29.20.