# Regio- and Enantioselective Monofunctionalization of Diols via Hemiboronic Acid Catalysis

by

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# Abstract

Polyhydroxylated compounds such as carbohydrates, glycerols and diols play an important role in biological chemistry and as pharmaceutical agents. Furthermore, diols are often useful starting materials and intermediates to prepare stereochemically complex molecules. However, hydroxy group site-selectivity in the functionalization of diols remains an important unmet challenge. Traditional methods toward diol functionalization include multi-step protection/deprotection strategies and the use of stoichiometric activation. These processes are inefficient from an atom economy standpoint and can often result in the production of hazardous waste. More recently, diol functionalization via catalysis has become an emerging approach to overcome these challenges.

Chapter 1 is a summary of common methods to functionalize diol-containing compounds. Various catalytic transformations have been developed in the regioselective derivatization of carbohydrates. Asymmetric catalysis has also been a common approach toward the preparation of optically active compounds from achiral diols, however few methods provide high enantioselectivities for a wide range of substrates and transformations. Boronic acids have emerged as attractive catalysts toward diol functionalization because of their ability to undergo reversible interactions with hydroxy functional groups to form boronic esters. Diol activation is achieved upon formation of a tetrahedral adduct by enhancing the nucleophilicity of the oxygen atoms in the boronic ester.

Chapter 2 describes the use of a bench-stable hemiboronic acid catalyst in the regioselective monofunctionalization of polyol substrates. Evidence for the formation of an active tetrahedral adduct, without the use of a Lewis base, is described. The stability of the catalyst is a considerable

improvement to current borinic acid catalyzed methods. Mechanistic considerations and efforts to control regioselectivity are discussed.

Chapter 3 summarizes the discovery of a novel chiral variant of the aforementioned hemiboronic acid toward the catalytic enantioselective desymmetrization of 1,3-diols. Reaction optimization and catalyst design leads to the synthesis of optically active alcohols from symmetrical diols with good enantioselectivity. In the end, a mild and practical method is a unique way to prepare useful, chiral building blocks. Favourable characteristics of the developed reaction, such as catalyst recyclability and use of a weak base, is discussed.

# Preface

Preliminary research described in Chapter 2 in the screening of boronic acid catalysts (Section 2.1.1) was conducted by K.-M. Vetter, a visiting research intern. A. Ponich (NSERC Undergraduate Student Research Award recipient) was an undergraduate student under my supervision that assisted with the preparation and scope of some substrates (**2-5**, **2-17** and **2-20**), and performing competition experiments relevant in Chapter 2. H.T. Ang was responsible for growing X-ray quality crystals for the X-ray crystal structure described in Chapter 2, which was analyzed by M. Ferguson (X-Ray Crystallography Laboratory, University of Alberta).

# Acknowledgments

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Finally, I would like to thank my sister, Vanessa Estrada, mother, Victoria Estrada, and father, Carlito Estrada, for their continuous love and support.

# List of Abbreviations

| | |
|---|---|
| Ac | Acetyl |
| Ad | Adamantyl |
| Ar | Aryl |
| BINOL | 1,1’-Bi-2-naphthol |
| Bn | Benzyl |
| Boc | *tert*-Butyloxycarbonyl |
| Bu | Butyl |
| Bz | Benzoyl |
| $CH_2Cl_2$ | Dichloromethane |
| Cy | Cyclohexyl |
| CyJohnPhos | 2-(Dicyclohexylphosphino)biphenyl |
| DAN | 1,8-Diaminonaphthyl |
| DBI | Dibromoisocyanuric acid |
| DBU | 1,8-Diazabicyclo[5.4.0]undec-7-ene |
| DDQ | 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone |
| DMA | *N*,*N*-Dimethylaniline |
| DMDO | Dimethyldioxirane |
| DME | 1,2-Dimethoxyethane |
| DMF | *N,N*-Dimethylformamide |
| DMSO | Dimethylsulfoxide |
| dppf | 1,1'-Bis(diphenylphosphino)ferrocene |
| ee | Enantiomeric excess |
| er | Enantiomeric ratio |
| ESI | Electrospray ionization |
| Et | Ethyl |
| h | Hour |
| Hex | Hexanes |
| HPLC | High-performance liquid chromatography |
| HRMS | High-resolution mass spectrometry |

| | |
|---|---|
| Int | Intermediate |
| *i*Pr | *iso*-Propyl |
| $K_a$ | Acid dissociation constant |
| MALDI | Matrix assisted laser desorption/ionization |
| Me | Methyl |
| MHz | Megahertz |
| min | Minutes |
| mol | Moles |
| Ms | methanesulfonyl |
| MS | Mass spectrometry |
| SPS | Solvent purification system |
| NMI | 1-Methylimidazole |
| Ph | Phenyl |
| pin | Pinacolato |
| PMP | 1,2,2,6,6-Pentamethylpiperidine |
| ppm | Parts per million |
| quant. | Quantitative |
| rr | Regiomeric ratio |
| *t*-amyl | 2-Methyl-2-butyl |
| TBDMS | *tert*-Butyldimethylsilyl |
| TBDPS | *tert*-Butyldiphenylsilyl |
| TBS | *tert*-Butyldimethylsilyl |
| TES | Triethylsilyl |
| Tf | Trifluoromethanesulfonyl |
| THF | Tetrahydrofuran |
| TLC | Thin-layer chromatography |
| TMEDA | *N*,*N*,*N'*,*N'*-Tetramethylethylenediamine |
| TOF | Time-of-flight |
| Ts | *p*-Toluenesulfonyl |

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# Chapter 1 – A Survey of Selective Diol Functionalization

## 1.1 Diols as Synthetic Building Blocks

The hydroxy functional group is one of the most ubiquitous and versatile functional groups in all of organic chemistry. Alcohols are important in chemical synthesis because they are readily available from a wide variety of natural sources, are inexpensive, and can undergo a plethora of reactions. Polyhydroxylated compounds are found in several important bioactive natural products and pharmaceuticals (Figure 1-1). For example, Amphotericin B is the key component in liposomal AmBisome used to treat fungal infections.[1] Voglibose is an α-glucosidase inhibitor used for treating diabetes.[2] Pseudomonic acid A is the principal component in Mupirocin that is used as a topical antibiotic in the treatment of skin infections.[3] Gemcitabine is a chemotherapy drug used to treat a number of types of cancer.[4]

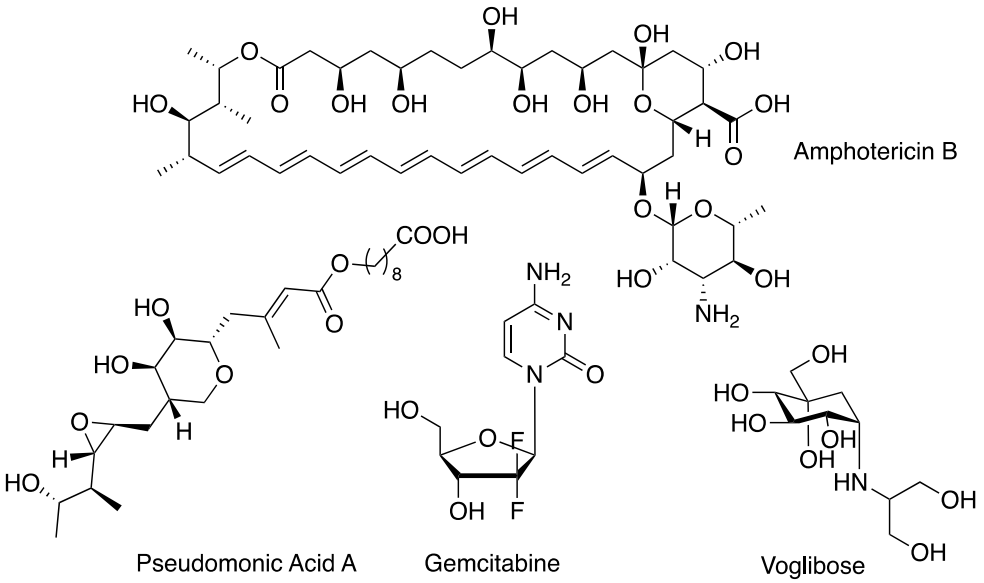



Figure 1-1: Examples of polyhydroxylated natural products and pharmaceutical drugs

Diols – commonly prepared by dihydroxylation of alkenes, epoxide-opening, reduction of dicarbonyls – are also very important synthetic building blocks in organic synthesis and are widely available and inexpensive (Figure 1-2). The diol moiety is also present in a wide variety of

naturally occurring compounds (Figure 1-2). Carbohydrates and other biological polyols are examples of highly abundant, stereoenriched polyhydroxylated compounds that are very useful starting materials in a chiral pool synthesis.

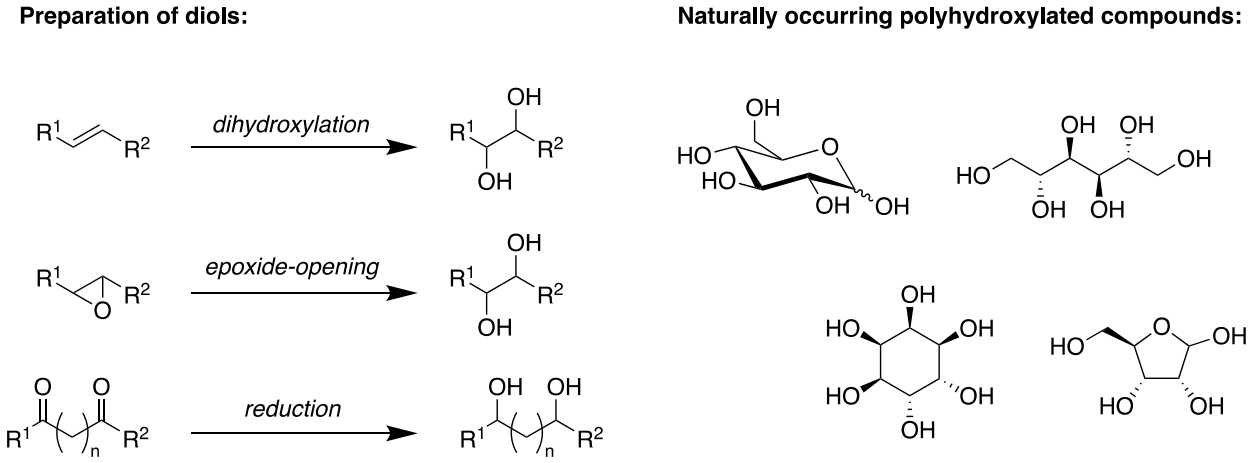



Figure 1-2: Examples of the preparation of diols and naturally occurring diols

Figure 1-3 shows examples of diol-containing starting materials and intermediates in the total synthesis of natural products. Vangala and co-workers used D-mannitol as the chiral precursor in the stereocontrolled total synthesis of (–)-lentiginosine.[5] A chiral aziridine **1-1** containing a 1,2-diol (made via asymmetric Sharpless alkene dihydroxylation) was used as an intermediate in the total synthesis of (–)-8-*epi*-swainsonine.[6]

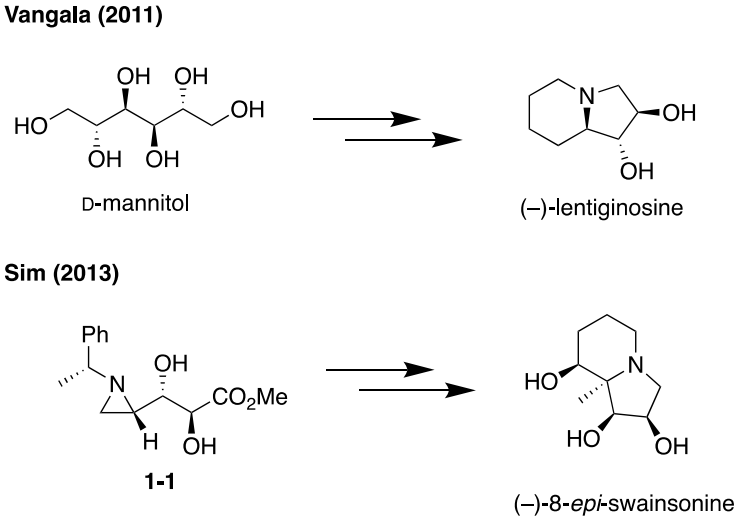



Figure 1-3: Examples of diols as building blocks in the total synthesis of natural products

To allow their selective transformations, compounds containing several nucleophilic sites are often orthogonally protected and deprotected. Common protecting groups for alcohols include esters, benzyl ethers, trityl ethers, silyl ethers, and sulfonates (Figure 1-4). In carbohydrate chemistry, the manipulation of a starting monosaccharide by orthogonal protection and deprotection of several hydroxy groups is essential toward building complex oligosaccharides. Ideally, manipulation of only a single hydroxy group in an unprotected monosaccharide is necessary. One of the greatest challenges organic chemists encounter is the site-selective functionalization of diol/polyol compounds (Figure 1-4).

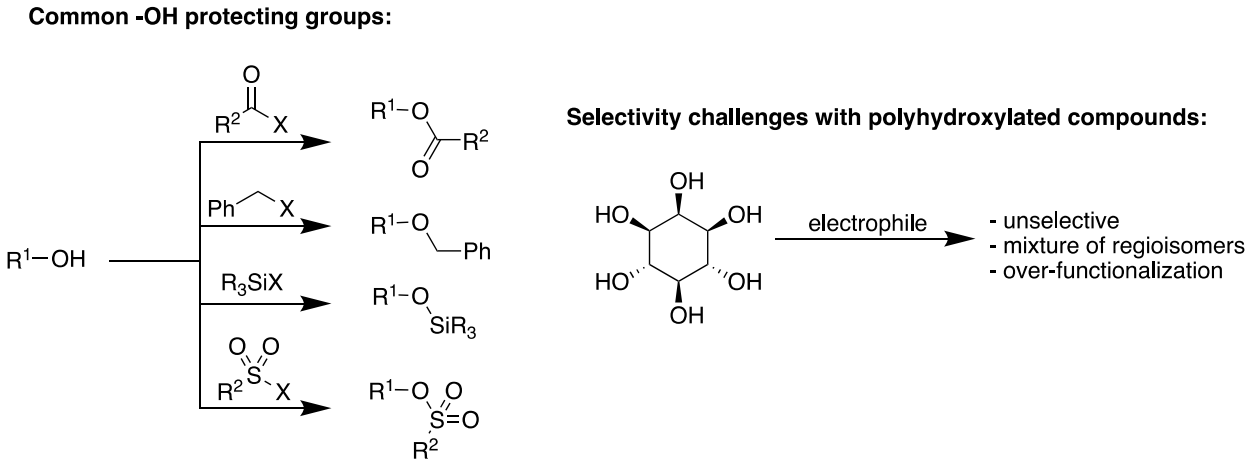



Figure 1-4: Common alcohol protecting groups and challenges in selective functionalization

Selectively derivatizing diol-containing compounds can be important in drug discovery when trying to synthesize various analogs, but distinguishing -OH groups of similar reactivity still remains a difficult task. For example, synthesis of pyranoside **1-2** could ideally be formed in one step upon direct substitution at the anomeric position (Figure 1-5). However, in reality, it is prepared in five steps involving a series of protection/deprotection and redox interchanges (Figure 1-5).[7] The use of multiple protecting groups to prevent further reactivity at the undesired sites, however, would be totally eliminated in an ideal synthesis.[8]

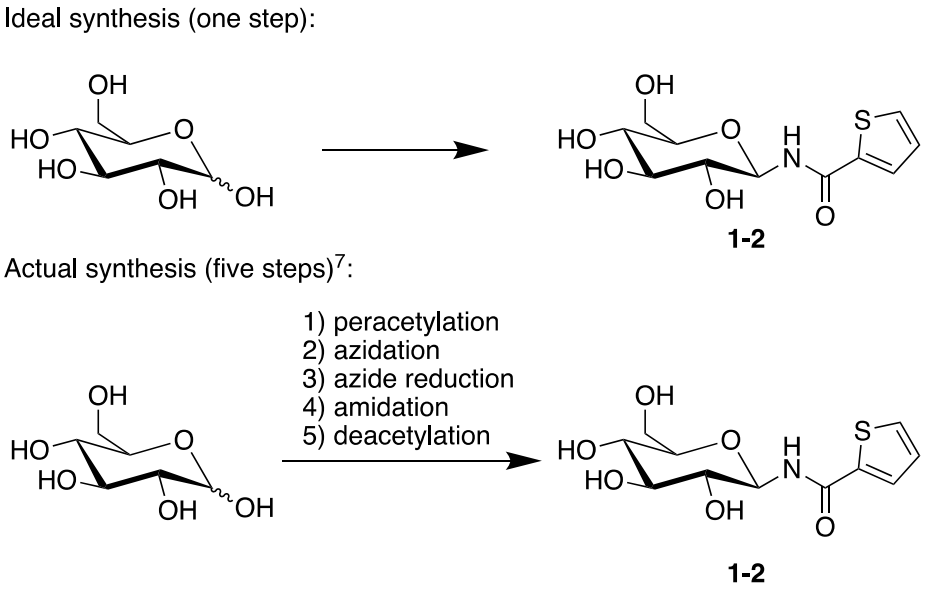


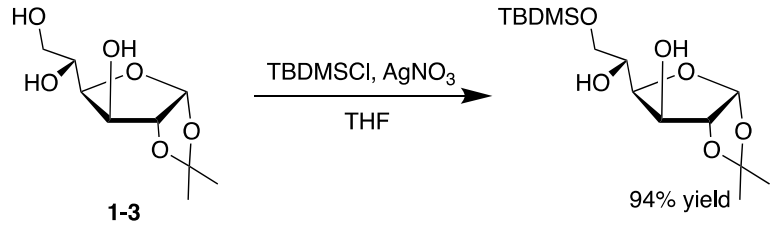

Figure 1-5: Ideal synthesis and actual synthesis of glucopyranoside **1-2**

It is therefore important to develop methodologies for diol functionalization that are highly selective and general. This introductory chapter will discuss some of the classical methods for diol functionalization. The first section will focus on stoichiometric and catalytic methods toward the selective functionalization of diols and carbohydrates. The second section will discuss recent catalytic methods toward enantioselective desymmetrization of achiral diols toward the synthesis of chiral building blocks. The use of organoboron compounds toward diol activation, and their advantages over other methods, will then be highlighted in this chapter.

## 1.2 Methods for Selective Diol Functionalization

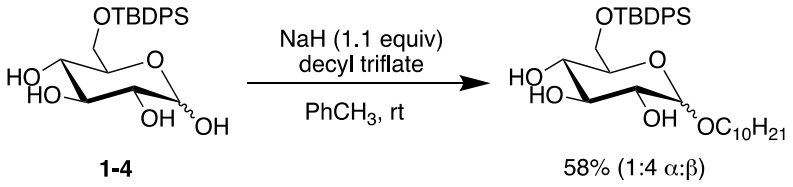
### 1.2.1 Relative Reactivities of -OH Groups

Over several decades, chemists have discovered ways to take advantage of the intrinsic reactivities of the -OH groups in polyhydroxylated compounds. For example, steric factors can create a strong bias in the functionalization of a single -OH, as exemplified in Scheme 1-1. Primary alcohols can often be selectively functionalized with bulky electrophiles in the presence of secondary alcohols (Scheme 1-1); secondary alcohols in the presence of a tertiary alcohol are selectively functionalized.[9,10]




Scheme 1-1: Selective *O*-6 silylation of glucofuranose **1-3**

Due to similar steric considerations, equatorial -OH groups in pyranosides, in general, are favoured toward functionalization over axial -OH groups. The positions of the hydroxy groups in carbohydrates are also differentiated by their relative acidities: the most acidic -OH group can be selectively functionalized depending on the strength of the base used.[11] For example, in the presence of a strong base, the anomeric -OH in glucopyranose **1-4** can be selectively alkylated due to its enhanced acidity relative to the -OH bonds (Scheme 1-2).



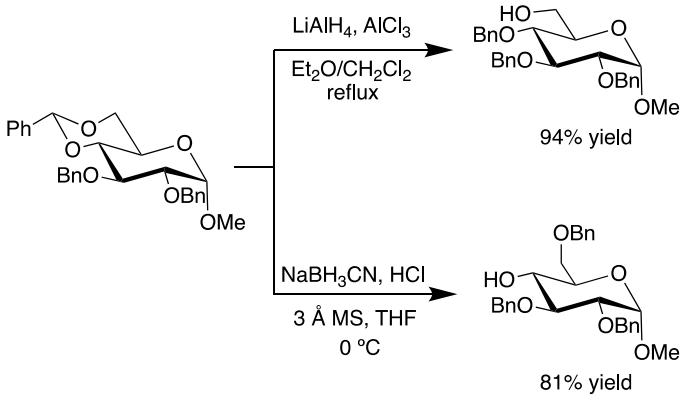

Scheme 1-2: Selective anomeric -OH alkylation of glucopyranose **1-4**

However, most often there are cases where there is less differentiation between two or more hydroxy groups. Therefore, extensive research has been conducted to develop methods to discover reagents that can interact with diol moieties to further activate them toward selective monofunctionalization.[12,13]

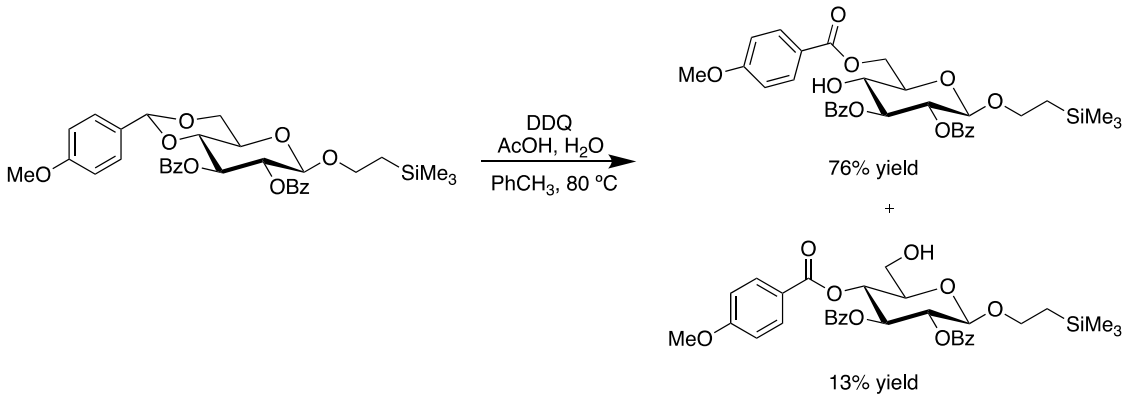
### 1.2.2 Stoichiometric Methods for Selective Functionalization of Diols

In the presence of a catalytic amount of acid, 1,2- and 1,3- diols can react with aldehydes and ketones to form cyclic acetals and ketals (Scheme 1-2). Acetals and ketals are an important class of protecting groups that are stable to a variety of transformations. While the formation of

isopropylidene ketals are generally selective toward 1,2-*cis*-diols to form a thermodynamically favoured 5-membered ring, arylidene acetals of 1,3-diol moieties are useful in the sense that opening of the 1,3-dioxane would formally produce a monofunctionalized diol. One of the advantages of such functional groups is that selective cleavage of an arylidene acetal can be achieved. In the example of 2,3-di-O-benzyl-4,6-O-benzylidenehexopyranoside, reduction using lithium aluminum hydride in the presence of aluminum trichloride would render a benzyl ether at the 5-position,[14] whereas reduction using sodium cyanoborohydride and HCl provides the protected 6-position (Scheme 1-3).[15] Another example is the selective oxidative cleavage of *p*-methoxybenzylidene acetals with DDQ has also been shown to provide *p*-methoxybenzoyl esters (Scheme 1-4).[16]

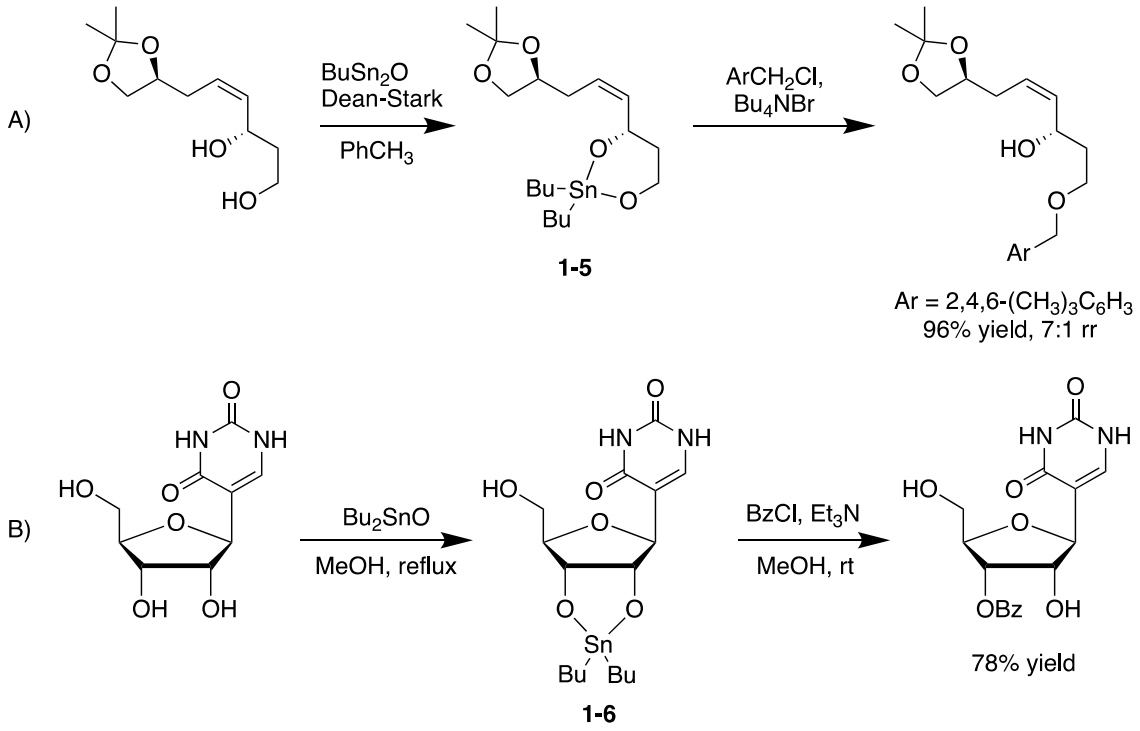



Scheme 1-3: Selective reductive ring cleavage of 2,3-di-*O*-benzyl-4,6-*O*-benzylidenehexopyranoside




Scheme 1-4: Selective oxidative ring cleavage of 2,3-di-*O*-benzoyl-4,6-*O*-methoxybenzylidenehexopyranoside

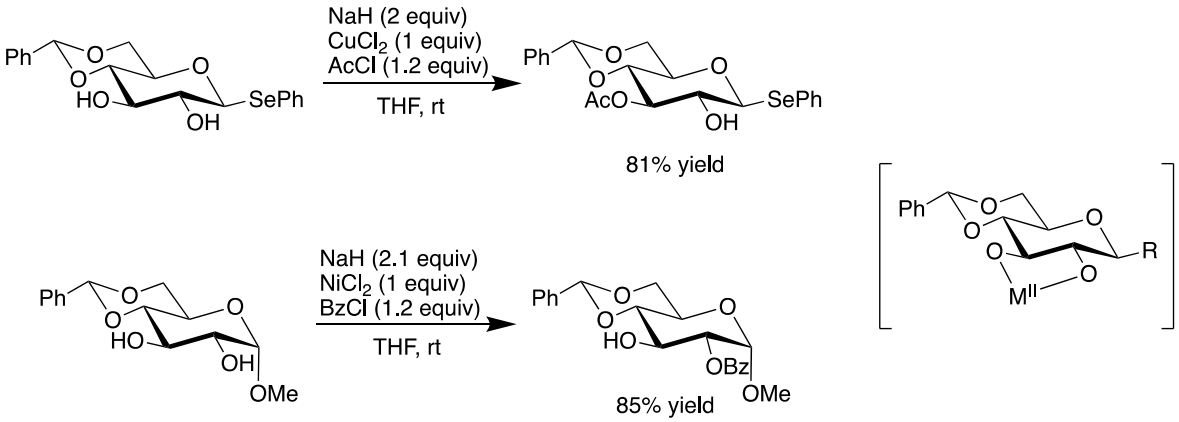
The use of organotin reagents is another classical general method toward selective diol functionalization. *cis*-Diol moieties can react with dibutyltin(IV) oxide to generate a cyclic stannylene acetal where the bound oxygen atoms acquire enhanced nucleophilicity.[17] The enhanced nucleophilicity may be a result of electron channeling from the tin atom to the bound oxygen atoms (i.e. an increased inductive effect).[17] Such stannylene acetals can further react with a variety of electrophiles to produce a monofunctionalized diol. In the asymmetric synthesis of *N*-acetylneuraminic acid, the stannylene acetal **1-5** generated from a 1,3-diol was reacted with 2,4,6-trimethylbenzyl chloride to selectively functionalize the primary alcohol (7:1 regioisomeric mixture, Scheme 1-5A).[18] Another example is the selective benzoylation of a secondary alcohol (in the presence of a primary -OH) of a ribonucleoside by reacting benzoyl chloride with the preformed 2',3'-*O*-stannylene acetal **1-6** (Scheme 1-5B).[19]




Scheme 1-5: Examples of organotin promoted diol functionalization

Transition metals have also been used to promote functionalization of *trans*-1,2-diol motifs. Chelation of a carbohydrate onto a metal center deactivates the dianion in the form of metal(II)

salt, and regioselectivity arises from reaction of the electrophile with the more nucleophilic anion (Scheme 1-6).[20] Examples of selective *O*-3 acylation and alkylation of partially protected glucopyranoside derivatives in the presence of copper(II) and nickel(II) salts have been demonstrated.[21,22]

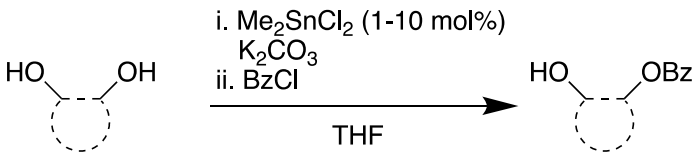



Scheme 1-6: Transition metal promoted selective acylation of 4,6-*O*-protected pyranosides

### 1.2.3 Catalytic Methods for Selective Functionalization of Diols

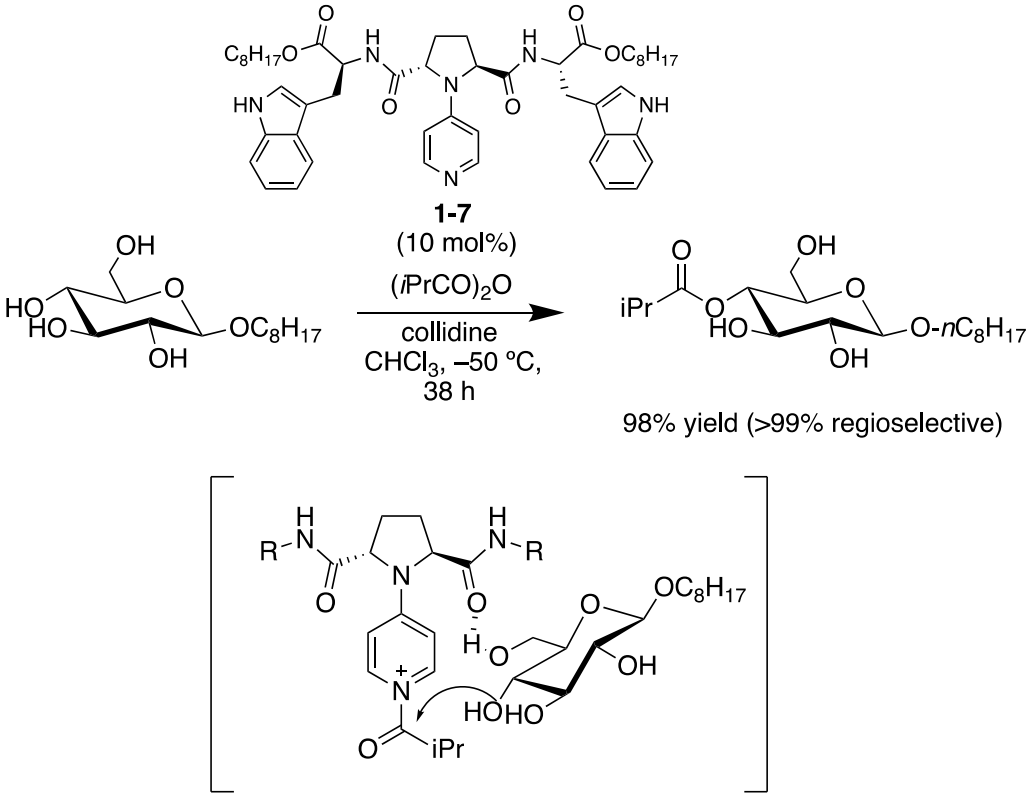
While the use of stoichiometric reagents to activate diols can be effective and general, pre-formation of an activated complex is still required, thereby increasing the number of steps in a synthesis. The generation of toxic and hazardous waste when using organotin reagents is also a key limitation. To address these issues, much progress has been made in discovering catalytic methods for diol functionalization.

With the generality and usefulness of the organostannane method, newer methods for diol activation using catalytic amounts of the tin(IV) reagent have been developed. For example, Matsamura developed the use of dimethyltin dichloride as a catalyst in the chemoselective monobenzoylation of diol substrates (Scheme 1-7).[23] Selective alkylation of carbohydrate derivatives has also been shown in the presence of tetrabutylammonium bromide or silver(I) oxide as additives. [24,25]



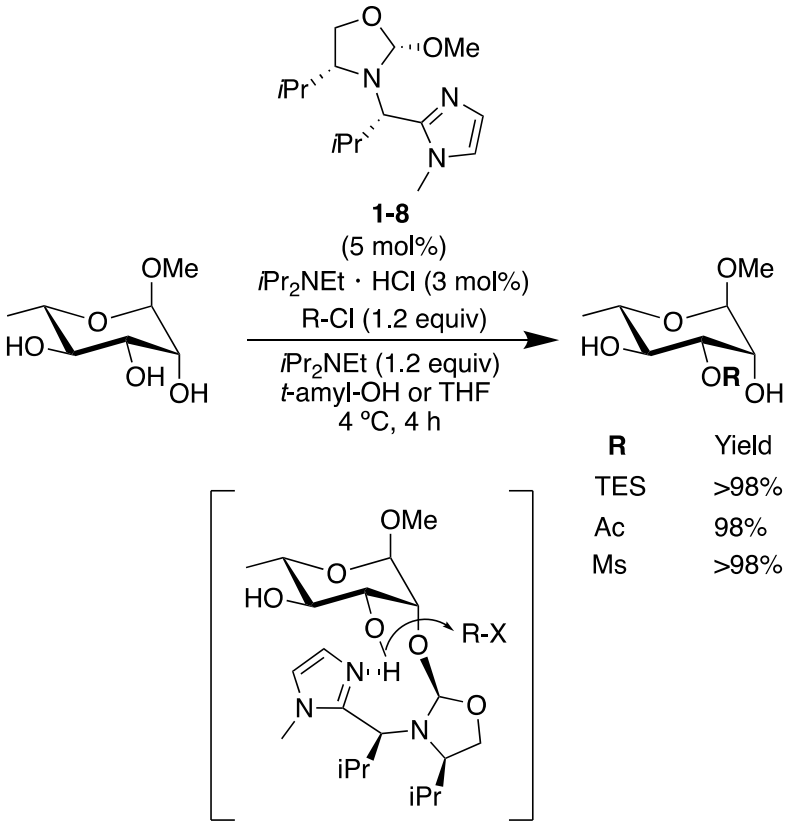

Scheme 1-7: Organotin(IV) catalyzed monofunctionalization of diols

Organocatalysts designed for substrate recognition toward site selective functionalization of diol substrates have also emerged in recent years. Kawabata and co-workers developed a chiral 4-pyrrolidinopyridine catalyst, **1-7**, in the monoesterification of unprotected pyranosides with excellent selectivity.[26] An example is shown in Scheme 1-8 where octyl β-glucopyranoside is selectively acylated at the 4-position. The authors proposed a key interaction between the primary hydroxyl group at the 6-position and the amide carbonyl in the catalyst, allowing for the nearest -OH to react with the intermediate acylpyridinium.[26]



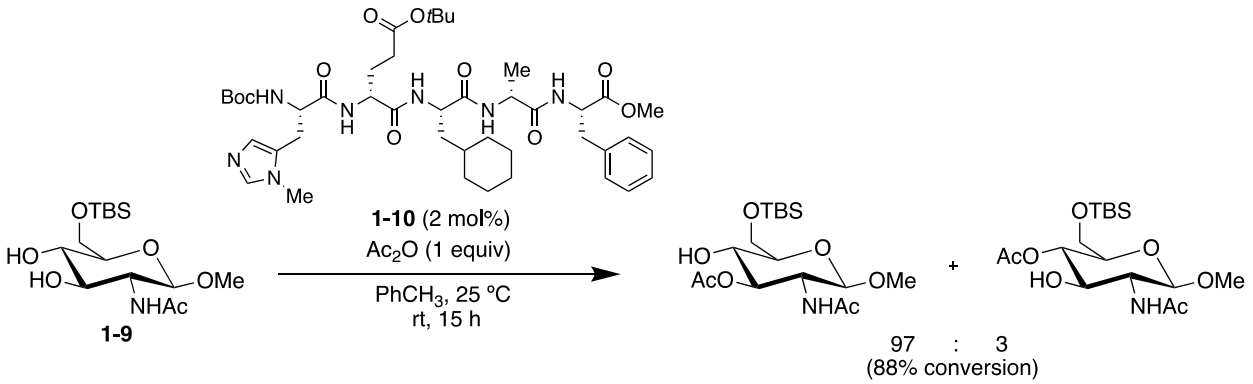

Scheme 1-8: Chiral 4-pyrrolidinopyridine catalyzed selective acylation of octyl β-glucopyranoside

Tan and co-workers developed a "scaffolding catalyst" in the site-selective functionalization of *cis*-1,2 diol moieties in carbohydrates. The chiral imidazole catalyst utilizes reversible, covalent interactions and proximal effects to selectively functionalize carbohydrates. For example, protection of methyl-α-L-rhamnose using catalyst **1-8** provides the 3-functionalized product with excellent selectivity for the silylation, acylation, and sulfonylation variants (Scheme 1-9).[27]




Scheme 1-9: Selective functionalization of methyl-α-L-rhamnose using a scaffolding catalyst

Miller and co-workers have demonstrated the use of peptide catalysts in the site-selective functionalization of carbohydrates and natural products.[28] For example, a high-throughput screen of a small library of peptides enabled their discovery of catalyst **1-10** that regioselectively acylated glucosamine **1-9** at the 3-position (Scheme 1-10).[29] The authors propose that the increased reactivity of the 3-OH may be due to interaction with the acetamide in **1-9** with hydrogen-bond donors and acceptors of the catalyst.




Scheme 1-10: Regioselective acylation of glucosamine **1-9** via peptide catalysis

Further derivatization of functionalized carbohydrate derivatives is a powerful method to introduce multiple stereocenters with high enantiopurity in a target synthesis. Other methods, such as enantioselective desymmetrization, can also be utilized to introduce chirality in a compound without pre-existing stereocenters in the substrate.

### 1.2.4 Enantioselective Desymmetrization of Achiral Diols

Asymmetric transformations of hydroxy-containing compounds are very important in the synthesis of enantioenriched materials (Figure 1-6). Kinetic resolution of racemic substrates is a very common method to exploit the relative catalyzed reaction rates between enantiomers to produce enantioenriched materials.[30] In the presence of a chiral catalyst, one enantiomer in a racemic mixture reacts faster than the opposite enantiomer resulting in non-racemic products. Organic compounds containing elements of symmetry can also be useful substrates to introduce chirality; desymmetrization of prochiral compounds removes an element of symmetry and results in a product that is optically active. In an asymmetric process, desymmetrization of prochiral substrates is especially useful since a stereogenic center can be formed in the process. Thus, in the presence of a chiral catalyst, discrimination between enantiotopic functional groups in the substrate is possible. Enantioselective group differentiation is more advantageous than a kinetic resolution since, in theory, quantitative yields can be achieved with high enantioselectivity, whereas in a kinetic resolution yields of up to 50% can only be achieved.

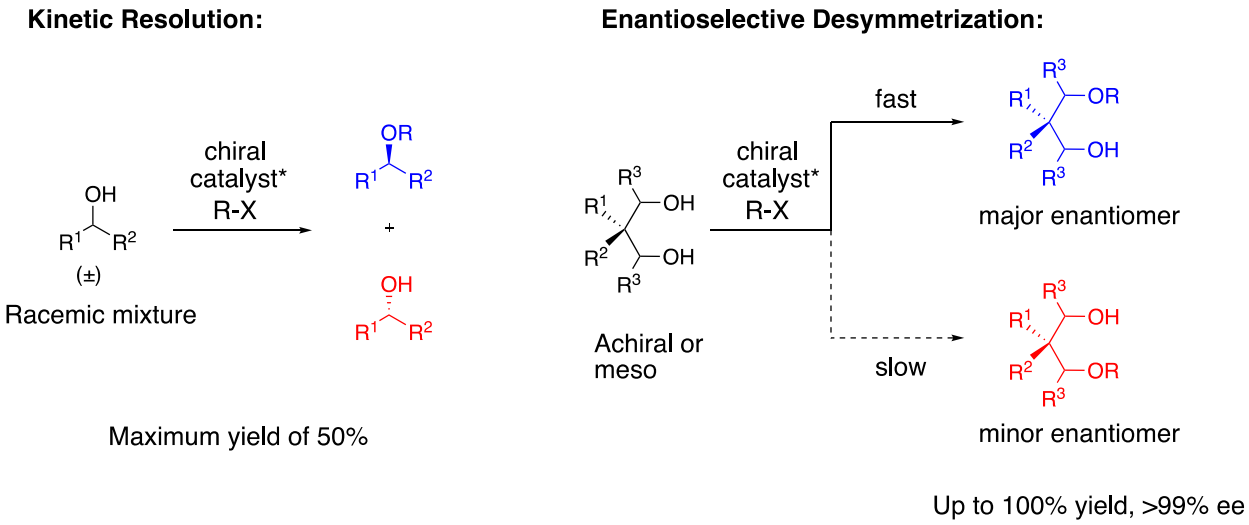
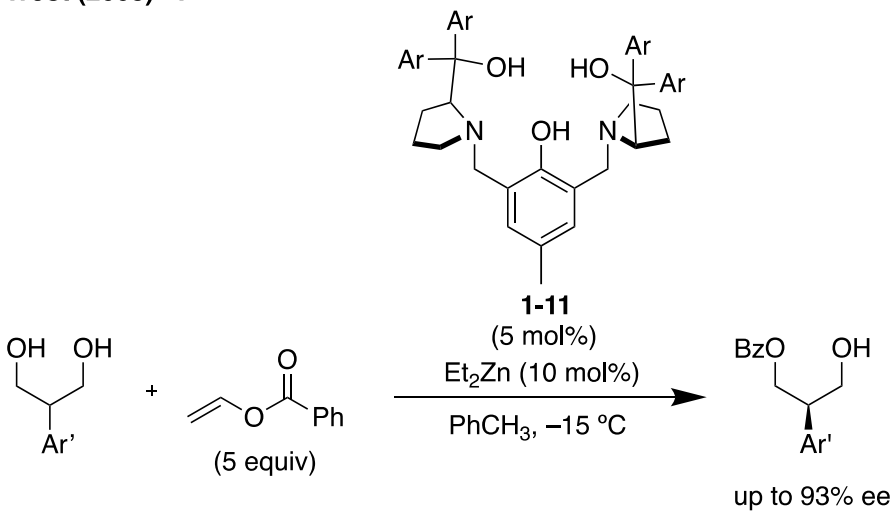



Figure 1-6: Catalyzed asymmetric transformations of alcohols/polyols

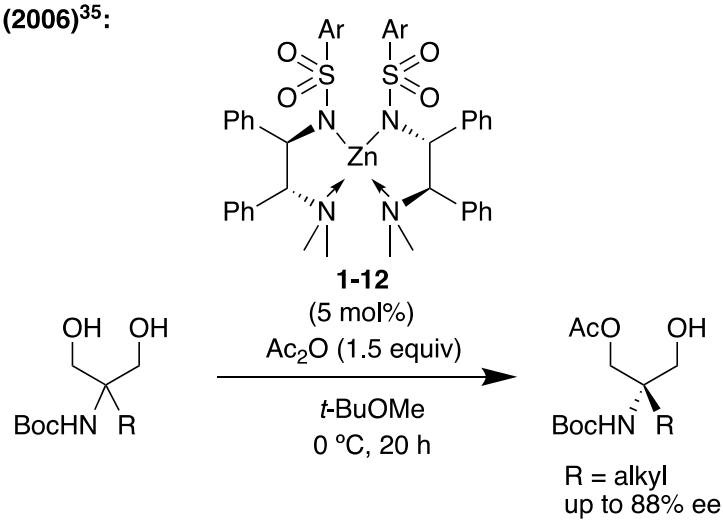
There are many examples of enzymatic desymmetrization of diols in the literature.[31] Although excellent enantioselectivities can be obtained, enzymatic methods are often limited by the structure of the substrate, and most often only one enantiomer can be accessed. Symmetrical diols have often been used as readily available substrates toward synthesizing chiral building blocks by nonenzymatic enantioselective group discrimination methods.[32,33] The most relevant methods will be reviewed here.

Trost developed a method toward the desymmetrization of 2-aryl-1,3-propanediols with the use of a chiral zinc catalyst generated from diethyl zinc and ProPhenol **1-11**. The diaryl carbinol units of the prolinol provide the chiral environment surrounding the diol, and excellent enantioselectivity can be obtained by selective esterification with vinyl acetate (Scheme 1-11).[34] Another example of a chiral zinc complex was shown in the enantioselective monoacetylation of 2-amino-1,3-propanediols. Similarly, coordination of the substrate with the sulfonamide–zinc complex **1-12** provides the chiral environment for the diol, which can then be selectively esterified using acetic anhydride (Scheme 1-11).[35]

**Trost (2003)[34]:**

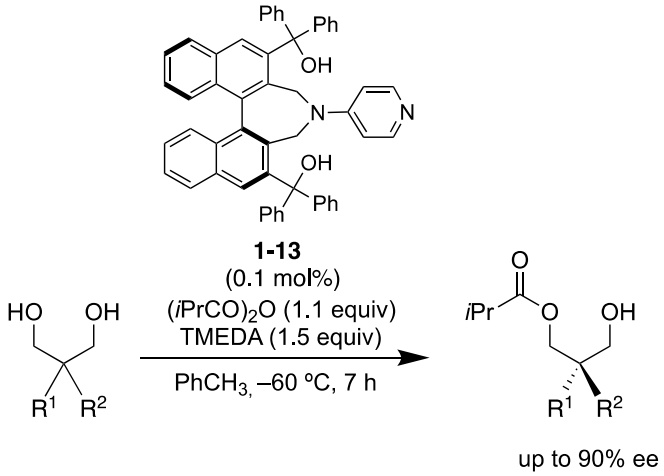



**Nagao (2006)[35]:**



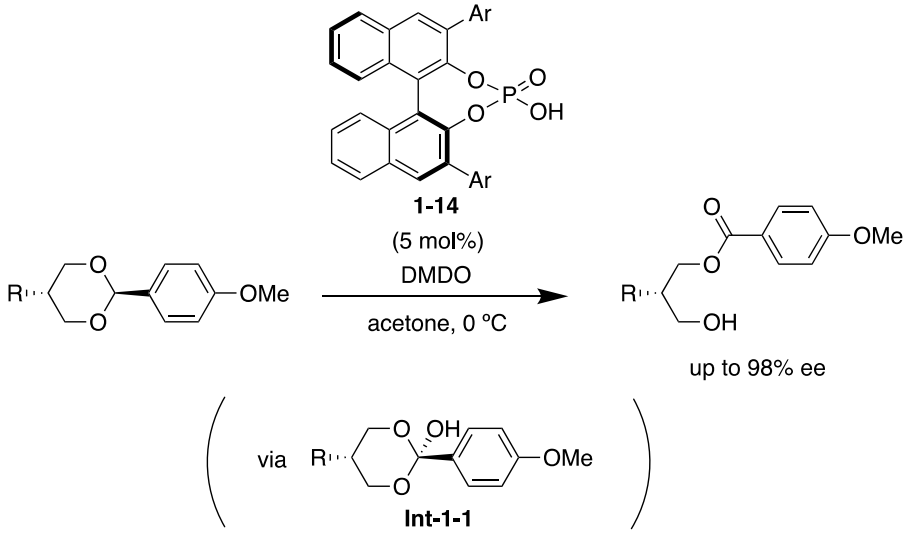

Scheme 1-11: Examples of enantioselective desymmetrization of 1,3-propanediols using a chiral-zinc catalyst

An enantioselective method developed by Suga and co-workers utilized a chiral DMAP-like derivative as an organocatalyst in the desymmetrization of 1,2-*meso*-diols, and more recently 2- and 2,2-disubstituted-1,3-propanediols (Scheme 1-12). The authors concluded that the two tertiary alcohol units of the $C_2$-symmetric catalyst **1-13** were important in achieving high levels of enantioselectivity in the monoacylation with isobutyric anhydride.[36,37]




Scheme 1-12: Organocatalytic enantioselective desymmetrization of 1,3-propanediols using a chiral DMAP derivative catalyst

Enantioselective oxidative cleavage of benzylidene acetals in the presence of a chiral phosphoric acid (CPA) **1-14** was achieved by Houk and co-workers. Oxidation by dimethyldioxirane (DMDO) to generate an ortho ester **Int-1-1** followed by proton transfer by the CPA yielded monoprotected 2,2-disubstituted 1,3-diols with high enantioselectivities (Scheme 1-13). According to DFT calculations, the rate determining step was determined to be oxidation of the acetal by DMDO, and key aryl–aryl interactions between substrate and catalyst lead to high levels of enantioselectivity.[38]




Scheme 1-13: Chiral phosphoric acid catalyzed enantioselective oxidative cleavage of *p*-methoxybenzylidene acetals

## 1.3 Organoboron Reagents

Organoboron compounds have seen an exponential increase in attention over recent years and are an important class of compounds in organic synthesis. The general structure of organoboron compounds has the boron center $sp^2$-hybridized, assuming a trigonal planar geometry with at least one carbon group attached: boronic acids contain one carbon unit and two hydroxy groups; borinic acids contain two carbon units and one hydroxy group (Figure 1-7). The presence of a vacant *p*-orbital makes organoboron compounds Lewis acids, and it is their ability to interact with various types of Lewis bases and nucleophiles that makes them sought after as reagents to promote a wide variety of transformations.

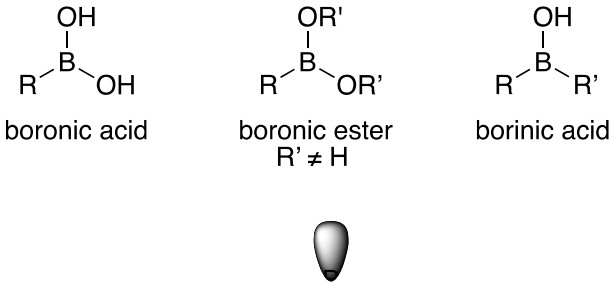



Figure 1-7: General structure and examples of organoboron compounds

Their low toxicity and increased stability make them more desirable to use as reagents compared to other highly reactive organometallic compounds. Organoboron compounds have also been of particular interest in the fields of medicinal chemistry, bioconjugation, carbohydrate chemistry, and materials chemistry as of late.[39]

Although boronic acids and their derivatives have been extremely useful as coupling partners in Suzuki–Miyaura reactions,[40] organic chemists have also taken advantage of their ability to interact reversibly with hydroxy functional groups to promote other types of transformations. Electrophilic activation of alcohols, carboxylic acids, and oximes is possible by way of coordination of an -OH group onto the boron center or exchange with a labile B-OH group. Catalytic transformations via

electrophilic activation using boronic acids include direct amidation of carboxylic acids, cycloadditions, rearrangement reactions, and Friedel-Crafts alkylations.[41] Nucleophilic activation is also possible upon formation of a tetrahedral adduct on a boron center as the electron density of the surrounding atoms is increased in the resulting anionic species. A well-known example of nucleophilic activation using organoboron is the 1,2-metallate shift of boronate complexes in which a species coordinated onto the boron can migrate onto an electrophilic α-center in a stereospecific manner (Figure 1-8).[42]

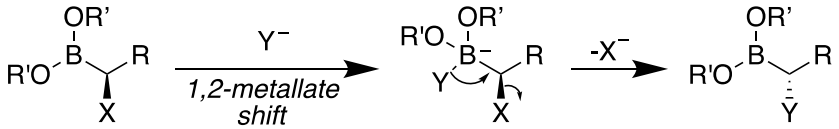



Figure 1-8: General scheme for the 1,2-metallate shift of boronate complexes

Boronic acids can form reversible covalent bonds with diols to form boronic esters. This property of boronic acids has been shown to be useful in fluorescent tagging in bioconjugation chemistry,[43] and are also important protecting groups for *cis*-1,2- and 1,3-diol moieties in oligosaccharide synthesis.[44] Benzoxaborole, a hemiboronic acid, has been shown to display superior carbohydrate-binding properties under physiological conditions compared to previously known boronic acids (Figure 1-9).[45,46] Other analogs of benzoxaboroles have emerged as useful compounds in many applications.[47]

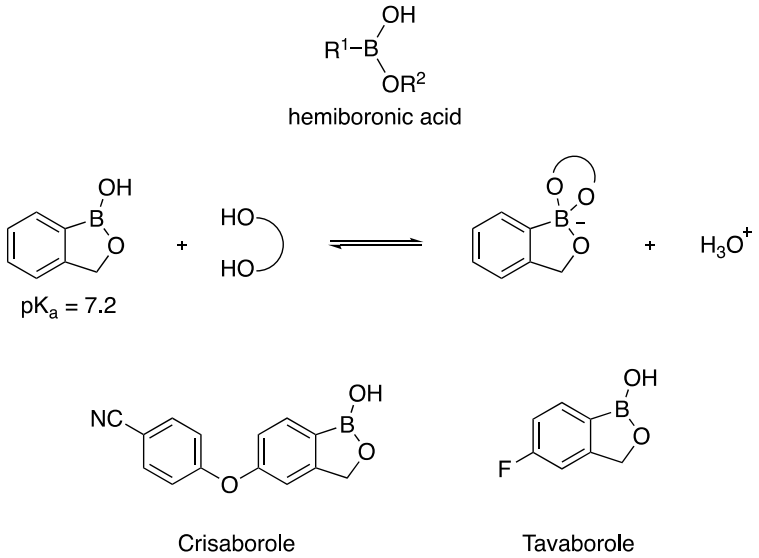
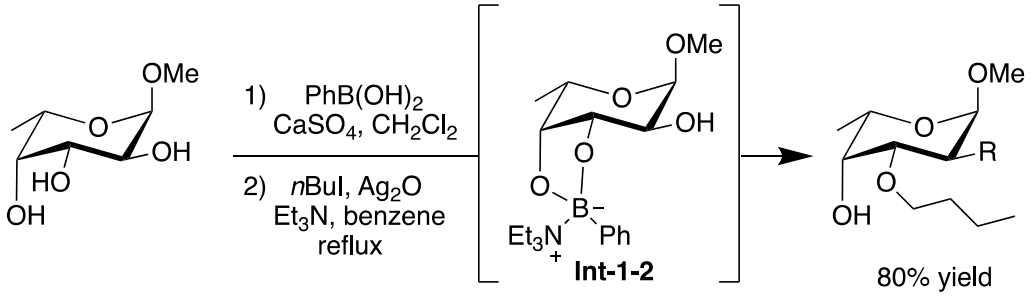



Figure 1-9: Benzoxaborole diol binding properties and examples of important benzoxaboroles

Crisaborole is an example of a benzoxaborole that serves is a topical medication is used to treat psoriasis and atopic dermatitis.[48] Tavaborole (5-fluorobenzoxaborole number), the first benzoxaborole drug, is a topical medication to treat onychomycosis. It was found to block protein synthesis in fungi by forming an adduct with the diol moiety in the adenosine site of $tRNA^{LEU}$.[49] The highly chemoselective recognition of polyhydroxylated compounds in medicinal applications prompted research in the synthetic utility of organoboron acids as either promoters or catalysts in the selective functionalization of diols.

### 1.3.1 Use of Organoboron Acids in Diol Functionalization

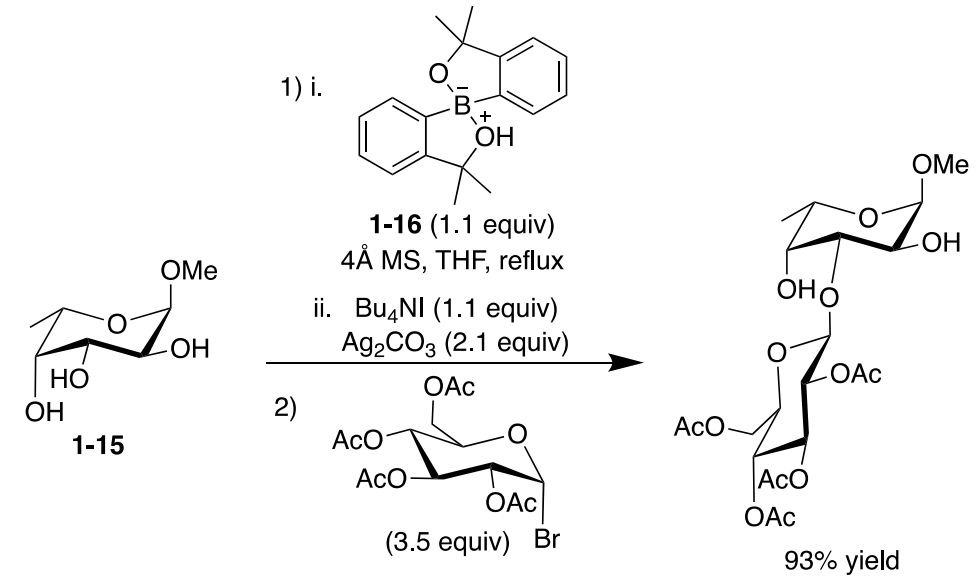
Aoyama showed one of the first examples of site-selective functionalization of carbohydrates using organoboron in the regioselective alkylation of methyl α-fuco- and β-arabinopyranosides (Scheme 1-14). Triethylamine serves as the Lewis base that coordinates onto a preformed carbohydrate-derived boronate ester to form the activated tetrahedral complex **Int-1-2**, which then undergoes selective *O*-alkylation at the equatorial 3-position of the carbohydrate.[50] The authors attribute the regioselectivity to be due to the formally less-hindered equatorial 3-OH in **Int-1-2** compared to the axial 4-OH that is also hindered by an adjacent methyl group.



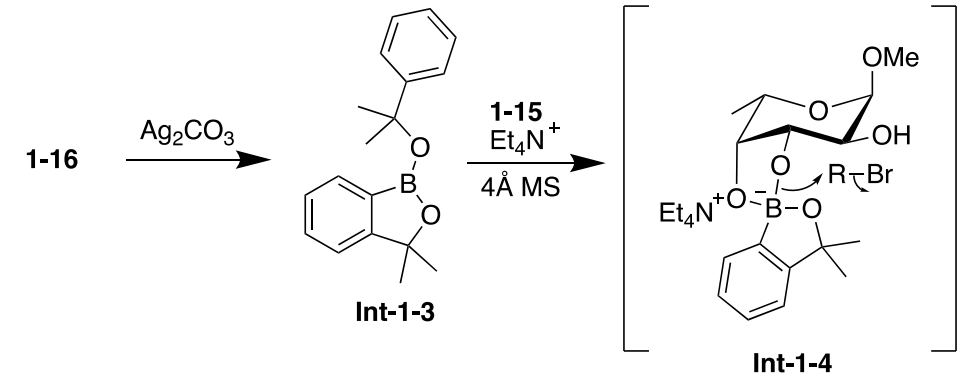

Scheme 1-14: Selective alkylation of a boronic ester of methyl α-fucopyranoside in the presence of triethylamine

Aoyama then reported the use of diarylborinic acid derivative **1-16** as a promoter in the selective glycosidation of unprotected sugars (Scheme 1-15). The authors propose that the C-B bond in arylborinic acid derivative **1-16**, in the presence of silver(I) carbonate, undergoes protonolysis to

generate **Int-1-3**. The 1,2-*cis*-diol moiety in carbohydrate **1-15** is then activated by the arylboron species where there is intramolecular coordination of the *ortho* alkoxy substituent (**Int-1-4**), which can then react which the glycosyl donor. Glycosidation of the benzyl oxygen on the organoboron is prevented due to steric hindrance from the two methyl groups.[51] Although stoichiometric amounts of organoboron were used in these methods, the work of Aoyama has inspired other research groups to develop catalytic methods using organoboron acids in the selective functionalization of diols.



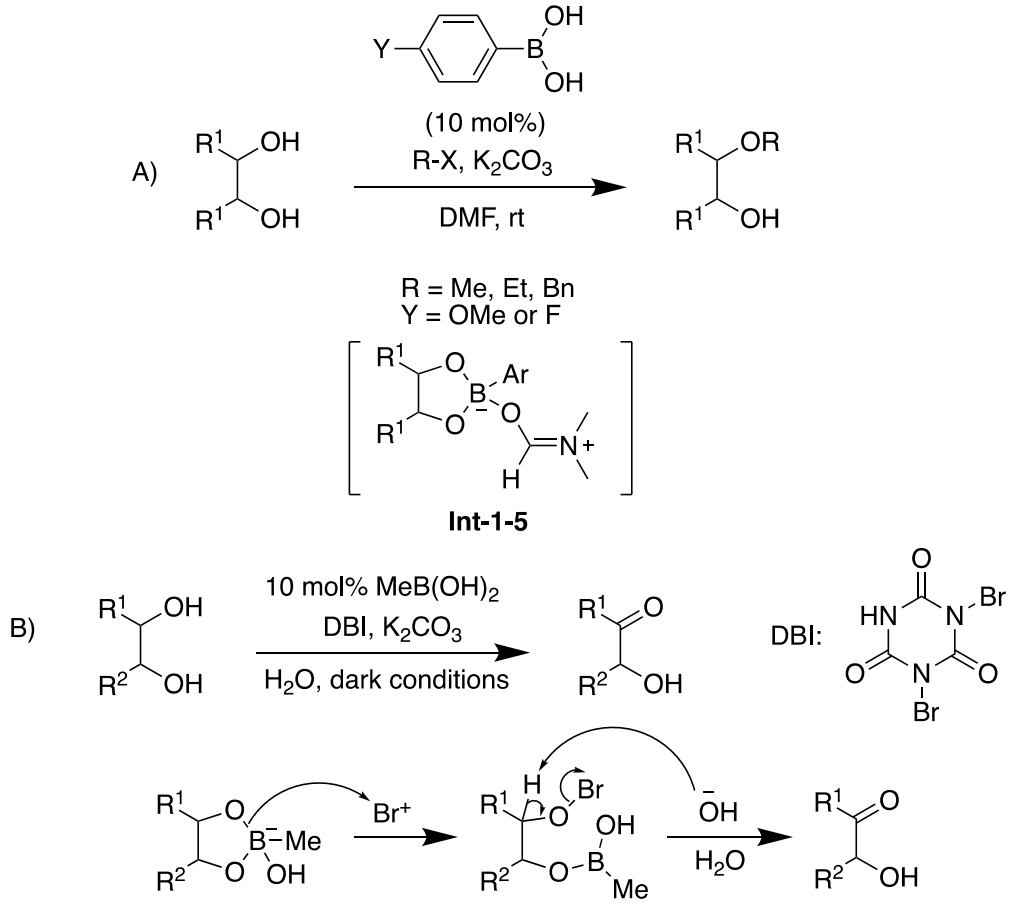

Proposed mechanism:




Scheme 1-15: Borinic acid derivative promoted selective glycosidation of unprotected methyl α-fucopyranoside **1-15**

Onomura and co-workers were the first to report examples of boronic acid catalyzed monoalkylation of 1,2-diols with alkyl halides in DMF (Scheme 1-16A). In their report, they found

that the choice of catalyst depended on the acidity of the hydroxyl groups on the diol: more acidic diols form a complex easily with an electron-rich boronic acid, and diols with lower acidity require a stronger Lewis acid (electron-poor boronic acid).[52] Although it is not proposed in their report, it is presumed that coordination by a molecule of DMF onto the boron center generates a tetrahedral adduct **Int-1-5** to produce the active catalytic species. Onomura then reported a recent example of a boronic acid-catalyzed selective oxidation of 1,2-diols in water (Scheme 1-16B). Acyclic and cyclic 1,2-diols were transformed into their corresponding α-hydroxy ketones in water via nucleophilic activation of the diol by methylboronic acid, followed by oxidation with dibromoisocyanuric acid (DBI).[53]




Scheme 1-16: A) Boronic acid catalyzed monoalkylation of 1,2-diols. B) Boronic acid catalyzed oxidation of 1,2-diols

Inspired by the work of Aoyama, Taylor and co-workers developed methods of catalytic regioselective acylation of *cis*-1,2-diols. Their initial studies looked at the catalytic activity of various organoboron compounds on cyclic vicinal diol substrates. They found that diphenylborinic acid, or its ethanolamine ester, showed superior catalytic activity compared to other boronic acids they had evaluated.[54] The diarylborinic acid-catalyzed selective monofunctionalization of diols was then extended onto carbohydrate derivatives and other diol substrates and was shown to be general toward acylation, alkylation, sulfonylation, and sulfation (Figure 1-10).[55–57] Further investigations into the reaction mechanism led them to propose the catalytic cycle depicted in Figure 1-10. The ethanolamine ester acts as a precatalyst to stabilize the otherwise air-sensitive borinic acid, and the ethanolamine ligand is released upon difunctionalization, followed by diol complexation to generate the active catalyst **Int-1-6**. They determined the reaction of the tetracoordinated boron with the electrophile to be the turnover-limiting step, with another molecule of diol responsible for catalyst turnover.[56] Protection of the 6-position in carbohydrates is, however, required in this system to prevent interaction of the boron species with the 1,3-diol moiety.

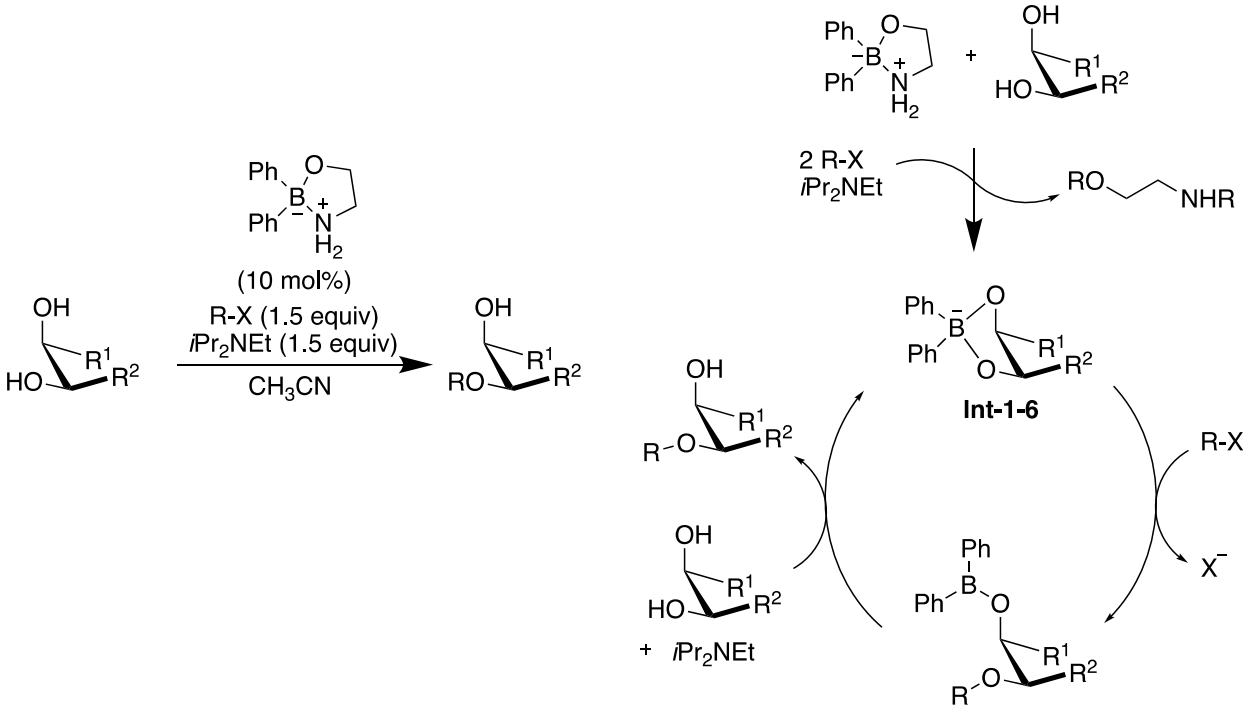
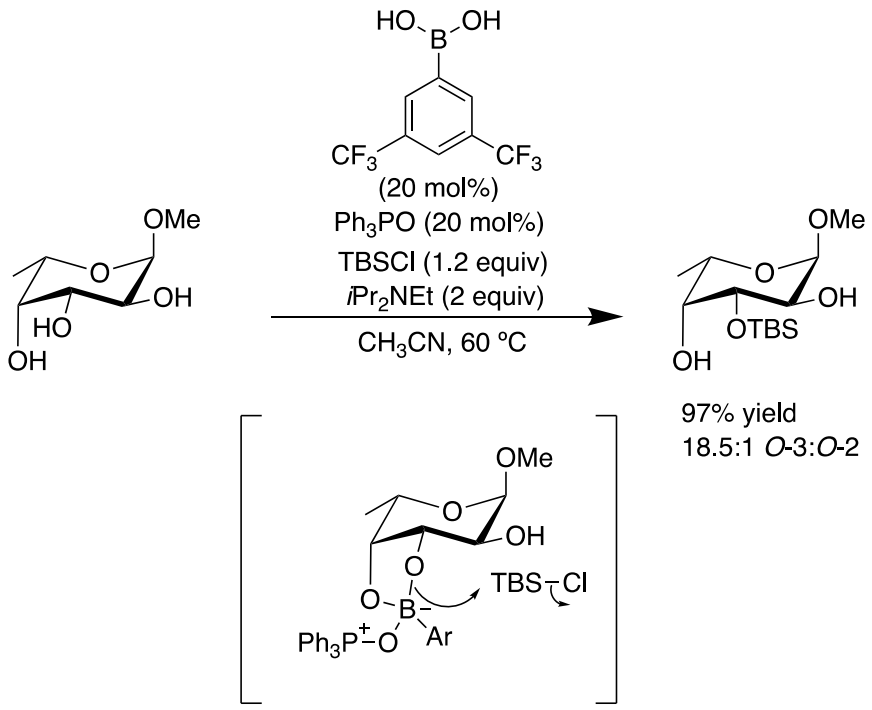


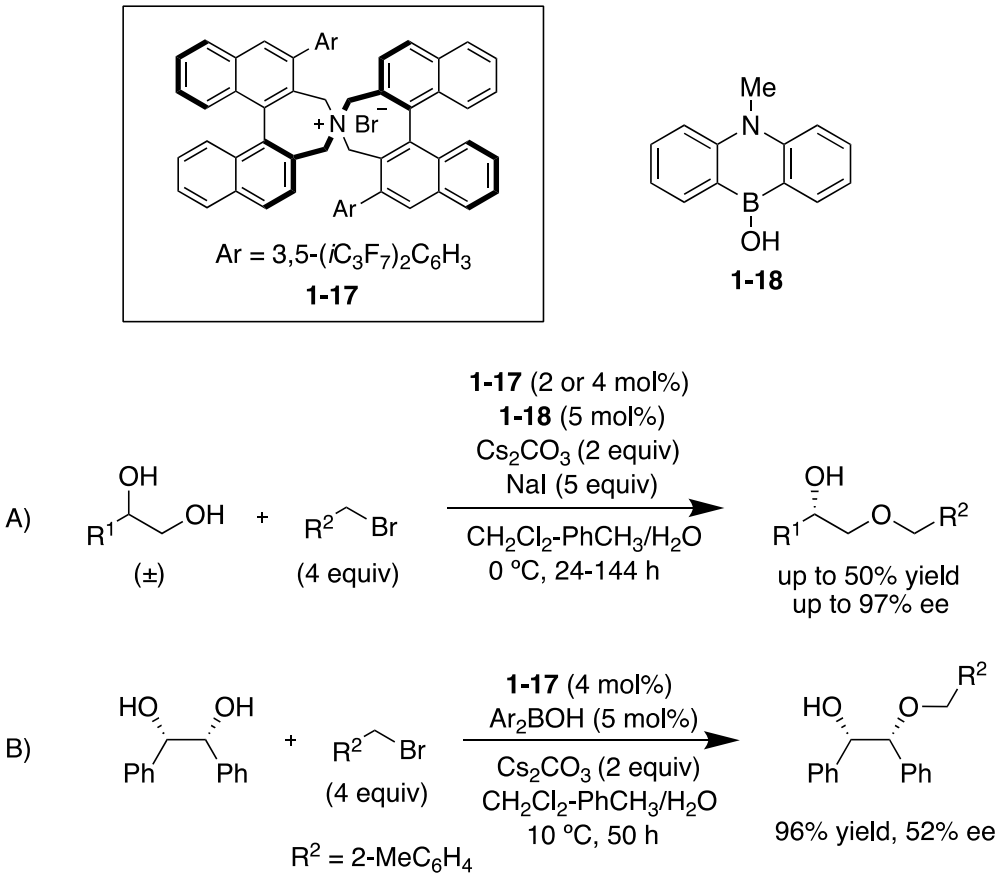

Figure 1-10: Borinic acid catalyzed selective functionalization of polyols developed by Taylor

In the case of silylation, borinic acid catalysts displayed lower activity and regioselectivity. However, in parallel with the work of Aoyama, Taylor was able to show an efficient co-catalytic system involving boronic acids and Lewis bases in the regioselective silylation of pyranosides (Scheme 1-17).[58]



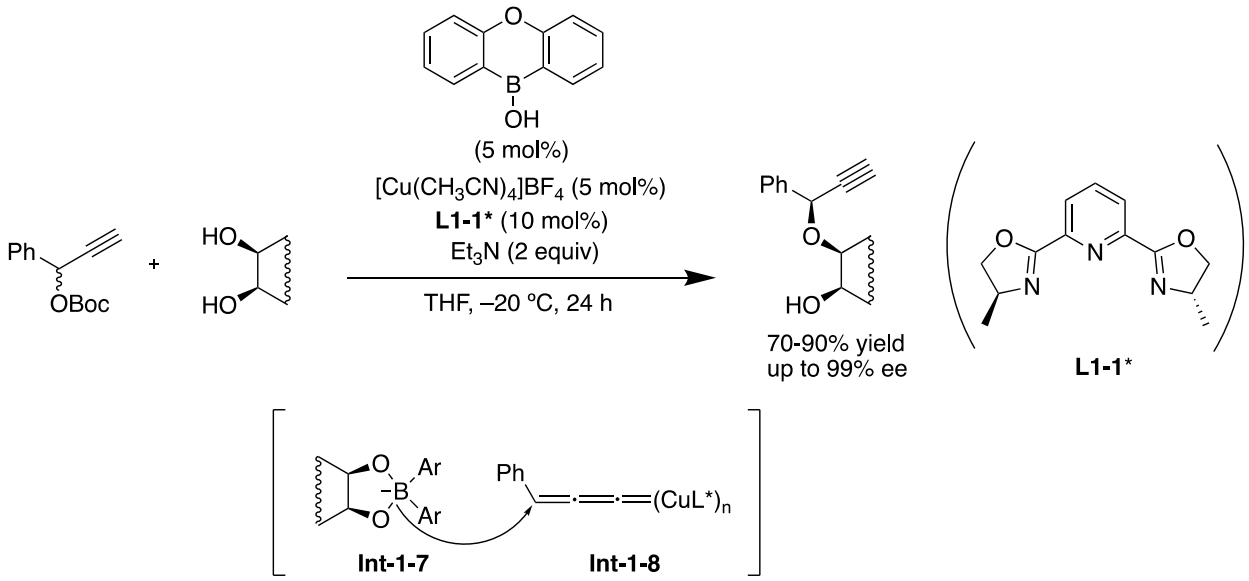

Scheme 1-17: Boronic acid-Lewis base co-catalyzed selective silylation of carbohydrates

Much progress has been made toward the selective functionalization of diols catalyzed by organoboron reagents. Maruoka and co-workers combined Taylor's borinic acid catalysis with chiral phase-transfer catalysis in the alkylative kinetic resolution of vicinal diols. Understanding that the key intermediate in diol activation is the anionic tetracoordinate boron, Maruoka employed a chiral ammonium counter-ion **1-17** to provide the chiral environment around the diol-boron adduct generated from **1-18** (Scheme 1-18). With their binaphthyl-based their phase-transfer catalyst (PTC), kinetic resolution of racemic terminal vicinal diols was achieved via alkylation of the primary alcohol (Scheme 1-18A). In their report, they also showed an example of desymmetrization of a *meso* diol using their PTC with moderate enantioselectivity (Scheme 1-18B).[59]



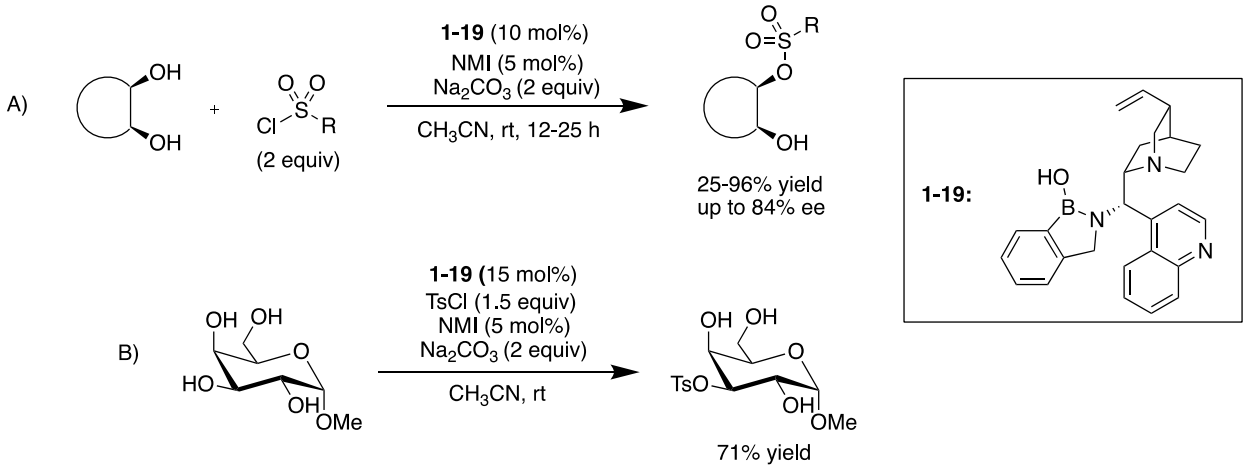

Scheme 1-17: A) Kinetic resolution of vicinal diols via borinic acid–chiral ammonium phase-transfer catalysis and B) desymmetrization of *meso*-1,2-diols

Another example of an asymmetric transformation of diols using borinic acids is the enantioselective propargylation via copper/borinic acid dual catalysis. Niu and co-workers developed a method to trap the nucleophilic borinic acid activated diol species **Int-1-7** with a chiral copper-allenylidene **Int-1-8** generated from propargyl carbonates to produce propargyl ethers with excellent enantioselectivity (Scheme 1-19).



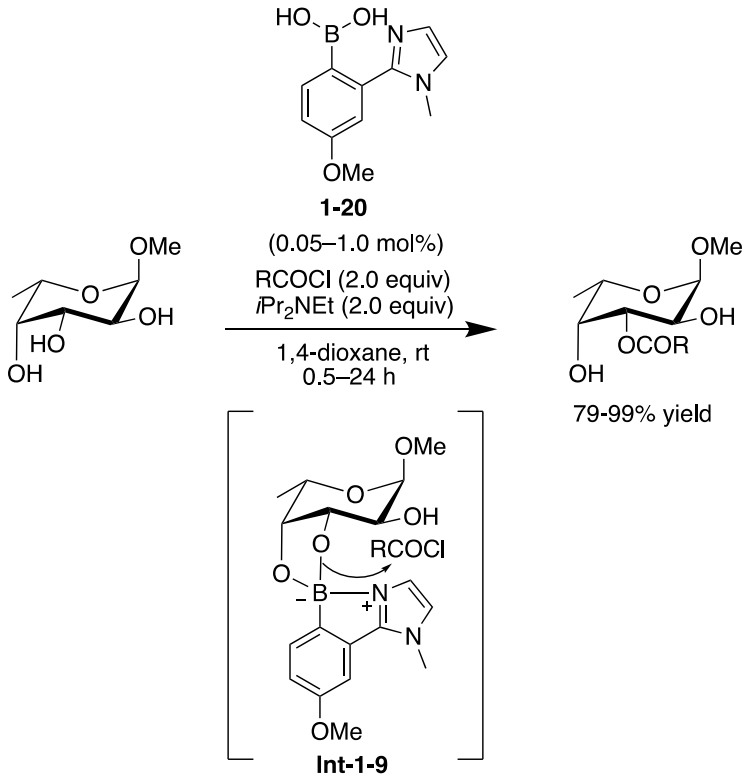

Scheme 1-19: Enantioselective propargylation of alcohols via copper-borinic acid dual catalysis

Arai and co-workers developed a chiral benzazaborole catalyst in the enantioselective desymmetrization of *cis*-1,2-diols. Monosulfonylation of *cis*-1,2-cyclohexanediol and other cyclic vicinal diols was achieved with good enantioselectivity catalyzed by their quinine-derived benzazaborole **1-19** with *N*-methylimidazole as a co-catalyst (Scheme 1-20A).[60] They later utilized their chiral organoboron catalyst in the regioselective sulfonylation of unprotected sugars. Secondary alcohols were selectively protected even in the presence of a primary alcohol in a wide variety of pyranosides (Scheme 1-20B).[61]




Scheme 1-20: Chiral benzazaborole catalyzed selective sulfonylation of diols

More recently, Makino and co-workers reported a boronic acid catalyzed site-selective acylation of carbohydrates (Scheme 1-21).[62] They designed a boronic acid **1-20** that contains and imidazole group at the ortho position that acts an internal Lewis base that activates the diol upon complexation (**Int-1-9**). Including an electron-donating group (-OMe) at the *para*-position allows for a more active catalyst, and several examples of selective acylation of *cis*-diols were shown with low catalyst loadings.




Scheme 1-21: Boronic acid catalyzed selective acylation of carbohydrates developed by Makino

## 1.4 Limitations of Current Methods

There are numerous methods for toward site-selective functionalization of diols. However, despite the number of examples in the literature, each method comes with its own limitations and drawbacks, and extensive research has been conducted by several groups to try to resolve some of the current issues and challenges. Selective cleavage of benzylidene acetals is a two-step protocol that first requires preformation of the cyclic moiety. Although the use of organotin(IV) for diol

functionalization has proven to be a reliable, general, and efficient method, much progress has been made in finding new methods that are catalytic, greener and mild to avoid hazardous and toxic reagents. Transition-metal promoted methods require a strong base to first generate a reactive dialkoxide, as well as protection of other -OH groups is necessary. Examples of organocatalytic reactions have shown to also be effective in the site-selective acylation of carbohydrates; however, synthesis of the organocatalysts require a number of steps and examples of monofunctionalization other than acylation are rare.

Current methods toward enantioselective desymmetrization of diols also have their drawbacks. Procedures using a chiral-zinc catalyst require the use of highly reactive and hazardous diethyl zinc (Scheme 1-11). The chiral-DMAP catalyzed method of 1,3-propanediol desymmetrization (Scheme 1-12) requires ten steps to synthesize the organocatalyst. The chiral phosphoric acid catalyzed method of cleaving cyclic acetals enantioselectively still requires preformation of the acetal and usage of a strong oxidizing agent prior to ring cleavage (Scheme 1-13). Although desymmetrization via monoesterification of diols is useful to provide chiral alcohols, there are few examples in the literature that describe installation of different, more desirable, *O*-protecting groups.

Recent methods using borinic acid derivatives as catalyst have proven to be general and effective. However, compared to boronic acids, borinic acids are relatively unstable, with limited storage potential, as they are prone to oxidation. Protection of the primary alcohol is typically required for borinic acid catalyzed functionalization of carbohydrate derivatives to avoid interaction with the 1,3-diol moiety. Functionalization of *cis*-diols have been extensively demonstrated under borinic acid catalysis, but there are limited methods for the functionalization of important *trans*-diol motifs in carbohydrates. With regards to enantioselective transformations, a major limitation in the use of borinic acids and their derivatives is the lack of methods to prepare these boron compounds within a chiral scaffold; chirality in the substrate is typically introduced by a chiral ligand or a chiral counterion.

Despite the numerous examples of methods for asymmetric diol functionalization, there is still a need for mild methods for catalytic enantioselective desymmetrization of achiral substrates using

organoboron reagents. The examples of asymmetric transformations via organoboron acid catalysis described in this chapter are some of the only examples found in the literature. Ideally, desymmetrization via functionalization of -OH containing substrates using a variety of electrophiles would render an extremely useful and general method to generate enantioenriched materials.

## 1.5 Thesis Objectives

One of the "Holy Grails" in chemistry is the site-selective functionalization of polyhydroxylated compounds.[63] Due to their high affinities toward diol moieties, boronic acids still have promising potential to be used in catalytic diol functionalization. Their use in carbohydrate derivatization could further advance the field of oligosaccharide synthesis. One of the objectives of this research is to develop a class of bench-stable boronic acid catalysts that have a distinct selectivity pattern toward site-selective functionalization of, ideally, unprotected polyol substrates. This strategy would enable a general, site-divergent method that would be highly efficient and advantageous to current protection/deprotection strategies. Chapter 2 will describe some of the progress made to address this objective using a hemiboronic acid catalyst. The second project objective is to develop chiral organoboron compounds to be used as catalysts in the enantioselective desymmetrization of symmetrical prochiral diol substrates. Use of a chiral boronic acid catalyst would provide an effective method to desymmetrize a variety of symmetrical diols to produce enantioenriched materials. Chapter 3 will describe the discovery of chiral hemiboronic acid catalysts, as well as the optimization of various parameters in the attempts to synthesize useful, optically active alcohols from simple achiral diol starting materials.

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# Chapter 2 – Hemiboronic Acid-Catalyzed Monofunctionalization of Diols

In this chapter, preliminary work on the screening of boronic acids as catalysts for the functionalization of diols will be described. The discovery of a known boron-oxygen heterocycle that is catalytically active in the transformation will be discussed. Various diol substrates that were examined, attempts at controlling selectivity, and some mechanistic investigations are further detailed in this chapter.

## 2.1 Introduction

### 2.1.1 Initial Screening of Organoboron Acid Catalysts in Diol Functionalization

As mentioned in Chapter One, alternative methods utilizing boronic acids as catalysts in diol functionalization are desired due to their increased stability relative to borinic acids. Another advantage is that electronic and steric modulations of boronic acids are easier to achieve (Figure 2-1A), whereas methods to modulate borinic acids are limited and challenging. For example, steric and electronic modifications were shown to be extremely important in finding a more active catalyst in the boronic acid catalyzed amidation of carboxylic acids demonstrated by Hall and co-workers (Figure 2-1B).[1] Another example is the boronic acid catalyzed monoalkylation of diols described by Onomura, where the choice of catalyst (electron-rich vs electron poor) depended on the acidity of the diol (Chapter One, Section 1.3.1).[2] For these reasons, identifying a boronic acid that can be a general catalyst toward the recognition of a variety of diols would be an improvement to current methods.

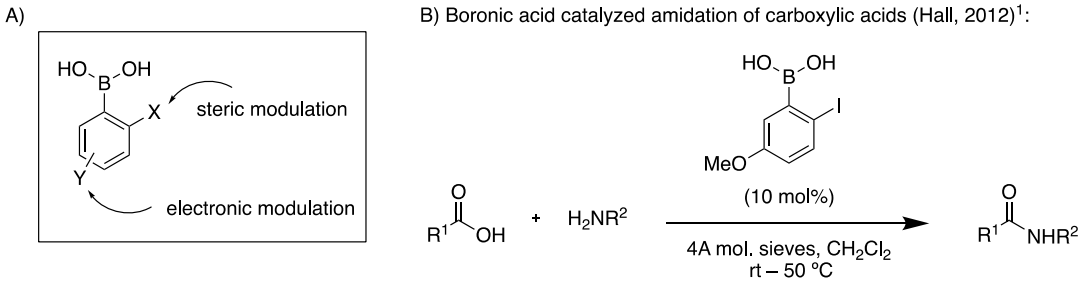
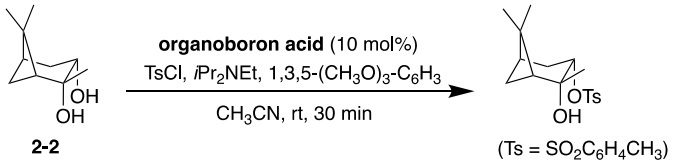


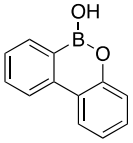

Figure 2-1: A) Steric and electronic modulations of arylboronic acids B) Application in boronic acid-catalyzed amidation reactions

Initial investigations in the evaluation of various organoboron acid catalysts were conducted in our laboratory by Kim Vetter.[3] To determine the potential for organoboronic acids to act catalytically, a model reaction was performed in comparison with diphenylborinic acid ethanolamine ester (**2-1a**), an organoboron species that is known to catalytically monofunctionalize diols (as described in Chapter One, Section 1.3.1). The model reaction used pinanediol **2-2** as the diol substrate and tosyl chloride as the electrophile (Table 2-1). For the purpose of screening, conversions and yields of the monosulfonylated product (determined by $^1$H-NMR using 1,3,5-trimethoxybenzene as an internal standard) were measured after a short reaction time period (30 minutes).



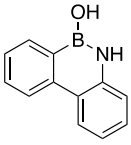

**2-2**

**2-1a**

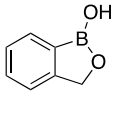


**2-1b**

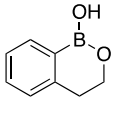
| Entry | **Organoboron acid** | Conversion[a] (%) | Yield[a] (%) |
|---|---|---|---|
| 1 | **none** | 3 | 0 |
| 2 | **2-1a** | 64 | 52 |
| 3 | **2-1b** | 51 | 47 |
| 4 | **2-1c** | 17 | 3 |
| 5 | **2-1d** | 26 | 9 |
| 6 | **2-1e** | 23 | 4 |
| 7 | **2-1f** | 74 | 53 |
| 8 | **2-1g** | 17 | 2 |
| 9 | **2-1h** | 44 | 27 |
| 10 | **2-1i** | 19 | 1 |
| 11 | **2-1j** | 15 | 3 |
| 12 | **2-1k** | 19 | 2 |



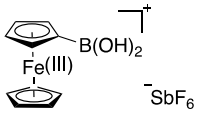
**2-1c**



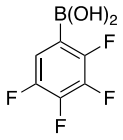
**2-1d**



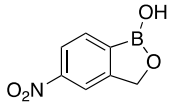
**2-1e**



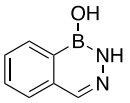
**2-1f**



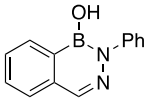
**2-1g**



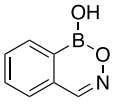
**2-1h**



**2-1i**



**2-1j**



**2-1k**

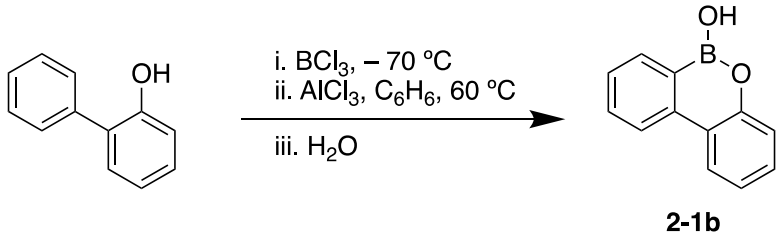
Table 2-1: Screening of organoboron acids in the monosulfonylation of pinanediol **2-2** (performed by Kim Vetter). [a]Determined by $^1$H-NMR using 1,3,5-trimethoxybenzene as an internal standard

Organoboron compounds evaluated in the model reaction included known compounds with low $pK_a$ values (<7), as it was initially proposed that a boronic acid with a relatively higher Lewis

acidity similar to that of diphenylborinic acid ($pK_a = 6.2$)[4] can be efficient catalysts due to tighter diol-binding with the organoboron species. These included electron-poor boronic acids (**2-1f**, **2-1g**) and benzoxaboroles (**2-1d**, **2-1h**), in addition to other known hemiboronic acids (**2-1b**, **2-1c**, **2-1e**, **2-1i**, **2-1j**, **2-1k**). Out of all the boronic acids screened, ferrocenium boronic acid **2-1f** and hemiboronic acids **2-1b** and **2-1h** were observed to provide yields of greater than 20% after 30 minutes (Table 2-1, entries 3,7 and 9). The progress of the reaction catalyzed by these organoboron acids were also compared, and it was observed that hemiboronic acid **2-1b** gave a similar profile as the diphenylborinic acid derivative (**2-1a**) catalyzed process. Organoboron **2-1b** (10-hydroxy-10,9-boroxarophenanthrene) was chosen to be explored further due to its ease of preparation and relative stability.

### 2.1.2 10-Hydroxy-10,9-boroxarophenanthrene (2-1b) in the Literature

Hemiboronic acid **2-1b** was first reported in 1959 by Dewar.[5] It was synthesized via an intramolecular Friedel-Crafts reaction of 2-phenylphenol in the presence of $BCl_3$ and $AlCl_3$ (Scheme 2-1). Further investigations on **2-1b** correlated its unusual stability toward strong acid, base and oxidation to the aromatic character of the boron-oxygen heterocyclic ring.[5,6]




**2-1b**

Scheme 2-1: First reported synthesis of 10-hydroxy-10,9-boroxarophenanthrene (Dewar, 1959)

Philp and co-workers investigated the solid-state and solution phase reactivity of **2-1b**.[7] It was observed that **2-1b** can undergo rapid and reversible exchange with alcohols and that transesterification is also possible when a different alcohol is introduced (Figure 2-2A). Philp and co-workers have also reported the chemistry of hemiboronic acid **2-1b** with diols.[8] With a mixture containing equimolar amounts of **2-1b** and 1,3-propanediol, a 2:1 complex was observed exclusively by MALDI-TOF mass spectrometry.[8] In solution, however, the authors observe a

relatively low chemical shift in the $^{11}$B-NMR spectrum (–0.4 ppm). A low $^{11}$B-NMR chemical shift typically indicates an sp$^3$-hybridized boron that is tetracoordinated, which suggests a 1:1 complex is also present (Figure 2-2B).[8]

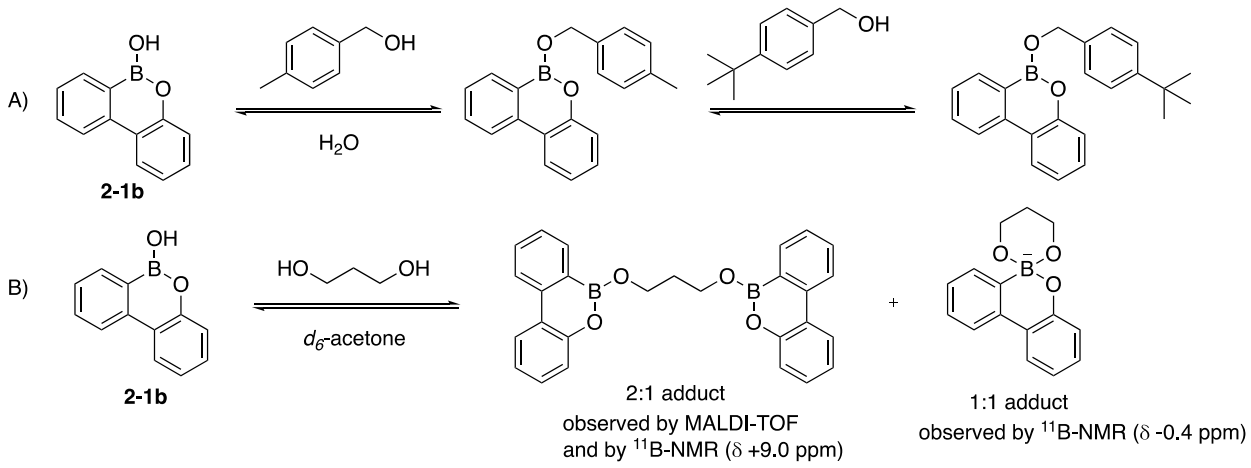



Figure 2-2: A) Reactivity of **2-1b** toward alcohol exchange B) Solution-phase reactivity of **2-1b** and 1,3-propanediol (Note: $^{11}$B-NMR in $d_6$-acetone referenced to B(OMe)$_3$, δ = 0.0 ppm)

Few applications of boron heterocycle **2-1b** have been shown in the literature. Examples include Suzuki-Miyaura cross-coupling to synthesize triaryls,[9] palladium-mediated CO insertion to prepare 3,4-benzocoumarins[9], and synthesis of *o*-phenylene oligomers[10] (Figure 2-3). The use of organoboron **2-1b** in catalysis, however, has not yet been reported in the literature.

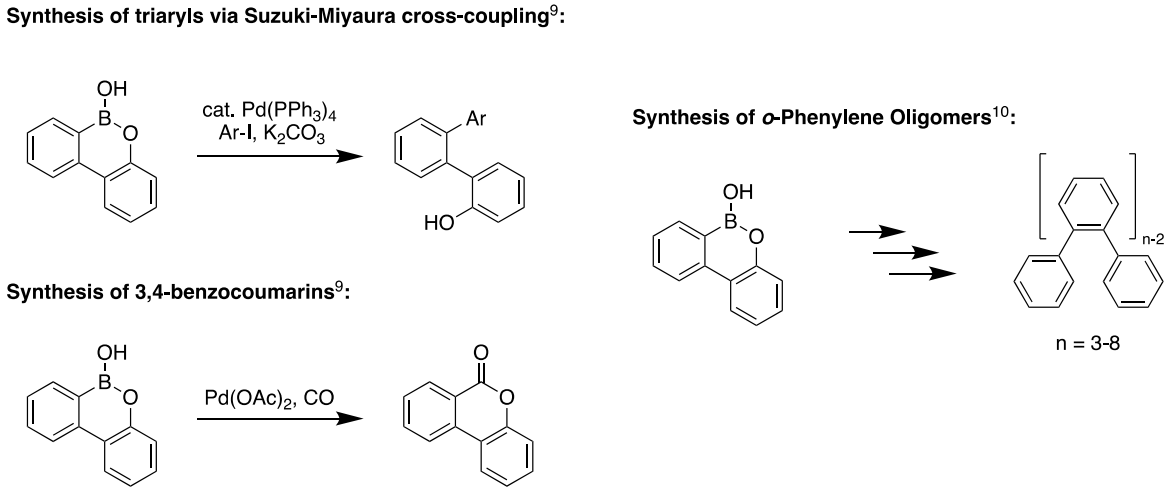
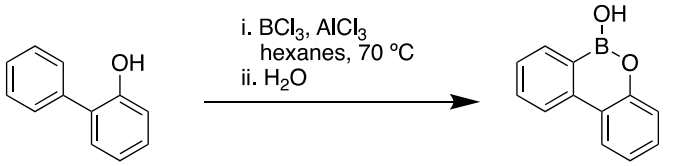



Figure 2-3: Synthetic applications of organoboron **2-1b**

## 2.2 Results & Discussion

### 2.2.1 Use of Hemiboronic Acid 2-1b as a Catalyst in the Monofunctionalization of Diols

As described before, due to its increased stability compared to borinic acid derivatives, as well as its simple preparation and ease of handling, organoboron **2-1b** was investigated further to explore the generality of the catalyzed diol functionalization reaction. Boroxarophenanthrene **2-1b** was synthesized according to literature procedure,[9] furnishing a white solid in 60% yield.




**2-1b**, 60% yield

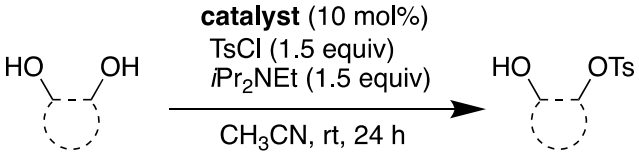
Scheme 2-2: Preparation of organoboron acid catalyst **2-1b**

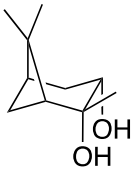
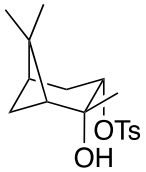
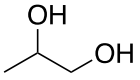
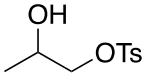
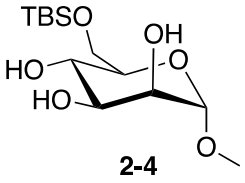
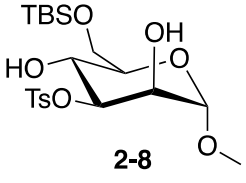
Previous experiments by Kim Vetter had only monitored the catalyzed reaction by $^{1}$H-NMR spectroscopy. I had then begun obtaining isolated yields of the monofunctionalized products. Following the general procedure reported by Taylor and co-workers,[11] 10 mol% of organoboron acid catalyst **2-1b** was added to a reaction mixture containing a diol substrate, electrophile, and a weak base in acetonitrile. Isolated yields were compared to the literature values obtained in the sulfonylation catalyzed by **2-1a**. Substrates examined include both cyclic and acyclic diols, as well as monosaccharides. Carbohydrate derivatives **2-4** and **2-5** were prepared by selectively protecting the primary 6-position with a silyl ether. This derivatization was planned so that potential interaction of organoboron **2-1b** with the 4,6-diol moiety can be avoided, in the same manner as reported by Taylor and co-workers.[12]

#### 2.2.1.1 Hemiboronic Acid-Catalyzed Monosulfonylation of Diols

Sulfonates are important orthogonal protecting groups for diols and carbohydrates[13] and for nucleophilic substitution reactions.[14] The generality of monosulfonylation of diols using *p*-

tolylsulfonyl chloride, catalyzed by hemiboronic acid **2-1b**, was first examined (Table 2-2). Overall, monotosylation of diols worked well in the presence of **2-1b** to provide excellent yields with good regioselectivity. Yields were comparable to the reported borinic acid catalyzed method. Pinanediol **2-2**, consistent with the results from the boronic acid screening (Table 2-2, entry 2), underwent sulfonylation selectively at the less hindered secondary alcohol (Table 2-2, entry 1). Hemiboronic acid **2-1b** was shown to catalyze the reaction within a shorter reaction time (88% yield after 6 hours, 96% yield after 24 hours) to provide the pinanediol derivative **2-6** in excellent yield as a single regioisomer (Table 2-2, entry 1). Similarly, 1,2-propanediol **2-3** was selectively tosylated at the primary alcohol (Table 2-2, entry 2). Silyl-protected methyl α-D-mannopyranoside **2-4** and methyl α-D-galactopyranoside **2-5** were functionalized at the equatorial 3-position in good yields and excellent regioselectivity (Table 2-2, entries 3 and 4). This observed regioselectivity for these substrates are nearly identical to the examples reported by Taylor and co-workers.[11]




| Entry | Diol | Product | Lit. Yield[11] (Catalyst: **2-1a**) | Yield[a] (Catalyst: **2-1b**) |
|---|---|---|---|---|
| 1 |  **2-2** |  **2-6** | 99% | 96% (88%) (single regioisomer) |
| 2 |  **2-3** |  **2-7** | 81% | 77% (3.27:1 rr) |
| 3 |  **2-4** |  **2-8** | 85% | 90% (single regioisomer) |

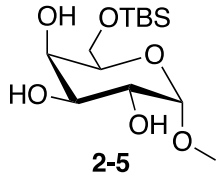
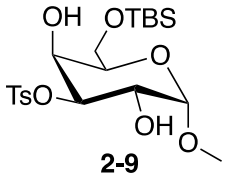
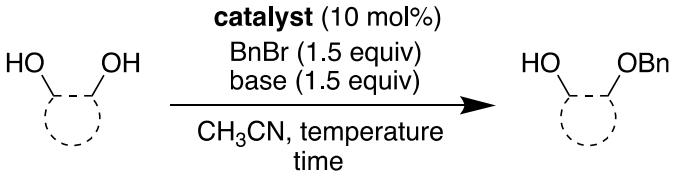
| | | | | |
|---|---|---|---|---|
| 4 |  **2-5** |  **2-9** | 83% | 83%[b] (13.07:1 *O*-3:O-4 rr) |

Table 2-2: Hemiboronic acid **2-1b** catalyzed monosulfonylation of diols. Regiomeric ratio determined by crude $^{1}$H-NMR. [a]Isolated yields. Values in parentheses are yields obtained after 6 hours. [b]Result for product **2-9** was obtained by Ashley Ponich

### 2.2.1.2 Hemiboronic Acid-Catalyzed Monobenzylation of Diols

Benzyl ethers are important orthogonal alcohol protecting groups, especially in carbohydrate chemistry, as they are tolerant to a variety of chemical transformations and can be easily cleaved under hydrogenation conditions.[13] However, traditional methods for alkylation typically require the use of strong bases to deprotonate alcohols ($pK_a \sim 16$), which may be problematic if there are other acidic sites in a substrate. Monobenzylation of diols was then explored using catalyst **2-1b** (Table 2-3). The organoboron-catalyzed monobenzylation was also carried out using optimized conditions reported by Taylor and co-workers.[12] Silver(I) oxide was employed as the base in the case of carbohydrate derivatives. Isolated yields after benzylation were also compared to the literature values obtained from the reaction catalyzed by **2-1a.** Overall, benzylation was also shown to work well in the presence of **2-1b** to provide monobenzylated diol products in good yields. Yields were comparable to the reported borinic acid catalyzed method. The regioselectivity observed in the monotosylation reaction (Table 2-2) was also consistent with the catalyzed monobenzylation reaction: secondary alcohols were selectively benzylated over tertiary alcohols (Table 2-3, entry 1), and benzyl ethers of carbohydrate derivates were produced selectively at the equatorial 3-position (Table 2-3, entries 1, 4, and 5). Benzylation of symmetrical 1,2- and 1,3-diols (**2-10** and **2-11**) were also shown to be productive in the presence of catalyst **2-1b** to produce monoalkylated (racemic) diols **2-13** and **2-14** in excellent yields (Table 2-3, entries 2, and 3).



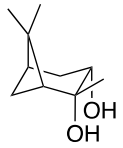
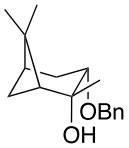
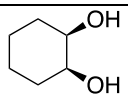
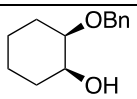
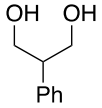
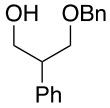
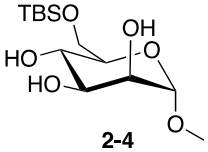
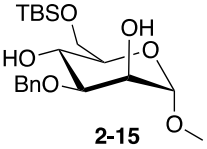
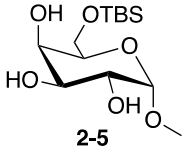
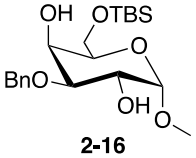

| Entry | Diol | Base | Temp. | Time (h) | Product | Lit. Yield[11,12] (Catalyst: **2-1a**) | Yield[a] (Catalyst: **2-1b**) |
|---|---|---|---|---|---|---|---|
| 1 |  **2-2** | $K_2CO_3$ | 60 ºC | 24 |  **2-12** | 78% | 82% (11.8:1 rr) |
| 2 |  **2-10** | $K_2CO_3$ | 60 ºC | 24 |  (±) **2-13** | >99% | 87% |
| 3 |  **2-11** | $iPr_2NEt$ | rt | 24 |  **2-14** | – | 69% |
| 4 |  **2-4** | $Ag_2O$ | 40 ºC | 48 |  **2-15** | 91 | 85% (4:1 *O*-3:O-4 rr) |
| 5 |  **2-5** | $Ag_2O$ | 40 ºC | 48 |  **2-16** | 77 | 82[b] Single regioisomer |

Table 2-3: Hemiboronic acid **2-1b** catalyzed monobenzylation of diols. Regiomeric ratio determined by crude $^1$H-NMR. [a]Isolated yields. [b]Result for product **2-16** was obtained by Ashley Ponich

### 2.2.2 Hemiboronic Acid Catalyzed Diol Functionalization – Mechanistic Considerations

It has been known that diphenylborinic acid readily form an "ate" complex with vicinal diols at neutral pH to form an "ate" complex due to their relatively low $pK_a$.[4] As mentioned in Chapter

One (Scheme 1-9), mechanistic investigations described by Taylor and co-workers had shown that the diol-bound tetrahedral adduct is the active catalytic species.[11] The generality toward diol functionalization catalyzed by hemiboronic acid **2-1b** is partially demonstrated in Section 2.2.1, providing a more advantageous alternative to borinic acid catalyzed processes due to the increased stability of **2-1b**. Experiments were then conducted to gain some insight for this catalytic transformation.

As mentioned in Section 2.1, other boronic acids with relatively low $pK_a$ values (<9) were screened as it was initially thought that organoboron compounds with a similar $pK_a$ to that of diarylborinic acids could also perform efficiently as catalysts in the diol functionalization reaction. The $pK_a$ of **2-1b** was measured in 1961 by Dewar and was estimated to be 9.1.[15] For the purpose of this study, the $pK_a$ was remeasured experimentally by $^{11}$B-NMR spectroscopy, a common, convenient method to determine the $pK_a$ of boronic acids by plotting the observed $^{11}$B-NMR chemical shift at varying pH.[16] The $pK_a$ is the inflection point of the curve of the pH plotted against the observed $^{11}$B-NMR chemical shift. A 16 mM solution of hemiboronic acid **2-1b** was prepared by dissolving the solid in a 1:1 ethanol:buffer solution (buffer solution: 0.1 M phosphate in 90:10 $H_2O/D_2O$). 1 mL of the hemiboronic acid solution was transferred to 16 separate vials and the pH was adjusted with 0.1 M HCl or 1% NaOH to obtain solutions with a pH range of 2 to 12. The solutions were transferred to NMR tubes for $^{11}$B-NMR analysis. After plotting the pH against the observed $^{11}$B-NMR chemical shift, the $pK_a$ of **2-1b** was determined by linear regression[17] to be 8.9, correlating well with the literature value (Figure 2-4).

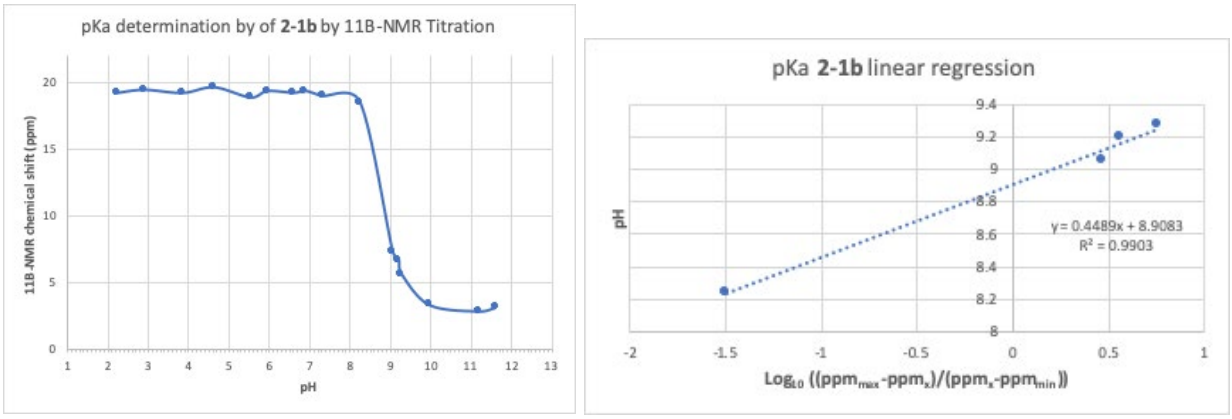



Figure 2-4: Determination of $pK_a$ of hemiboronic acid **2-1b** by $^{11}$B-NMR titration ($pK_a$ = 8.9)

It was previously observed (Table 2-1) that boronic acids with even lower $pK_a$ values than **2-1b** did not perform efficiently as catalysts in the diol functionalization reaction. Since the observed $pK_a$ of hemiboronic acid **2-1b** is more than two orders of magnitude different than **2-1a** ($pK_a$ = 6.2), there appears to be no obvious correlation between $pK_a$ and catalytic activity as **2-1b** performs as efficiently as the more acidic borinic acid derivative **2-1a**. The catalytic activity of hemiboronic acid **2-1b** may be attributed to its ability to form a reactive tetrahedral "ate" species.

To confirm the presence of a four-coordinate boron intermediate, a $^{11}$B-NMR spectrum of a mixture of **2-1b**, 2-phenyl-1,3-propanediol **2-11** and a weakly coordinating base $K_2CO_3$ in $d_3$-acetonitrile was obtained (Figure 2-5). After stirring the mixture for 18 hours, the reaction mixture was filtered and transferred to an NMR tube. A comparison of the spectrum to that of only **2-1b** (Figure 2-5A) reveals a low-shift resonance that indicates the presence of a four-coordinate boron species **Int-2-1** (Figure 2-5B). An ESI-HRMS was obtained from this sample to further support the presence of **Int-2-1**, and the most abundant peak detected is one that corresponds well with the mass for the tetrahedral adduct of the boron-diol species.

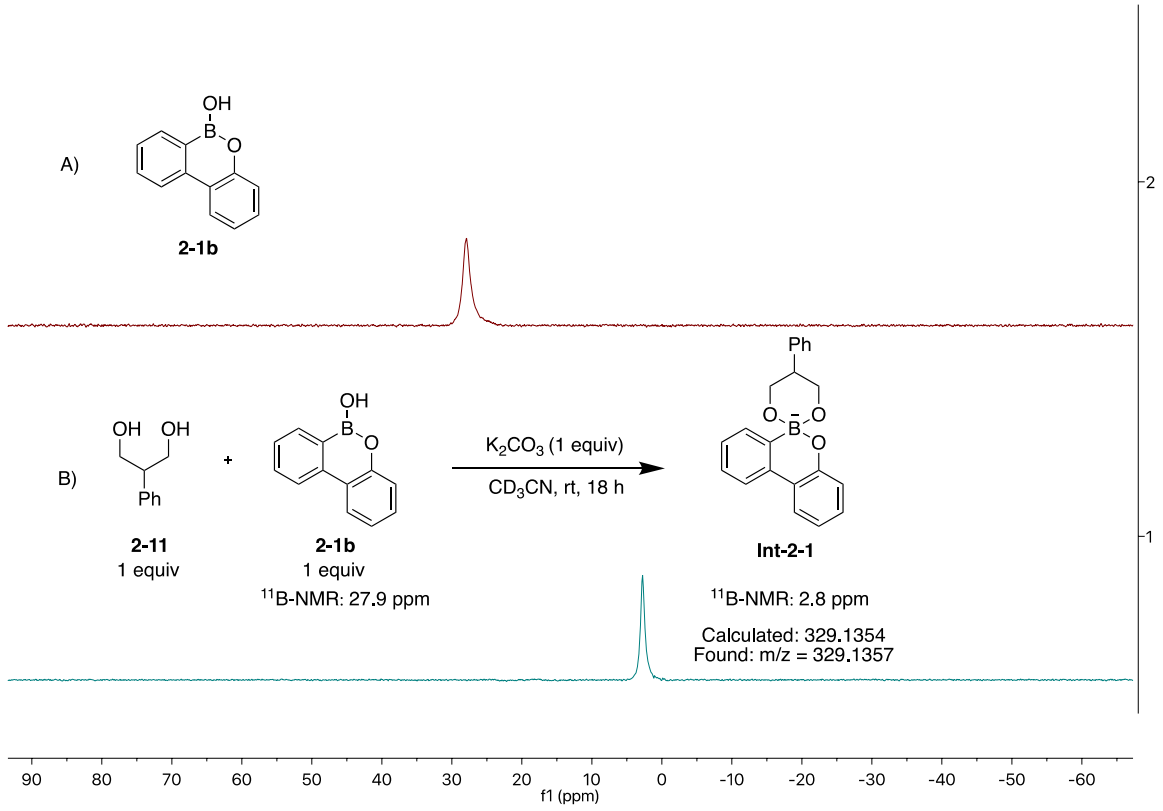



Figure 2-5: Comparison of (A) $^{11}$B-NMR spectra of **2-1b** and (B) a mixture of **2-1b** and diol **2-11**

Formation of the four-coordinate boron center was further confirmed by X-ray crystallography when **2-1b** was reacted with 2,2-dimethyl-1,3-propanediol in the presence of tetrabutylammonium hydroxide as a base (Figure 2-6). From the X-ray structure of **2-1b**, the six-membered boron-diol adduct assumes a chair-like conformation where the aryl oxygen-boron bond (B1-O1) occupies the axial position and the aryl carbon-boron bond (B1-C12) is placed equatorially (Figure 2-6).

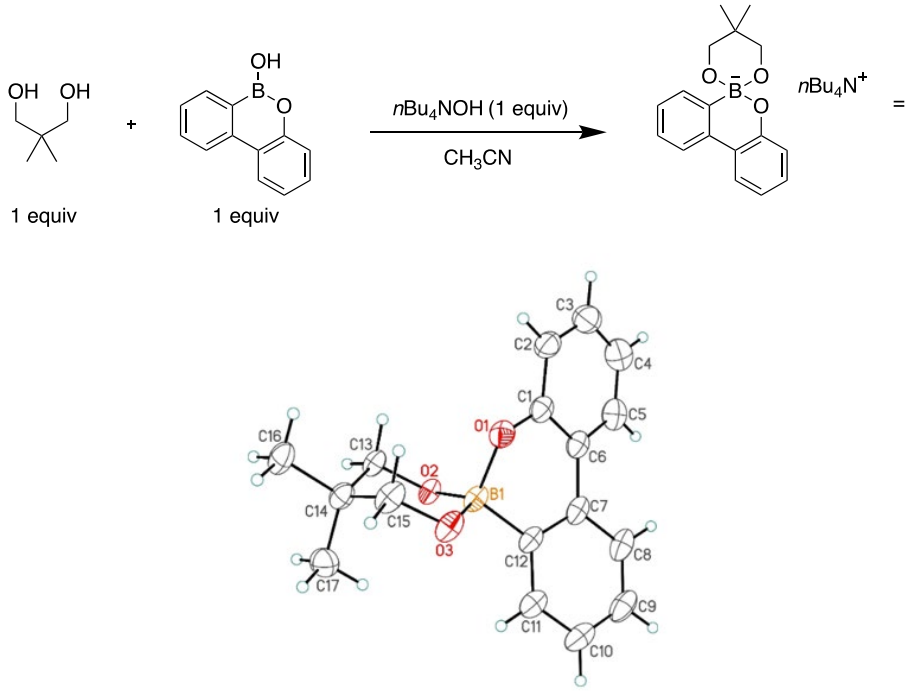



Figure 2-6: ORTEP diagram of boron "ate" complex of **2-1b** and 2-dimethyl-1,3-propanediol (obtained by Hwee Ting Ang)

From these observations, a mechanism resembling that described by Taylor is proposed (Figure 2-7). Diol activation upon coordination to **2-1b** forms the active catalytic species **Int-2-2** and water as a by-product, followed by functionalization of one of the bound oxygens with an electrophile to generate a boronic ester **Int-2-3**, which can then be turned over by another molecule of diol and base.

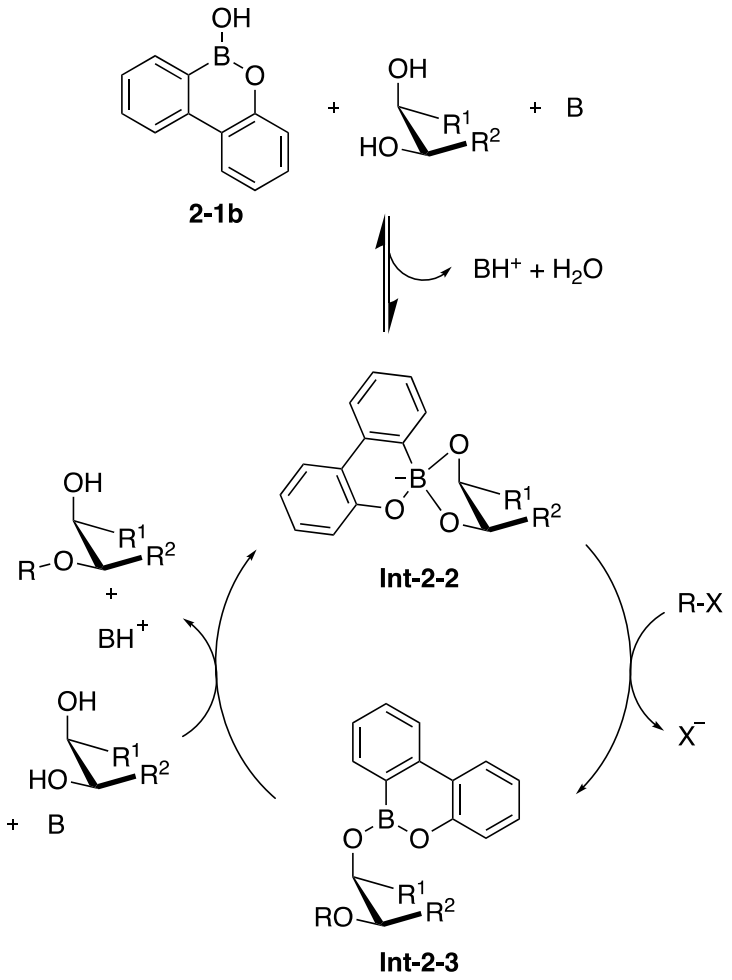
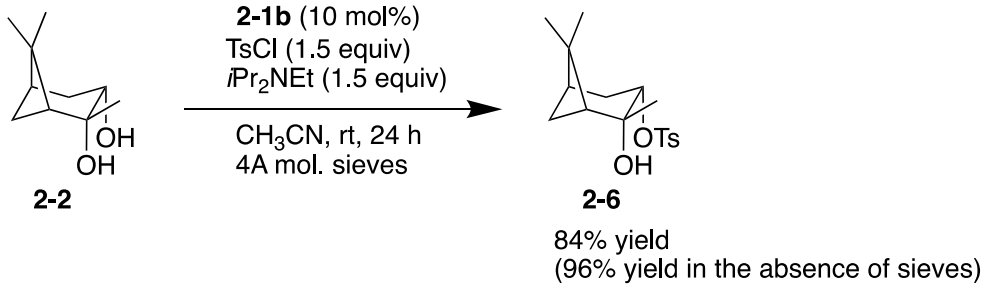



Figure 2-7: Proposed mechanism for the hemiboronic acid catalyzed monofunctionalization of diols

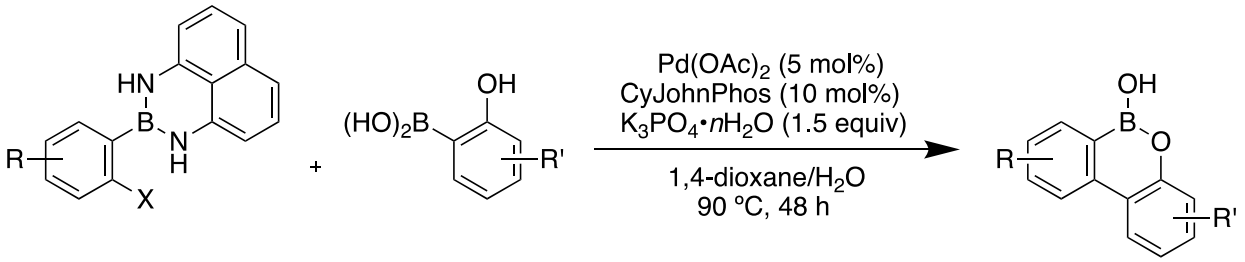
The presence or absence of water can be detrimental or advantageous in boronic acid catalyzed reactions.[18] Therefore, the role of water in the diol functionalization reaction was investigated. Removing water by employing molecular sieves into the monosulfonylation reaction with pinanediol slightly decreased the yield of **2-6** (84% yield compared to 96% yield in the absence of molecular sieves, Scheme 2-3). This may suggest that the diol substrate and base are adequate for catalyst turnover, but a small amount of water may also assist in regenerating the active catalytic species. Excess water may, however, inhibit catalysis by hydrolyzing the active boron catalyst species.[19]




Scheme 2-3: Monosulfonylation of pinanediol **2-2** in the presence of molecular sieves

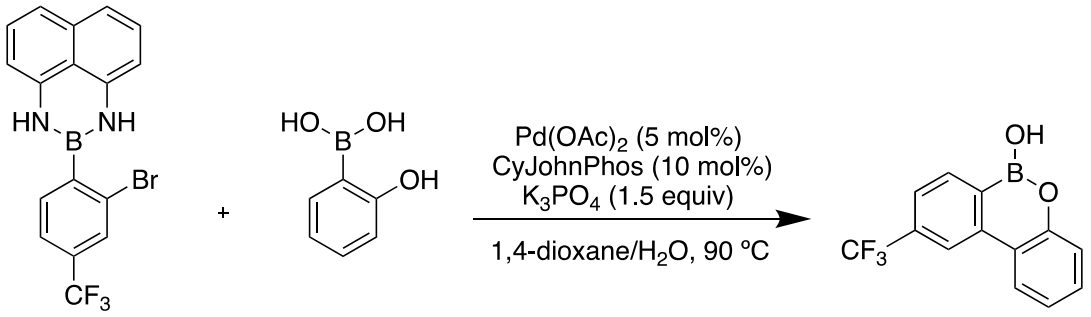
### 2.2.3 Attempts at Controlling the Selectivity in the Hemiboronic Acid Catalyzed Diol Monofunctionalization

Structural modifications to the catalyst **2-1b** were also attempted in an effort to control the selectivity of functionalization. Electronic and/or steric modulation may influence the regioselectivity of functionalization of the bound oxygen atoms from the tetrahedral boron-diol adduct. Introducing electron-withdrawing groups to the arene may produce a more active intermediate Lewis acidic boron center that can more readily bind with diols and stabilize the resulting anionic intermediate. Alternatively, electron-donating groups may generate a more nucleophilic boron adduct that would increase the reactivity of the diol oxygens. Tuning the electronics may also result in differentiation between the nucleophilicity of the two bound oxygens and may affect the regioselective outcome. Conveniently, Hosoya and co-workers reported a protocol to synthesize analogs of **2-1b** by a boron-selective cross-coupling–cyclization strategy (Scheme 2-4).[20]

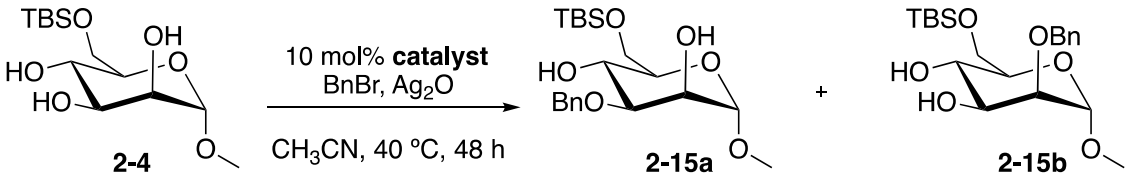



Scheme 2-4: Cross-coupling–cyclization strategy for the synthesis of boroxarophenanthrene analogs (Hosoya)

Using this strategy, a *p*-trifluoromethyl analog **2-1l**, albeit low yielding, was synthesized (Scheme 2-5) and employed as a catalyst in the benzylation of mannopyranoside **2-4**. Electronic modification of the hemiboronic acid, however, did not appear to affect the regioselectivity nor the reactivity of the reaction as the yield and ratio of *O*-2:*O*-3 benzylation (**2-15a** : **2-15b**) remained unaffected (Table 2-4).



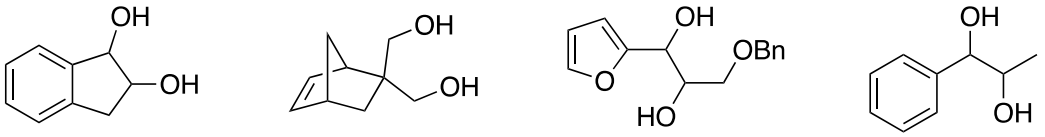

Scheme 2-5: Synthesis of hemiboronic acid analog **2-1l** by Suzuki-Miyaura cross-coupling–cyclization strategy




| Entry | **catalyst** | *O*-3:*O*-2 (**2-15a:2-15b**) | Yield of **2-15a** (%) |
|---|---|---|---|
| 1 | **2-1b** | 3:1 | 71 |
| 2 | **2-1l** | 3:1 | 71 |

Table 2-4: Comparing the regioselectivity and yields in the hemiboronic acid catalyzed benzylation of mannopyranoside **2-4**

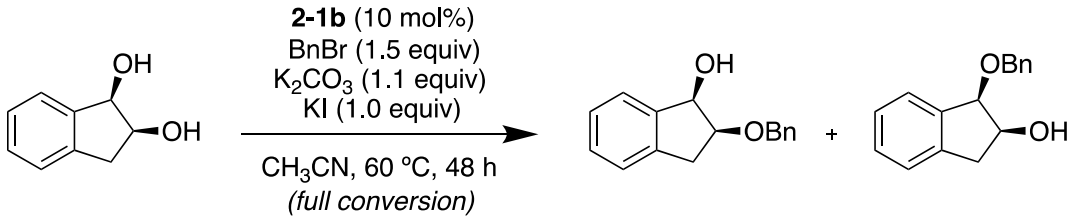
From the attempted reactions for the selected substrates shown in Tables 2-2 and 2-3, there was negligible observed difference in the regioselectivity of functionalization compared with previously reported diarylborinic acid catalyzed examples. To further contribute to the field of catalyzed diol functionalization, and in an attempt to find an application in which **2-1b** provides a regioselectivity advantage over **2-1a**, other substrates with less bias in the reactivity of the hydroxy groups were screened (Figure 2-8). Selective functionalization of unbiased diols is very challenging and a method that can distinguish -OH groups of similar reactivity would be a great improvement to current methods. The chosen model substrates include diols **2-17**, **2-19**, **2-20** that contain two secondary alcohols, as well as diol **2-18** that contains two primary alcohols (Figure 2-8).




**2-17** **2-18** **2-19** **2-20**

Figure 2-8: Selected challenging, less biased diol substrates

In the case of indane-1,2-diol **2-17** containing a benzylic and an alkyl secondary alcohol, selective benzylation was attempted. Using catalyst **2-1b**, the reaction did not appear to be selective as equal amounts of benzyl ethers **2-17a** and **2-17b** were observed upon $^{1}$H-NMR spectroscopic analysis of the crude mixture (Scheme 2-6).

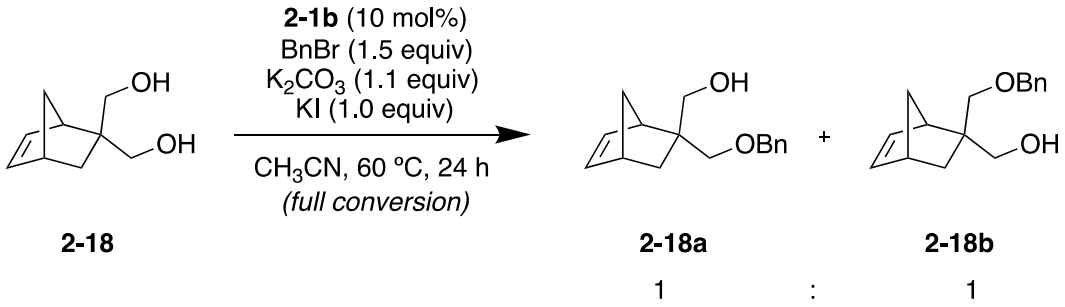



**2-17** **2-17a** : **2-17b**

1 : 1

Scheme 2-6: Monobenzylation of indane-1,2-diol **2-17** (performed by Ashley Ponich). Product ratio determined by crude $^{1}$H-NMR.

Norbornene diol derivative **2-18** was also chosen as a model unbiased diol substrate, one that contains two nonequivalent primary hydroxy moieties. Selective benzylation was attempted here as well but was not successful as a 1:1 regioisomeric mixture of **2-18a** and **2-18b** was observed, indicating that the catalyst is unable to induce a preference for nucleophilic attack from the substrate (Scheme 2-7).

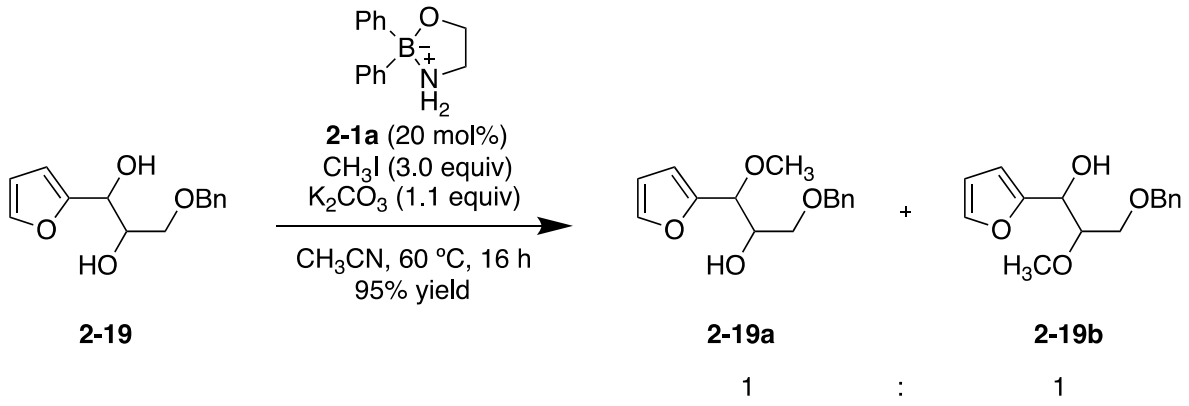



Scheme 2-7: Monobenzylation of norbornene diol **2-18** (performed by Ashley Ponich). Product ratio determined by crude $^{1}$H-NMR.

Another substrate of interest was furfural-derived diol **2-19**. Selective functionalization of this substrate had previously been explored by Lowary and co-workers.[21] The authors had explored various alkylating conditions in an attempt to selectively methylate the homobenzylic alcohol. Use of the 2-aminoethyl diphenylborinate catalyst **2-1a** was found to be their optimal method, albeit, it provided an inseparable 1:1 mixture of **2-19a** and **2-19b** (Scheme 2-8A).

There was room for improvement in the selectivity for this reaction, and so hemiboronic acid **2-1b** was instead evaluated as a catalyst. Unfortunately, the same 1:1 regioselectivity was observed (Scheme 2-8B).

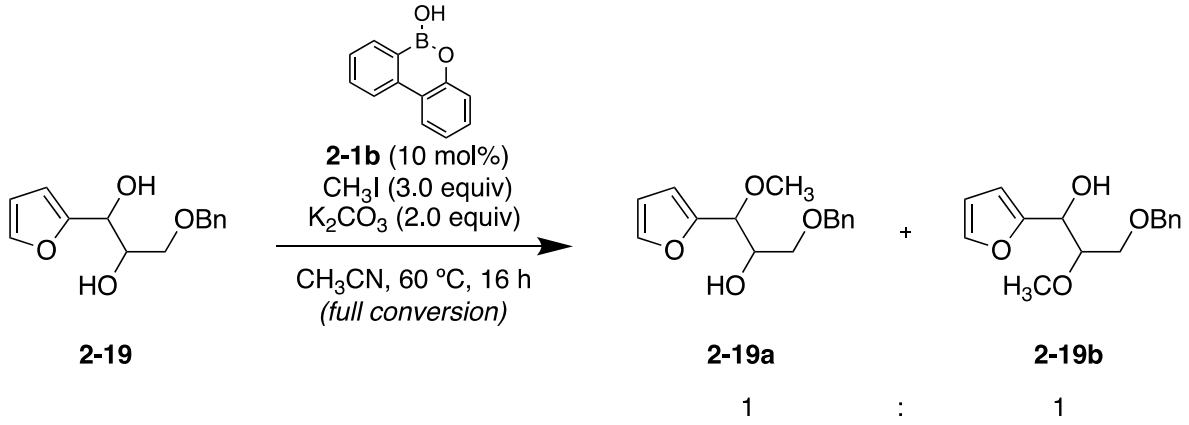
**A) Attempted literature example for selective alkylation (Lowary)[21]:**




**2-19** **2-19a** : **2-19b**

1 : 1

**B) Attempted alkylation with hemiboronic acid 2-1b:**

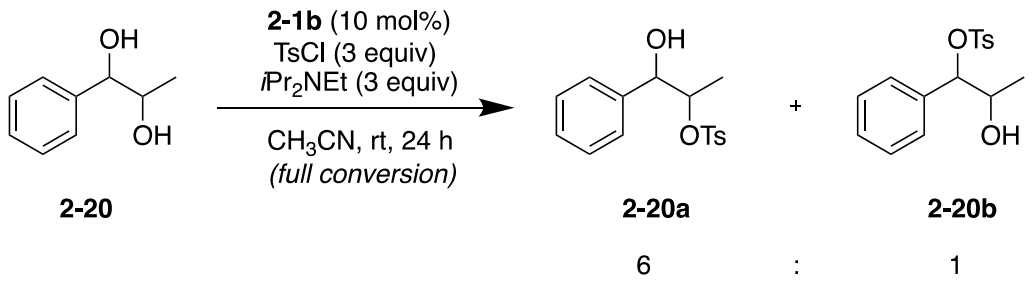



**2-19** **2-19a** : **2-19b**

1 : 1

Scheme 2-8: Attempt at selective methylation of furan diol **2-19**. Product ratio determined by crude $^{1}$H-NMR.

Acyclic diol **2-20** was another substrate that was attempted for selective functionalization (Scheme 2-9). From the results obtained from the previously described substrates above, there was no observed selectivity toward monoalkylation. Sulfonylation was instead attempted with 1-phenyl-1,2-propanediol **2-20**. In the presence of **2-1b**, although not significantly selective, there appeared to be some preference for sulfonylation at the homobenzylic position as a 6:1 regioisomeric ratio of **2-20a** to **2-20b** was observed (Scheme 2-9)




Scheme 2-9: Monosulfonylation of 1-phenyl-1,2-propanediol **2-20** (performed by Ashley Ponich). Product ratio determined by crude $^{1}$H-NMR.

It can be seen from the examined unbiased diol substrates that boron catalyst **2-1b** does not appear to significantly affect the regioselectivity of monofunctionalization and that differentiation between similarly reactive hydroxyl groups is difficult. Selective monofunctionalization of these substrates remains an unmet challenge.

### 2.2.4 Hemiboronic Acid Catalyzed Diol Functionalization – Competition Experiments

Competition experiments were then performed on structurally similar diol substrates in an attempt to observe any preference toward functionalization when catalyzed by **2-1b**. Competition experiments have been previously reported by Taylor and co-workers to evaluate the ability for diarylborinic ester **2-1a** to distinguish similar diols (Figure 2-9).[11,22] The authors observed the high preference for *cis*-diol moieties to undergo functionalization in the presence of *trans*-diol moieties, high chemoselectivity toward diol moieties in the presence of monoalcohols, and a strong preference to form a 5-membered borinate from 1,2-diols compared to formation of a 6-membered ring from 1,3-diols.

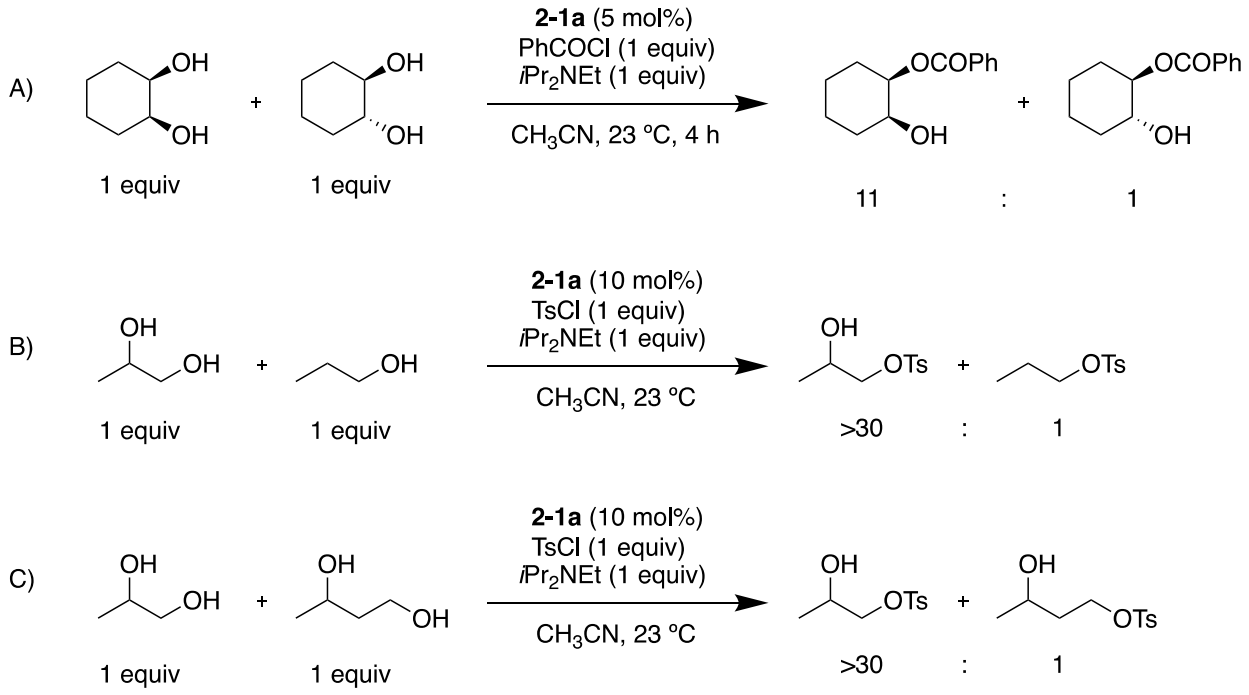



Figure 2-9: Reported examples of competition experiments in the borinic acid catalyzed functionalization of diols (Taylor)[11,12]

Similar competition experiments were performed to compare **2-1a** and **2-1b** as catalysts (Figure 2-10). In this study, comparable observations to those reported by Taylor were observed when using borinic acid derivative **2-1a** as a catalyst under sulfonylating conditions where there is a strong preference for **2-1a** to recognize *cis*-diols.

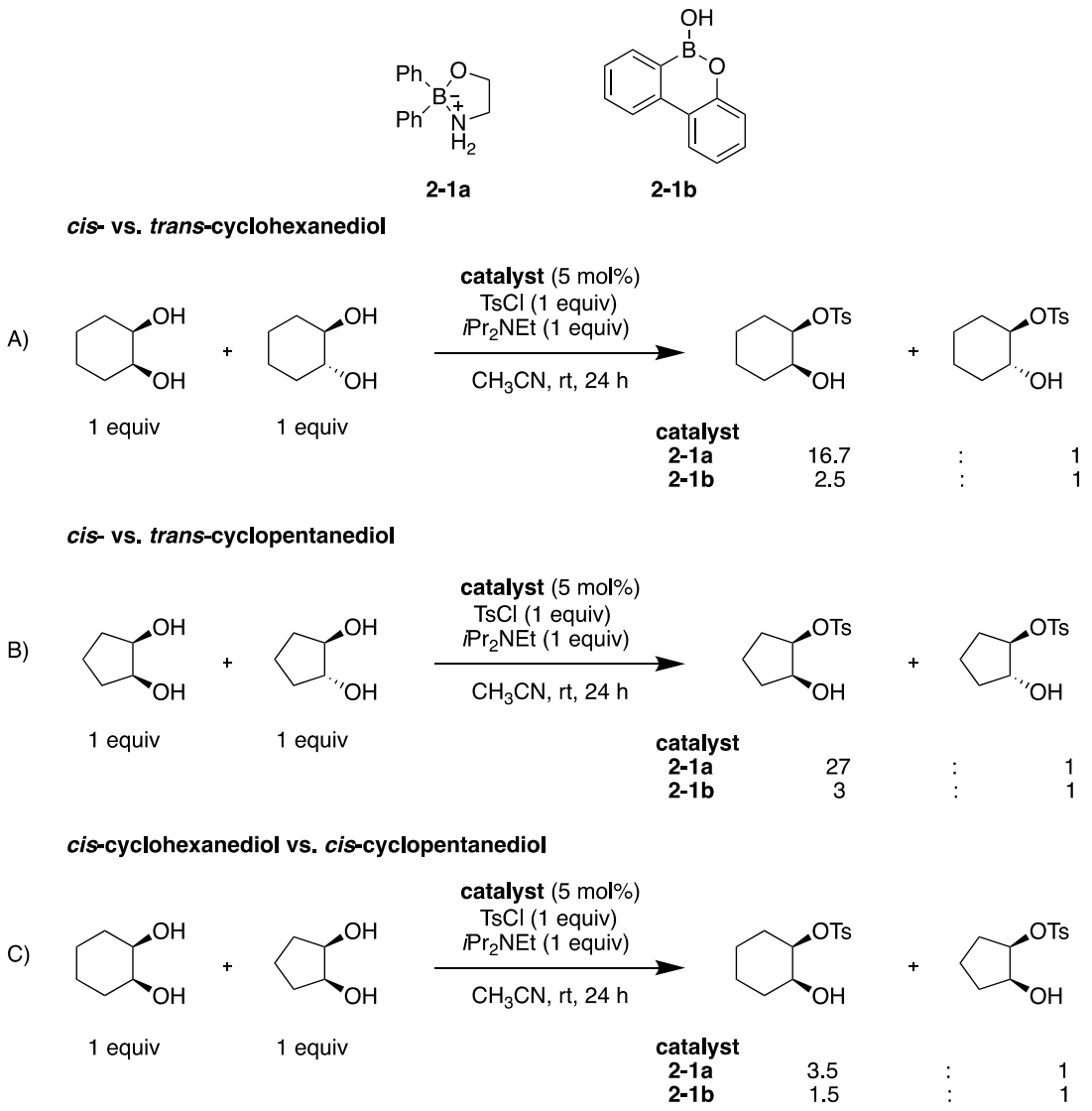
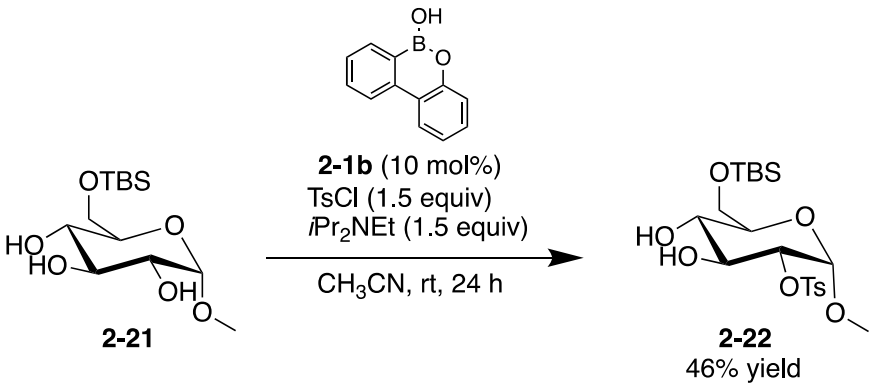



Figure 2-10: Competition experiments comparing **2-1a** and **2-1b** in diol recognition (performed by Ashley Ponich). Product ratio determined by crude $^{1}$H-NMR.

Interestingly, there appears to be less preference toward *cis*-diol functionalization in the presence of a *trans*-diol when **2-1b** is utilized as a catalyst (Figures 2-10A, 2-10B). *trans*-Diol recognition and monofunctionalization is also very challenging, and there are only a few methods in the literature that promote transformations for these types of substrates. The potential for catalyst **2-1b** to also recognize *trans*-diol moieties can provide a significant advantage over the diarylborinic acid catalysis method since it is limited to *cis*-diol substrates and would also provide a more general method toward diol functionalization.

To test this hypothesis, glucopyranoside derivative **2-21** was used as a *trans*-diol model substrate. Site-selective functionalization of minimally protected glucopyranosides under mild conditions still remains a difficult task, and discovery of a simple and mild method to functionalize them would be a great advancement in carbohydrate chemistry. Thus, 6-*O*-silyl protected glucopyranoside **2-21** was initially subjected to sulfonylation conditions. Analysis of the crude mixture by $^{1}$H-NMR spectroscopy after stirring for 48 hours at room temperature revealed a sulfonylated product. After purification by silica gel chromatography, a monosulfonylated glucopyranoside product was isolated in 46% yield. Further analysis by two-dimensional $^{1}$H-NMR spectroscopy (COSY, HSQC, HMBC) confirmed the product to be the 2-*O*-tosyl glucopyranoside **2-22** (Scheme 2-10).




Scheme 2-10: Monosulfonylation of 6-*O*-TBS-methyl α-D-glucopyranoside (performed by Ashley Ponich)

This result led us to propose a different mechanism in which catalyst **2-1b** can potentially activate *trans*-diols and other diols. Alcohol exchange of **2-1b** with one of the hydroxy groups of the diol may introduce hydrogen bonding between the cyclic oxygen from **2-1b** with an adjacent -OH (**Int-2-4**), which may increase its nucleophilicity to react more readily with electrophiles without forming a tetrahedral borate intermediate (Figure 2-11).

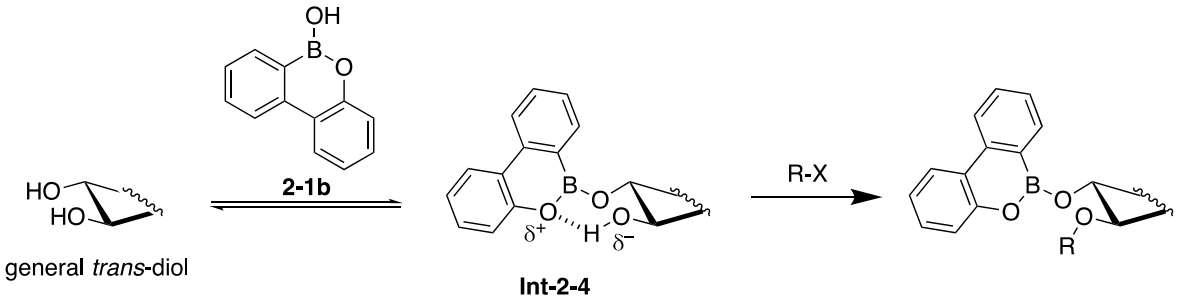



Figure 2-11: Proposed activation of *trans*-diols by hemiboronic acid **2-1b**

Unfortunately, efforts to reproduce and optimize the result obtained from the selective sulfonylation of **2-21** were unsuccessful. Attempts at troubleshooting the reaction included using excess base, distilling the base and increasing the temperature. However, only complex reaction mixtures were obtained as observed by the crude $^{1}$H-NMR spectra upon workup of the reaction. The 46% yield of product **2-22** that was first obtained may have been a result of deprotonation of the most acidic O-H at the 2-position.

As sulfonylation of a *trans*-diol substrate was less successful, selective functionalization of glucopyranoside **2-21** was then attempted with other electrophiles. Esterification and alkylation reactions, unfortunately, gave complex crude mixtures as observed by $^{1}$H-NMR spectroscopy. Benzoylation resulted in low yields and a mixture of regioisomers. Benzylation was also attempted, but also resulted in low yields and poor regioselectivity (Figure 2-12).

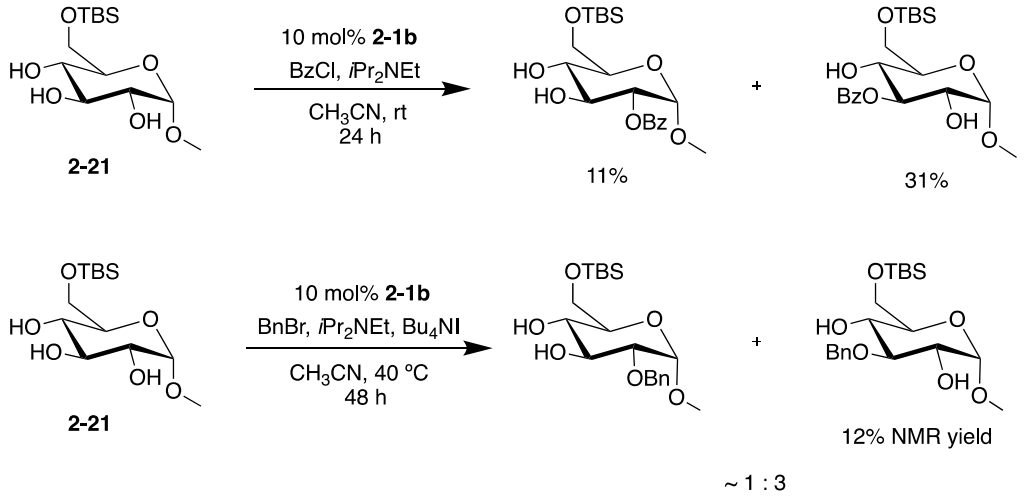
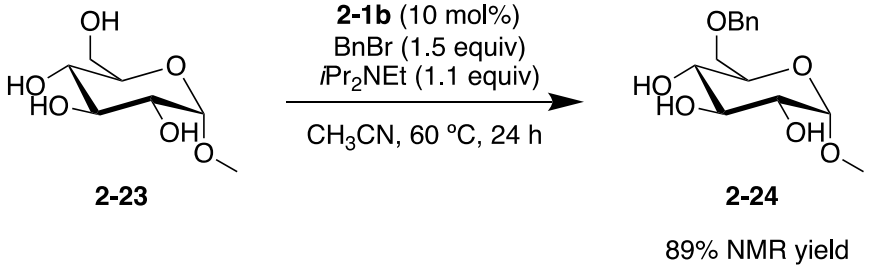



Figure 2-12: Attempts at selective benzoylation and benzylation of pyranoside **2-21**

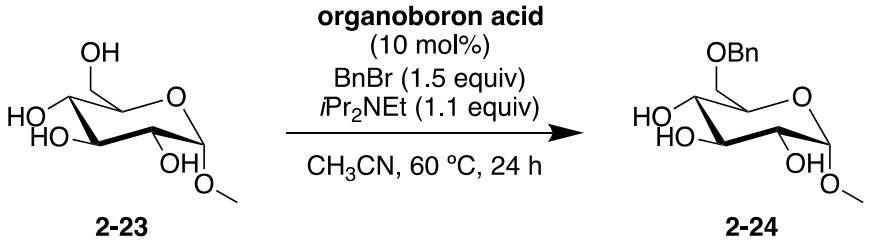
### 2.2.5 Attempts at Functionalization of Unprotected Carbohydrates

In another attempt to discover an advantage that hemiboronic acid **2-1b** may have over borinic acid derivative **2-1a** as a catalyst, a fully unprotected carbohydrate substrate (methyl α-D-glucopyranoside **2-23**) was examined. As discussed in Chapter One, selective functionalization of free primary alcohols in sugars can be achieved easily in the presence of a bulky electrophile. Benzylation was chosen as a model reaction, as selective installation of benzyl ethers on nonprotected carbohydrates without the use of a strong base is challenging. Interestingly, in the presence of **2-1b**, the 6-*O*-benzyl ether was observed in 89% NMR yield (Scheme 2-11).




Scheme 2-11: Selective benzylation of unprotected pyranoside **2-23**

Catalyst **2-1b** was compared to other organoboron acids (Table 2-5). Not surprisingly, borinic acid derivative **2-1a** was shown to be an effective catalyst (Table 2-5, entry 2). Phenylboronic acid only provided the product in 18% yield under the same reaction conditions. Benzoxaborole **2-1d**, which is also capable of forming an active tetrahedral adduct, yielded benzyl ether **2-24** in a lower yield (Table 2-5, entry 3). This result is consistent with that obtained in the initial organoboron acid screen (Table 2-1) where benzoxaboroles **2-1d** and **2-1h** were relatively less efficient as catalysts.




**2-23** **2-24**

| Entry | **catalyst** | Yield (%)[a] |
|---|---|---|
| 1 | **2-1b** | 89 |
| 2 | **2-1a** | >99 |
| 3 | **2-1d** | 36 |
| 4 | $PhB(OH)_2$ | 18 |

Table 2-5: Screening of organoboron acids in the selective monobenzylation of unprotected pyranoside **2-23**. 0.2 mmol scale. [a]NMR yields using 1,3,5-trimethoxybenzene as an internal standard

Although formation of a tetrahedral adduct is possible upon complexation of a diol with benzoxaborole **2-1d**, alkylation of the benzyl oxygen of the boroxole can be competing (**Int-2-5**, Figure 2-13A). This issue was also mentioned by Aoyama in the borinic acid promoted glycosidation of carbohydrates when benzoxaborole **2-1d** is used as a promoter (see Section 1.2). This competition may be less likely to occur when **2-1b** is used as a catalyst since the aryl oxygen is relatively less nucleophilic than the bound alkoxy groups from the diol substrate (**Int-2-6**, Figure 2-13B). Aromaticity is also regained in **Int-2-8** when one of the alkoxy groups from the tetrahedral adduct reacts with an electrophile.

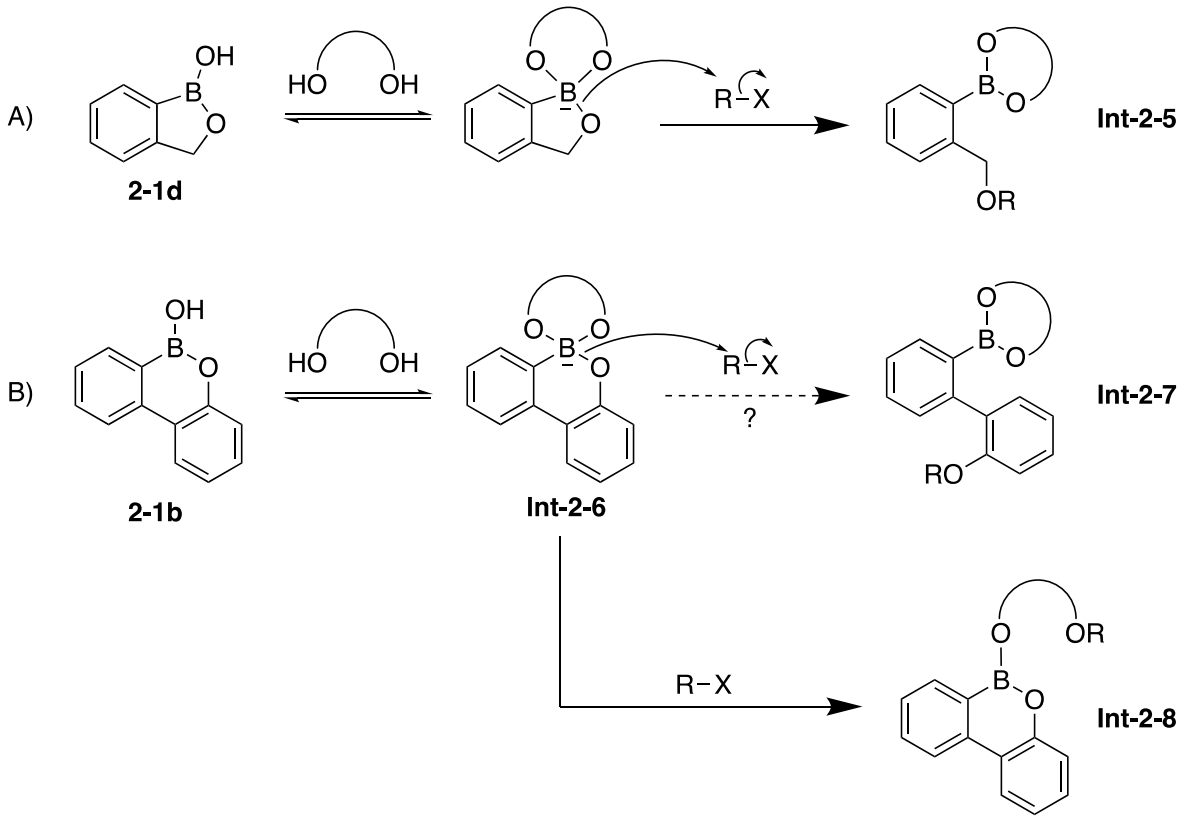



Figure 2-13: Possible alkylation pathways of diols upon activation by benzoxaborole **2-1d** (A) and hemiboronic acid **2-1b** (B)

Since it is possible that **Int-2-7** is produced in the reaction, synthesis of boronic acid **2-26** was attempted to find out if it can also be used as a catalyst in the diol functionalization reaction (Figure 2-14). Interestingly, after lithiation–borylation of bromoarene **2-25** and purification by sorbitol phase-switch extraction,[23] the only product isolated that contained boron was hemiboronic acid **2-1b**. This may occur through substitution of the benzyl ether of **2-26** under basic conditions to promote intramolecular cyclization to form product **2-1b**. This observation may suggest that benzylation of the aryl oxygen of **2-1b** may be reversible, and that rearomatization of **Int-2-6** to the boronic ester intermediate **Int-2-8** upon functionalization of one of the diol oxygens may be more favourable in the catalyzed process.

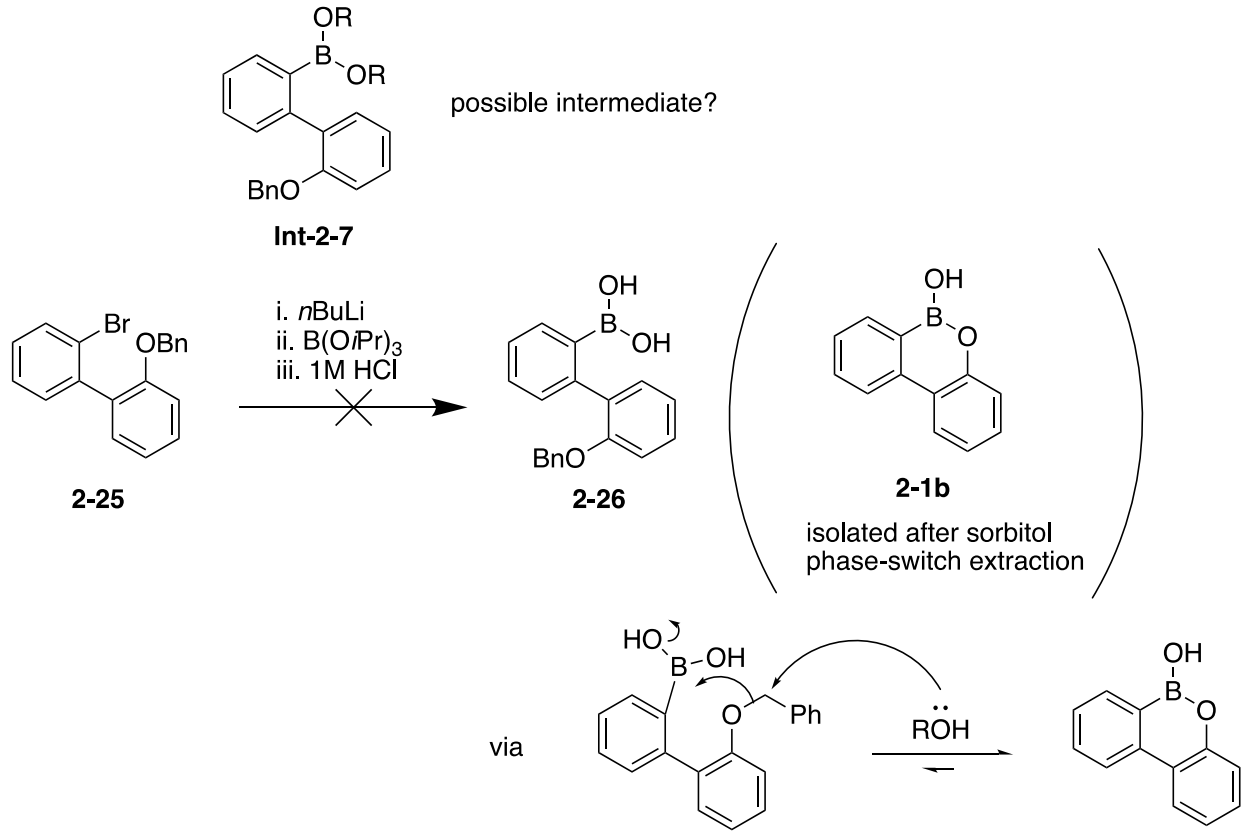
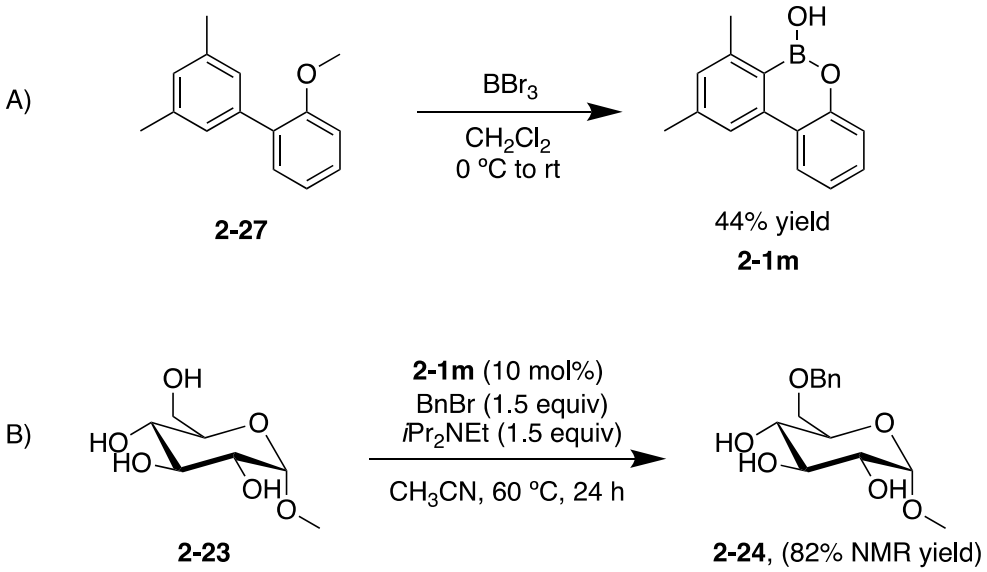



Figure 2-14: Attempted synthesis of boronic acid **2-26**

Next, I looked into controlling the regioselectivity in the benzylation of unprotected monosaccharide **2-23**. It is believed that benzyl ether **2-24** is formed from interaction of the 1,3-diol moiety in **2-23** with organoboron **2-1b** to generate a six-membered adduct, followed by nucleophilic attack of the less hindered primary *6*-OH to the benzyl electrophile. In an attempt to control the regioselectivity in the benzylation of glucopyranoside **2-23** (*O*-4 vs. *O*-6), another analog of hemiboronic acid **2-1b** was synthesized. Similar to the synthesis of **2-1b,** 5,7-dimethyl analog **2-1m** was synthesized by reacting biaryl **2-27** with $BBr_3$ (Scheme 2-12A). Introduction of two methyl groups increases electron density and sterics about the boron atom which may influence the reactivity and regioselectivity toward alkylation of the boron-diol adduct. This was not the case, however, as the crude $^1$H-NMR spectrum from the benzylation of polyol **2-23** catalyzed by **2-1m** looked similar to the spectrum of the crude mixture of the reaction catalyzed

by unsubstituted hemiboronic acid **2-1b**. Similar NMR yield (82%) was also observed (Scheme 2-12B).




Scheme 2-12: A) Synthesis of hemiboronic acid analog **2-1m**. B) Attempt at selective benzylation of **2-23** catalyzed by hemiboronic acid analog **2-1m**

## 2.3 Summary

This chapter describes the use of known boron-heterocycle 10-hydroxy-10,9-boroxarophenanthrene **2-1b** as a catalyst in the monofunctionalization of diols. Sulfonylation and benzylation of various diol substrates (acyclic, cyclic, carbohydrate-derived) in the presence of a weak base worked well under hemiboronic acid catalysis. Use of organoboron **2-1b** is advantageous to borinic acids and their derivatives due to its increased stability and ease of preparation. The regioselective outcome upon functionalization of diol substrates catalyzed by **2-1b** was observed to be nearly identical to those reported in borinic acid catalyzed processes. Preliminary structural modifications to the core structure of **2-1b** did not lead to any changes in regioselectivity. $^{11}$B-NMR experiments and X-ray crystallography confirm the presence of a tetrahedral boron adduct as the likely active catalytic species. Since the B-O-phenanthrene-type structure of **2-1b** has been demonstrated to activate diols toward effective monofunctionalization

reactions, there is promise and potential for enantioselective transformations catalyzed by a chiral variant of catalyst **2-1b** (Chapter Three).

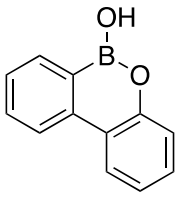
## 2.4 Experimental

### 2.4.1 General Information

Unless otherwise stated, all reactions were performed in flame-dried glassware under a nitrogen atmosphere. Molecular sieves were activated by drying under high vacuum over a 120 ºC oil bath for 48 hours, then stored in a 100 ºC oven. Acetonitrile was distilled from calcium hydride and stored over activated 3Å molecular sieves. Dioxane was distilled over sodium. Dichloromethane ($CH_2Cl_2$), tetrahydrofuran (THF) and toluene were purified using an MBraun MS SPS* solvent system. All other solvents were purchased from Sigma Aldrich and used as received. Unless stated otherwise, *N,N*-diisopropylethylamine (Sigma Aldrich) was used as received. 2-aminoethyl diphenylborinate (**2-1a**) was purchased from Sigma-Aldrich and was used as received. All other chemicals were purchased from Strem, Sigma Aldrich, Oakwood Chemicals or Combi-Blocks and used as received. Thin layer chromatography (TLC) was performed on silica gel 60 F254 plates and visualized using UV light, potassium permanganate ($KMnO_4$) and/or phosphomolybdic acid (PMA) stains. Flash chromatographic separations were performed with silica gel 60 using ACS grade solvents. $^{1}H$ NMR, $^{13}C$ NMR, $^{19}F$ NMR and $^{11}B$ NMR spectroscopy experiments were performed on 400 MHz, 500 MHz, 600 MHz or 700 MHz instruments. The residual solvent ($CDCl_3$, $CD_3OD$, or $(CD_3)_2O$) protons ($^{1}H$) and carbons ($^{13}C$) were used as internal references. $^{1}H$ NMR data is presented as follows: chemical shift in ppm (δ) (multiplicity, coupling constant, integration). The following abbreviations are used in reporting the $^{1}H$ NMR data: s, singlet; br s, broad singlet; app s, apparent singlet; d, doublet; t, triplet; app t, apparent triplet; dd, doublet of doublet; dddd, doublet of doublet of doublet of doublet; app dtd, apparent doublet of triplet of doublet; m, multiplet. The error of coupling constants from $^{1}H$ NMR spectra is estimated to be 0.3 Hz. High-resolution mass spectra were recorded by the University of Alberta Mass Spectrometry Services using electron ionization (EI) or electrospray ionization (ESI) techniques.

Compounds **2-4**,[22] **2-5**,[22] **2-17**,[24] **2-19**,[25] **2-20**,[26] **2-21**,[22] and **2-25**[27] were prepared according to literature procedures. Spectral data for these compounds matched that previously reported.

### 2.4.2 Preparation and Characterization of Hemiboronic acid 2-1b and Analogs 2-1l, 2-1m:



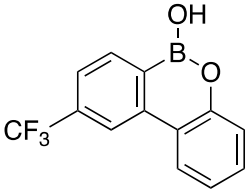

**10-Hydroxy-10,9-boroxarophenanthrene (2-1b):**

Synthesized according to literature procedure[9] from 2-phenylphenol (841 mg, 4.94 mmol). Purification by column chromatography (10% ethyl acetate in hexanes) afforded a white crystalline solid (2.80 g, 60% yield). All spectral data matched that previously reported.[9]

**$^{1}$H NMR** (500 MHz, $CDCl_3$): δ 8.18 (d, *J* = 8.4 Hz, 1H), 8.14 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.07 (dd, *J* = 7.4, 1.8 Hz, 1H), 7.72 (ddd, *J* = 8.2, 7.3 1.5 Hz, 1H), 7.48 (app. td, *J* = 7.3, 1.0 Hz, 1H), 7.38 (ddd, *J* = 8.2, 7.1, 1.6 Hz, 1H), 7.28 (d, *J* = 8.1, 1.4 Hz, 1H), 7.23 (ddd, *J* = 8.0, 7.1, 1.4 Hz, 1H), 4.61 (s, 1H).

**$^{13}$C NMR** (125 MHz, $CDCl_3$): δ 151.2, 140.4, 133.4, 132.6, 129.0, 127.3, 123.6, 123.0, 122.7, 121.7, 119.6. The boron-bound carbon was not detected due to the quadrupolar relaxation of boron.

**$^{11}$B NMR** (160 MHz, $CDCl_3$): δ 28.3.




**9-(Trifluoromethyl)-6*H*-dibenzo[*c*,*e*][1,2]oxaborinin-6-ol (2-1l):**

Following a literature procedure[19], 1,8-diaminonaphthalene-protected 2-bromo-4-(trifluoromethyl)-phenylboronic acid (101 mg, 0.26 mmol, 1.00 equiv), 2-hydroxyphenylboronic acid (54 mg, 0.39 mmol, 1.50 equiv), and potassium phosphate tribasic (82.8 mg, 0.39 mmol, 1.50 equiv) were added to a 15 mL pressure tube. The flask was evacuated and backfilled with $N_2$ three times. CyJohnPhos (9.1 mg, 0.026 mmol, 0.10 equiv) and palladium(II) diacetate (2.9 mg, 0.013

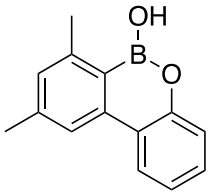
mmol, 0.05 equiv) were then added followed by dioxane (2 mL) and water (0.2 mL, degassed with $N_2$ needle). The flask was capped and the reaction mixture was stirred at 100 ºC for 65 hours. The reaction mixture was cooled to room temperature, then 2M HCl (6 mL) was added and stirred at room temperature for 1 hour. The mixture was extracted with ethyl acetate (20 mL), washed with $H_2O$ (2 x 10 mL) and brine (10 mL). The organic layer was dried with $MgSO_4$, filtered and concentrated. The residue was purified by silica gel chromatography (20% ethyl acetate in hexanes) to yield a brown solid (11.7 mg, 17%).

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 8.38 (s, 1H), 8.20 (d, *J* = 7.8 Hz, 1H), 8.14 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.72 (ddd, *J* = 8.2, 7.3 1.5 Hz, 1H), 7.43 (ddd, *J* = 8.5, 7.1, 1.6 Hz, 1H), 7.38 (ddd, *J* = 8.2, 7.1, 1.6 Hz, 1H), 7.31–7.25 (m, 2H), 4.81 (br s, 1H).

**$^{11}$B NMR** (160 MHz, $CDCl_3$): δ 27.8.

**$^{19}$F NMR** (376 MHz, $CDCl_3$): –63.0

**HRMS** (ESI-TOF) for $C_{13}H_7BF_3O_2$ $(M - H)^-$: calc. 263.0497; found 263.0508.




**7,9-Dimethyl-6*H*-dibenzo[*c*,*e*][1,2]oxaborinin-6-ol (2-1m):**

2-Bromoanisole (376 mg, 2.02 mmol, 1.00 equiv), 3,5-dimethylphenylboronic acid (333.0 mg, 2.22 mmol, 1.10 equiv), potassium carbonate (838.0 mg, 6.06 mmol, 3.00 equiv) and palladium(II) diacetate (18 mg, 0.081 mmol, 0.040 equiv) were added to a 25 mL round bottom flask. The flask was evacuated and backfilled with $N_2$ two times before adding DMF (7 mL) and $H_2O$ (7 mL, degassed with $N_2$). The reaction mixture was stirred for 19.5 hours at room temperature, then transferred to a separatory funnel. After extraction with ethyl acetate (3 x 20 mL), the organic layer was washed with $H_2O$ (3 x 20 mL), brine (10 mL), dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (1% to 5% ethyl acetate in hexanes) to yield 2-(3,5-dimethylphenyl)-anisole **2-27** as a clear oil (386 mg, 90%).

Following a literature procedure[9], 2-(3,5-dimethylphenyl)-anisole **2-27** was added to a flame-dried 50 mL round-bottom flask and dissolved in $CH_2Cl_2$ (20 mL). The solution was cooled to 0 ºC (ice-bath), then $BBr_3$ was slowly added under $N_2$. The reaction was stirred overnight (19 hours),

gradually warming to room temperature. $H_2O$ (10 mL) was slowly added to quench, followed by addition of saturated aqueous $NaHCO_3$. The mixture was extracted with diethyl ether (20 mL), washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was dried with $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (5% ethyl acetate in hexanes to 100% ethyl acetate) to yield a brown solid (137 mg, 44%).

**$^1$H NMR** (400 MHz, $d_6$-acetone): δ 8.24 (dd, $J$ = 8.2, 1.6 Hz, 1H), 8.04 (s, 0.5H, B-O*H*), 7.97 (s, 1H), 7.38–7.31 (m, 1H), 7.21–7.15 (m, 2H), 7.13 (app s, 1H), 2.71 (s, 3H), 2.45 (s, 3H).

**$^{13}$C NMR** (126 MHz, $d_6$-acetone): δ 152.2, 147.0, 142.8, 142.3, 131.6, 129.5, 124.9, 124.0, 123.1, 120.6, 119.7, 28.2, 21.8. The boron-bound carbon was not detected due to the quadrupolar relaxation of boron.

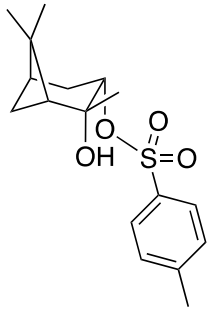
**$^{11}$B NMR** (160 MHz, $d_6$-acetone): δ 27.8.

**HRMS** (ESI-TOF) for $C_{14}H_{13}BO_2$ $(M - H)^-$: calc. 223.0936; found 223.0935.

### 2.4.3 General Procedure 2A – Hemiboronic Acid Catalyzed Monosulfonylation of Diols:

Following a literature procedure[11], diol (1.0 equiv), hemiboronic acid **2-1b** (0.10 equiv) and *p*-toluenesulfonyl chloride (1.5 equiv) were added to a round-bottom flask. Acetonitrile (0.2 M) was then added, followed by *N*,*N*-diisopropylethylamine (1.5 equiv). The reaction was stirred at room temperature for 24 hours. The mixture was diluted with ethyl acetate (10 mL) and transferred to a separatory funnel. The organic layer was washed with $H_2O$ (10 mL) then brine (10 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. The residue was then purified by silica gel chromatography.

#### 2.4.3.1 Characterization of Monosulfonated Diols

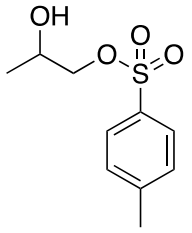


**(1*R*,2*R*,3*S*,5*R*)-3-*O*-(4-Toluenesulfonyl)-pinanediol (2-6):**

Synthesized according to General Procedure 2A using diol **2-2** (170 mg, 1.0 mmol). The crude oil was purified by silica gel chromatography (10% to 20% ethyl acetate in pentane) to afford a clear colourless oil (310 mg, 96%) that solidified after storage in a 4 ºC fridge. All spectral data matched that previously reported.[11]

**$^1$H NMR** (500 MHz, $CDCl_3$): δ 7.84 (m, 2H, AA' part of AA'BB'), 7.36 (m, 2H, BB' part of AA'BB'), 4.88 (dd, *J* = 9.7, 6.0 Hz, 1H), 2.46 (s, 1H), 2.27 (dddd, *J* = 13.7, 9.8, 3.9, 2.5 Hz, 1H), 2.20 (dddd, *J* = 10.5, 5.9, 5.9, 2.5 Hz, 1H), 2.00 (dd, *J* = 5.8, 5.8 Hz, 1H), 1.88 (dddd, *J* = 6.1, 6.1, 3.9, 2.6 Hz, 1H), 1.80 (ddd, *J* = 14.1, 6.0, 2.3 Hz, 1H), 1.26 (s, 3H), 1.21 (s, 3H), 0.92 (s, 3H).

**$^{13}$C NMR** (101 MHz, $CDCl_3$): δ 145.0, 133.9, 129.9, 127.9, 79.9, 73.6, 54.1, 40.5, 38.5, 35.2, 29.4, 28.4, 27.9, 24.4, 21.7.

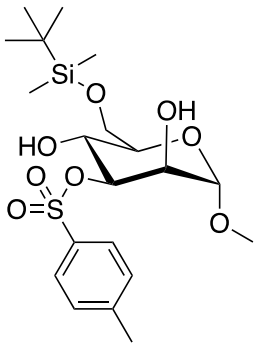



**1-*O*-(4-Toluenesulfonyl)-2-propanol (2-7):**

Synthesized according to General Procedure 2A using diol **2-3** (76 mg, 1.0 mmol). The crude oil was purified by silica gel chromatography (15% ethyl acetate in hexanes) to afford a white solid (177 mg, 77%). All spectral data matched that previously reported.[11]

**$^1$H NMR** (500 MHz, $CDCl_3$): δ 7.80 (m, 2H, AA' part of AA'BB'), 7.36 (m, 2H, BB' part of AA'BB'), 4.08–4.02 (m, 1H), 4.00 (dd, *J* = 10.1, 3.1 Hz, 1H), 3.86 (dd, *J* = 10.0, 7.3 Hz, 1H), 2.46 (s, 3H), 2.06 (br s, 1H), 1.16 (d, *J* = 6.4 Hz, 3H)

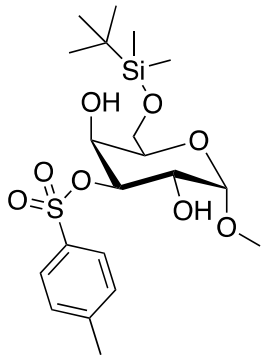
**$^{13}$C NMR** (125 MHz, $CDCl_3$): δ 145.06, 132.59, 129.93, 127.90, 74.74, 65.55, 21.61, 18.52.



**Methyl-6-(*tert*-butyldimethylsilyloxy)-3-*O*-(4-toluenesulfonyl)-α-D-mannopyranoside (2-8):** Synthesized according to General Procedure 2A using diol **2-4** (154 mg, 0.500 mmol). The crude oil was purified by silica gel chromatography (10% to 20% ethyl acetate in hexanes) to afford a pale yellow oil (209 mg, 90%). All spectral data matched that previously reported.[11]

**$^1$H NMR** (500 MHz, $CD_3OD$): δ 7.84 (m, 2H, AA' part of AA'BB'), 7.41 (m, 2H, BB' part of AA'BB'), 4.55 (d, $J$ = 1.9 Hz, 1H), 4.49 (dd, $J$ = 9.5, 3.3 Hz, 1H), 3.90 (dd, $J$ = 11.2, 2.0 Hz, 1H), 3.90 (dd, $J$ = 3.9, 1.9 Hz, 1H), 3.75 (m, 2H), 3.46 (ddd, $J$ = 9.7, 6.2, 2.0 Hz, 1H), 3.34 (s, 1H), 2.45 (s, 3H), 0.90 (s, 9H), 0.07 (s, 6H).

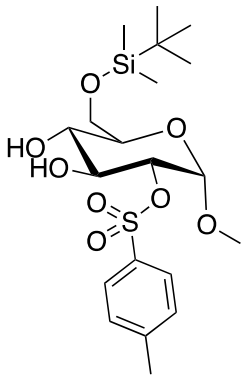
**$^{13}$C NMR** (125 MHz, $CD_3OD$): δ 146.3, 135.4, 130.8, 129.2, 102.4, 84.0, 75.1, 70.3, 65.7, 64.2, 55.1, 26.4, 21.6, 19.2, -5.2.



**Methyl-6-(*tert*-butyldimethylsilyloxy)-3-*O*-(4-toluenesulfonyl)-α-D-galactopyranoside (2-9):** Synthesized according to General Procedure 2A using diol **2-5** (62 mg, 0.20 mmol). The crude oil was purified by silica gel chromatography (20% ethyl acetate in hexanes) to afford a white solid (75 mg, 83%). All spectral data matched that previously reported.[11]

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.84 (m, 2H, AA' part of AA'BB'), 7.32 (m, 2H, BB' part of AA'BB'), 4.78 (d, $J$ = 3.9 Hz, 1H), 4.63 (dd, $J$ = 9.9, 3.0 Hz, 1H), 4.19 (dd, $J$ = 3.1, 1.1 Hz, 1H),

4.05 (dd, *J* = 9.9, 3.9 Hz, 1H), 3.84 (dd, *J* = 10.5, 5.8 Hz, 1H), 3.79 (dd, *J* = 10.5, 5.0 Hz, 1H), 3.72 (dd, *J* = 5.4, 5.4 Hz), 3.38 (s, 3H), 2.42 (s, 3H), 2.29 (br s, 2H), 0.87 (s, 9H), 0.05, (s, 6H).
**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 145.0, 133.7, 129.8, 127.9, 99.6, 81.7, 69.6, 69.1, 66.7, 62.7, 55.4, 25.8, 21.7, 18.2, –5.48, –5.51.



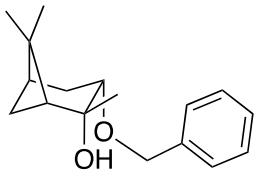

**Methyl-6-(*tert*-butyldimethylsilyloxy)-2-*O*-(4-toluenesulfonyl)-α-D-glucopyranoside (2-22):** Synthesized according to General Procedure 2A using diol **2-21** (62 mg, 0.20 mmol). The crude oil was purified by silica gel chromatography (20% ethyl acetate in hexanes) to afford a yellow oil (43 mg, 46%).
**$^{1}$H NMR** (600 MHz, $CDCl_3$): δ 7.83 (m, 2H, AA' part of AA'BB'), 7.35 (m, 2H, BB' part of AA'BB'), 4.69 (d, *J* = 3.7 1H), 4.27 (dd, *J* = 9.7, 3.6 Hz, 1H), 3.95 (dd, *J* = 9.2, 9.2 Hz, 1H), 3.84 (dd, *J* = 10.8, 4.9 Hz, 1H), 3.79 (dd, *J* = 10.8, 4.9 Hz, 1H), 3.59 (ddd, *J* = 9.5, 4.7, 4.7 Hz, 1H), 3.51 (dd, *J* = 9.2, 9.2 Hz, 1H), 3.28 (s, 3H), 3.05 (br s, 1H), 2.64 (br s, 1H), 2.44 (s, 3H), 0.89 (s, 9H), 0.07 (s, 6H).
**$^{13}$C NMR** (150 MHz, $CDCl_3$): δ 145.3, 133.5, 130.0, 128.2, 114.8, 97.3, 79.5, 72.4, 71.3, 70.2, 63.8, 55.5, 26.0, 21.8, 18.4, –5.30, –5.33.
**HRMS** (ESI-TOF) for $C_{20}H_{34}NaO_8SSi$ $(M+Na)^+$: calc. 485.1636; found 485.1630.

### 2.4.4 General Procedure 2B – Hemiboronic Acid Catalyzed Monobenzylation of Diols

Following a literature procedure[12], diol (1.0 equiv), hemiboronic acid **2-1b** (0.10 equiv), base, and an iodide additive (if stated) were added to a round-bottom flask. Acetonitrile (0.2 M) was then added, followed by the benzyl electrophile. The reaction was stirred at the stated temperature for 24 hours. Carbohydrate derivatives were stirred for 48 hours. If silver(I) oxide was used as the

base, the mixture was filtered through a short pad of Celite, eluted with $CH_2Cl_2$ (10 mL), and concentrated *in vacuo*. Otherwise, the mixture was diluted with ethyl acetate (10 mL) and transferred to a separatory funnel. The organic layer was washed with $H_2O$ (10 mL) then brine (10 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. The residue was then purified by silica gel chromatography.

### 2.4.4.1 Characterization of Monobenzylated Diols

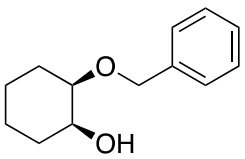



**(1*R*,2*R*,3*S*,5*R*)-3-(Benzyloxy)-pinanediol (2-12):**

Synthesized according to General Procedure 2B using diol **2-2** (34 mg, 0.20 mmol, 1.0 equiv), potassium carbonate (30 mg, 0.22 mmol, 1.1 equiv), potassium iodide (33 mg, 0.20 mmol, 1.0 equiv), and benzyl bromide (36 µL, 0.30 mmol, 1.50 equiv). The crude oil was purified by silica gel chromatography (10% ethyl acetate in hexanes) to afford a yellow oil (46 mg, 87%). All spectral data matched that previously reported.[11]

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.40–7.29 (m, 5H), 4.70 (d, *J* = 11.6 Hz, 1H), 4.61 (d, *J* = 11.7 Hz, 1H), 3.80 (s, 1H), 3.75 (dd, *J* = 9.2, 5.1 Hz, 1H), 2.39 (dddd, *J* = 13.7, 9.3, 3.6, 2.4 Hz, 1H), 2.18 (app dtd, *J* = 10.3, 6.1, 2.4 Hz, 1H), 1.97 (dd, *J* = 5.8, 5.8 Hz, 1H), 1.94–1.90 (m, 1H), 1.78 (ddd, *J* = 13.7, 5.1, 2.5 Hz), 1.46 (d, 10.3 Hz, 1H), 1.27 (s, 3H), 1.26 (s, 3H), 0.89 (s, 3H).

**$^{13}$C NMR** (101 MHz, $CDCl_3$): δ 138.0, 128.5, 127.9, 76.3, 73.4, 72.1, 53.9, 40.4, 38.4, 35.3, 30.8, 28.3, 27.9, 24.3.



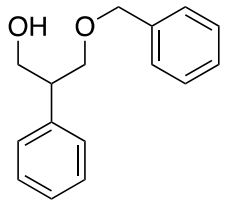

***cis*-2-(Benzyloxy)cyclohexanol (2-13):**

Synthesized according to General Procedure 2B using diol **2-10** (12 mg, 0.10 mmol, 1.0 equiv), *N*,*N*-diisopropylethylamine (30 µL, 0.17 mmol, 1.7 equiv), and benzyl bromide (18 µL, 0.15 mmol, 1.5 equiv). The crude oil was purified by silica gel chromatography (10% ethyl acetate in

hexanes) to afford a clear, colourless oil (18 mg, 87%). All spectral data matched that previously reported.[11]

**$^{1}$H NMR** (400 MHz, $CDCl_3$): δ 7.40–7.27 (m, 5H), 4.63 (d, *J* = 11.7 Hz, 1H), 4.52 (d, *J* = 11.8 Hz, 1H), 3.86 (app dt, *J* = 6.8, 3.2 Hz, 1H), 3.52 (app dt, *J* = 8.1, 3.2 Hz, 1H), 2.21 (br s, 1H), 1.91–1.75 (m, 2H), 1.69–1.47 (m, 4H), 1.36–1.23 (m, 2H).

**$^{13}$C NMR** (101 MHz, $CDCl_3$): δ 138.7, 128.5, 127.7, 127.6, 78.2, 70.2, 68.8, 30.5, 26.6, 22.2, 21.3.

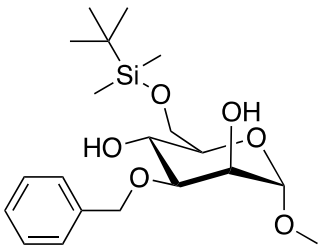



**2-Benzyl-3-(benzyloxy)propan-1-ol (2-14):**

Synthesized according to General Procedure 2B using diol **2-11** (30 mg, 0.20 mmol, 1.0 equiv), *N*,*N*-diisopropylethylamine (52 μL, 0.30 mmol, 1.5 equiv), and benzyl bromide (36 μL, 0.30 mmol, 1.5 equiv). The crude oil was purified by silica gel chromatography (20% ethyl acetate in hexanes) to afford a clear oil (34 mg, 69%). All spectral data matched that previously reported.[28]

**$^{1}$H NMR** (600 MHz, $CDCl_3$): δ 7.42–7.22 (m, 10H), 4.59 (s, 2H), 4.04 (dd, *J* = 10.9, 7.4 Hz, 1H), 3.91 (dd, *J* = 11.1, 5.3 Hz, 1H), 3.85 (dd, *J* = 8.9, 8.9 Hz, 1H, A part of ABM), 3.79 (dd, *J* = 9.3, 5.2 Hz, 1H, B part of ABM), 3.25 (dddd, *J* = 8.6, 7.4, 5.2, 5.2 Hz, 1H), 2.47 (br s, 1H).

**$^{13}$C NMR** (101 MHz, $CDCl_3$): δ 139.6, 137.9, 128.7, 128.5, 128.0, 127.8, 127.7, 127.1, 118.0, 73.6, 73.5, 66.5, 47.8.



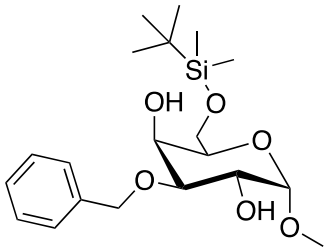

**Methyl-6-(*tert*-butyldimethylsilyloxy)-3-*O*-benzyl-α-D-mannopyranoside (2-15):**

Synthesized according to General Procedure 2B using diol **2-8** (62 mg, 0.20 mmol, 1.0 equiv), silver(I) oxide (51 mg, 0.22 equiv, 1.1 equiv) and benzyl bromide (36 μL, 0.30 mmol, 1.5 equiv).

The crude oil was purified by silica gel chromatography (7.5% to 15% ethyl acetate in hexanes) to afford a yellow oil (68 mg, 85%). All spectral data matched that previously reported.[12]

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.42–7.28 (m, 5H), 4.74 (d, *J* = 1.7 Hz, 1H), 4.71 (s, 2H), 3.97 (dd, *J* = 3.4, 1.7 Hz, 1H), 3.92–3.84 (m, 3H), 3.69 (dd, *J* = 9.1, 3.4 Hz, 1H), 3.60 (app dt, *J* = 10.1, 5.3 Hz, 1H), 3.37 (s, 3H), 2.95 (br s, 1H), 2.38 (br s, 1H), 0.91 (s, 9H), 0.10 (s, 6H).

**$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 138.0, 128.6, 128.1, 128.0, 100.4, 79.5, 72.2, 70.8, 69.3, 67.9, 64.8, 54.9, 25.9, 18.3, -5.4.

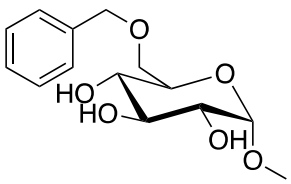



**Methyl-6-(*tert*-butyldimethylsilyloxy)-3-*O*-benzyl-α-D-galactopyranoside (2-16):**

Synthesized according to General Procedure 2B using diol **2-2** (62 mg, 0.20 mmol, 1.0 equiv), silver(I) oxide (51 mg, 0.22 equiv, 1.1 equiv) and benzyl bromide (36 μL, 0.30 mmol, 1.5 equiv). The crude oil was purified by silica gel chromatography (10% to 30% ethyl acetate in hexanes) to afford a yellow oil (66 mg, 82%). All spectral data matched that previously reported.[12]

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.42–7.47 (m, 5H), 4.81 (d, *J* = 3.9 Hz, 1H), 4.75 (d, *J* = 11.9 Hz, 1H), 4.71 (d, *J* = 11.9 Hz, 1H), 4.06 (dd, *J* = 3.3, 1.2 Hz), 4.01 (dd, *J* = 9.7, 4.0 Hz, 1H), 3.87 (dd, *J* = 10.3, 6.1 Hz, 1H), 3.87 (dd, *J* = 10.3, 6.1 Hz, 1H), 3.79 (dd, *J* = 10.3, 5.6 Hz, 1H), 3.71 (app t, *J* = 6.8 Hz, 1H), 3.61 (dd, *J* = 9.7, 3.2 Hz, 1H), 3.41 (s, 3H), 2.56 (br s, 1H), 2.06 (br s, 1H), 0.90 (s, 9H), 0.08 (s, 6H).

**$^{13}$C NMR** (101 MHz, $CDCl_3$): δ 138.0, 128.6, 128.0, 127.9, 99.5, 78.6, 72.0, 70.1, 68.7, 66.9, 62.6, 55.2, 25.9, 18.31, -5.37, -5.42.




**Methyl-6-*O*-benzyl-α-D-glucopyranoside (2-24):**

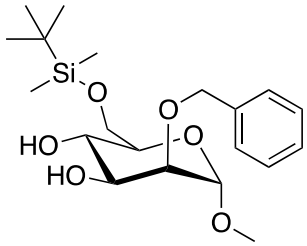
Synthesized according to General Procedure 2B using diol **2-23** (38 mg, 0.20 mmol, 1.0 equiv), *N*,*N*-diisopropylethylamine (52 µL, 0.30 mmol, 1.5 equiv), and benzyl bromide (36 µL, 0.30 mmol, 1.5 equiv). The crude oil was purified by silica gel chromatography (8% methanol in dichloromethane) to afford a white solid upon trituration with hexanes.

**$^1$H NMR** (600 MHz, $CD_3OD$): δ 7.38–7.30 (m, 4H), 7.29–7.24 (m, 1H), 4.67 (d, *J* = 3.7 Hz, 1H), 4.58 (app s, 2H), 3.79–3.75 (m, 1H), 3.68 (m, 2H), 3.61 (app t, *J* = 9.3, 1H), 3.42–3.38 (m, 4H) 3.36–3.32 (m, 1H).

**$^{13}$C NMR** (176 MHz, $CD_3OD$): δ 139.7, 129.3, 128.8, 128.6, 101.3, 75.2, 74.5, 73.5, 72.5, 71.9, 70.9, 55.6.

**HRMS** (ESI-TOF) for $C_{14}H_{20}NaO_6$: calc. 307.1152; found: 307.1149.

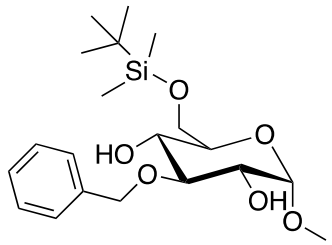
### 2.4.5 Characterization of isolated minor products




**Methyl-6-(*tert*-butyldimethylsilyloxy)-2-*O*-benzyl-α-D-mannopyranoside**

**$^1$H NMR** (700 MHz, $CDCl_3$): δ 7.39–7.28 (m, 5H), 4.77 (d, *J* = 1.4 Hz, 1H), 4.72 (d, *J* = 11.7 Hz, 1H), 4.57 (d, *J* = 1.4 Hz, 1H), 3.88 (d, *J* = 5.3 Hz, 2H), 3.79 (m, 1H), 3.74 (app t, *J* = 9.3 Hz, 1H), 3.71 (dd, , *J* = 3.7, 1.5 Hz, 1H), 3.55 (app dt, *J* = 9.5, 5.2, 1H), 3.5 (s, 3H), 2.94 (br s, 1H), 2.28 (br s, 1H), 0.91 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H).

**$^{13}$C NMR** (101 MHz, $CDCl_3$), δ 137.8, 128.6, 128.0, 127.8, 110.0, 98.1, 73.0, 71.5, 71.1, 70.8, 64.4, 54.8, 31.0, 25.9, 18.3, -5.4, -9.1.




**Methyl-6-(*tert*-butyldimethylsilyloxy)-3-*O*-benzyl-α-D-glucopyranoside**

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 8.13–8.05 (m, 2H), 7.59–7.52 (m, 1H), 7.47–7.40 (m, 2H), 5.24 (dd, *J* = 9.8, 8.8 Hz, 1H), 4.81 (d, *J* = 3.8 Hz, 1H), 3.93 (dd, *J* = 10.7 Hz, 4.7 Hz, 1Hz), 3.88 (dd, *J* = 10.7 Hz, 4.4 Hz, 1Hz), 3.81–3.68 (m, 3H), 3.47 (s, 3H), 3.11 (d, *J* = 3.4 Hz, 1H), 2.25 (d, *J* = 10.9 Hz, 1H), 0.91 (s, 9H), 0.10 (s, 6H).

## 2.5 References

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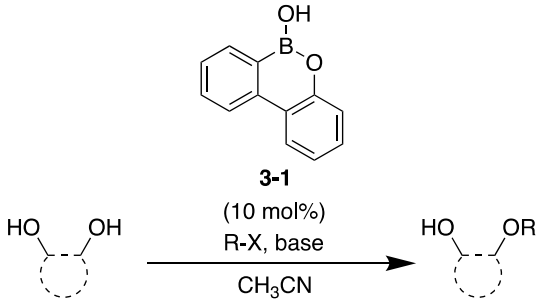
# Chapter 3 – Chiral Hemiboronic Acid-Catalyzed Enantioselective Desymmetrization of Diols

## 3.1 Introduction

As discussed in Chapter One, diol substrates can often be very useful starting materials in the synthesis of stereochemically complex molecules. Kinetic resolution of racemates and enantioselective desymmetrization of achiral diols are common methods to prepare optically active alcohols. There are numerous catalytic methods for these types of transformations (see examples in Chapter One), but there is still a need for complementary methods for catalytic enantioselective reactions for a variety of substrates using organoboron reagents.

Boronic acids and their derivatives are useful as catalysts for diol functionalization due to their advantageous properties, in particular, their stability, and high affinity toward diol moieties. Protocols to structurally modify boronic acids are far more numerous than their borinic acid counterparts. However, enantioselective transformations of diol substrates using organoboron compounds as catalysts are rare. Even more limited are methods that utilize chiral organoboron catalysts. In this chapter, the design of chiral hemiboronic acids as catalysts in the enantioselective desymmetrization of achiral diols to synthesize optically active alcohols will be discussed.

Chapter Two described the use of hemiboronic acid **3-1** as a catalyst in the regioselective monofunctionalization of diol substrates (Scheme 3-1). This method was shown to be regioselective for simple diol and carbohydrate derivatives toward alkylation and sulfonylation.




Scheme 3-1: Hemiboronic acid **3-1** catalyzed regioselective monofunctionalization of diols

Symmetrical diols **3-2** and **3-3** were among the substrates examined in the catalyzed monobenzylation. In these reaction, benzyl ether products **3-4** and **3-5** were obtained in racemic form since the catalyst used in the reaction was not chiral; there is no differentiation between the bound oxygen atoms in the reactive boron-diol intermediate **Int-3-1** (Figure 3-1A). From these results, however, we were optimistic to find a chiral variant of hemiboronic acid (**3-1***) to be used as a catalyst (Figure 3-1B). Chirality may be introduced into the core structure of **3-1** for possible stereoinduction into the tetrahedral boron-diol species **Int-3-1*** (Figure 3-1B). If differentiation of two enantiotopic -OH groups can be achieved, such a process would render non-racemic products as a result of enantioselective desymmetrization.

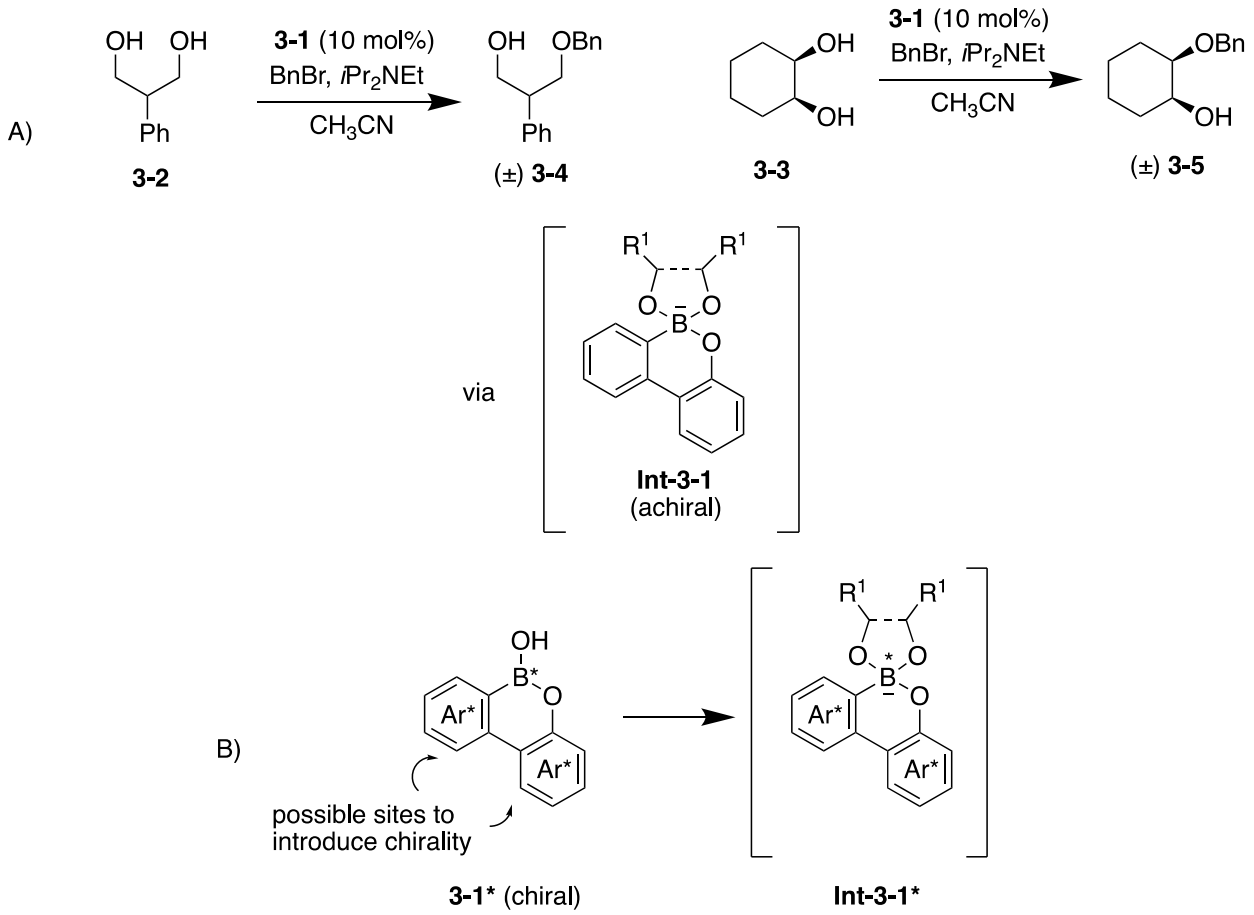
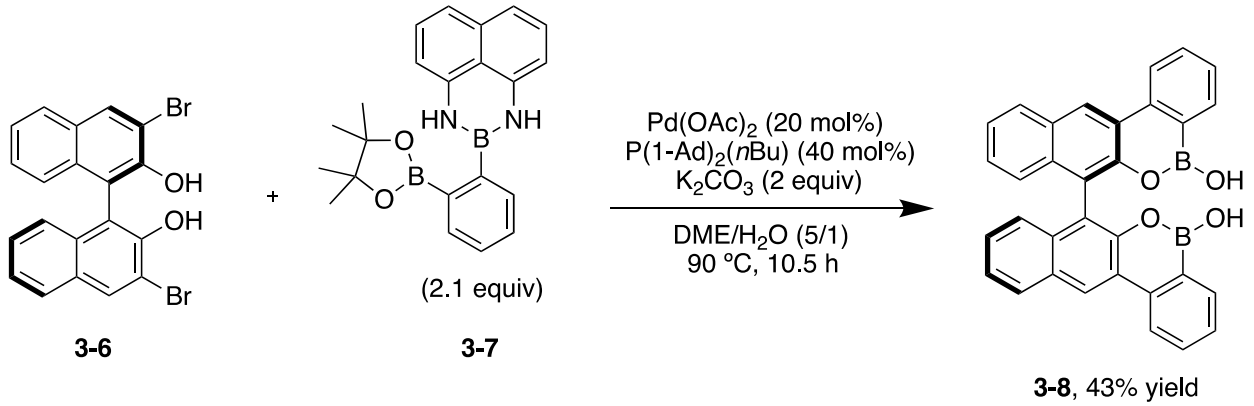



Figure 3-1: A) Monobenzylation of symmetrical diols catalyzed by hemiboronic acid **3-1**. B) Potential application of a chiral hemiboronic acid **3-1*** for enantioselective catalysis

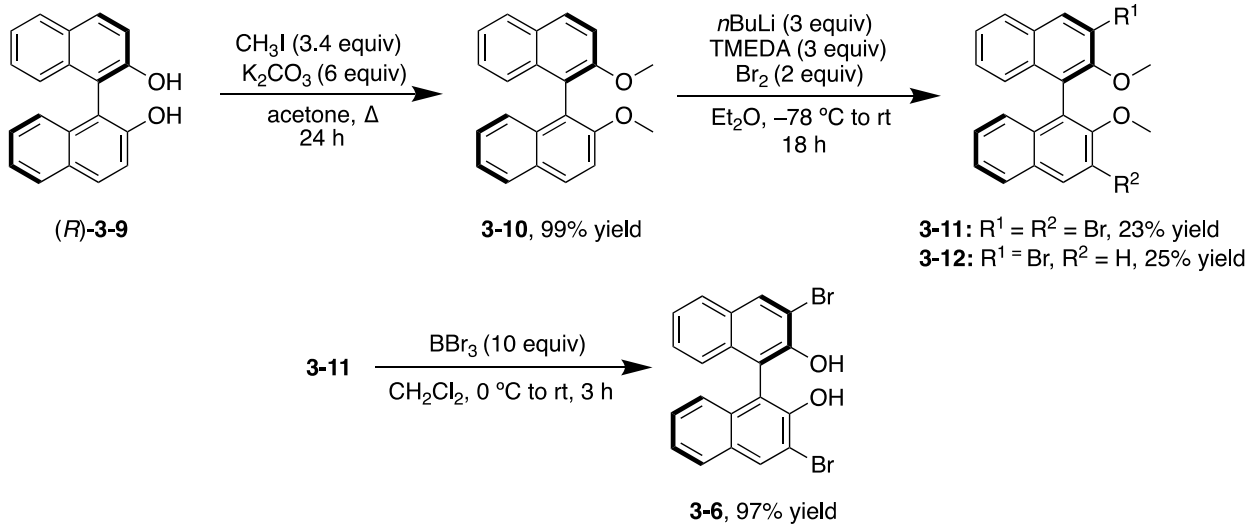
### 3.1.1 Literature Precedence of a Chiral Hemiboronic Acid

A literature search was first conducted to identify if there were any reported examples of a chiral variant of hemiboronic acid **3-1**. To our delight, Hosoya and co-workers had reported such an example using their boron-selective cross-coupling–cyclization strategy, as discussed in Chapter Two.[1] Using this methodology, the authors had reported an example of a chiral bis-hemiboronic acid, **3-8**, synthesized from (*R*)-BINOL-derived bromoarene **3-6** and 1,2-diboron **3-7** (Scheme 3-2).[1]



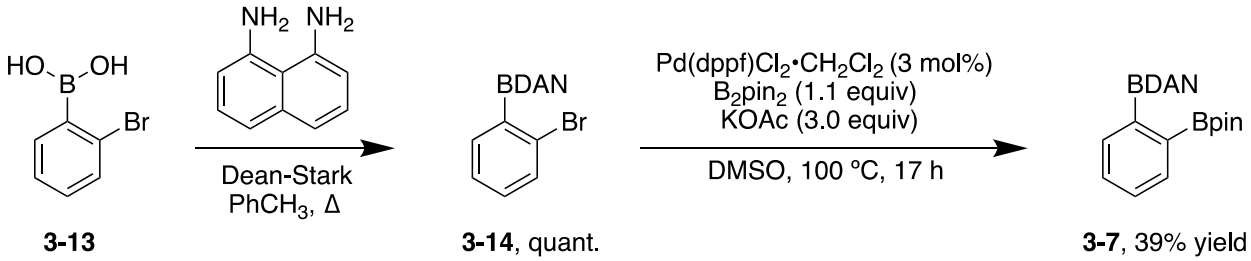

Scheme 3-2: Literature example for the synthesis of a chiral hemiboronic acid **3-8** (Hosoya)[1]

The project was initiated by first attempting to reproduce the literature procedure to prepare **3-8** to be used later as a chiral catalyst. First, the cross-coupling partners (**3-6** and **3-7**) were synthesized. Aryl bromide **3-6** was prepared starting from enantiopure (*R*)-BINOL **3-9** (Scheme 3-3).[2] Methylation of the phenolic oxygens, followed by *ortho*-directed lithiation–halogenation of **3-10**, yielded a mixture of aryl bromides **3-11** and **3-12**. Preparation of the desired dibromo compound **3-12** was not optimized, and low yields may have been due to insufficient lithiation that is also evident in the recovery of starting material. Although low yielding, the obtained material was used to prepare **3-6** after $BBr_3$-mediated demethylation in excellent yield.



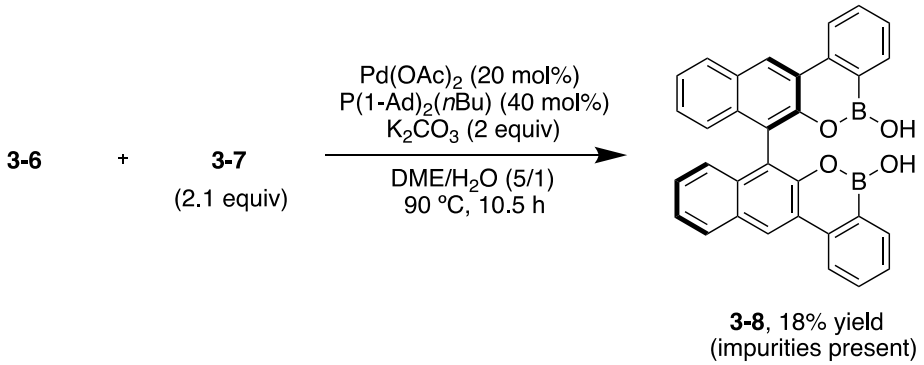

Scheme 3-3: Synthesis of (*R*)-2,2'-dibromo-BINOL **3-6**

The 1,2-diboryl species was then synthesized starting from 2-bromophenylboronic acid **3-13**. Protection of the boron atom in **3-13** with 1,8-diaminonaphthalene (DAN), followed by Miyaura borylation of the resulting BDAN **3-14** yielded boronic ester **3-7** in 39% yield (Scheme 3-4).




Scheme 3-4: Synthesis of 1,2-diboryl compound **3-7**

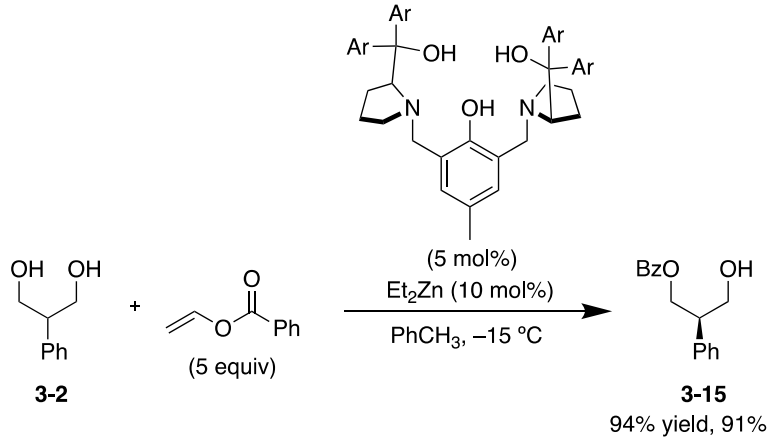
With the two coupling partners in hand, the synthesis of chiral organoboron **3-8** was attempted following the literature procedure (Scheme 3-5). However, only 18% yield of the desired chiral compound was isolated. The lower than expected yield may have been attributed to insufficient deprotection of the BDAN protecting group upon acidification, in addition to difficult separation of a complex crude mixture as observed by thin-layer chromatography (TLC). The isolated compound also contained some minor impurities (as observed by $^{1}$H-NMR) but was nevertheless used as a catalyst in an attempt at enantioselective desymmetrization.




Scheme 3-5: Reproducing literature procedure to synthesize chiral bis-hemiboronic acid **3-8**

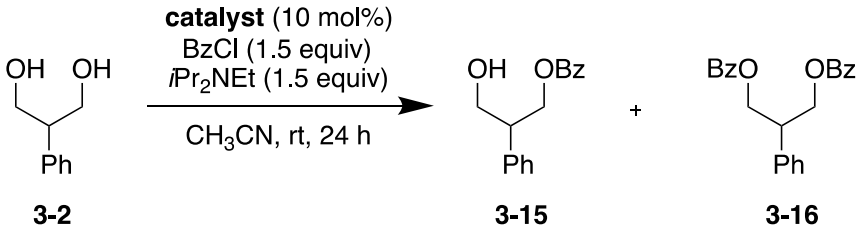
## 3.2 Initial Results in the Enantioselective Desymmetrization using a Chiral Hemiboronic Acid

Inspired by the examples of enantioselective desymmetrization of diols in the literature (see Section 1.2.4), 2-substituted-1,3-propanediol **3-2** was chosen as a model prochiral substrate. Stereoselective functionalization of such substrates can be challenging due to the remoteness of the prostereogenic center from the reacting -OH groups. Trost and co-workers reported the enantioselective desymmetrization of diol **3-2** via benzoylation using a dinuclear chiral zinc-ProPhenol catalyst to produce the monobenzoylated product **3-15** in 91% ee (Scheme 3-6).[3] Monobenzoylation was initially chosen as a model proof-of-concept reaction to attempt under hemiboronic acid catalysis conditions as the desymmetrized product **3-15** is known in the literature.




Scheme 3-6: Desymmetrization of 1,3-diols method developed by Trost[3]

Beginning with the racemic reaction, diol **3-2** was monobenzoylated using benzoyl chloride in the presence of base and hemiboronic acid **3-1** in moderate yield (Table 3-1, entry 1). With the success of the racemic reaction, the asymmetric reaction was then attempted with the obtained chiral organoboron **3-8**. Under the same conditions, employing 10 mol% of **3-8** as a catalyst provided the desymmetrized product in 34% ee (Table 3-1, entry 2).




**3-2** **3-15** **3-16**

| Entry | **catalyst** | Yield of **3-15** (%)[a] | %ee (of **3-15**)[c] |
|---|---|---|---|
| 1 | **3-1** | 45[b] | – |
| 2 | **3-8** | 44[c] | 34 |

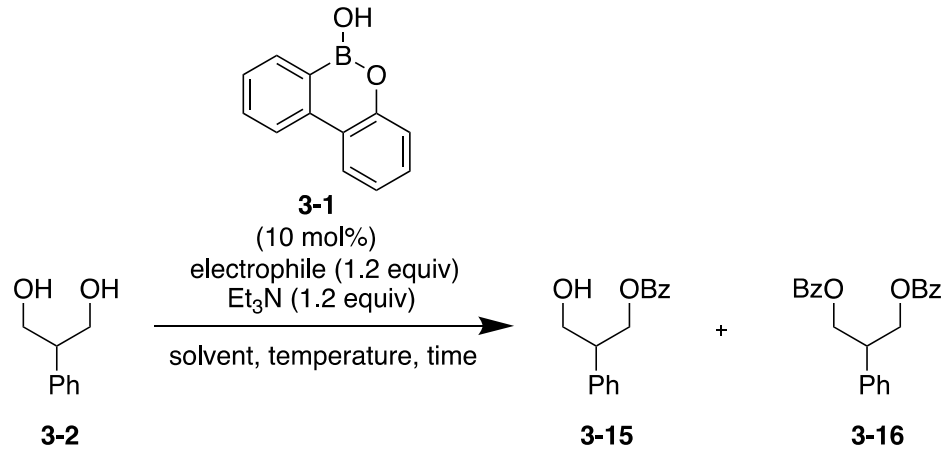
Table 3-1: Initial result in the enantioselective desymmetrization catalyzed by chiral organoboron **3-8**. [a]Isolated yield of **3-15**. [b]34% of dibenzoate **3-16** observed by $^1$H-NMR. [c]Determined by HPLC on a chiral stationary phase.

### 3.2.1 Optimization of the Chiral Hemiboronic Acid Catalyzed Monobenzoylation

Encouraged by the modest enantioinduction by catalyst **3-8**, efforts were then made to optimize the reaction and improve the enantioselectivity. One observation from the benzoylation reaction that may contribute to the relatively low yield of the monofunctionalized diol **3-15** is the presence of the symmetrical dibenzoylated product **3-16**. The relatively low enantiomeric excess may be attributed to the uncatalyzed background reaction competing with the catalyzed process.

Using achiral catalyst **3-1,** optimization of some of the reaction parameters were first attempted to decrease the amount of the dibenzoylated diol **3-16** (Table 3-2). Use of a relatively less reactive benzoylating agent was also attempted since the formation of the diester **3-16** is due to the facile reaction between two reactive species: a primary alcohol (**3-15**) and an acid chloride. Using

benzoic anhydride in non-polar solvent appeared to reduce slightly the amount of the dibenzoate formed while improving the yield of the desired monobenzoate **3-15** (Table 3-2, entry 1).




**3-2** **3-15** **3-16**

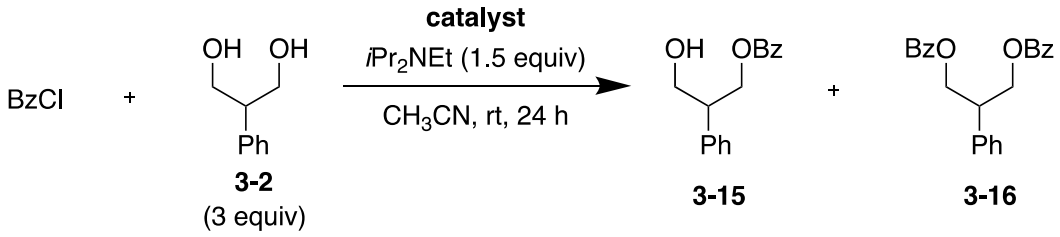
| Entry | Electrophile | Solvent | Temperature | Time | Yield of **3-15** (%)[a] | Yield of **3-16** (%)[a] |
|---|---|---|---|---|---|---|
| 1 | $Bz_2O$ | $PhCH_3$ | rt | 24 h | 53 | 15 |
| 2 | $Bz_2O$ | $PhCH_3$ | 0 ºC | 17 h | 38 | 6 |
| 3 | vinyl benzoate | $PhCH_3$ | rt | 17 h | n.d. | n.d. |

Table 3-2: Optimization of the monobenzylation catalyzed by hemiboronic acid **3-1**. [a]Yields determined by $^1$H-NMR using 1,3,5-trimethoxybenzene as an internal standard. n.d.: Not detected.

Lowering the temperature also showed an improvement in reducing the amount of difunctionalized **3-16**, but however decreased the yield of monoester **3-15** since the overall rate of the reaction is slower at 0 ºC (Table 3-2, entry 2). An attempt at using a different benzoylating agent (vinyl benzoate) was not successful as neither functionalized product was observed (Table 3-2, entry 3).

Since the attempts at decreasing the amount of dibenzoate **3-16** did not provide any improvement on increasing the amount of the desired monobenzoate **3-15,** the initial benzoylation conditions were revisited. Use of excess acylating agent may also be problematic in the formation of the symmetrical product. In an attempt to resolve this issue, the stoichiometry of the reagents was reversed where instead benzoyl chloride was limiting and the diol **3-2** was employed in excess.

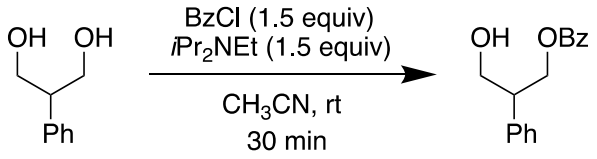
This modification was shown to be successful, as the amount of **3-15** formed relative to **3-16** was significantly increased (Table 3-3, entry 1). To probe the rate of the catalyzed reaction versus the rate of the background reaction, the procedure was performed without the organoboron catalyst. Under the same reaction conditions, and in the absence of a catalyst, monofunctionalization still proceeded to produce monobenzoate **3-15** in slightly lower yield than the catalyzed reaction (Table 3-3, entry 2). Although inconclusive, the small difference in the yield of monobenzoate **3-15** may suggest that the uncatalyzed background reaction competes significantly.




| Entry | **catalyst** | Yield of **3-15** (%)[a] | Yield of **3-16** (%)[a] |
|---|---|---|---|
| 1 | **3-1** (10 mol%) | 93 | 6 |
| 2 | none | 80 | 3 |

Table 3-3: Comparison of yields obtained in the presence and absence of catalyst. [a]Yields determined by $^1$H-NMR using 1,3,5-trimethoxybenzene as an internal standard.

The reaction time may also contribute to the amount of **3-16** observed. To get a sense of how fast hemiboronic acid **3-1** was catalyzing the reaction, the amount of product **3-15** formed after a short reaction time was determined by $^1$H-NMR. Unfortunately, even in the absence of a catalyst, after 30 minutes product **3-15** was observed in quantitative yield (Table 3-4).




**3-2** **3-15**

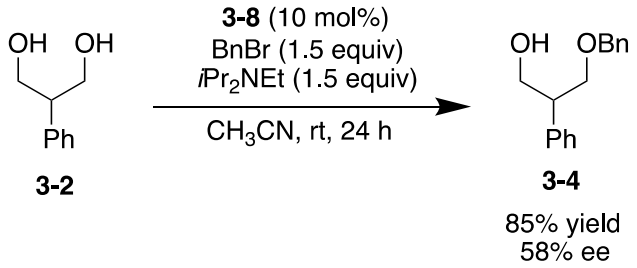
| Entry | **catalyst** | Yield of **3-15** (%)[a] |
|---|---|---|
| 1 | **3-1** (10 mol%) | >99 |
| 2 | none | >99 |

Table 3-4: Comparison of yields obtained in the presence and absence of catalyst after 30 minutes. [a]Yields determined by $^1$H-NMR using 1,3,5-trimethoxybenzene as an internal standard.

The competing uncatalyzed background reaction is problematic in the enantioselective process since the racemic product produced in the uncatalyzed process would negatively affect the observed enantioselectivity of the reaction catalyzed by a chiral catalyst. As indicated by the results of Table 3-3 and Table 3-4, enantioselective desymmetrization of diols via benzoylation catalyzed by **3-8** may be challenging to achieve high levels of enantioselectivity due to the competing uncatalyzed process. Therefore, desymmetrization via alkylation was instead attempted, as an alkylation process may be competing less as a background reaction when only a weak base is present.

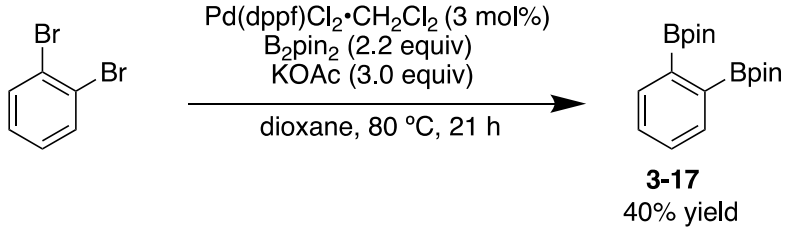
## 3.3 Enantioselective Desymmetrization via Benzylation

Chiral organoboron **3-8** was employed as a catalyst in the benzylation of 2-phenyl-1,3-propanediol **3-2**. Fortunately, monobenzyl ether **3-4** was formed in good yield with a higher enantiomeric excess than the attempted benzoylation reaction (Scheme 3-7). With an improved model reaction toward enantioselective desymmetrization, efforts were made to optimize the asymmetric reaction to obtain useful enantioselectivities.



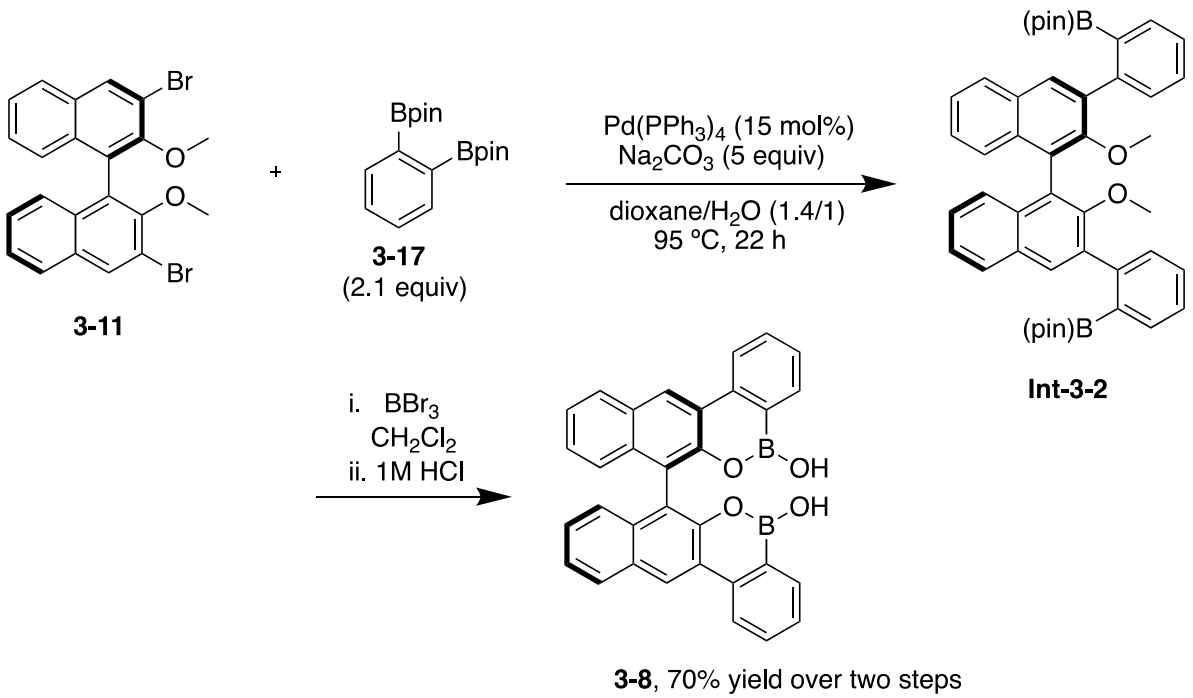

Scheme 3-7: Initial result in the enantioselective desymmetrization via benzylation catalyzed by chiral organoboron **3-8**

In order to screen reaction conditions for further optimization, the synthesis of the chiral catalyst **3-8** needed to be improved so as to provide larger amounts with higher purity. Rather than deprotecting the methoxy groups of **3-11** to prepare the required cross-coupling partner **3-6**, it was envisioned that the dibromo compound **3-11** can be used directly for cross-coupling. Masking one of the boron atoms in **3-7** with a diaminonaphthalene-protecting group was also not necessary since the cross-coupling step in preparation of chiral hemiboronic acid **3-8** does not need to be boron-selective (ie. Bpin vs BDAN). Symmetrical 1,2-diboryl compound **3-17** was instead prepared by two-fold Miyaura borylation of 1,2-dibromobenzene (Scheme 3-8).




Scheme 3-8: Synthesis of symmetrical 1,2-diboryl compound **3-17**

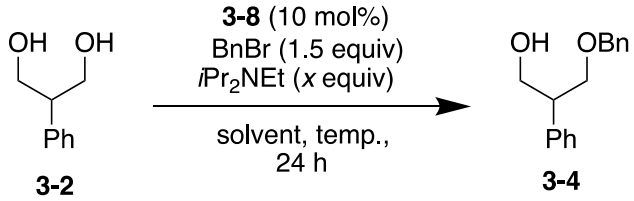
Suzuki-Miyaura cross-coupling of dibromo compound **3-11** with **3-17**, followed by demethylation with $BBr_3$ and acidification to remove the pinacol protecting groups and promote cyclization. The crude material was purified by a phase-switch extraction protocol described by Hall and co-workers for the purification of boronic acids[4] to yield organoboron **3-8** in much improved yield and purity (as observed by $^1$H-NMR).




Scheme 3-9: Modified synthesis of chiral organoboron **3-8**

### 3.3.1 Optimization of the Chiral Hemiboronic Acid Catalyzed Monobenzylation – Solvent Screen

With a more efficient route to prepare chiral catalyst **3-8**, screening of reaction conditions for the enantioselective monobenzylation of **3-2** then proceeded. Various solvents were first screened (Table 3-5). In general, polar solvents provided greater yields with relatively higher enantiomeric excess than when less polar solvents were used in the reaction.




| Entry | *x* | solvent | temperature | Yield (%)[a] | % ee[b] |
|---|---|---|---|---|---|
| 1 | 1.5 | $PhCH_3$ | rt | 14 | 50 |
| 2 | 1.5 | THF | rt | 15 | 52 |
| 3 | 1.7 | $CH_3CN$ | rt | 97 | 60 |
| 4 | 1.7 | DMF | rt | 75 | 56 |
| 5 | 1.7 | $CH_3NO_2$ | rt | 55 | 62 |
| 6 | 1.7 | $CH_2Cl_2$ | rt | 16 | 56 |
| 7 | 1.7 | $CH_3CN$ | 0 ºC | 23 | 68 |

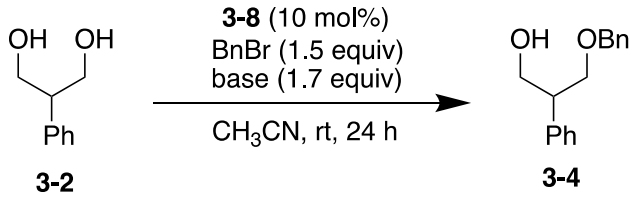
Table 3-5: Enantioselective desymmetrization via alkylation catalyzed by chiral organoboron **3-8** – solvent screen. [a]Isolated yields. [b]Determined by HPLC on a chiral stationary phase. Data obtained from a single experiment.

Slightly increasing the amount of base relative to the electrophile also improved the yield of the reaction (Table 3-5, entry 3). Lowering the temperature of the reaction in an attempt to increase the enantioselectivity also proved to be beneficial, although it provided the product in significantly lower yields (Table 3-5, entry 7). From the results of Table 3-5, acetonitrile was chosen as the optimal solvent to provide the product in both excellent yields and good enantioselectivity.

### 3.3.2 Optimization of the Chiral Hemiboronic Acid Catalyzed Monobenzylation – Base Screen

The effect of the base was also examined (Table 3-6). Overall, the reaction and the enantioselectivity appeared to be sensitive to the identity of the base used. Triethylamine, while improving the enantioselectivity, provided a much lower yield of the desymmetrized product **3-4** (Table 3-6, entry 4). This is likely due to a competing substitution reaction of the less hindered trialkylamine base with benzyl bromide to generate an ammonium salt under the reaction conditions. This competing reaction was also present when dimethylaniline (DMA) was used as a

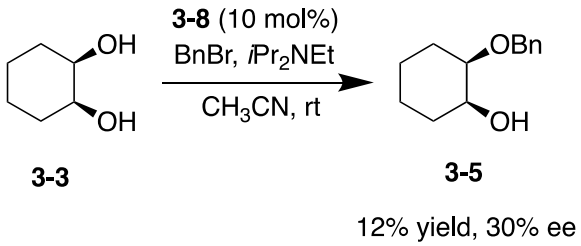
base as it completely shut down the desired benzylation reaction (Table 3-6, entry 3). Pyridine bases were shown to also be less effective in improving either yield or enantioselectivity (Table 3-6, entry 2 and 6). The reaction is optimized when the more hindered *N*,*N*-diisopropylethylamine is used as a base. From the results obtained in the solvent and base screen, further optimization of the reaction was continued using acetonitrile and *N*,*N*-diisopropylethylamine with chiral catalyst **3-8**.




| Entry | base | Yield (%)[a] | % ee[b] |
|---|---|---|---|
| 1 | *i*Pr$_2$NEt | 97 | 60 |
| 2 | 2,6-lutidine | 16 | 45 |
| 3 | DMA | n.r. | – |
| 4 | Et$_3$N | 11 | 74 |
| 5 | DBU | <10 | n.d. |
| 6 | PMP | 74 | 54 |

Table 3-6: Enantioselective desymmetrization via alkylation catalyzed by chiral organoboron **3-8** – base screen. [a]Isolated yields. [c]Determined by HPLC on a chiral stationary phase. n.d. = Not determined. Data obtained from a single experiment.

In hopes of successfully applying the asymmetric reaction to other types of diols, such as 1,2-diols, another model substrate was explored. In the case of *cis*-1,2-cyclohexanediol **3-3** however, benzylation was less effective at room temperature and was not as enantioselective compared to when 1,3-diol **3-2** is used as a substrate (Scheme 3-10). The low yield may be due to the presence of relatively hindered secondary alcohols that may react slower under the reaction conditions. The lower enantioselectivity may be attributed to the five-membered boronate ring formed with 1,2-diol **3-3** that may adopt multiple conformations, as opposed to a six-membered adduct from a 1,3-diol that would form a stable chair-like conformation (see Section 2.2.2).

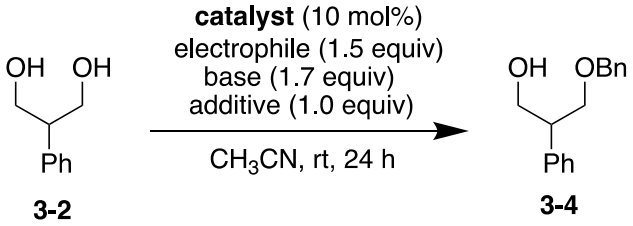



Scheme 3-10: Desymmetrization of 1,2-*cis*-cyclohexanediol **3-3** catalyzed by chiral organoboron **3-8**.

From the results obtained in the solvent and base screen, further optimization of the reaction was continued with model substrate **3-2** using acetonitrile and *N*,*N*-diisopropylethylamine with chiral catalyst **3-8**.

### 3.3.3 Optimization of the Chiral Hemiboronic Acid Catalyzed Monobenzylation – Additive Effects

Although an uncatalyzed process may be less problematic in the case of benzylation, the background reaction was still investigated (Table 3-7). In the absence of a catalyst, benzylation was less productive. However, a small amount of the product can still be observed (Table 3-7, entry 1). If the background reaction is competing even slightly with the catalyzed process, this racemic process could significantly impact the observed enantiomeric excess of the product. Efforts were then made to reduce the rate of the background reaction. When using a less electrophilic benzyl chloride, the desymmetrized product was observed in only trace amounts in both the presence and absence of chiral catalyst **3-8** (Table 3-7, entry 2 and 3).




**3-2** **3-4**

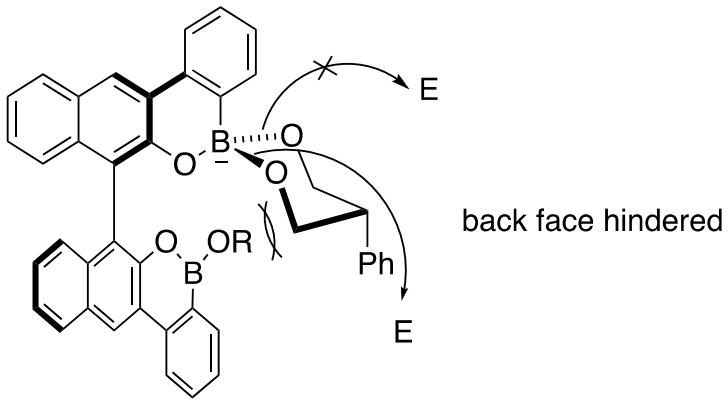
| Entry | Catalyst | Electrophile | Base | Additive | Yield (%) | % ee[c] |
|---|---|---|---|---|---|---|
| 1 | none | BnBr | *i*Pr$_2$NEt | none | 13[a] | – |
| 2 | none | BnCl | *i*Pr$_2$NEt | none | <1[a] | – |
| 3 | **3-8** | BnCl | *i*Pr$_2$NEt | none | 3[a] | – |
| 4 | **3-8** | BnCl | *i*Pr$_2$NEt | *n*Bu$_4$NI | 43[b] | 66 |
| 5 | none | BnCl | $K_2CO_3$ | KI | 8 | – |
| 6 | **3-8** | BnCl | $K_2CO_3$ | KI | 99[b] | 66 |

Table 3-7: Iodide additive effects on the monobenzylation reaction. [a]Yields determined by $^1$H-NMR using 1,3,5-trimethoxybenzene as an internal standard. [b]Isolated yields. [c]Determined by HPLC on a chiral stationary phase.

Additives were then explored to increase the rate of the benzylation reaction when benzyl chloride is used at the alkylating agent. This was achieved by adding a source of iodide to the reaction, which is a common method to generate a more reactive electrophile benzyl iodide *in situ* for when benzylation reactions are sluggish. Employing stoichiometric tetrabutylammonium iodide to the reaction improved the efficiency of benzylation, increasing both the yield and enantioselectivity (Table 3-7, entry 4). Taylor and co-workers had found that the use of potassium iodide, in the presence of potassium carbonate, to be effective in the monoalkylation of 1,2-diols.[5] This system was applied in the enantioselective benzylation of **3-2** and was shown to significantly improve the reaction efficiency while maintaining good levels of enantioselectivity (Table 3-7, entry 6).

From the structure of catalyst **3-8**, it was not known if the presence of two boron-containing functionalities, rather than just one, was required for catalysis. It was hypothesized that the diol forms a tetrahedral adduct with one of the boron atoms in **3-8**, while the other heteroaromatic unit in the catalyst serves as a "steric block" to prevent alkylation of one of the two faces of intermediate **Int-3-2** (Figure 3-2). The chair-like conformation of the six-membered tetrahedral boron-diol

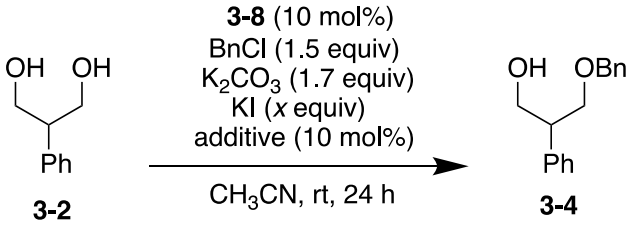
adduct where the B-$O_{aryl}$ bond is axial is supported by an X-ray crystallographic structure obtained from achiral **3-1** and a 1,3-diol (see Section 2.2.2); the phenyl substituent is assumed to occupy the equatorial position. This steric bias to favour alkylation of the less hindered oxygen may explain the observed moderate enantioselectivity.




**Int-3-3**

Figure 3-2: Proposed stereochemical model for the benzylation of diol **3-4** catalyzed by chiral organoboron **3-8**.

It was hypothesized that exchange of a bulky alcohol or diol with one of the hemiboronic acid units may provide greater steric hindrance that would better discriminate the bound oxygens in the borate species (Figure 3-2, **Int-3-2**, R ≠ H). Alcohol additives were thus investigated (Table 3-8). A screen of a few bulky diol additives, however, did not appear to significantly improve the enantioselectivity of the reaction.



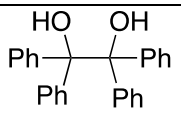
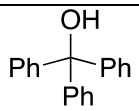
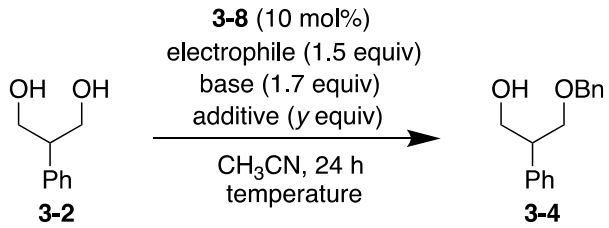

| Entry | *x* | diol additive | Yield (%)[a] | % ee[b] |
|---|---|---|---|---|
| 1 | 0.5 |  | 66 | 66 |
| 2 | 1.0 |  | 85 | 68 |
| 3 | 1.0 |  | 52 | 68 |

Table 3-8. Alcohol additive effects on the enantioselectivity of the benzylation reaction. [a]Isolated yields. [b]Determined by HPLC on a chiral stationary phase. Data obtained from a single experiment.

The temperature of the benzylation reaction was then fine-tuned in an attempt to improve the enantioselectivity. It had been observed under previously optimized conditions that although the rate of the benzylation reaction is slower at lower temperature, the enantioselectivity of the reaction had increased (Table 3-5, entry 7). Employing the potassium carbonate/potassium iodide system at lower temperatures, however, did not show any improvement in the yield or enantioselectivity of the reaction, which may be due to the limited solubility of KI and $K_2CO_3$ in acetonitrile at 0 ºC (Table 3-9, entry 2). Instead, benzylations were then attempted using benzyl bromide and tetrabutylammonium iodide to generate a more reactive system at lower temperatures.




| Entry | Electrophile | Base | Additive ($y$ equiv) | Temperature | Yield (%)[a] | % ee[b] |
|---|---|---|---|---|---|---|
| 1 | BnCl | $K_2CO_3$ | KI (1.0) | rt | 99 | 66 |
| 2 | BnCl | $K_2CO_3$ | KI (1.0) | 0 ºC | 37 | 70 |
| 3 | BnBr | *i*Pr$_2$NEt | none | 0 ºC | 23 | 68 |
| 3 | BnBr | *i*Pr$_2$NEt | *n*Bu$_4$NI (1.0) | 0 ºC | 72 | 72 |
| 4 | BnBr | *i*Pr$_2$NEt | *n*Bu$_4$NI (1.0) | –10 ºC | 23 | 70 |

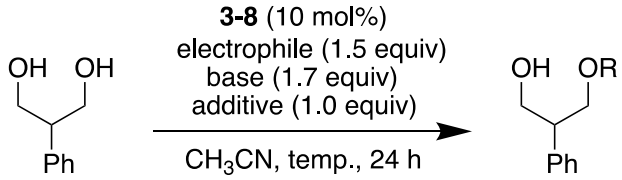
Table 3-9: Effect of additive and temperature on the benzylation of **3-2** catalyzed by chiral organoboron **3-8**. [a]Isolated yields. [b]Determined by HPLC on a chiral stationary phase. Data obtained from a single experiment.

Employing stoichiometric tetrabutylammonium iodide as an additive to the reaction at 0 ºC improved the efficiency of benzylation as the yield was increased from 23% to 72% while also improving the enantioselectivity (Table 3-9, entry 3). Cooling the reaction further, however, did not prove to be beneficial as the benzyl ether **3-4** was obtained in lower yields with no significant change in the enantioselectivity (Table 3-9, entry 4).

### 3.3.4 Optimization of the Chiral Hemiboronic Acid Catalyzed Monobenzylation – Effect of the Electrophile and Substrate

The nature of the electrophile was also explored in another attempt to increase the enantioselectivity of the reaction (Table 3-10). Approach of a larger electrophile to the active catalyst may also improve facial discrimination of the two bound oxygens (Figure 3-2). Using 2-(bromomethyl)naphthalene as an electrophile was shown to be compatible in the enantioselective alkylation reaction while also improving the enantioselectivity (Table 3-10, entry 1). Cooling the reaction down further to –20 ºC did not show any improvement in the % ee of product **3-18** (Table 3-10, entry 2). Regioisomeric 1-(bromomethyl)naphthalene was also attempted as a hindered

benzylic electrophile but was shown to be less selective (Table 3-10, entry 3). Use of benzhydryl chloride as another hindered electrophile dramatically decreased the enantioselectivity of the reaction (Table 3-10, entry 4). This lower selectivity may be due to a competing uncatalyzed $S_N1$ reaction upon generation of a stable dibenzylic carbocation that may react readily with unbound diol. A competing $S_N1$ process was also evident when trityl chloride is used at the electrophile where the obtained trityl ether **3-21** was observed in only 8% ee (Table 3-10, entry 5).




**3-2**

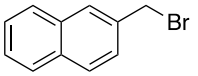
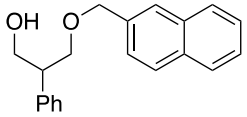
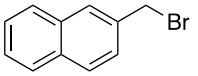
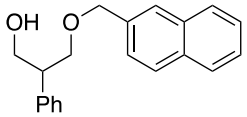
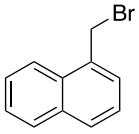
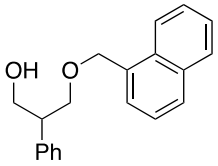
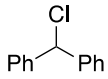
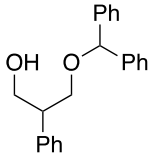
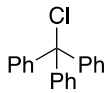
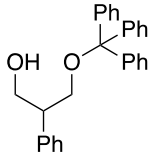
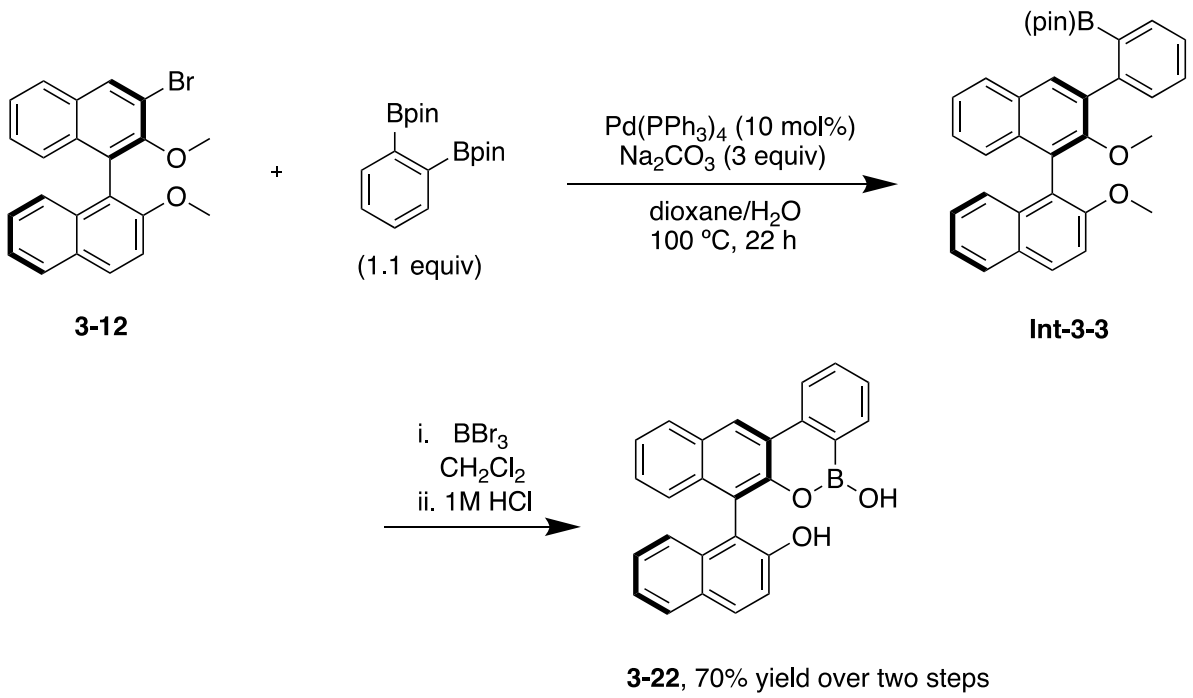
| Entry | electrophile | base | additive | temp. | Product | Yield (%)[a] | % ee[b] |
|---|---|---|---|---|---|---|---|
| 1 |  | *i*Pr$_2$NEt | *n*Bu$_4$NI | 0 ºC |  **3-18** | 55 | 78 |
| 2 |  | *i*Pr$_2$NEt | *n*Bu$_4$NI | –20 ºC |  **3-18** | 40 | 78 |
| 3 |  | *i*Pr$_2$NEt | *n*Bu$_4$NI | 0 ºC |  **3-19** | 78 | 68 |
| 4 |  | $K_2CO_3$ | KI | rt |  **3-20** | 42 | 6 |
| 5 |  | *i*Pr$_2$NEt | – | rt |  **3-21** | 47 | 8 |

Table 3-10: Effect of the electrophile on the enantioselectivity of the desymmetrization reaction. [a]Isolated yields. [b]Determined by HPLC on a chiral stationary phase. Data obtained from a single experiment.

Although desymmetrization of diol **3-2** via alkylation can be obtained with good levels of enantioselectivity, there appeared to be a threshold in the enantioinduction that catalyst **3-8** can introduce (< 80% ee). Efforts to increase the enantioselectivity of the benzylation reaction by lowering the temperature did not show any significant improvements. A mild, more practical set of conditions (inexpensive reagents, room temperature) can however provide moderate levels of enantioselectivity. Therefore, structural modifications to the catalyst was deemed to be desirable in an attempt to obtain greater levels of enantioselectivities under mild reaction conditions.

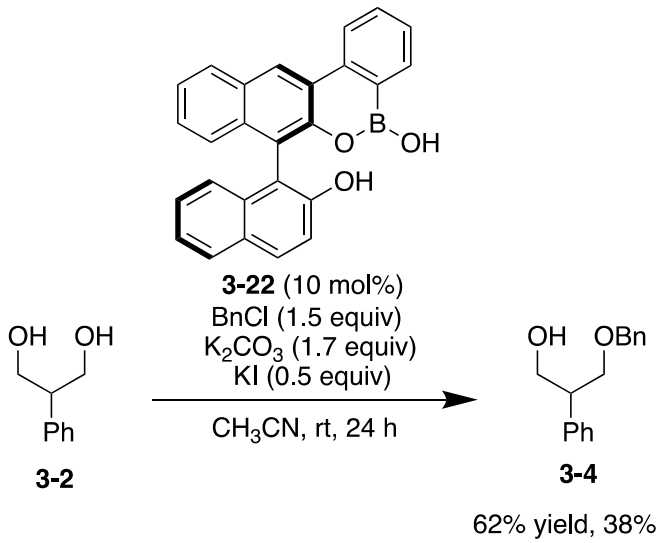
### 3.3.5 Optimization of the Chiral Hemiboronic Acid Catalyzed Monobenzylation – Catalyst Screen

To determine if the two boron atoms are crucial to achieving moderate levels of enantioselectivity, a control reaction was performed with chiral catalyst **3-22**. Synthesis of organoboron **3-22** followed a similar procedure optimized to synthesize chiral catalyst **3-8** where instead aryl bromide **3-12** was used as the coupling partner (Scheme 3-11).



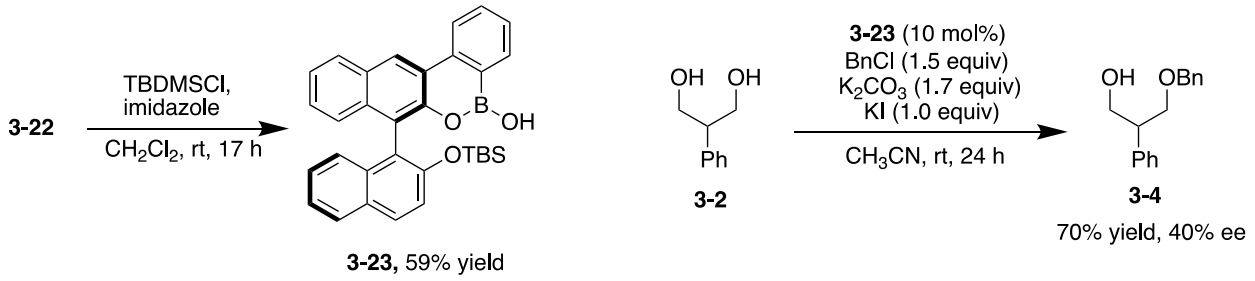

Scheme 3-11: Synthesis of chiral organoboron **3-22**

Employing organoboron **3-22** as a catalyst at room temperature provided benzyl ether **3-4** with lower enantioselectivity (Scheme 3-12). This result may suggest that the second cyclic boron unit in **3-8** is not necessary in catalyzing the reaction but may be necessary to achieve higher levels of enantioselectivity due to greater -OH group discrimination.




Scheme 3-12: Monobenzylation of diol **3-2** catalyzed by chiral organoboron **3-22**

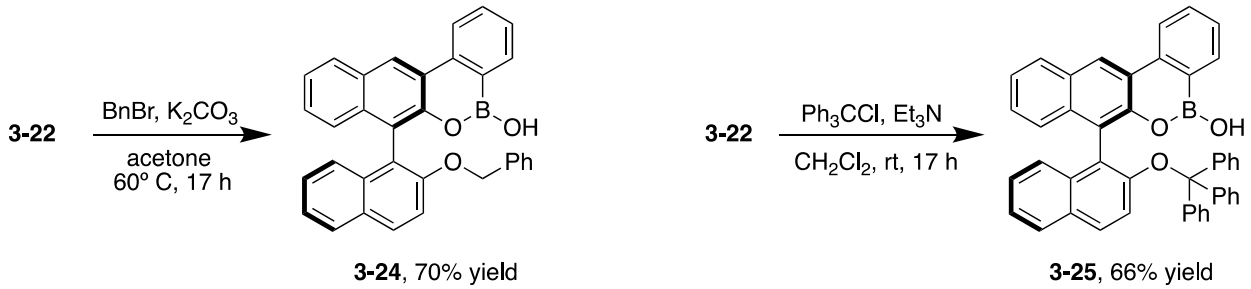
Chiral organoboron **3-22** contains a free phenol, and etherification of the hydroxy group to install a large motif may provide a catalyst that can differentiate the two oxygen atoms bound to the boron atom upon diol complexation. Thus, installation of a bulky silyl ether was first attempted (Scheme 3-13). Silylation of phenol **3-22** with *tert*-butyldimethylsilyl chloride resulted in clean conversion of **3-23** as observed by the $^{1}$H-NMR spectrum of the crude mixture. However, purification of the obtained material to remove any excess silyl chloride lead to desilylation of **3-23**. Instead, the crude material obtained after silylation was used as a catalyst in the desymmetrization reaction. Interestingly, the reaction using the bulkier silyl ether catalyst **3-23** was unexpectedly less enantioselective (Scheme 3-13). This may indicate that the desilylation of **3-23** also occurs during the course of the reaction, producing **3-22** *in situ*. This possible side-reaction is also evident in the observed enantiomeric excess of the product as it is similar to that when phenol **3-22** is used as a catalyst.



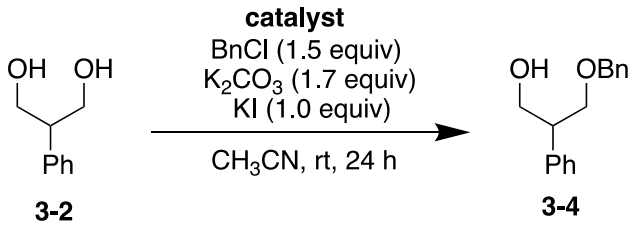

Scheme 3-13: Monobenzylation of diol **3-2** catalyzed by chiral organoboron **3-23**

Next, as an attempt to form more robust catalysts, installation of a benzyl and trityl ether onto the phenol of **3-22** resulted in chiral hemiboronic acids **3-24** and **3-25** respectively (Scheme 3-14). Employing these organoboron compounds as catalysts in the desymmetrization reaction revealed an interesting correlation (Table 3-11). With the exception of silyl ether **3-20**, as the size of the functionalized phenol became larger, the enantioselectivity of the reaction also increased. One reason that benzyl ether **3-24** gave a lower enantioselectivity than the bis-boron **3-8** may be that the benzyl ether is smaller and less rigid than the B-O heterocyclic moiety in **3-8**. Satisfactorily, trityl ether **3-25** provided the desymmetrized product **3-4** in excellent yield with higher enantiomeric excess (Table 3-11, entry 5). Chiral organoboron **3-25** can be obtained in good yields

after simple installation of the trityl group and can be easily purified by silica gel chromatography to remove the excess trityl chloride.




Scheme 3-14: Synthesis of chiral hemiboronic acid derivatives **3-24** and **3-25**




| Entry | **catalyst** | Yield (%)[a] | % ee[b] |
|---|---|---|---|
| 1 | **3-8** | 99 | 66 |
| 2 | **3-22** | 62 | 38 |
| 3 | **3-23** | 70 | 40 |
| 4 | **3-24** | 83 | 58 |
| 5 | **3-25** | 94 | 86 |

Table 3-11: Enantioselective desymmetrization via alkylation catalyzed by chiral organoboron derivatives – catalyst screen. [a]Isolated yields. [b]Determined by HPLC on a chiral stationary phase. Data obtained from a single experiment.

Rationalization for the observed predominant enantiomer formed in excess can be explained in a manner similar to the analysis of **Int-3-3** Figure 3-2. In the stereochemical model, the trityl ether in **Int-3-4** provides a greater "steric block" such that there is enhanced differentiation of the bound oxygen atoms (Figure 3-3). Optimized equilibrium geometry of structure **Int-3-2** also clearly shows that one of the bound oxygens is less hindered relative to the oxygen that is closer to the trityl moiety (Figure 3-3).

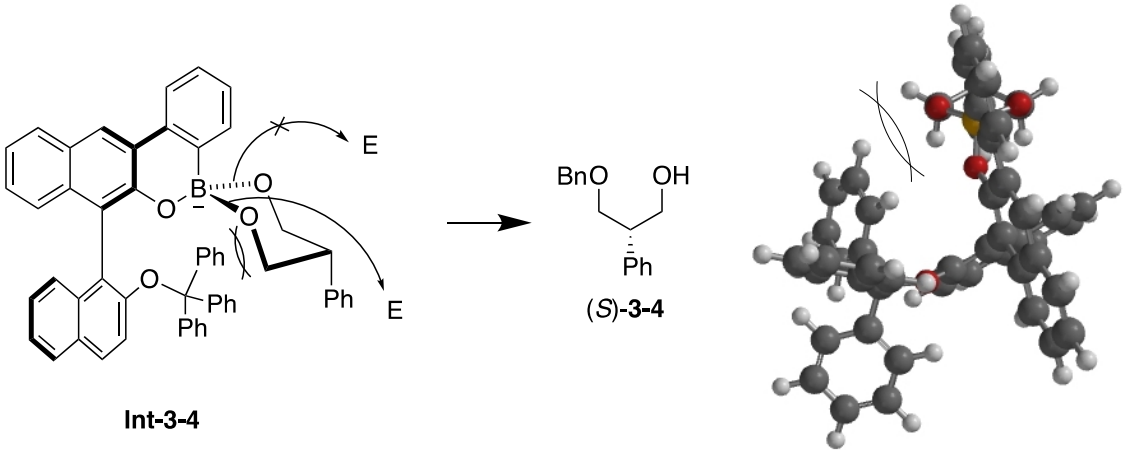
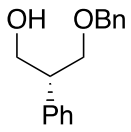



Figure 3-3: Proposed stereochemical model for the benzylation of diol **3-4** catalyzed by chiral organoboron **3-25** (Semi-empirical (PM3) calculation of **Int-3-4** optimized on MacSpartan 18).

If the 2-substituent is equatorial, alkylation of the less hindered oxygen would result in formation of the (*S*)-enantiomer. This is confirmed by stereochemical assignment of **3-4** by comparison with the known specific rotation for the (*R*)-enantiomer reported in the literature[6] where the obtained product **3-4** in 86% ee was observed to rotate plane-polarized light in the opposite direction, indicating the opposite stereoisomer is produced (Figure 3-4).




(*R*)-3-(benzyloxy)-2-phenylpropan-1-ol

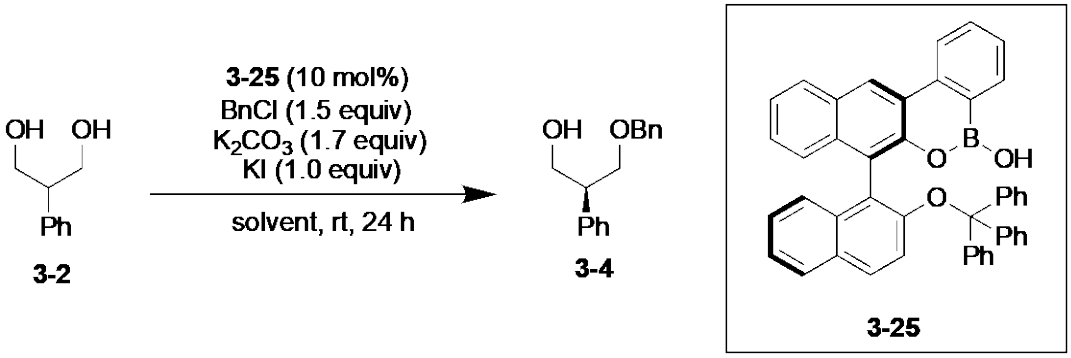
Literature: $[\alpha]_D^{25}$ = +24.8 °(c = 1.0, $CHCl_3$)

Experimental (86% ee): $[\alpha]_D^{25}$ = –18.9 °(c = 1.0, $CHCl_3$)

Figure 3-4: Determination of the absolute configuration of benzyl ether **3-4**

### 3.3.6 Optimization of the Enantioselective Desymmetrization Catalyzed by Chiral Hemiboronic Acid 3-25

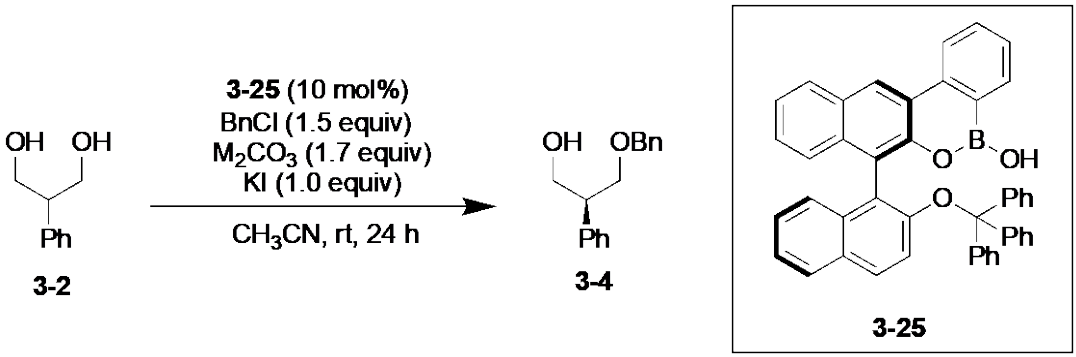
Some re-optimization of the asymmetric reaction was necessary using chiral hemiboronic acid **3-25** as a catalyst. A few polar solvents were screened in the benzylation reaction catalyzed by **3-25** (Table 3-12). Similar results to Table 3-5 were observed where acetonitrile appeared to be the optimal solvent that provided benzyl ether **3-4** in both good yield and enantioselectivity.




| Entry | solvent | Yield (%)[a] | % ee[b] |
|---|---|---|---|
| 1 | $CH_3CN$ | 94 | 86 |
| 2 | DMF | 78 | 76 |
| 3 | $CH_3NO_2$ | 25 | 83 |
| 4 | EtCN | 46 | 80 |

Table 3-12: Enantioselective desymmetrization via alkylation catalyzed by chiral organoboron **3-25** – solvent screen. [a]Isolated yields. [b]Determined by HPLC on a chiral stationary phase. Data obtained from a single experiment.

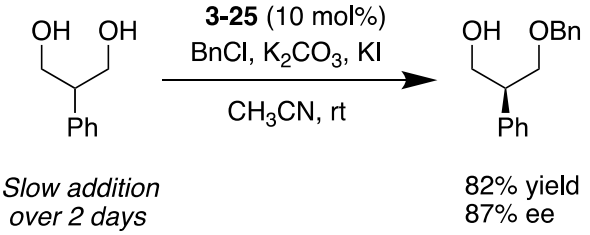
A screen of the carbonate base was also performed (Table 3-13). Use of sodium carbonate as the base was shown to be as efficient as potassium carbonate (Table 3-13, entry 2). Lithium carbonate as a base did not provide the product **3-4** in useful yield (Table 3-13, entry 1). When cesium carbonate was used as a base, the % ee **3-4** was decreased (Table 3-13, entry 4). These results suggest that the size of the counter cation may not play a role in the enantioselectivity, but that the increasing solubility of the base in acetonitrile may contribute to a competing background reaction to produce racemic **3-4** that would affect the observed % ee.




| Entry | M | Yield (%)[a] | % ee[c] |
|---|---|---|---|
| 1 | Li | 9[b] | n.d. |
| 2 | Na | 73 | 82 |
| 3 | K | 94 | 86 |
| 4 | Cs | 47 | 74 |

Table 3-13: Enantioselective desymmetrization via alkylation catalyzed by chiral organoboron **3-25** – carbonate base screen. [a]Isolated yields. [b]Determined by $^1$H-NMR using 1,3,5-trimethoxybenzene as an internal standard. [c]Determined by HPLC on a chiral stationary phase.

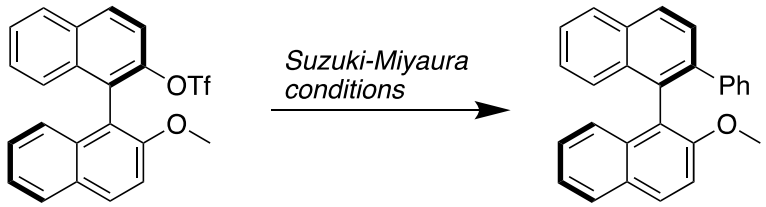
To determine whether a background benzylation reaction is competing when potassium carbonate is used as a base, the reaction was performed with slow addition of the diol **3-2** (Scheme 3-15). Slow addition of the diol would maximize the concentration of the nucleophilic dialkoxyboronate adduct relative to free alcohol. This experiment resulted in the same observed % ee result of **3-4** than when the diol is not slowly added, which may suggest that the background reaction is not competing under these conditions, and that the desired catalyzed process appreciably is faster.




Scheme 3-15: Enantioselective desymmetrization via alkylation catalyzed by chiral organoboron **3-25** – slow addition experiment

### 3.3.7 Attempts at Preparing Hindered Chiral Hemiboronic Acids

Attempts at installing an aryl group at the 1-position by derivatization of (*R*)-BINOL was briefly investigated. Installation of an aryl group was thought to provide even greater steric shielding about the hemiboronic acid moiety. Unfortunately attempts at an early palladium-catalyzed Suzuki-Miyaura cross-coupling of precursor **3-26** with phenylboronic acid were unsuccessful (Table 3-14). Low yields of the desired biaryl product may be attributed to the difficult cross-coupling reaction of the sterically hindered aryl-triflate **3-26**. This route was not further explored, and a different strategy was explored.

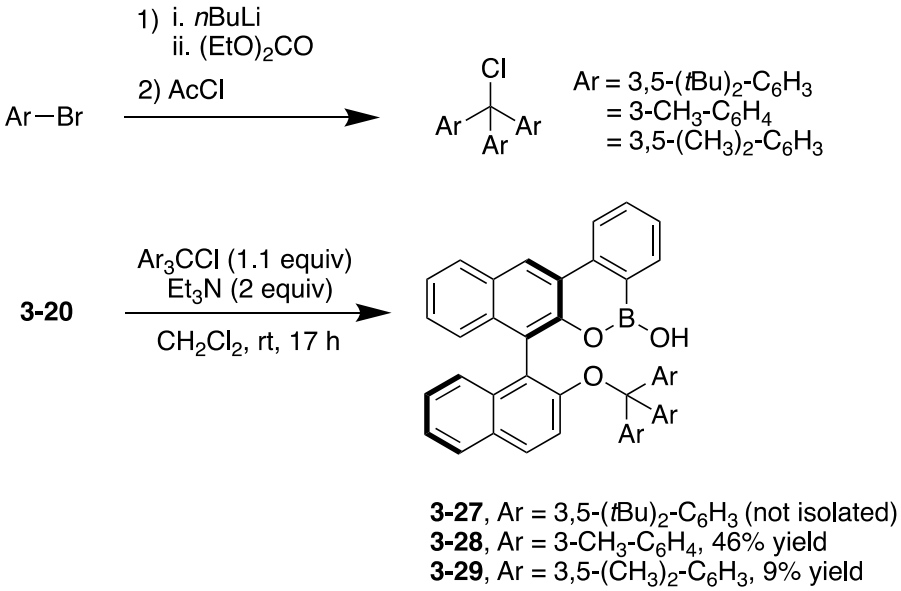



**3-26**

| Entry | *conditions* | Yield (%) |
|---|---|---|
| 1 | $Pd(PPh_3)_4$, $PhB(OH)_2$, $K_2CO_3$<br>DMF, 90 ºC, 15 h | 13 |
| 2 | $Pd(OAc)_2$, $PCy_3$, $PhB(OH)_2$, KF<br>THF, rt | 0 |
| 3 | $Pd(PPh_3)_4$, $PhB(OH)_2$, CsF<br>DMF, 115 ºC, 24 h | 6 |

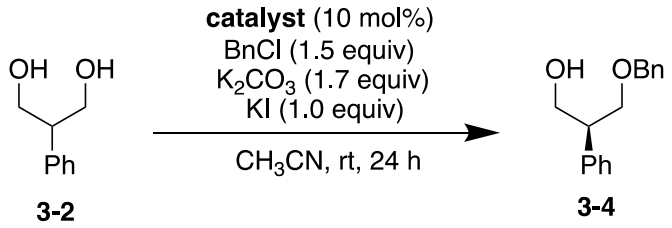
Table 3-14: Attempted Suzuki-Miyaura reactions of aryl triflate **3-26**

Instead, attempts at increasing the sterics about the structure of catalyst **3-25** were made (Scheme 3-16). This was accomplished by introducing alkyl substitutents on the trityl fragment of the catalyst. The corresponding triarylmethyl chlorides were prepared by aryl lithium addition to diethyl carbonate, followed by chloride substitution of the triarylmethanols.




Scheme 3-16: Synthesis of chiral hemiboronic acid analogs **3-28** and **3-29**

With the triarylmethyl chlorides in hand, etherification with **3-20** was then attempted. As the size of the triarylmethyl chlorides became larger, etherification with the phenol in **3-22** became more challenging. In the case of derivative **3-27**, the increased lability of the C-O bond became apparent when the trityl ether was cleaved upon routine silica gel purification and could not be isolated. Although the reactions to prepare derivatives **3-28**, and **3-29** were low yielding, enough material was obtained to perform the asymmetric benzylation reaction (Table 3-15). Overall, these catalysts were shown to only slightly improve the enantioselectivity of the reaction, albeit, likely within the error margin of HPLC analysis.

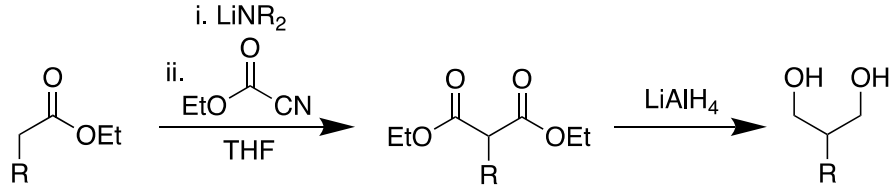



| Entry | **catalyst** | Yield (%)[a] | % ee[b] |
|---|---|---|---|
| 1 | **3-25** | 94 | 86 |
| 2 | **3-27** | 85 | 87 |
| 3 | **3-28** | 68 | 88 |

Table 3-15: Enantioselective desymmetrization via alkylation catalyzed by chiral organoboron analogs – catalyst screen. [a]Isolated yields. [b]Determined by HPLC on a chiral stationary phase. Data obtained from a single experiment.

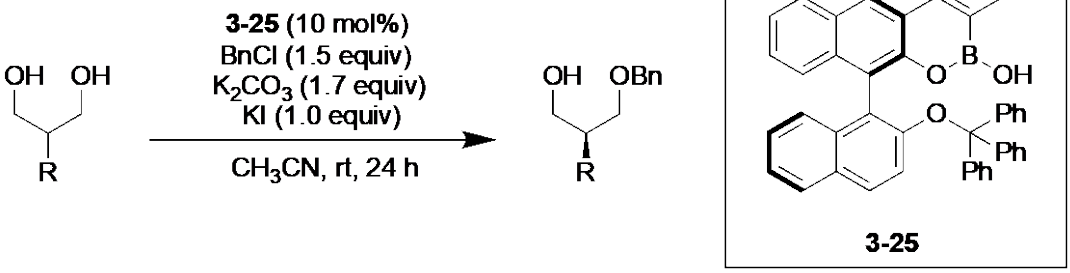
### 3.3.8 Enantioselective Desymmetrization via Benzylation – Substrate Scope

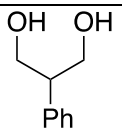
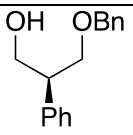
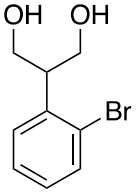
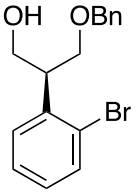
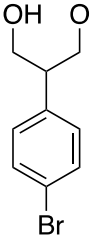
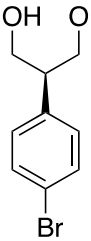
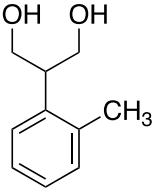
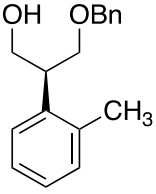
The route to prepare chiral hemiboronic acids **3-28** and **3-29** required synthesis of the corresponding triarylmethyl chlorides and was generally low yielding. For these reasons, benzylation catalyzed by chiral hemiboronic acid **3-25** was chosen to be the optimal and most practical method and was applied to a variety of substrates. The required 2-substituted-1,3-propanediol substrates were prepared by reduction of their corresponding 2-substituted diethyl malonates (Scheme 3-17).




Scheme 3-17: Preparation of 2-substituted-1,3-propanediols

In general, the enantioselective desymmetrization catalyzed by chiral hemiboronic acid **3-25** tolerates 2-aryl-1,3-propanediols with varying substitution (Table 3-16). The absolute stereochemistry of these examples was assigned by analogy to **3-4**.




| Entry | Substrate | Product | Yield (%)[a] | % ee[b] |
|---|---|---|---|---|
| 1 |  **3-2** |  **3-4** | 94 | 86 |
| 2 |  **3-30** |  **3-36** | 75 | 84 |
| 3 |  **3-31** |  **3-37** | 50 | 82 |
| 4 |  **3-32** |  **3-38** | 77 | 88 |

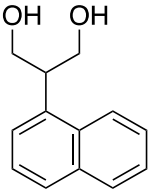
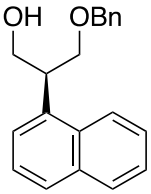
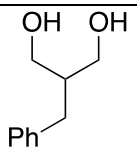
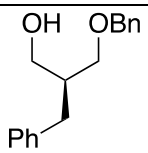
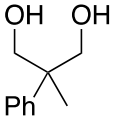
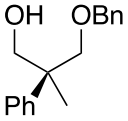
| | | | | |
|---|---|---|---|---|
| 5 |  **3-33** |  **3-39** | 89 | 82 |
| 6 |  **3-34** |  **3-40** | 90 | 43 |
| 7 |  **3-35** |  **3-41** | 99 | 56 |

Table 3-16: Substrate scope of the enantioselective desymmetrization via alkylation catalyzed by chiral organoboron **3-25**. [a]Isolated yields. [b]Determined by HPLC on a chiral stationary phase. Data obtained from a single experiment.

The enantioselectivity of the reaction is, however, less selective when the 2-position is alkyl substituted (Table 3-16, entry 6). This outcome may be due to a smaller difference in the energies of the diol-catalyst adducts in which the alkyl substituent may assume either an axial or equatorial position (Figure 3-5). If the substituent at the 2-position is axial, benzylation of the less hindered oxygen would result in the formation of the opposite enantiomer. This problem is also evident in the attempt to generate an all-carbon quaternary center enantioselectively for 2,2-disubstituted diol **3-35**, where a relatively lower enantiomeric excess of product **3-41** was observed (Table 3-16, entry 7).

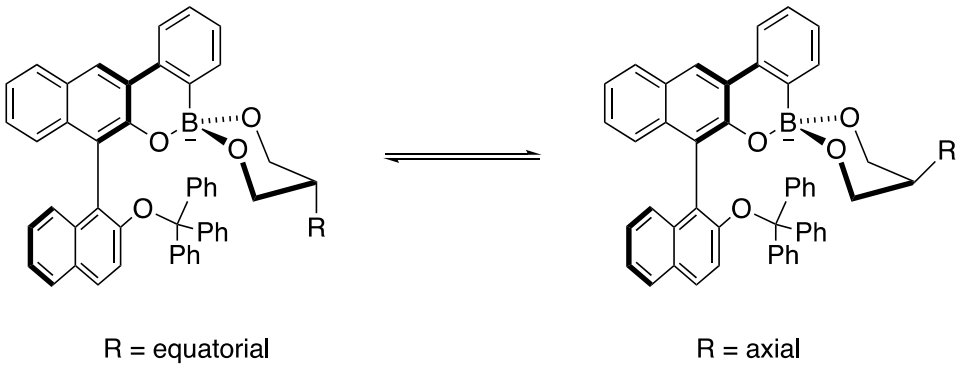
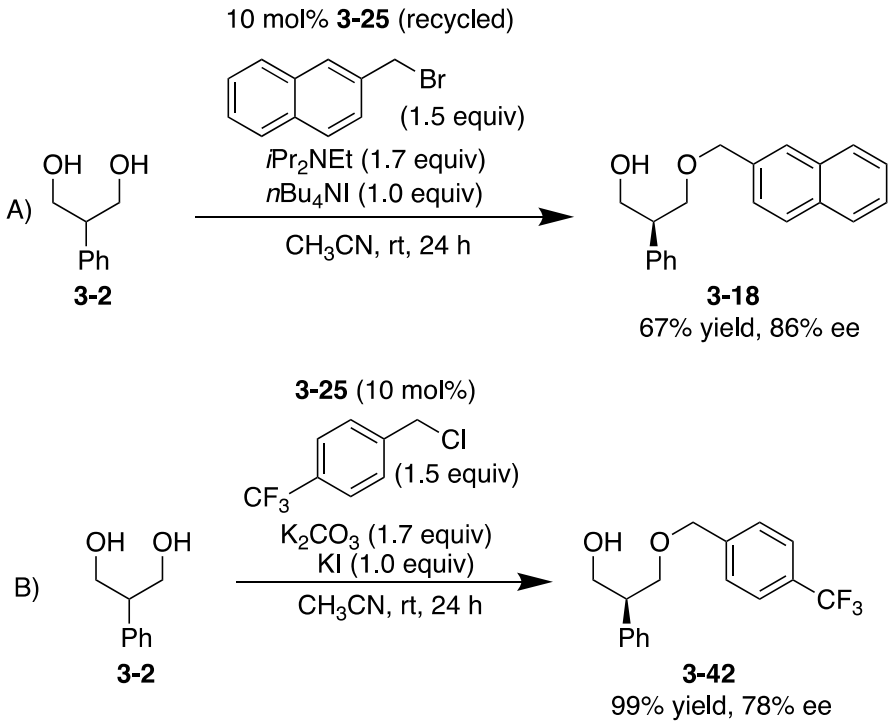



Figure 3-5: Possible conformational equilibrium in diol-catalyst adduct when R = alkyl

One advantage of this method is that the catalyst **3-25** can be quantitatively recovered via a simple chromatographic separation. For example, catalyst **3-25** was recycled to install 2-naphthyl ether in product **3-18** without loss of activity while maintaining good enantioselectivity (Scheme 3-18A). A 4-trifluoromethylbenzyl ether was also installed with moderate enantioselectivity (Scheme 3-18B).




Scheme 3-18: A) Enantioselective naphthylation of diol **3-2** using recovered catalyst **3-25**. B) Enantioselective benzylation using 4-trifluoromethylbenzyl chloride

## 3.4 Summary

This chapter describes the use of chiral hemiboronic acid **3-25** as a catalyst in the enantioselective desymmetrization of 2-substituted-1,3-propanediols via benzylation. Several novel chiral hemiboronic acids (derived from (*R*)-BINOL) were screened in the asymmetric reaction and it is proposed that the role of a sterically hindered catalyst is crucial in providing high levels of enantioselectivity. Discrimination of the enantiotopic -OH groups in the substrate is possible upon complexation with organoboron **3-25** where one of the hydroxy groups is effectively blocked by a trityl group in the catalyst. The reaction, however, appears to be sensitive to the nature of the substituent at the 2-position in the substrate. Nonetheless, the asymmetric reaction was shown to be effective on prochiral diol substrates to prepare optically active alcohols with good levels of enantioselectivity. Future work includes the expansion of the substrate scope to include electron-donating and withdrawing groups in the arene substituent of the substrate to determine their effect on the enantioselectivity. Further improvement to the structure of the catalyst to increase the enantioselectivity of the benzylation reaction (ex. introducing a methyl group *ortho* to the boron atom) should also be explored (Chapter 4).

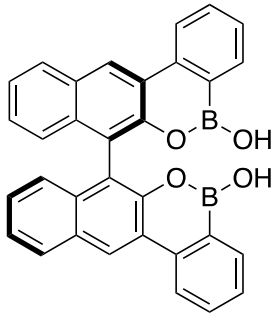
## 3.5 Experimental

### 3.5.1 General Information

Unless otherwise stated, all reactions were performed in flame-dried glassware under a nitrogen atmosphere. Molecular sieves were activated by drying under high vacuum over a 120 ºC oil bath for 48 hours, then stored in a 100 ºC oven. Acetonitrile was distilled from calcium hydride and stored over activated 3Å molecular sieves. Dioxane was distilled over sodium. *N*,*N*,-dimethylformamide (DMF), dichloromethane ($CH_2Cl_2$), tetrahydrofuran (THF) and toluene were purified using an MBraun MS SPS* solvent system. All other solvents were purchased from Sigma Aldrich and used as received. Unless stated otherwise, *N*,*N*-diisopropylethylamine (Sigma Aldrich) was used as received. All other chemicals were purchased from Strem, Sigma Aldrich, Oakwood Chemicals or Combi-Blocks and used as received. 2-Aryl-1,3-propanediol substrates were prepared according to a literature procedure.[7] Thin layer chromatography (TLC) was

performed on silica gel 60 F254 plates and visualized using UV light, potassium permanganate ($KMnO_4$) and/or phosphomolybdic acid (PMA) stains. Flash chromatographic separations were performed with silica gel 60 using ACS grade solvents. $^{1}H$ NMR, $^{13}C$ NMR, $^{19}F$ NMR and $^{11}B$ NMR spectroscopy experiments were performed on 400 MHz, 500 MHz, 600 MHz or 700 MHz instruments. The residual solvent ($CDCl_3$, $CD_3OD$, or $(CD_3)_2O$) protons ($^{1}H$) and carbons ($^{13}C$) were used as internal references. $^{1}H$ NMR data is presented as follows: chemical shift in ppm (δ) (multiplicity, coupling constant, integration). The following abbreviations are used in reporting the $^{1}H$ NMR data: s, singlet; br s, broad singlet; d, doublet; t, triplet; dd, doublet of doublet; dddd, doublet of doublet of doublet of doublet; dddddd, doublet of doublet of doublet of doublet of doublet of doublet; m, multiplet. The error of coupling constants from $^{1}H$ NMR spectra is estimated to be 0.3 Hz. High-resolution mass spectra were recorded by the University of Alberta Mass Spectrometry Services using electrospray ionization (ESI) techniques. Optical rotations were measured using a 1 mL cell with a 10 cm length on a polarimeter by the University of Alberta analytical and instrumental laboratories. The enantiomeric excess ratios for optically enriched compounds were determined using a HPLC Agilent instrument with a Chiralpak AS/IA/IB/IC or Chiralcel OD column.

### 3.5.2 Procedure and Characterization of Chiral Hemiboronic Acids




**(7*R*)-5,5'-Dihydroxy-5*H*,5'*H*-7,7'-bibenzo[c]naphth[2,3-e][1,2]oxaborin (3-8):**

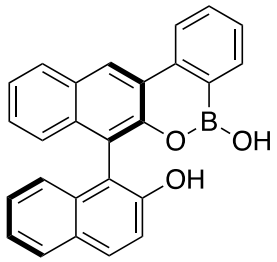
To a 15 mL pressure tube was added 3,3'-dibromo-2,2'-dimethoxy-1,1'-binaphthalene **3-11** (350 mg, 0.741 mmol), 1,2-benzenediboronic acid bis(pinacol) ester **3-17** (515 mg, 1.56 mmol), and sodium carbonate (393 mg, 3.71 mmol). The reaction flask was evacuated and backfilled with nitrogen, then $Pd(PPh_3)_4$ (128 mg, 0.111 mmol) was added. The reaction flask was evacuated and backfilled with nitrogen three more times before adding dioxane (7.4 mL) and $H_2O$ (5.3 mL,

degassed with $N_2$). The flask was sealed with a screw cap and the reaction was stirred at 100 ºC for 18 hours. The reaction mixture was cooled to room temperature, extracted with ethyl acetate (3 × 5 mL), washed with $H_2O$ (2 × 10 mL) and brine (10 mL). The organic layer was dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude oil was then subjected to a silica plug and eluted with 5% to 8% ethyl acetate/hexanes (~500 mL). Removal of volatiles afforded a white foam that was used in the next step. The obtained material from the first step was transferred to a flame-dried 250 mL flask and was dissolved in $CH_2Cl_2$ (50 mL). The flask was cooled to 0 ºC, and $BBr_3$ (714 µL, 10.0 mmol) was added dropwise and was stirred for 2 hours, gradually warming to room temperature. The reaction was quenched with 1M HCl (20 mL) at 0 ºC and was stirred for an additional 30 minutes. The mixture was transferred to a separatory funnel and was extracted with $CH_2Cl_2$ (2 × 10 mL). The organic layer was dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude material was purified by sorbitol phase-switch extraction[4]: dissolved residue with ethyl acetate (25 mL) and extracted with a solution of sorbitol (1 M sorbitol/1 M $Na_2CO_3$). The aqueous layer was acidified with 5 M HCl until pH 2, back-extracted with ethyl acetate (20 mL), washed with $H_2O$ (10 mL), brine (10 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. Removal of solvent yielded a clear film which can be triturated with hexanes to afford a beige solid (189 mg, 52% over two steps). Spectral data are in agreement with that previously reported.[1]

**$^1$H NMR** (500 MHz, , $d_6$-acetone, $D_2O$ drop): δ 9.08 (s, 2H), 8.66 (d, $J$ = 8.2 Hz, 2H), 8.17 (d, $J$ = 8.3 Hz, 1H), 8.08 (dd, $J$ = 7.4, 1.5, 2H), 7.82 (ddd, $J$ = 8.2, 7.3, 1.5 Hz, 2H), 7.53 (app td, $J$ = 7.3, 0.9 Hz, 2H), 7.43 (ddd, $J$ = 8.1, 6.7, 1.2 Hz, 2H), 7.24 (ddd, $J$ = 8.6, 6.6, 1.3 Hz), 7.11 (d, $J$ = 8.5, Hz, 2H).

**$^{13}$C NMR** (126 MHz, $d_6$-acetone, $D_2O$ drop): δ 148.6, 141.4, 134.34, 134.33, 133.3, 130.5, 129.5, 128.4, 127.3, 126.0, 125.2, 124.6, 124.2, 123.2, 122.0. The boron-bound carbon was not detected due to the quadrupolar relaxation of boron.

**$^{11}$B NMR** (160 MHz, $d_6$-acetone, $D_2O$ drop): δ 28.5 (br s).




**Chiral hemiboronic acid derivative (*R*)-3-22:**

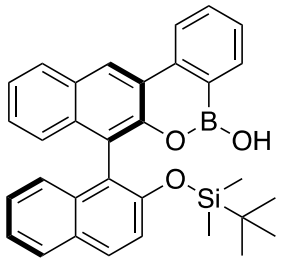
To a 25 mL pressure tube was added 3-bromo-2,2'-dimethoxy-1,1'-binaphthalene **3-12** (389 mg, 0.989 mmol), 1,2-benzenediboronic acid bis(pinacol) ester **3-17** (360 mg, 1.09 mmol), and sodium carbonate (315 mg, 2.97 mmol). The reaction flask was evacuated and backfilled with nitrogen, then $Pd(PPh_3)_4$ (114 mg, 0.0989 mmol) was added. The reaction flask was evacuated and backfilled with nitrogen three more times before adding dioxane (10 mL) and $H_2O$ (7 mL, degassed with $N_2$). The flask was sealed with a screw cap and the reaction was stirred at 100 ºC for 17 hours. The reaction mixture was cooled to room temperature, extracted with ethyl acetate (3 × 5 mL), washed with $H_2O$ (2 × 10 mL) and brine (10 mL). The organic layer was dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude oil was then subjected to a silica plug and eluted with 5% ethyl acetate/hexanes (600 mL). Removal of volatiles afforded a white foam that was used in the next step. The obtained material from the first step was transferred to a flame-dried 100 mL flask and was dissolved in $CH_2Cl_2$ (25 mL). The flask was cooled to 0 ºC, and $BBr_3$ (952 µL, 10.0 mmol) was added dropwise and was stirred for 3 hours, gradually warming to room temperature. The reaction was quenched with 1M HCl (10 mL) at 0 ºC and was stirred for an additional 30 minutes. The mixture was transferred to a separatory funnel and was extracted with $CH_2Cl_2$ (2 × 10 mL). The organic layer was dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude material was purified by silica gel chromatography (10% to 12% ethyl acetate/hexanes) to afford a clear film, which can be triturated with hexanes to afford a white solid (251 mg, 65% over two steps).

**$^1$H NMR** (500 MHz, *d*$_6$-acetone, $D_2O$ drop): δ 9.02 (s, 1H), 8.62 (d, *J* = 8.1 Hz, 1H), 8.13 (d, *J* = 8.3 Hz, 1H), 8.10 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.98 (d, *J* = 9.0 Hz, 1H), 7.93 (app d, *J* = 7.7 Hz, 1H), 7.81 (ddd, *J* = 8.2, 7.3, 1.5 Hz, 1H), 7.53 (app td, *J* = 7.3, 0.9 Hz, 1H), 7.43 (ddd, *J* = 8.1, 6.7, 1.2 Hz, 1H), 7.40 (d, *J* = 8.9 Hz, 1H), 7.32–7.25 (m, 2H), 7.17 (ddd, *J* = 8.3, 6.7, 1.4 Hz, 1H), 7.14 (app d, *J* = 8.5 Hz, 1H), 7.01 (app d, 8.5 Hz, 1H).

**$^{13}$C NMR** (126 Hz, $d_6$-acetone, $D_2O$ drop): 153.8, 149.4, 141.6, 135.4, 134.7, 134.4, 133.4, 130.8, 130.2, 129.8, 129.6, 128.9, 128.5, 127.4, 127.0, 126.0, 125.6, 125.3, 125.0, 124.6, 123.7, 123.2, 121.0, 119.5, 116.5. The boron-bound carbon was not detected due to the quadrupolar relaxation of boron.

**$^{11}$B NMR** (160 MHz, $d_6$-acetone, $D_2O$ drop): δ 27.7.

**HRMS** (ESI-TOF) for $C_{26}H_{17}BO_3$ $(M–H)^-$: calc. 387.1198; found 387.1198.



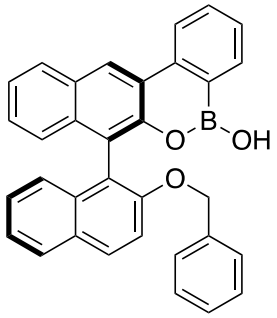

**Chiral hemiboronic acid *O*-TBS derivative (3-23):**

Organoboron **3-22** (24 mg, 0.063 mmol), imidazole (9.0 mg, 0.13 mmol) and *t*-butyldimethylsilylchloride (19 mg, 0.13 mmol) were added to a 25 mL round-bottom flask. Dichloromethane (4 mL) was then added and the reaction was stirred at room temperature for 17 hours. The mixture was transferred to a separatory funnel and was extracted with $CH_2Cl_2$ (3 × 5 mL). The organic layer was washed with $H_2O$ (10 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude solid (~59% yield) was used without further purification (*t*-butyldimethylsilylchloride impurity was however present).

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 8.85 (s, 1H), 8.44 (d, $J$ = 8.2 Hz, 1H), 8.07 (d, $J$ = 8.2 Hz, 1H), 8.02 (dd, $J$ = 7.3, 1.5 Hz, 1H), 7.94 (d, $J$ = 8.9 Hz, 1H), 7.88 (d, $J$ = 8.2 Hz, 1H), 7.78 (app td, $J$ = 8.2, 7.8, 1.6 Hz, 1H), 7.51 (td, $J$ = 6.9, 1.0 Hz, 1H), 7.49–7.45 (m, 1H), 7.38 (d, $J$ = 8.9 Hz, 1H), 7.35 (dd, $J$ = 3.6, 1.0 Hz, 2H), 7.31 (ddd, $J$ = 8.1, 6.7, 1.2 Hz, 1H), 7.19 (ddd, $J$ = 8.2, 6.8, 1.3 Hz, 1H), 7.04 (dd, $J$ = 8.5, 1.1 Hz, 1H), 0.73 (s, 9H), -0.33 (s, 3H), -0.57 (s, 3H).

**$^{13}$C NMR** (176 MHz, $CDCl_3$): δ 151.3, 149.0, 140.3, 134.2, 134.0, 133.4, 132.5, 129.83, 129.82, 129.4, 128.7, 128.0, 127.9, 127.4, 126.5, 125.1, 125.0, 124.8, 124.4, 124.2, 123.3, 122.0, 117.7, 117.5, 115.3, 29.8, 25.4, -3.5, -4.6. The boron-bound carbon was not detected due to the quadrupolar relaxation of boron.

**$^{11}$B NMR** (128 MHz, $CDCl_3$): δ 26.6 (br s).




**Chiral hemiboronic acid *O*-benzyl derivative (3-24):**

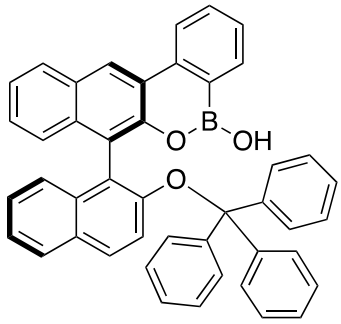
Organoboron **3-22** (13 mg, 0.033 mmol), benzyl bromide (4 µL, 0.03 mmol) and potassium carbonate (7.0 mg, 0.22 mmol) were added to a 25 mL round-bottom flask. Acetone (2 mL) was then added and the reaction was stirred at 60 ºC for 17 hours. The reaction mixture was extracted with ethyl acetate (2 × 5 mL), and the organic layer was washed with $H_2O$ (5 mL), brine (5 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (10% ethyl acetate/hexanes) to afford a clear film. Trituration with hexanes afforded a white solid (11 mg, 70% yield).

**$^1$H NMR** (500 MHz, $d_6$-acetone, $D_2O$ drop): δ 9.02 (s, 1H), 8.61 (d, $J$ = 8.2 Hz, 1H), 8.13 (d, $J$ = 8.3 Hz, 1H), 8.11–8.06 (m, 2H), 7.97 (d, $J$ = 8.3 Hz, 1H), 7.80 (ddd, $J$ = 8.5, 7.3, 1.5 Hz, 1H), 7.63 (d, $J$ = 9.1 Hz, 1H), 7.51 (app td, $J$ = 7.3, 0.9 Hz, 1H), 7.42 (ddd, $J$ = 8.1, 6.7, 1.2 Hz, 1H), 7.37–7.29 (m, 2H), 7.27 (ddd, $J$ = 8.1, 6.7, 1.3 Hz, 1H), 7.22 (ddd, $J$ = 8.2, 6.7, 1.3 Hz, 1H), 7.12 (d, $J$ = 5.4 Hz, 1H), 7.10 (d, $J$ = 5.3 Hz, 1H), 7.07–6.99 (m, 5H), 5.16 (d, $J$ = 12.6 Hz, 1H), 5.13 (d, $J$ = 12.5 Hz, 1H).

**$^{13}$C NMR** (126 MHz, $d_6$-acetone, $D_2O$ drop): δ 155.3, 148.5, 141.4, 138.5, 135.0, 134.4, 134.3, 133.3, 130.6, 130.3, 130.2, 129.5, 128.87, 128.85, 128.4, 128.0, 127.6, 127.5, 127.3, 127.22, 127.17, 126.04, 125.97, 125.1, 124.6, 124.5, 124.1, 123.2, 122.1, 121.1, 116.7, 71.5. The boron-bound carbon was not detected due to the quadrupolar relaxation of boron.

**$^{11}$B NMR** (128 MHz, $d_6$-acetone, $D_2O$ drop): δ 27.8 (br s).

**HRMS** (ESI-TOF) for $C_{33}H_{23}BO_3$ $(M–H)^-$: calc. 478.1740; found 478.1733.



**Chiral hemiboronic acid *O*-trityl derivative (3-25):**

Organoboron **3-22** (72.6 mg, 0.187 mmol) and triphenylmethyl chloride (62 mg, 0.22 mmol) were added to a 10 mL round-bottom flask. $CH_2Cl_2$ (3 mL) was then added, followed by triethylamine (34 μL, 0.24 mmol), and the reaction was stirred at room temperature for 17 hours. The reaction mixture was transferred to a separatory funnel, followed by addition of $H_2O$ (5 mL) and was extracted with $CH_2Cl_2$ (2 × 5 mL). The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (5% to 10% ethyl acetate/hexanes) to afford a white solid foam (78 mg, 66% yield).

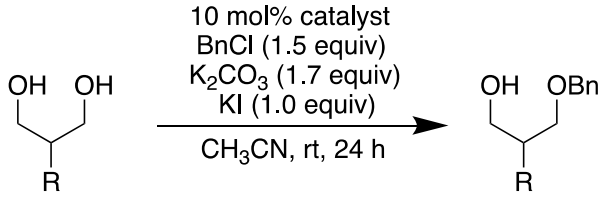
**$^1$H NMR** (500 MHz, $d_6$-acetone, $D_2O$ drop): δ 9.05 (s, 1H), 8.68 (d, $J$ = 8.1 Hz, 1H), 8.16–8.09 (m, 2H), 7.87–7.80 (m, 2H), 7.56 (d, $J$ = 9.4 Hz, 1H), 7.53 (dd, $J$ = 7.3, 0.9 Hz, 1H), 7.40 (ddd, $J$ = 8.1, 6.7, 1.2 Hz, 1H), 7.35–7.26 (m, 2H), 7.20–7.14 (m, 8H), 7.06–7.00 (m, 10H), 6.89 (d, $J$ = 9.2 Hz, 1H).

**$^{13}$C NMR** (176 Hz, $d_6$-acetone, $D_2O$ drop): 152.5, 149.0, 145.2, 141.6, 134.8, 134.4, 134.1, 133.4, 130.6, 129.6, 129.5, 129.2, 129.0, 128.7, 128.4, 127.8, 127.7, 126.94, 126.87, 126.3, 126.0, 125.1, 124.7, 124.4, 124.0, 123.2, 122.7, 122.6, 120.9, 89.8. The boron-bound carbon was not detected due to the quadrupolar relaxation of boron.

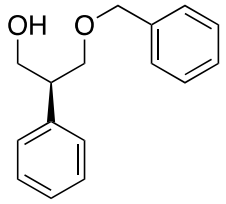
**$^{11}$B NMR** (160 MHz, $d_6$-acetone, $D_2O$ drop): δ 27.6 (br s).

**HRMS** (ESI-TOF) for $C_{45}H_{31}BO_3$ $(M–H)^-$: calc. 630.2366; found 630.2373.

### 3.5.3 General Procedure 3A for the Desymmetrization of 2-Substituted-1,3-Propanediols



To a flame-dried 5 mL round-bottom flask was added the 1,3-diol (1.0 equiv), organoboron catalyst **3-1** or **3-25** (0.10 equiv), potassium carbonate (1.7 equiv) and potassium iodide (1.0 equiv). Acetonitrile (0.2 M) was then added, followed by benzyl chloride (1.5 equiv). The flask was sealed, and the reaction was stirred at room temperature for 24 hours. The reaction mixture was diluted with ethyl acetate and transferred to a separatory funnel. The organic layer was washed with $H_2O$ (2 × 5 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography.

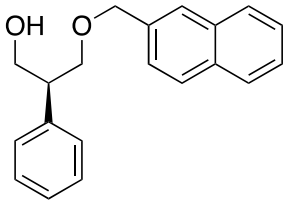



**(*S*)-2-Phenyl-3-(benzyloxy)propan-1-ol (3-4)**

(For procedure and characterization data of the racemic product, see Chapter Two, Section 2.4.4.1). Enantioselective synthesis according to General Procedure 3A from diol **3-2** (15 mg, 0.10 mmol). Purified by silica gel chromatography (10% ethyl acetate in hexanes) to yield a pale-yellow oil (23 mg, 94%). Spectral data are in agreement with that previously reported.[8]

**$[\alpha]_D^{25}$**: –18.9 (c 1.00, $CHCl_3$).

**HPLC** (Chiralpak IC): 5:95 *i*PrOH/Hex, 20 °C, 0.7 mL/min, λ = 254 nm, $T_{(S)}$ = 11.9 min, $T_{(R)}$ = 12.9 min, er = 93:7.




**(*S*)-2-Phenyl-3-(2-naphthyloxy)propan-1-ol (3-18)**

Synthesized according to General Procedure 3A with slight modifications: using diol **3-2** (15 mg, 0.10 mmol, 1.0 equiv), *N*,*N*-diisopropylethylamine (29 µL, 0.30 mmol, 1.7 equiv), 2-(bromomethyl)naphthalene (33 mg, 0.15 mmol, 1.5 equiv), tetrabutylammonium iodide (36 mg, 0.10 mmol, 1.0 equiv) and recovered catalyst **3-25** (4.9 mg, 0.010 mmol). The crude oil was

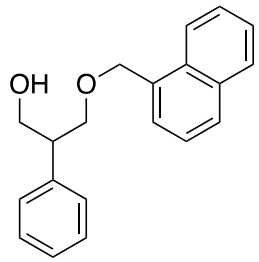
purified by silica gel chromatography (5% to 20% to 50% ethyl acetate in hexanes) to afford a pale-yellow oil (19 mg, 67%).

**$^1$H NMR** (500 MHz, $CDCl_3$): δ 7.86–7.79 (m, 3H), 7.74 (s, 1H), 7.51–7.46 (m, 2H), 7.33–7.29 (m, 2H), 7.44 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.28–7.24 (m, 2H), 7.24–7.21 (m, 2H), 4.72 (s, 2H), 4.04 (ddd, *J* = 10.9, 7.3, 4.8 Hz, 1H), 3.89 (ddd, *J* = 10.9, 7.2, 5.4 Hz, 1H), 3.86 (dd, *J* = 8.5 Hz, 8.5 Hz, 1H, A part of ABM), 3.82 (dd, *J* = 9.2, 5.2 Hz, 1H, B part of ABM), 3.25 (dddd, *J* = 11.9, 6.4, 5.3, 5.3 Hz, 1H), 2.36 (dd, *J* = 7.2, 4.9 Hz, 1H).

**$^{13}$C NMR** (126 MHz, $CDCl_3$): δ 139.6, 135.4, 133.3, 133.1, 128.7, 128.4, 128.1, 127.9, 127.8, 127.2, 126.6, 126.2, 126.0, 125.6, 73.6, 66.6, 47.9.

**HRMS** (ESI-TOF) for $C_{20}H_{20}NaO_2$ $(M+Na)^+$**:** calc. 315.1355; found 315.1356.

**HPLC** (Chiralpak AS): 15:85 *i*PrOH/Hex, 20 °C, 0.5 mL/min, λ = 210 nm, $T_{(S)}$ = 15.2 min, $T_{(R)}$ = 16.5 min, er = 92.6:7.4.




**2-Phenyl-3-(1-naphthyloxy)propan-1-ol (3-19):**

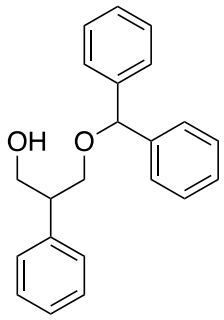
Synthesized according to General Procedure 3A with slight modifications: using diol **3-2** (15 mg, 0.10 mmol, 1.0 equiv), *N*,*N*-diisopropylethylamine (30 μL, 0.30 mmol, 1.7 equiv), 1-(bromomethyl)naphthalene (33 mg, 0.15 mmol, 1.5 equiv), tetrabutylammonium iodide (37 mg, 0.10 mmol, 1.0 equiv) and organoboron catalyst **3-8** (4.9 mg, 0.010 mmol, 0.10 equiv). The reaction was performed at 0 ºC. The crude oil was purified by silica gel chromatography (10% ethyl acetate in hexanes) to afford a pale-yellow oil (23 mg, 78%).

**$^1$H NMR** (500 MHz, $CDCl_3$): δ 8.10–8.06 (m, 1H), 7.92–7.87 (m, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.56–7.50 (m, 2H), 7.48 (dd, *J* = 6.9, 1.5 Hz, 1H), 7.44 (dd, *J* = 8.0, 6.9 Hz, 1H), 7.34–7.29 (m, 2H), 7.29–7.25 (m, 1H), 7.25–7.21 (m, 2H), 5.03 (d, *J* = 12.0 Hz, 1H), 5.00 (d, *J* = 12.0 Hz, 1H), 4.00 (dd, *J* = 10.9, 7.1 Hz, 1H), 3.92–3.84 (m, 2H, AB part of ABM), 3.90–3.87 (m, B part of ABM), 3.87 (dd, *J* = 5.3, 2.1 Hz, 1H). 3.86 (dd, *J* = 9.2, 5.3 Hz, 1H), 3.23 (dddd, *J* = 7.6, 7.6, 5.4, 5.4 Hz), 2.24 (br s, 1H).

**$^{13}$C NMR** (176 MHz, $CDCl_3$): δ 139.7, 133.8, 133.3, 131.7, 128.9, 128.7, 128.6, 128.1, 127.1, 126.6, 126.4, 125.9, 125.2, 123.9, 73.5, 72.1, 66.4, 47.9.

**HRMS** (ESI-TOF) for $C_{20}H_{20}NaO_2$ $(M+Na)^+$**:** calc. 315.1354; found 315.1356.

**HPLC** (Chiralpak IB): 15:85 *i*PrOH/Hex, 20 °C, 0.5 mL/min, λ = 210 nm, $T_{major}$ = 9.2 min, $T_{minor}$ = 10.0 min, er = 84:16.




**2-Phenyl-3-(diphenylmethyloxy)propan-1-ol (3-20):**

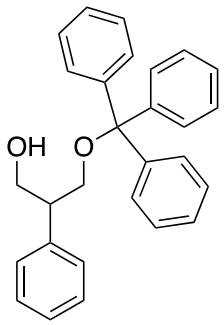
Synthesized according to General Procedure 3A using diol **3-2** (15 mg, 0.10 mmol). Purified by silica gel chromatography (10% ethyl acetate in hexanes) to yield a pale-yellow oil (14 mg, 42%).

**$^{1}$H NMR** (600 MHz, $CDCl_3$): δ 7.35–7.28 (m, 10H), 7.28–7.20 (m, 5H), 5.28 (s, 1H), 4.07 (dd, *J* = 10.8, 7.4 Hz, 1H), 3.92 (ddd, *J* = 10.2, 4.5, 4.5 Hz 1H), 3.80 (dd, *J* = 8.8, 8.8 Hz, 1H, A part of ABM), 3.76 (dd, *J* = 9.2, 5.0 Hz, 1H, B part of ABM), 3.26 (dddd, *J* = 8.5, 7.1, 5.3, 5.3 Hz, 1H), 2.29 (br s, 1H).

**$^{13}$C NMR** (151 MHz, $CDCl_3$): δ 141.9, 141.8, 139.7, 128.7, 128.6, 128.5, 128.1, 127.6, 127.6, 127.1, 126.9, 84.4, 72.3, 66.4, 48.1.

**HRMS** (ESI-TOF) for $C_{22}H_{22}NaO_2$ $(M+Na)^+$**:** calc. 341.1513; found 341.1512.

**HPLC** (Chiralcel OD): 10:90 *i*PrOH/Hex, 20 °C, 0.5 mL/min, λ = 220 nm, $T_{major}$ = 18.7 min, $T_{minor}$ = 25.1 min, er = 53:47.




**2-Phenyl-3-(triphenylmethyloxy)propan-1-ol (3-21):**

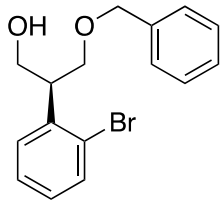
Synthesized according to General Procedure 3A using diol **3-2** (30.4 mg, 0.10 mmol, 1.0 equiv), *N*,*N*-diisopropylethylamine (30 μL, 0.17 mmol, 1.7 equiv), triphenylmethyl chloride (42 mg, 0.15 mmol, 1.5 equiv) and organoboron catalyst **3-8** (4.9 mg, 0.010 mmol, 0.10 equiv). The crude oil was purified by silica gel chromatography (10% ethyl acetate in hexanes) to afford a clear oil (18 mg, 47%).

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.49–7.38 (m, 6H), 7.36–7.21 (m, 12H), 7.21–7.14 (m, 2H), 4.02 (dd, *J* = 10.9, 7.0 Hz, 1H), 3.90 (dd, *J* = 10.4, 5.7 Hz, 1H), 3.51 (dd, *J* = 9.3, 5.3 Hz, 1H), 3.45 (dd, *J* = 9.3, 8.0 Hz, 1H), 3.17 (dddd, *J* = 7.9, 7.9, 6.0, 6.0 Hz), 2.15 (br s, 1H).

**$^{13}$C NMR** (101 MHz, $CDCl_3$): δ 143.8, 139.9, 128.7, 128.6, 128.2, 127.9, 127.1, 127.0, 87.2, 66.6, 65.9, 48.4.

**HRMS** (ESI-TOF) for $C_{28}H_{26}NaO_2$ $(M+Na)^+$: calc. 417.1825; found 417.1826.

**HPLC** (Chiralpak AS): 15:85 *i*PrOH/Hex, 20 °C, 0.5 mL/min, λ = 210 nm, $T_{major}$ = 11.1 min, $T_{minor}$ = 12.2 min, er: 54:46.




**(*S*)-2-(*o*-bromophenyl)-3-benzyloxypropan-1-ol (3-36):**

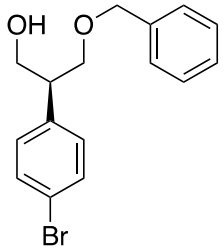
Synthesized according to General Procedure 3A from diol **3-29** (23 mg, 0.10 mmol). Purified by silica gel chromatography (5% to 10% ethyl acetate in hexanes) to yield a clear oil (26 mg, 75%).

**$^1$H NMR** (500 MHz, $CDCl_3$): δ 7.37–7.29 (m, 7H), 7.26–7.20 (m, 2H), 4.56 (s, 2H), 4.02 (dd, *J* = 10.9, 7.3 Hz, 1H), 3.88 (dd, *J* = 10.9, 5.3 Hz, 1H), 3.82 (dd, *J* = 9.1, 9.1 Hz, 1H, A part of ABM), 3.78 (dd, *J* = 9.2, 5.3, 1H, B part of ABM), 3.22 (dddd, *J* = 13.2, 8.0, 5.2, 5.2 Hz, 1H)

**$^{13}$C NMR** (126 MHz, $CDCl_3$): δ 139.6, 137.9, 128.7, 128.5, 128.0, 127.8, 127.7, 127.1, 73.7, 73.5, 66.6, 47.8.

**HRMS (EI)** for $C_{16}H_{18}O_2$ $(M–Br)^{\cdot+}$: calc. 242.1307; found 242.1309.

**HPLC** (Chiralpak IC): 5:95 *i*PrOH/Hex, 20 °C, 0.7 mL/min, λ = 210 nm, $T_{(S)}$ = 11.3 min, $T_{(R)}$ = 12.3 min, er = 91.7:8.3




**(*S*)-2-(*p*-bromophenyl)-3-benzyloxypropan-1-ol (3-37):**

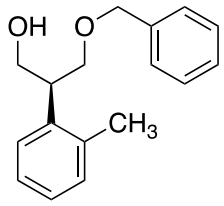
Synthesized according to General Procedure 3A from diol **3-30** (23 mg, 0.10 mmol). Purified by silica gel chromatography (5% to 15% ethyl acetate in hexanes) to yield a clear oil (16 mg, 50%).

**$^{1}$H NMR** (500 MHz, $CDCl_3$): δ 7.43 (d, *J* = 8.4 Hz, 2H), 7.39–7.27 (m, 5H), 7.11 (d, *J* = 8.4 Hz, 2H), 4.54 (s, 2H), 3.96 (dd, *J* = 10.9, 7.0 Hz, 1H), 3.85 (dd, *J* = 10.9, 5.3 Hz, 1H), 3.81–3.71 (m, 2H, AB part of ABM), 3.15 (ddd, *J* = 12.8, 7.3, 5.4, 5.4 Hz, 1H), 2.24 (br s, 1H).

**$^{13}$C NMR (176 MHz, $CDCl_3$):** δ 138.8, 137.8, 131.7, 129.8, 128.6, 127.9, 127.7, 120.9, 73.6, 73.0, 66.0, 47.4.

**HRMS** (ESI-TOF) for $C_{16}H_{17}BrNaO_2$ $(M+Na)^+$: calc. 343.0304; found 343.0304.

**HPLC** (Chiralpak IC): 5:95 *i*PrOH/Hex, 20 °C, 0.7 mL/min, λ = 210 nm, $T_{(S)}$ = 9.7 min, $T_{(R)}$ = 10.6 min, er = 91.1:8.9.




**(*S*)-2-(*o*-tolyl)-3-benzyloxypropan-1-ol (3-38):**

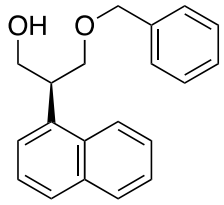
Synthesized according to General Procedure 3A from diol **3-31** (17 mg, 0.10 mmol). Purified by silica gel chromatography (5% to 10% ethyl acetate in hexanes) to yield a clear oil (20 mg, 77%).

**$^{1}$H NMR** (500 MHz, $CDCl_3$): δ 7.39–7.28 (m, 5H), 7.20–7.09 (m, 4H), 4.57 (s, 2H), 4.04 (dd, *J* = 10.9, 7.7 Hz, 1H), 3.86 (dd, *J* = 11.0, 4.9 Hz, 1H), 3.81 (dd, *J* = 9.2, 9.2 Hz, 1H), 3.74 (ddd, *J* = 9.2, 4.5 Hz, 1H), 3.51 (dddd, *J* = 9.3, 7.6, 4.7, 4.7 Hz, 1H), 2.54 (br s, 1H), 2.38 (s, 3H).

**$^{13}$C NMR** (126 MHz, $CDCl_3$): δ 137.9, 137.6, 136.5, 130.7, 128.5, 127.8, 127.7, 126.8, 126.3, 126.2, 73.9, 73.5, 66.5, 43.0, 19.7.

**HRMS** (ESI-TOF) for $C_{17}H_{20}NaO_2$ $(M+Na)^+$: calc. 279.1356; found 279.1355.

**HPLC** (Chiralpak IC): 5:95 *i*PrOH/Hex, 20 °C, 0.7 mL/min, λ = 220 nm, $T_{(S)}$ = 8.9 min, $T_{(R)}$ = 10.2 min, er = 93.7:6.3.




**(*S*)-2-(1-naphthyl)-3-benzyloxypropan-1-ol (3-39)**

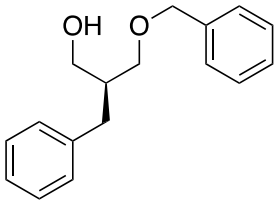
Synthesized according to General Procedure 3A from diol **3-32** (21 mg, 0.10 mmol). Purified by silica gel chromatography (8% to 20% ethyl acetate in hexanes) to yield a clear oil (26 mg, 88%).

**$^1$H NMR** (500 MHz, $CDCl_3$): δ 8.15 (d, *J* = 8.4 Hz, 1H), 7.87 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.76 (d, *J* = 8.2 Hz, 1H), 7.57–7.47 (m, 2H), 7.42 (dd, *J* = 8.2, 7.2 Hz, 1H), 7.38–7.28 (m, 6H), 4.61 (s, 2H), 4.18 (dd, *J* = 10.0, 6.9 Hz, 1H), 4.11 (ddd, *J* = 11.1, 7.4, 4.2 Hz, 1H), 4.05 (dd, *J* = 10.0, 3.8 Hz, 1H), 3.98 (dd, *J* = 8.7, 8.7 Hz, 1H, A part of ABM), 3.94 (dd, *J* = 9.1, 4.5 Hz, 1H, B part of ABM), 2.65 (br s, 1H).

**$^{13}$C NMR** (126 MHz, $CDCl_3$): δ 137.8, 135.4, 134.1, 131.8, 129.1, 128.6, 127.9, 127.8, 127.6, 126.4, 125.7, 125.4, 124.0, 123.0, 74.1, 73.7, 66.8, 42.0.

**HRMS** (ESI-TOF) for $C_{20}H_{20}NaO_2$ $(M+Na)^+$: calc. 315.1356; found 315.1356.

**HPLC** (Chiralpak IC): 5:95 *i*PrOH/Hex, 20 °C, 0.7 mL/min, λ = 220 nm, $T_{(S)}$ = 12.1 min, $T_{(R)}$ = 15.8 min, er = 90.9:9.1.




**(*S*)-2-benzyl-3-benzyloxypropan-1-ol (3-40):**

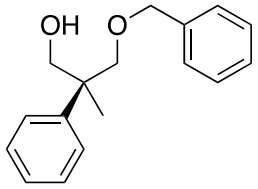
Synthesized according to General Procedure 3A from diol **3-33** (6.8 mg, 0.040 mmol). Purified by silica gel chromatography (5% to 10% ethyl acetate in hexanes) to yield a clear oil (10 mg, 90%). Spectral data are in agreement with that previously reported.[5]

**$^1$H NMR** (700 MHz, $CDCl_3$): δ 7.35 (dd, *J* = 8.0, 6.8 Hz, 2H), 7.33–7.25 (m, 5H) 7.20 (app t, *J* = 7.4 Hz, 1H), 7.16 (app d, *J* = 7.9 Hz, 2H), 4.51 (d, *J* = 11.9 Hz, 1H), 4.47 (d, *J* = 11.9 Hz, 1H),

3.74 (dd, *J* = 10.9, 3.7 Hz, 1H), 3.65 (dd, *J* = 10.9, 6.5 Hz, 1H), 3.59 (dd, *J* = 9.2, 4.2 Hz, 1H), 3.49 (dd, *J* = 9.2, 6.7 Hz, 1H), 2.68 (dd, *J* = 13.7, 7.5 Hz, 1H) 2.65 (dd, *J* = 13.7, 7.6 Hz, 1H), 2.44 (br s, 1H), 2.15 (dddddd, *J* = 7.3, 7.3, 7.3, 7.3, 3.9, 3.9 Hz, 1H).

**$^{13}$C NMR** (176 MHz, $CDCl_3$): δ 140.0, 138.0, 129.1, 128.5, 128.4, 127.8, 127.7, 126.1, 73.5, 72.9, 65.4, 42.6, 34.6.

**HPLC** (Chiralpak IC): 5:95 *i*PrOH/Hex, 20 °C, 0.7 mL/min, λ = 220 nm, $T_{(S)}$ = 9.2 min, $T_{(R)}$ = 8.4 min, er = 71.5:28.5.




**(*S*)-2-methyl-2-phenyl-3-benzyloxypropan-1-ol (3-41):**

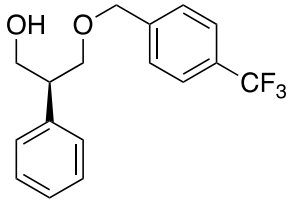
Synthesized according to General Procedure 3A from diol **3-34** (16 mg, 0.10 mmol). Purified by silica gel chromatography (5% to 50% ethyl acetate in hexanes) to yield a clear oil (25 mg, 99%).

**$^{1}$H NMR** (500 MHz, $CDCl_3$): δ 7.44–7.40 (m, 2H), 7.40–7.29 (m, 7H), 7.29–7.24 (m, 1H), 4.59 (d, *J* = 12.2 Hz, 1H), 4.56 (d, *J* = 12.1 Hz, 1H), 3.97 (dd, *J* = 11.9, 3.4 Hz, 1H), 3.86 (d, *J* = 9.1 Hz, 1H), 3.82 (dd, *J* = 11.8, 3.3 Hz, 1H), 3.66 (d, *J* = 9.1 Hz, 1H), 2.34 (br s, 1H), 1.38 (s, 3H).

**$^{13}$C NMR** (126 MHz, $CDCl_3$): δ 143.6, 138.0, 128.49, 128.46, 127.8, 127.6, 126.58, 126.56, 77.6, 73.6, 70.4, 44.0, 21.2.

**HRMS** (ESI-TOF) for $C_{17}H_2NaO_2$ $(M+Na)^+$**:** calc. 279.1356; found 279.1356.

**HPLC** (Chiralpak IA): 2:98 *i*PrOH/Hex, 20 °C, 0.5 mL/min, λ = 210 nm, $T_{(S)}$ = 16.2 min, $T_{(R)}$ = 17.9 min, er = 77.9:22.1.




**(*S*)-2-phenyl-3-(*p*-trifluoromethylbenzyloxy)propan-1-ol (3-42):**

Synthesized according to General Procedure 3A from diol **3-2** (9.2 mg, 0.060 mmol). Purified by silica gel chromatography (5% to 20% ethyl acetate in hexanes) to yield a yellow oil (19 mg, 99%).

**$^{1}$H NMR** (700 MHz, $CDCl_3$): δ 7.59 (d, *J* = 7.9 Hz, 2H), 7.40 (d, *J* = 7.9 Hz, 2H), 7.33 (dd, *J* = 8.2, 6.9 Hz, 2H), 7.28 – 7.25 (m, 1H), 7.23 (d, *J* = 8.4 Hz, 2H), 4.61 (d, *J* = 13.2 Hz, 1H), 4.59 (d, *J* = 13.2 Hz, 1H), 4.02 (dd, *J* = 10.9, 7.0 Hz, 1H), 3.90 (dd, *J* = 11.0, 5.6 Hz, 1H), 3.84 (dd, *J* = 9.3, 8.2 Hz, 1H), 3.79 (dd, *J* = 9.2, 5.3 Hz, 1H), 3.22 (dddd, *J* = 7.8, 7.8, 5.6, 5.6 Hz, 1H), 2.01 (br s, 1H).

**$^{13}$C NMR** (176 MHz, $CDCl_3$): δ 142.1, 139.5, 130.0 (q, *J* = 32.3 Hz), 128.8, 128.1, 127.5, 127.2, 125.4 (q, *J* = 3.8 Hz), 124.2 (q, *J* = 271.8 Hz), 73.6, 72.6, 66.1, 48.0.

**$^{19}$F NMR** (376 MHz, $CDCl_3$): δ –62.5.

**HRMS (EI)** for $C_{17}H_{17}O_2F_3$: calc. 310.1181; found 310.1179.

**HPLC** (Chiralpak IC): 2:98 *i*PrOH/Hex, 20 °C, 0.5 mL/min, λ = 220 nm, $T_{(S)}$ = 16.7 min, $T_{(R)}$ = 17.5 min, er = 88.8:11.2

## 3.6 References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# Chapter 4 – Conclusions

## 4.1 Conclusions and Future Directions

The diol moiety is present in a variety of important natural products and drugs. Structurally complex molecules can also be derived from diol-containing compounds. Traditional stoichiometric diol functionalization methods result in hazardous wastes and/or require preformation of the substrate into a more activated compound. Therefore, there is still a need for mild methods to selectively functionalize diol/polyol compounds. Boronic acids have emerged as useful catalysts in nucleophilic activation reactions, especially in diol functionalization due to their advantageous properties and high affinity toward diol moieties.

In Chapter 2, the discovery of known hemiboronic acid 10-hydroxy-10,9-boroxarophenanthrene (**2-1b**) was demonstrated to be useful as a catalyst in the selective monofunctionalization of diols. The hemiboronic acid is easy to prepare and can form a tetrahedral adduct with diols in the presence of a weak base. The reactivity and selectivity profile were similar to known diarylborinic acid catalyzed processes where a key tetrahedral diol-boron adduct was observed to be the active catalytic species. Monobenzylation and monosulfonylation were demonstrated for several diol/polyol substrates. This method is however optimal for substrates containing *cis*-1,2-diol moieties. Future work includes discovering a boronic acid that can recognize *trans*-diol moieties for stereoselective functionalization reactions. Furthermore, a class of boronic acids to be used in catalyst-controlled regioselective functionalization of unprotected carbohydrate derivatives would also greatly advance the field of carbohydrate chemistry. 10-Hydroxy-10,9-boroxarophenanthrene **2-1b** may also be useful in photocatalytic transformations of alcohols to activate α-C-H bonds toward homolytic cleavage that may further react with radical acceptors (Figure 4-1). Work along these lines is currently ongoing in the Hall Laboratory.

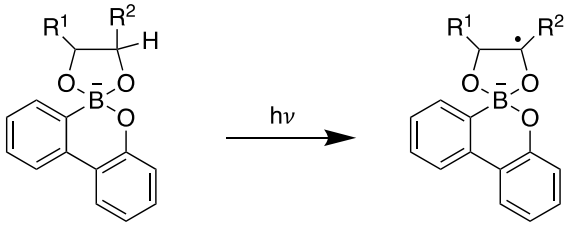


Figure 4-1: Potential C-H activation from a boron-diol complex

Chapter 3 described an extension of the work described in Chapter Two where a chiral hemiboronic acid derivative was used in asymmetric catalysis. The use of a chiral organoboron catalyst toward enantioselective transformations of diols is currently limited. The synthesis of novel chiral hemiboronic acids were achieved, and a trityl-containing catalyst (**3-25**) was shown to be effective in enantioselective desymmetrization of achiral diols via *O*-benzylation. This mild method can be performed at room temperature and only a weak inorganic base is needed. The sterically hindering trityl moiety in **3-25** is believed to be responsible for the discrimination of the enantiotopic hydroxy groups. In this process, 2-aryl-1,3-propanediol analogs were optimal substrates to achieve enantioselectivities greater than 80% in the formation of monobenzylated 1,3-diols in excellent yields. Future work includes the design and synthesis of a chiral hemiboronic acid catalyst that achieve even greater levels of enantioselectivity (>90% ee). A potential approach to achieve higher levels of enantioselectivity is to introduce a methyl group *ortho* to the boron atom in the chiral catalyst to act as a conformational steric block (Figure 4-2). Preliminary calculations show a larger difference in the energy (ΔE = 10.6 kJ/mol) of the two conformers if an *ortho* methyl substituent is present that would heavily favour the substituent at the 2-position of the diol to be equatorial (Figure 4-2).

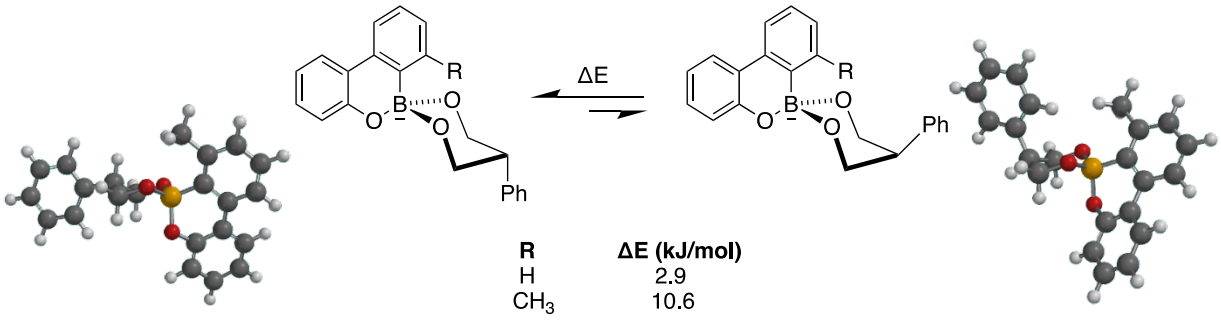


Figure 4-2: Possible *ortho*-substituted hemiboronic acid catalyst

Desymmetrization of other useful prochiral diol substrates should also be investigated. Chiral hemiboronic acid catalysts may also have application in selective functionalization of carbohydrates where the regioselectivity profile may be heavily influenced (ie. equatorial vs. axial -OH functionalization). Dual catalysis/cooperative catalysis should also be explored to develop a method that can produce other useful enantioenriched intermediates using other electrophiles than just benzyl halides (Figure 4-3). Application of this methodology may be useful in the asymmetric synthesis of a natural product or drug.

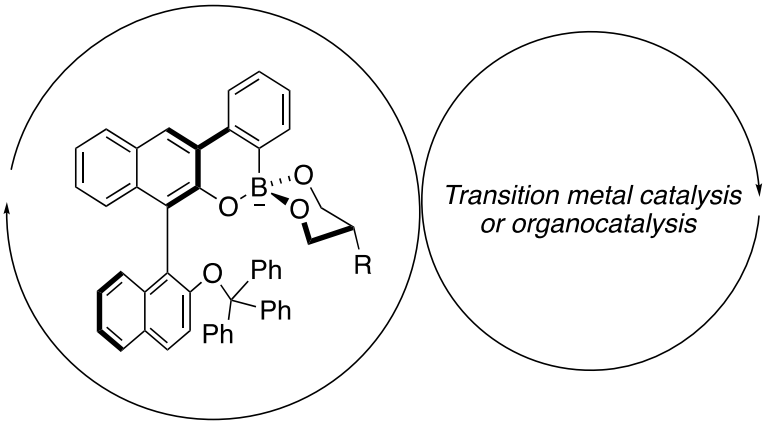


Figure 4-3: Potential application of a hemiboronic acid catalyzed process in dual catalysis/cooperative catalysis

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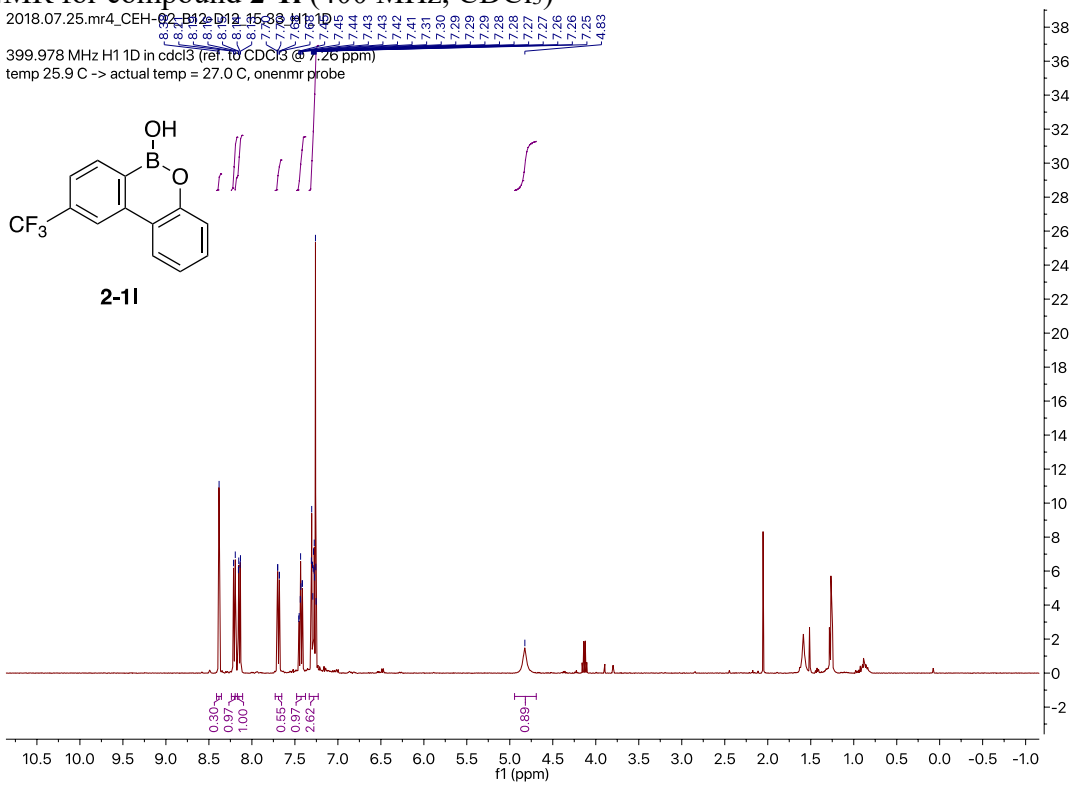
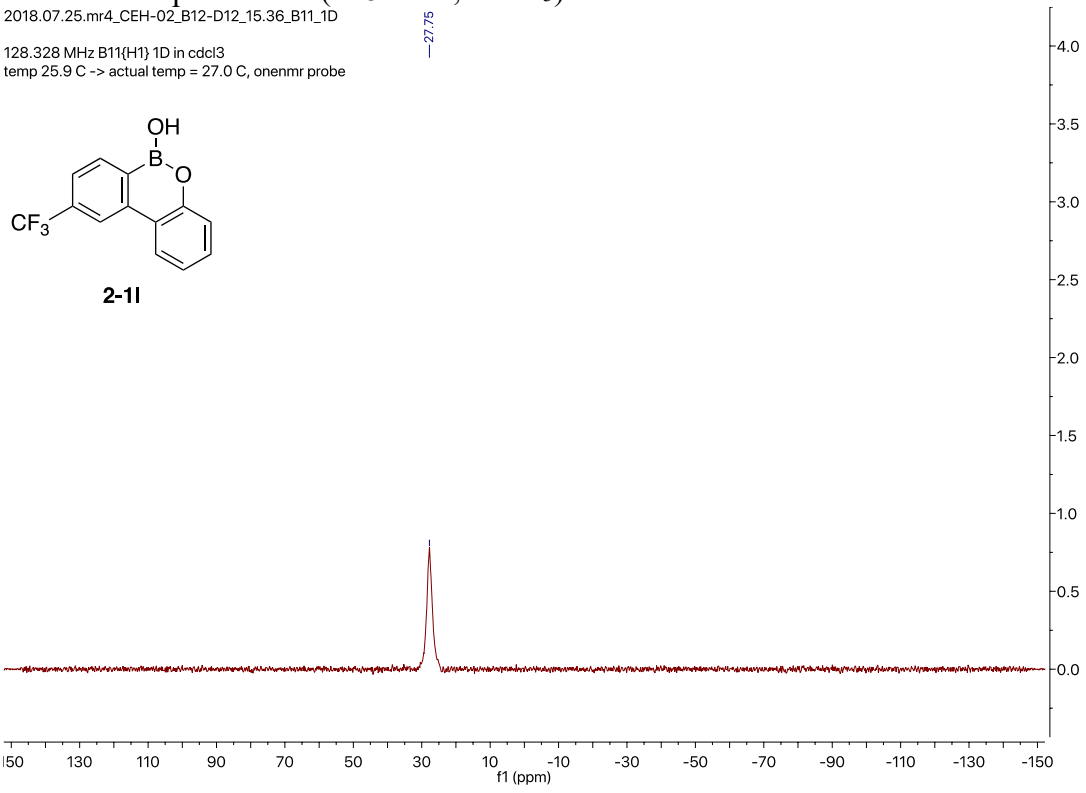
# Appendices

## Appendix 1: Select Copies of NMR Spectra of Compounds in Chapter Two

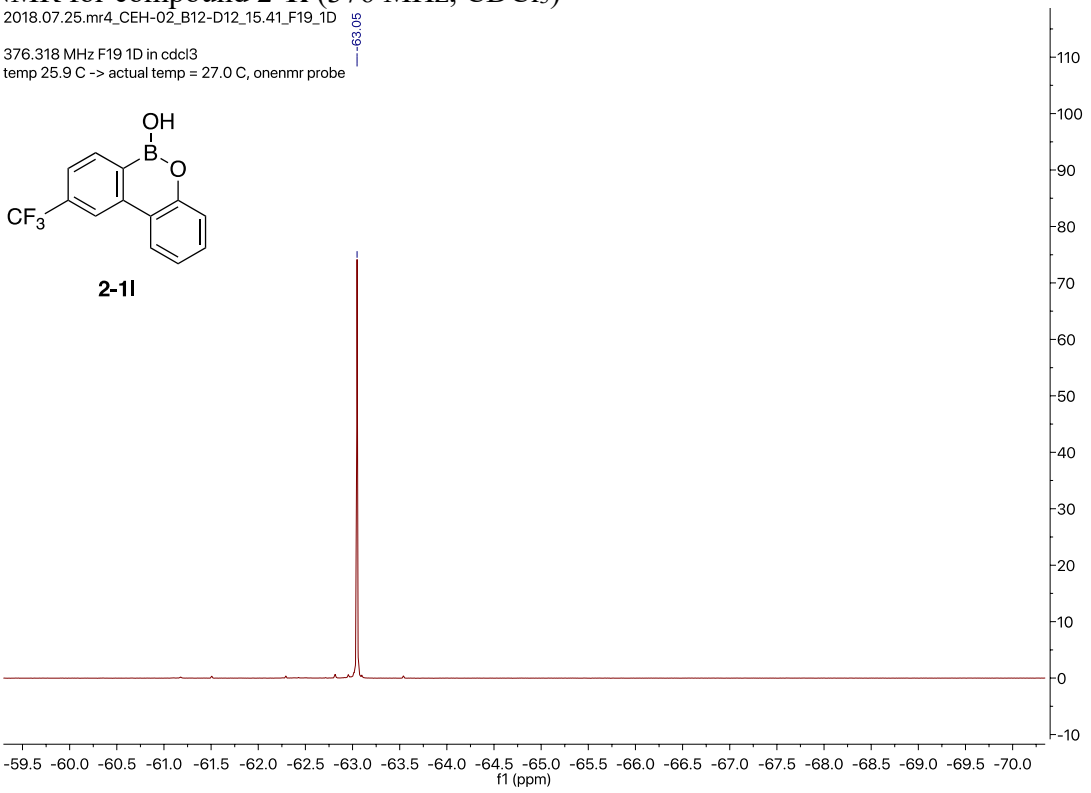
$^{1}$H-NMR for compound **2-1l** (400 MHz, $CDCl_3$)



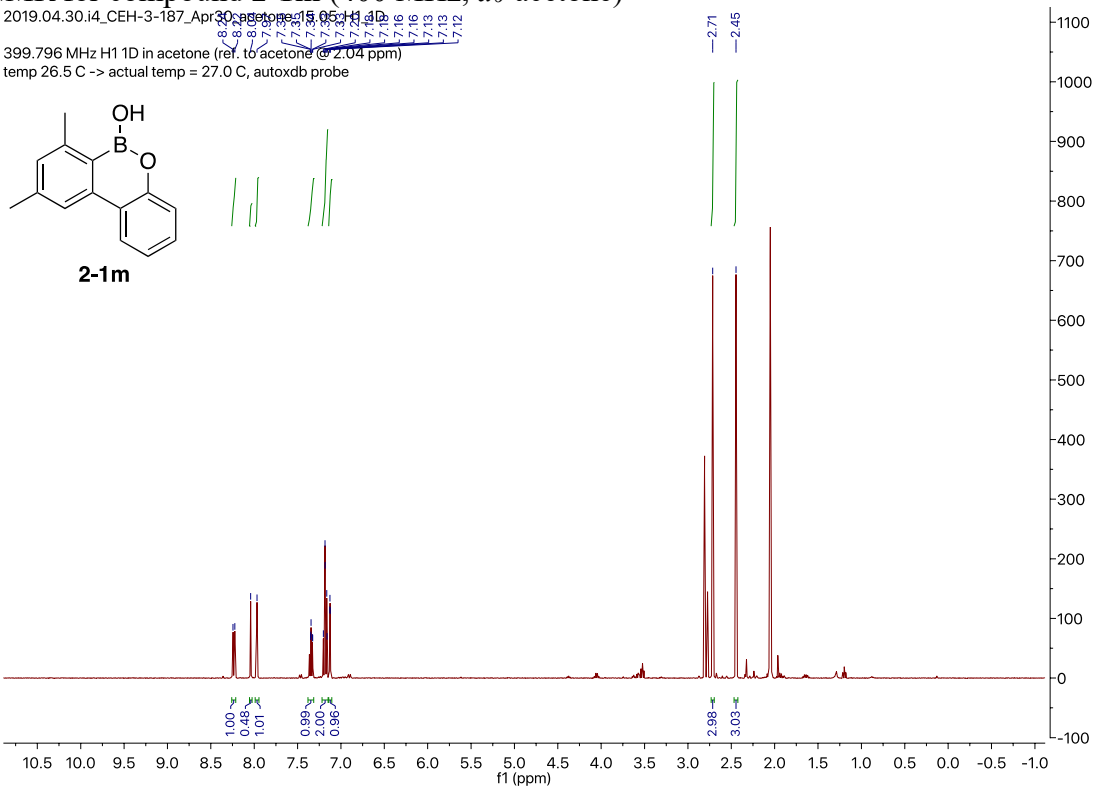

$^{11}$B-NMR for compound **2-1l** (128 MHz, $CDCl_3$)



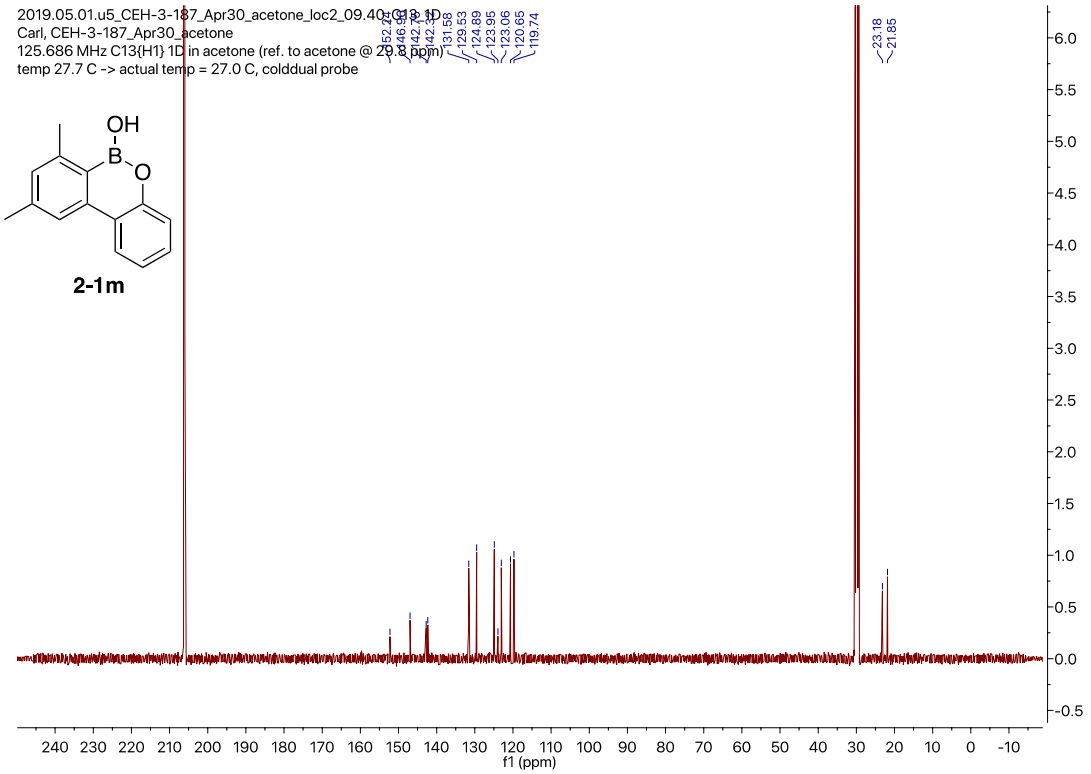
$^{19}$F-NMR for compound **2-1l** (376 MHz, $CDCl_3$)



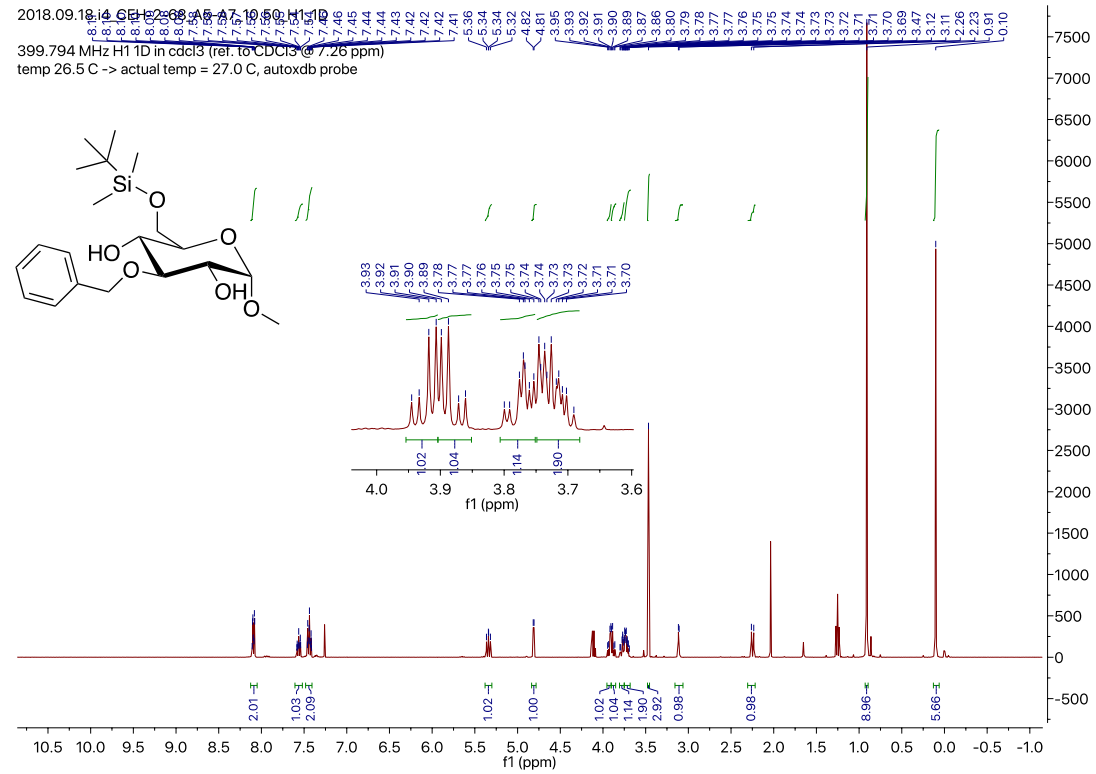

$^{1}$H-NMR for compound **2-1m** (400 MHz, *d*$_6$-acetone)



$^{13}$C-NMR for compound **2-1l** (126 MHz, *d*$_6$-acetone)

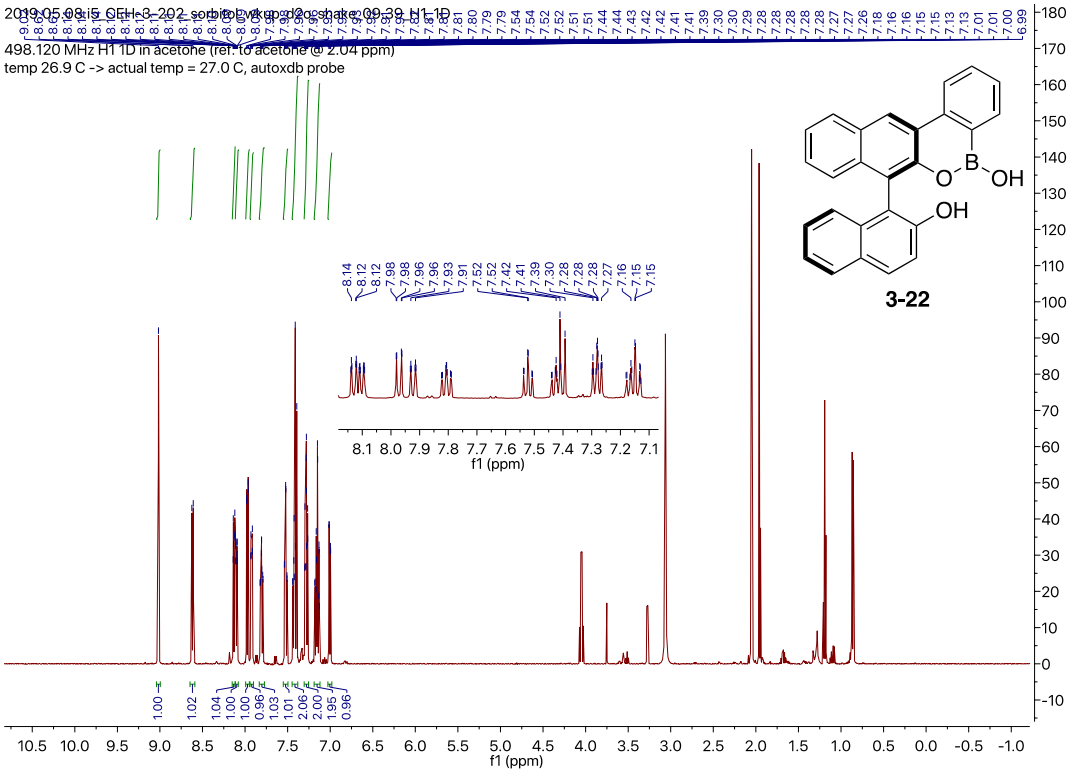



$^{1}$H-NMR for compound **methyl-6-(tert-butyldimethylsilyloxy)-3-O-benzyl-α-D-glucopyranoside** (400 MHz, $CDCl_3$)

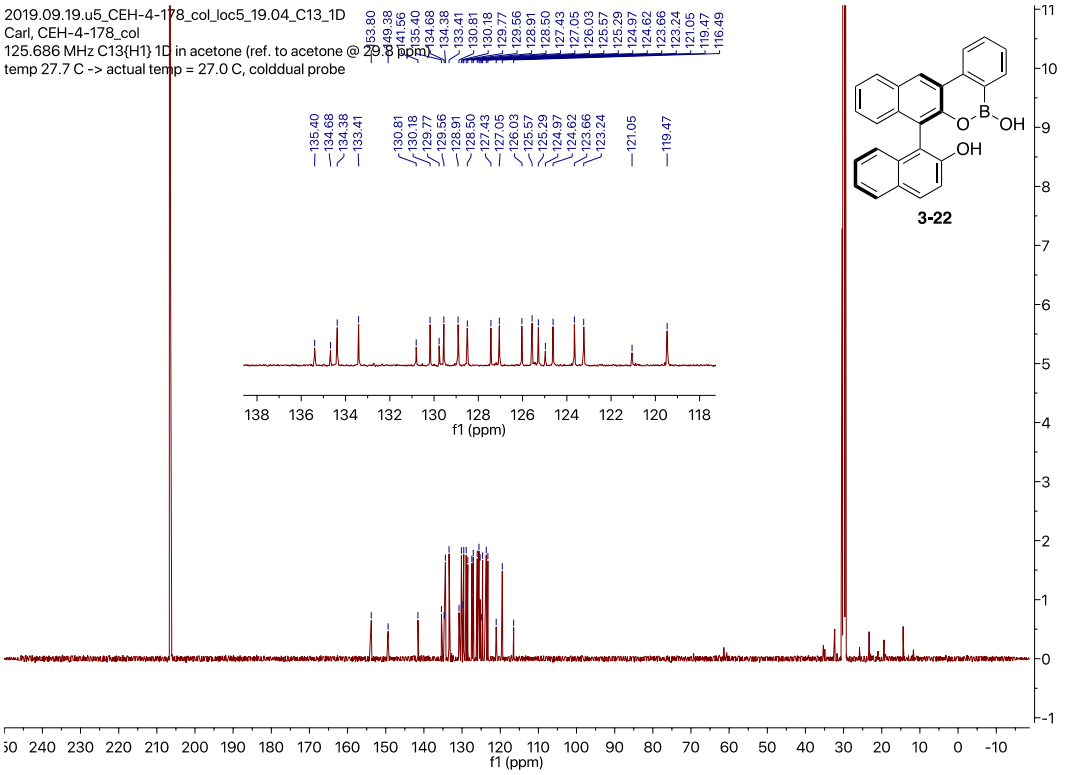


## Appendix 2: Select Copies of NMR Spectra of Compounds in Chapter Three

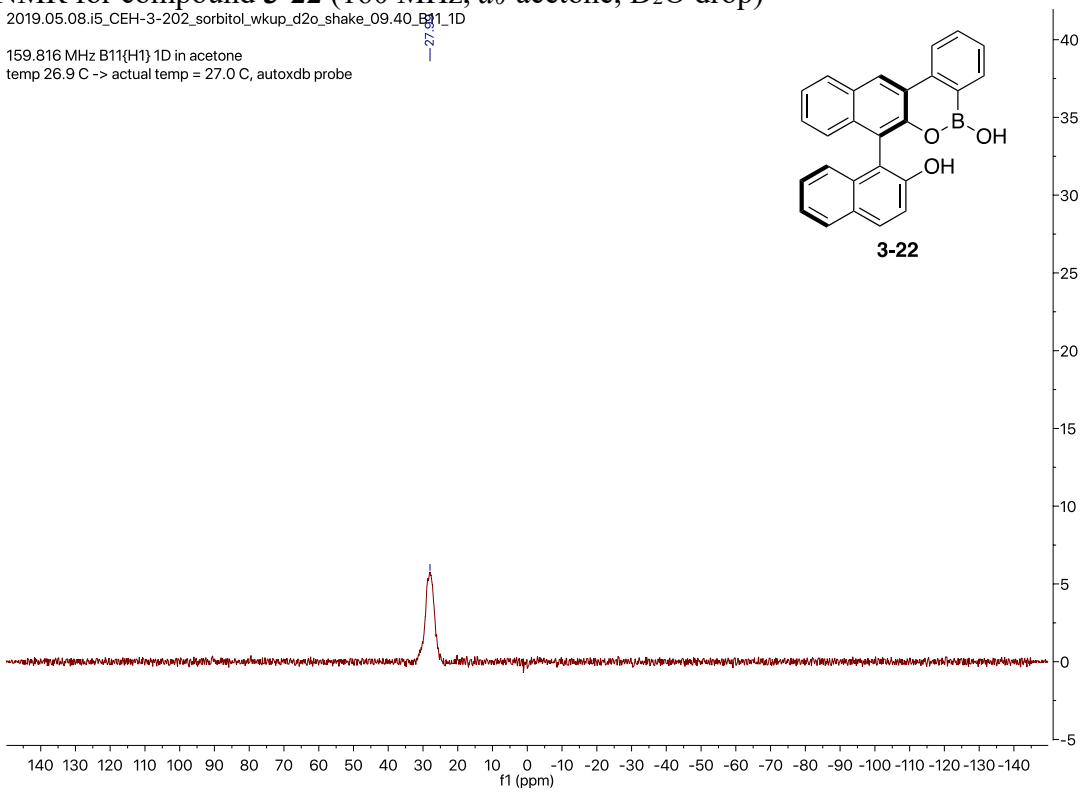
$^{1}$H-NMR for compound **3-22** (500 MHz, *d*$_6$-acetone, D$_2$O drop)



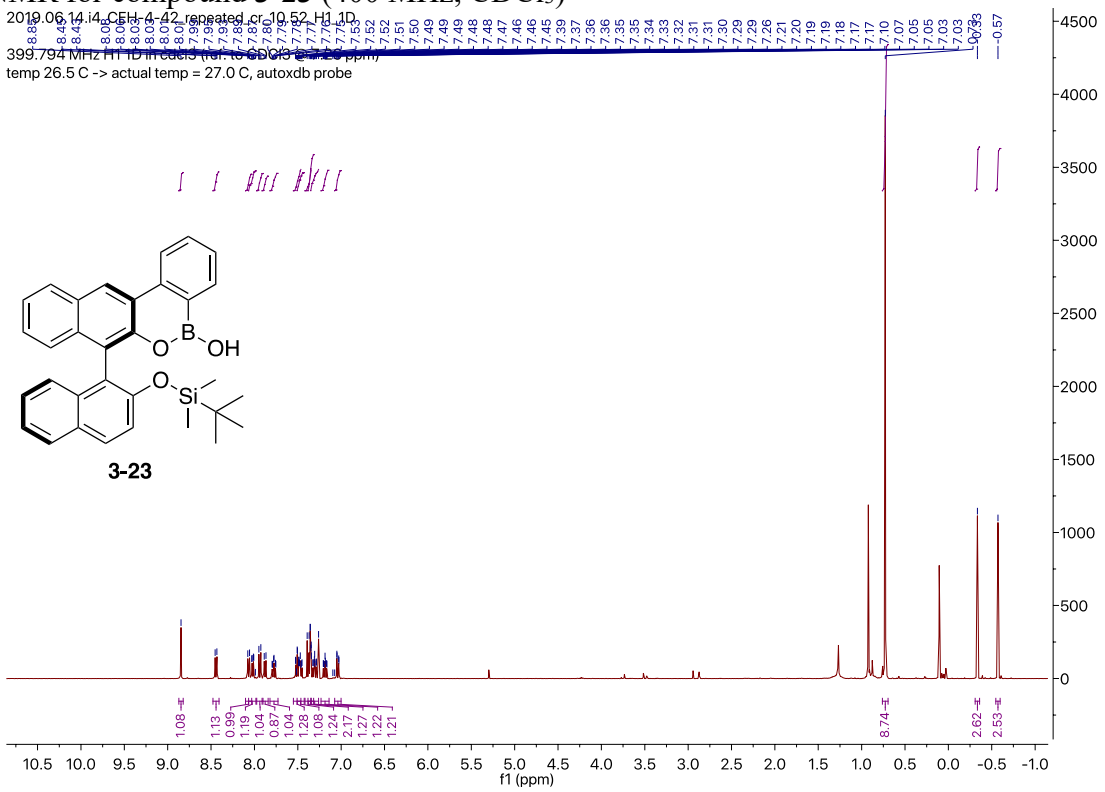

$^{13}$C-NMR for compound **3-22** (126 MHz, *d*$_6$-acetone, D$_2$O drop)



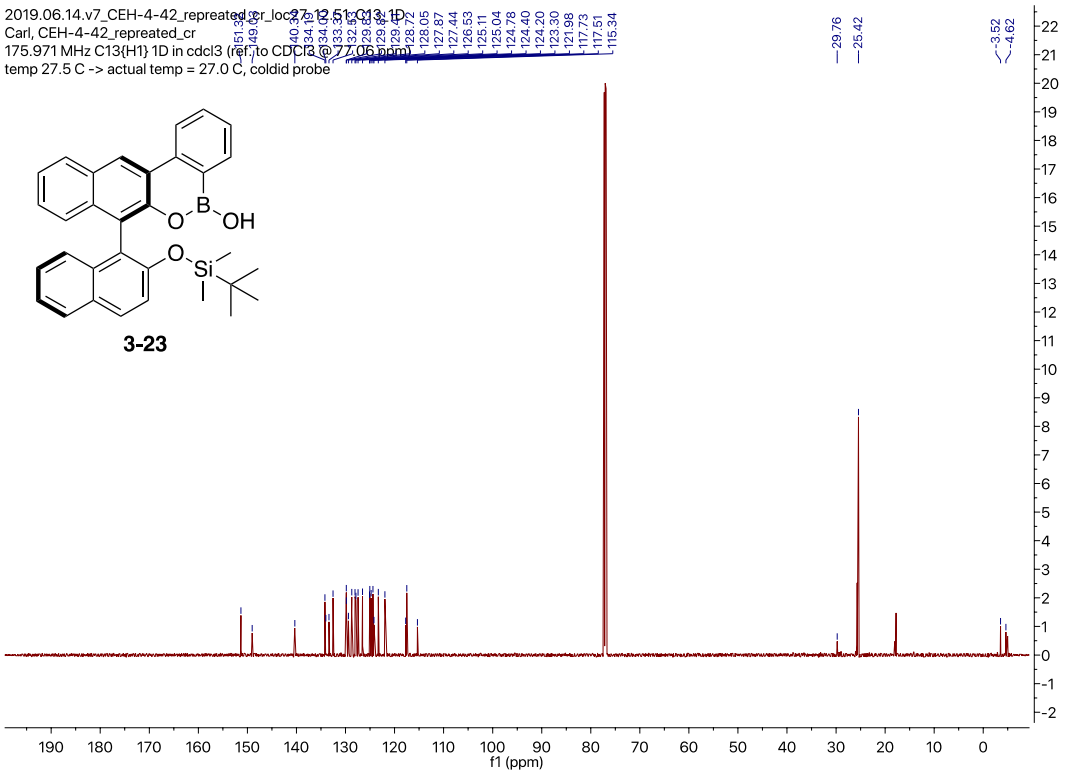
$^{11}$B-NMR for compound **3-22** (160 MHz, *d*$_6$-acetone, D$_2$O drop)



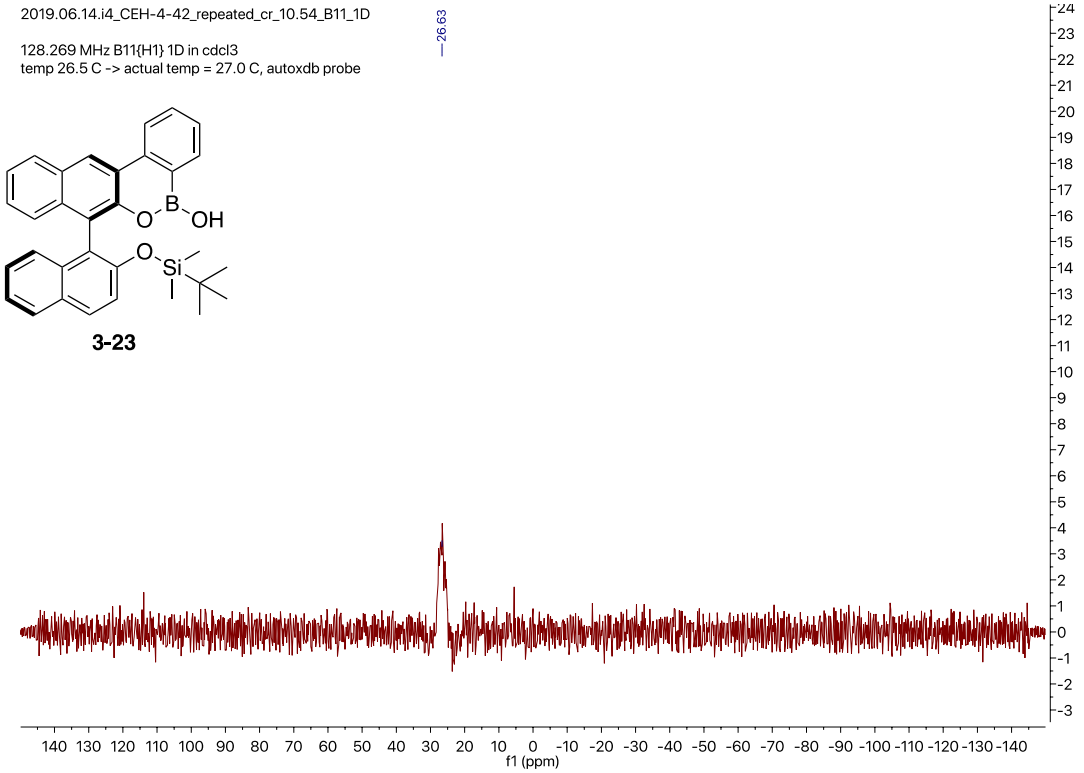

$^{1}$H-NMR for compound **3-23** (400 MHz, CDCl$_3$)



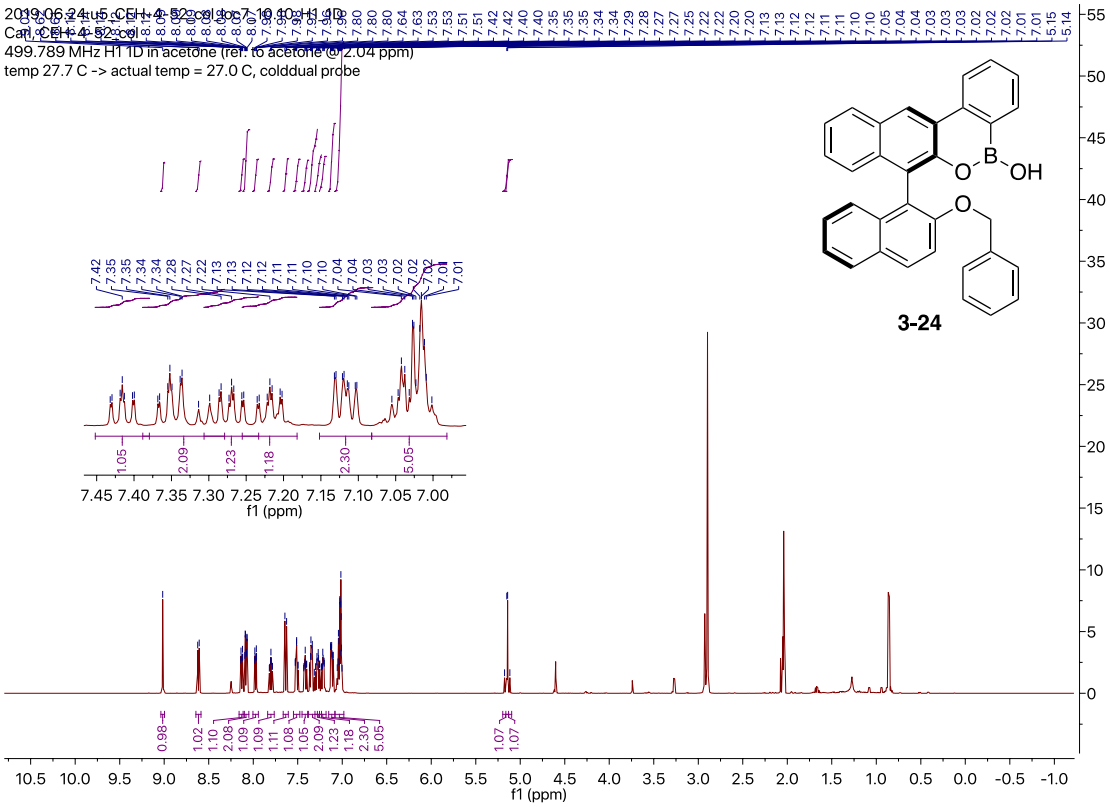
$^{13}$C-NMR for compound **3-23** (176 MHz, $CDCl_3$)



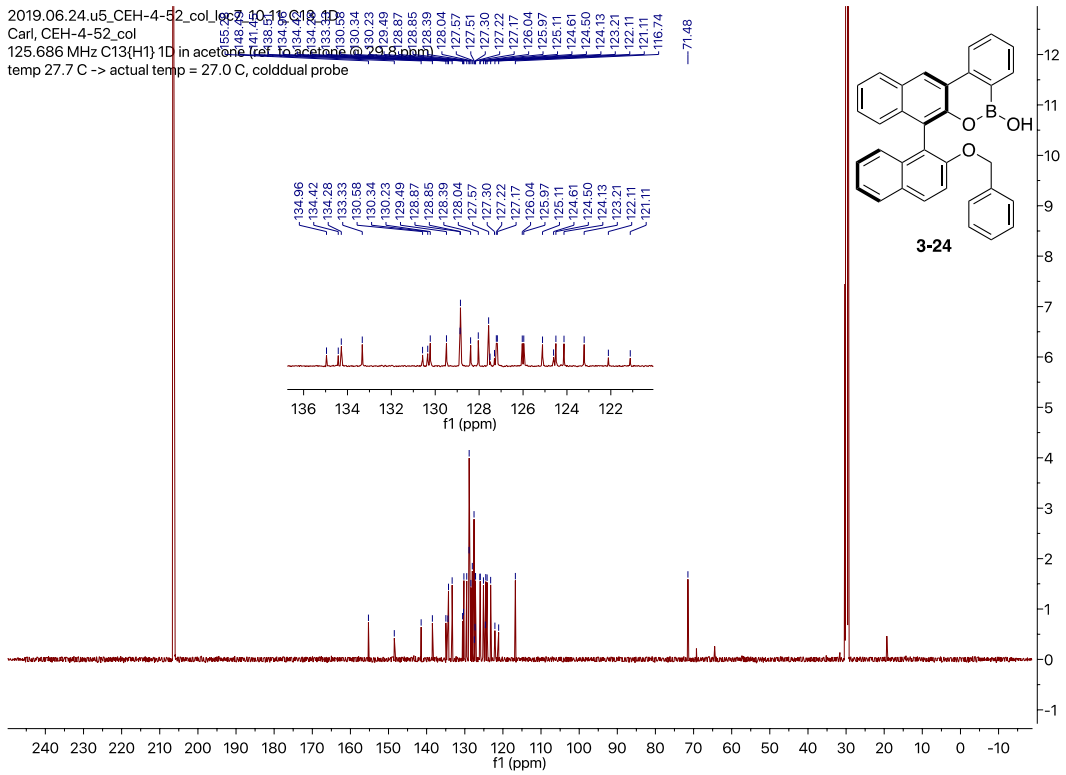

$^{11}$B-NMR for compound **3-23** (128 MHz, $CDCl_3$)



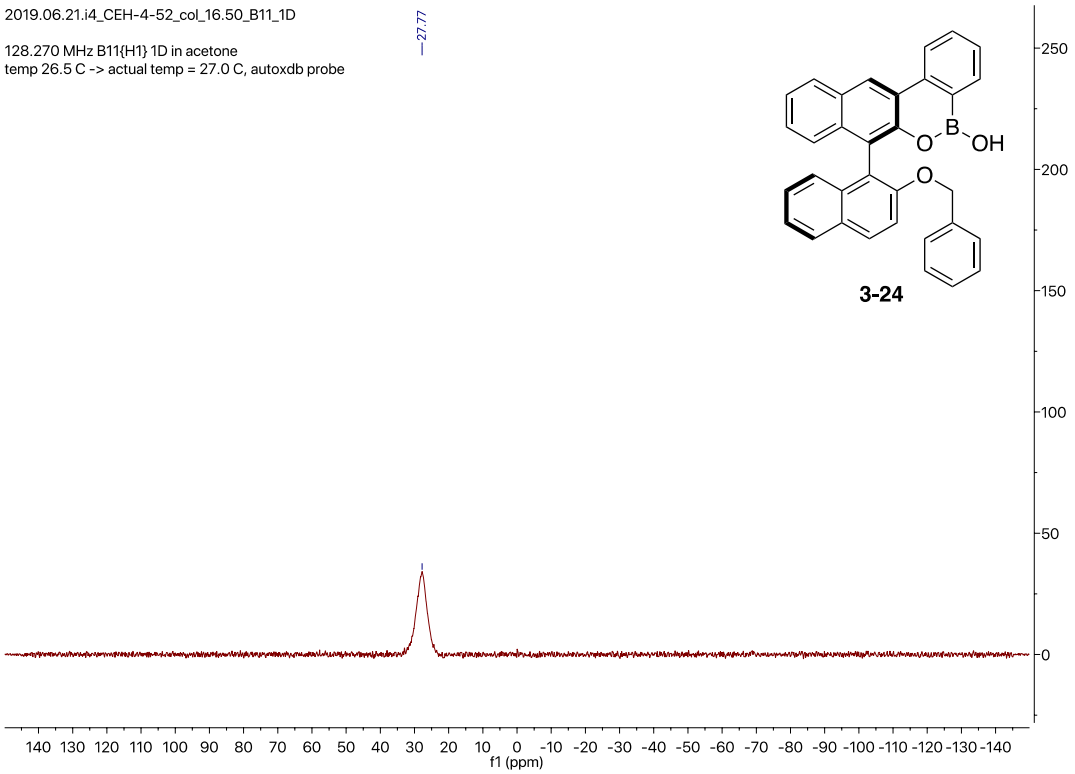
[1]H-NMR for compound **3-24** (500 MHz, *d*6-acetone, D2O drop)



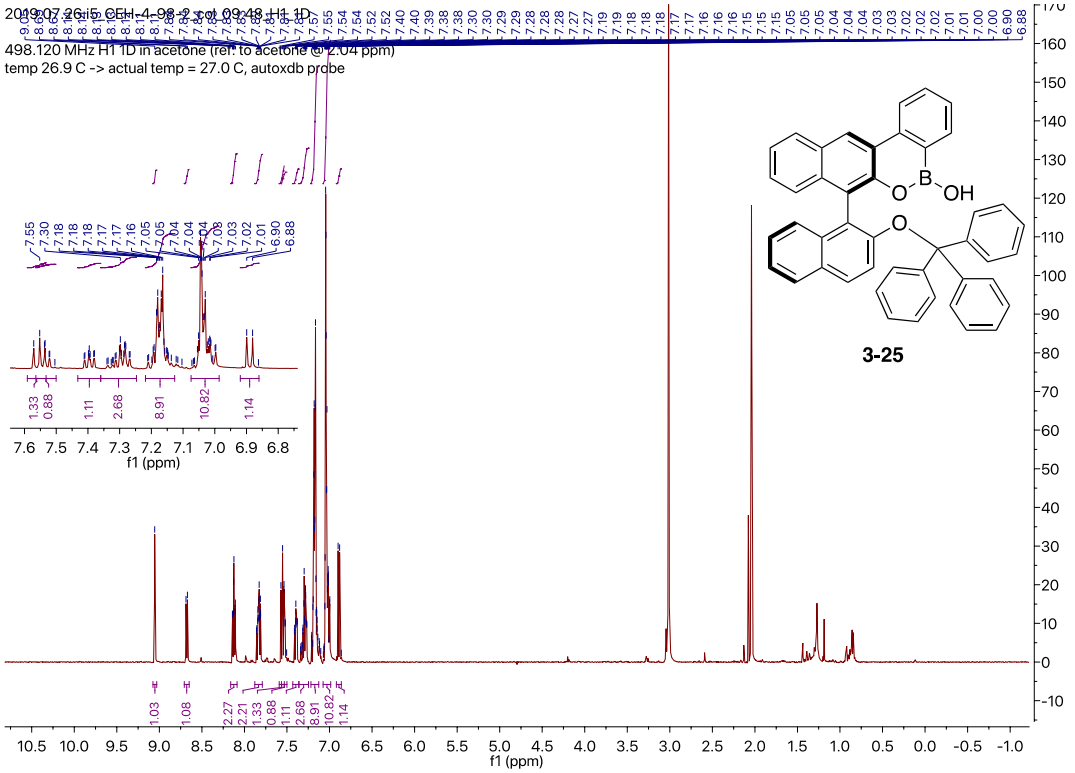

[13]C-NMR for compound **3-24** (126 MHz, *d*6-acetone, D2O drop)



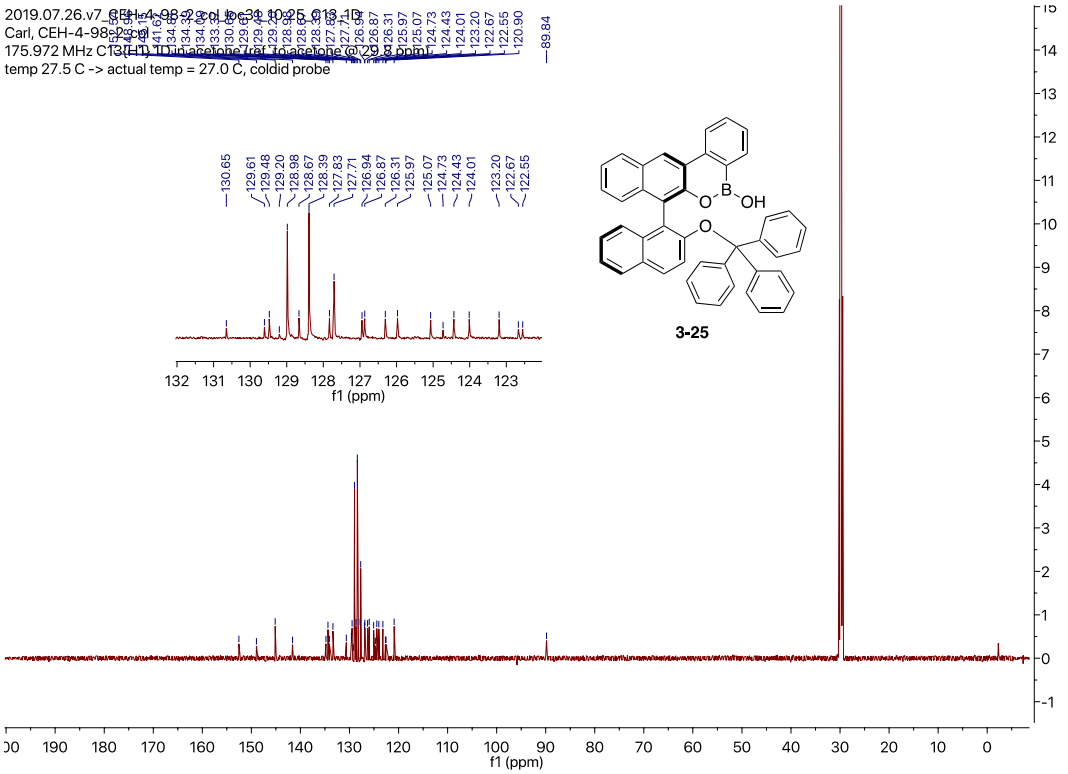
$^{11}$B-NMR for compound **3-24** (128 MHz, *d*$_6$-acetone, D$_2$O drop)



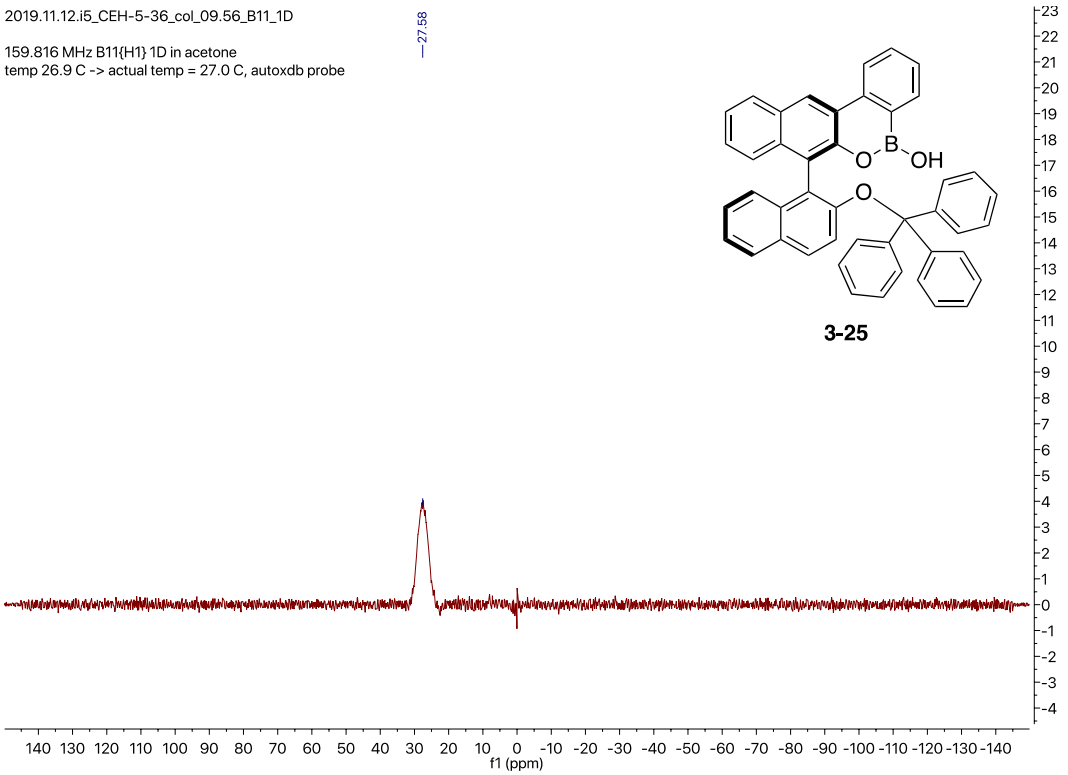

$^{1}$H-NMR for compound **3-25** (500 MHz, *d*$_6$-acetone, D$_2$O drop)



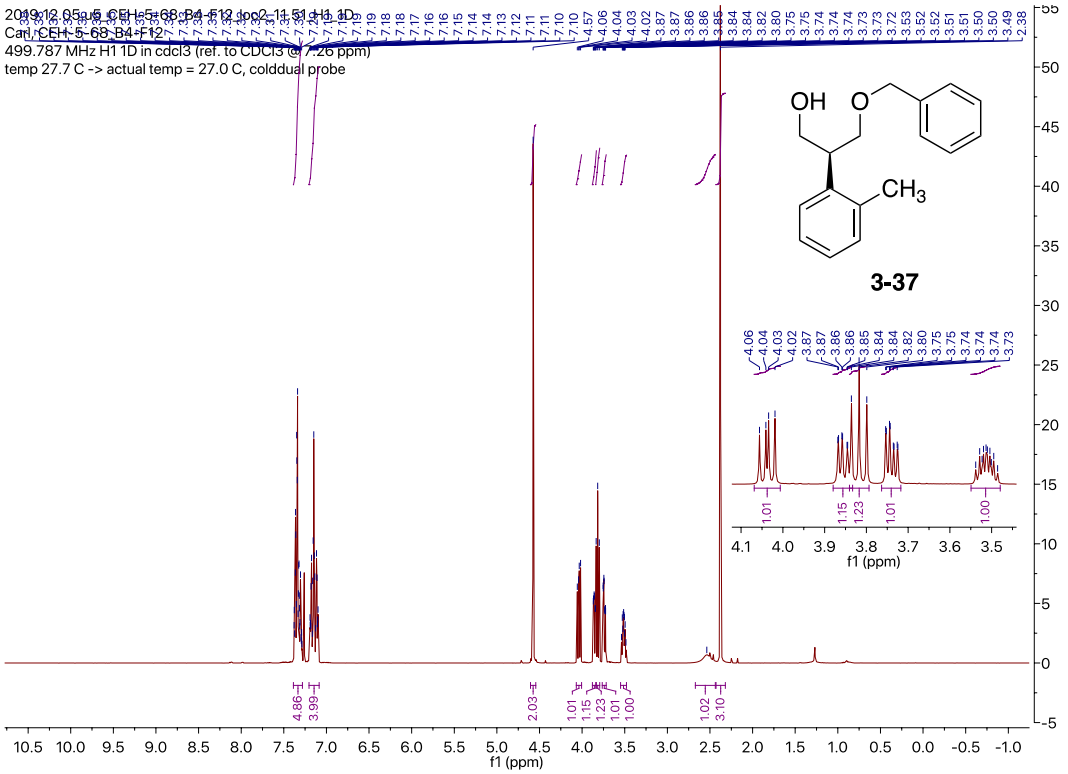
$^{13}$C-NMR for compound **3-25** (126 MHz, $d_6$-acetone, $D_2O$ drop)



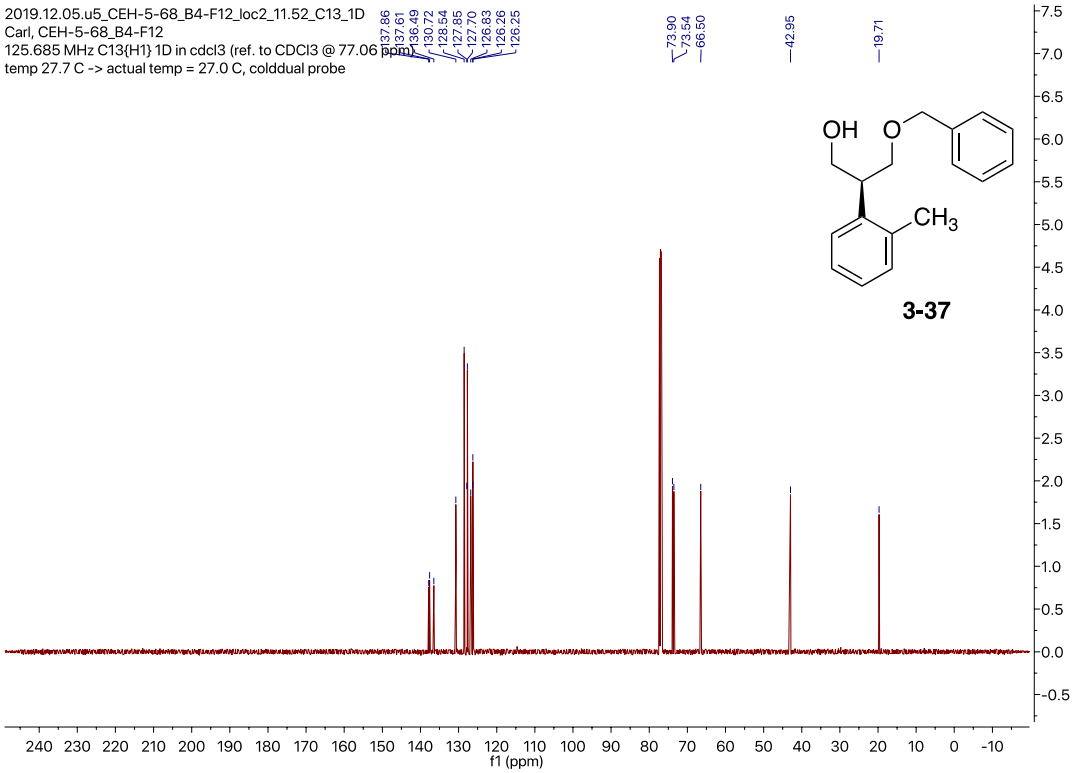

$^{11}$B-NMR for compound **3-25** (160 MHz, $d_6$-acetone, $D_2O$ drop)



$^{1}$H-NMR for compound **3-37** (500 MHz, $CDCl_3$)

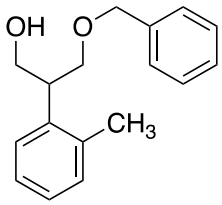


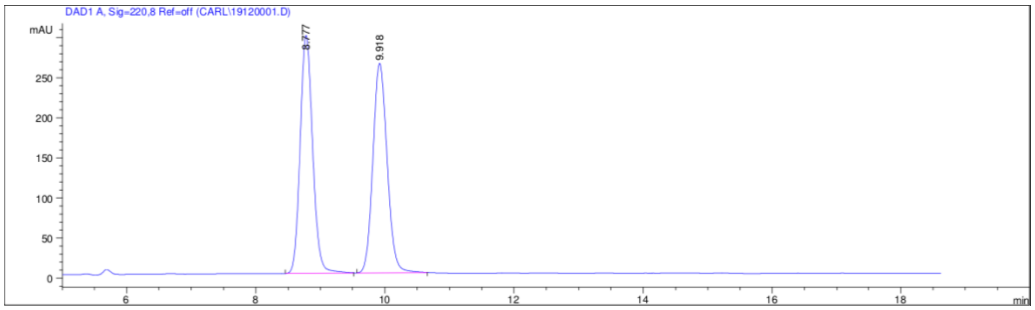

$^{13}$C-NMR for compound **3-37** (126 MHz, $CDCl_3$)



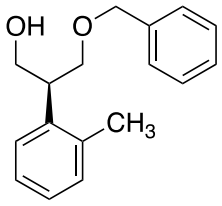
## Appendix 3: Select Copies of Chromatograms for Enantiomeric Excess Measurement

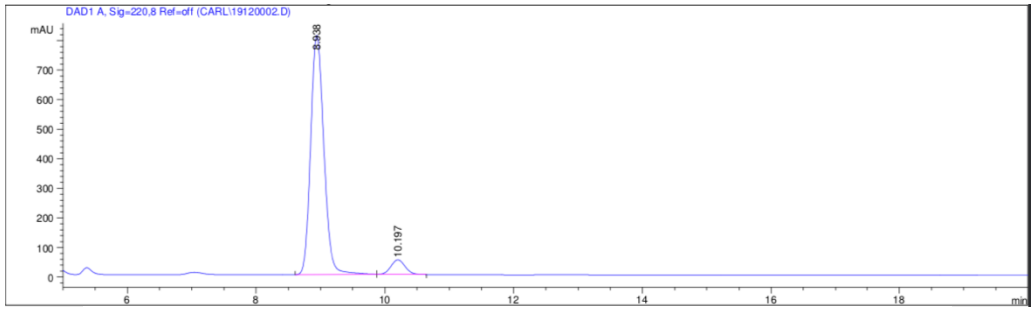
HPLC data for racemic and chiral for compound **3-37**




| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 8.777 | BB | 0.2103 | 4031.09131 | 297.09723 | 49.9999 |
| 2 | 9.918 | BB | 0.2396 | 4031.10010 | 261.90750 | 50.0001 |
| Totals : | | | | 8062.19141 | 559.00473 | |




| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 8.938 | BV | 0.2233 | 1.16088e4 | 809.49902 | 93.6868 |
| 2 | 10.197 | VB | 0.2430 | 782.27167 | 49.87885 | 6.3132 |
| Totals : | | | | 1.23911e4 | 859.37788 | |

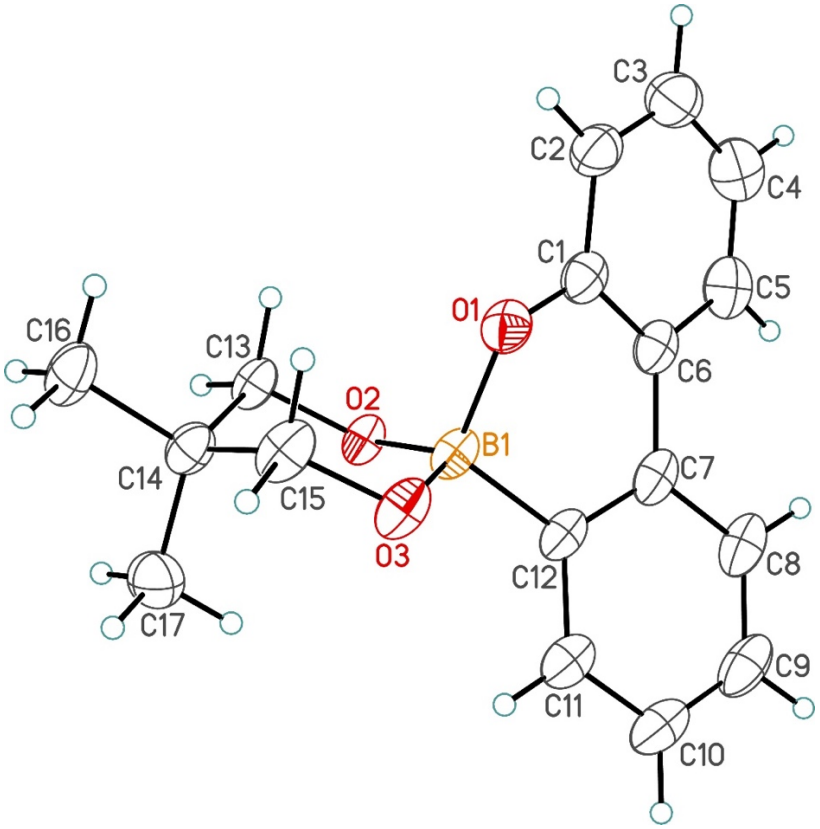
**Appendix 4: Crystal Structure Report**

**XCL Code:** DGH1919 **Date:** 15 November 2019

**Compound:** tetrabutylammonium 5',5'-dimethylspiro[dibenzo[1,2]oxaborinine-6,2'-[1,3,2]dioxaborinan]-6-uide

**Formula:** $C_{33}H_{54}BNO_3$

**Supervisor:** D. G. Hall **Crystallographer:** M. J. Ferguson

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