PART I: SYNTHESIS AND CROSS-COUPLING OF THE C1-C12 PRIMARY ORGANOBORANE BUILDING BLOCK OF AMPHOTERICIN B;

PART II: SITE- AND STEREORETENTIVE CROSS-COUPLING OF UNACTIVATED SECONDARY BORONIC ACIDS INSPIRED BY AMPHOTERICIN B

BY

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DISSERTATION
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Abstract

In contrast to peptides, oligonucleotides, and increasingly oligosaccharides, which can be rapidly and flexibly assembled in a systematic fashion from pre-fabricated building blocks, the synthesis of small molecules has remained a relatively slow, complex, and unsystematized process. With the potential of addressing these limitations, an analogous building block-based approach for making small molecules has been proposed in our group. In the idealized limit, a collection of off-the-shelf boronic acid-based building blocks having all of the required functional groups pre-installed in the correct oxidation states and with the desired stereochemical relationships are readily assembled using only a single cross-coupling reaction repeatedly.

Such an iterative cross-coupling (ICC) strategy has been applied in our proposed total synthesis of clinically valuable polyene natural product amphotericin B (AmB). In our retrosynthetic analysis, AmB is disconnected into four bifunctional building blocks and these building blocks are assembled via an iterative deprotection/cross-coupling fashion. Boronic acid-based cross-coupling reactions (Suzuki-Miyaura reaction) are most commonly executed to form Csp²-Csp² bond. In practice, due to the lack of consecutive Csp² centers on C1-C19 AmB skeleton, Csp³-Csp² cross-coupling is required to assemble the polyol subunit BB1.
The synthesis of BB1 turned out to be challenging. Moreover, a Csp$^3$-Csp$^2$ cross-coupling reaction was not readily available for the connection of BB1 and the rest of the molecule. Three generations of syntheses were developed and finally we reached a modular and efficient solution of the synthesis and assembly of BB1. Our total synthesis of the doubly-C13 labeled protected AmB is a good example to showcase the power of the ICC approach to small molecule synthesis. Also from the synthesis, it is clear that building block scopes for ICC are currently restricted to primarily Csp$^2$ organoborons.

Unactivated Csp$^3$ organoborons are often unstable and methods to access these building blocks are limited. In addition, at present, unactivated Csp$^3$ organoborons cannot be cross-coupled with the same levels of efficiency that is now accessible with many of their Csp$^2$ and activated Csp$^3$ hybridized counterparts. In order to address these challenges, in my thesis research, I developed three novel methods to make Csp$^3$ organo-N-methyliminodiacetic acid (MIDA) boronate building blocks that are indefinitely bench-top stable. Additionally, inspired by our ongoing total synthesis of AmB, I discovered a solution to the long-standing problem of site-, and stereoretentive cross-coupling of unactivated secondary Csp$^3$ boronic acids.
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Ac  acetate

AmB  amphotericin B

BIDA  \(((1S,2S)-\text{N-2-(benzyloxy)cyclopentyl})\text{-imino-diacetic~acid}\)

C35deOAmB  C35-deoxy amphotericin B

(R)-CBS  \((R)-(+)\text{-2-Methyl-CBS-oxazaborolidine}\)

CMPT  2-chloro-6-methyl-pyridinium triflate

CSA  \((\pm)-10\text{-camphorsulfonic~acid}\)

DCM  dichloromethane

DIBAL  diisobutylaluminum hydride
<table>
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<tr>
<th>Abbreviation</th>
<th>Chemical Name</th>
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<tbody>
<tr>
<td>DMAP</td>
<td>4-(dimethylamino)-pyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethyl formamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
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<tr>
<td>dppf</td>
<td>1,1’-bis(diphenylphosphino)ferrocene</td>
</tr>
<tr>
<td>FMOC-OSu</td>
<td>9-fluorenylmethyl $N$-succinimidyl carbonate</td>
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<td>HPLC</td>
<td>high performance liquid chromatography</td>
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<tr>
<td>MeCN</td>
<td>acetonitrile</td>
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<td>MIDA</td>
<td>$N$-methyliminodiacetic acid</td>
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<tr>
<td>S-Phos</td>
<td>2-dicyclohexylphosphino-2’,6’-dimethoxybiphenyl</td>
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<tr>
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<tr>
<td>SPhos-Pd-Cycle G2</td>
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<tr>
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<td>X-Phos</td>
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Chapter 1

Introduction

Organic synthesis is considered by many a form of art.¹ Indeed, target oriented total synthesis requires exquisite design based on established reactions and more often, the invention of new methodologies to close the gap from the unknown. For the past few years, I have had the opportunity to work with my colleagues on the synthesis of the interesting structurally-complex, biologically-active polyene macrolide natural product amphotericin B (AmB).
The thesis is structured into two parts. In chapters 2 to 4, I will discuss our efforts towards an iterative cross-coupling (ICC) based strategy for the total synthesis of polyene macrolide natural product AmB. In particular, I will focus on my synthesis of the C1-C12 building block (BB1) and a series of attempts to couple this building block to the C13-C23 bifunctional building block (BB2) that was synthesized by my colleagues. To establish the coupling between BB1 and BB2 required a primary Csp³ organoboron-based cross-coupling reaction that turned out to be very challenging. I went through three generations of synthesis to finally reach an efficient route to establish the C1-C23 skeleton of AmB.

![Diagram](image)

The experience encouraged us to search for a general solution to cross-couple both primary and secondary Csp³ boronic. Such a methodology would greatly expand the power of the ICC strategy in small molecule synthesis. Building on methods of primary boronic acid cross-coupling that is described in chapter 3, I will discuss my discovery of a stereoretentive cross-coupling of unactivated secondary Csp³ boronic acids in chapter 5.
1.1 An introduction to the biology and chemistry of amphotericin B (AmB)

1.1.1 Invasive fungal infections and polyene macrolides

The incidence of systemic fungal infections has continued to rise over the past three decades. The infectious diseases can be life threatening particularly to patients with compromised immune systems. From 1979 to 2000, the annual number of cases of sepsis caused by fungal organisms increased by an astonishing 207%. In fact, infections stemming from the pathogenic yeast *Candida albicans* represent the fourth most common cause of hospital-acquired bloodstream infections, and the mortality rate for these infections is 40%. Battling this lethal disease has cost the healthcare system a heavy economic burden. In 1998 alone, the United States spent $2.6 billion on treating systemic fungal infections. In addition, the occurrence of mycoses may be significantly underestimated due to the difficulties to diagnose fungal pathogens, resulting in a high ratio of false negative results for fungal blood cultures. Finally, challenges from microbial resistance have become increasingly common that development of safe and effective antifungal therapies is constantly needed.

**Table 1.1.** Estimated world incidence and mortality rates of some systemic fungal infections. Data from the Fungal Research Trust, How common are fungal diseases? Fungal Research Trust 20th Anniversary Meeting. June 18th 2011.
Currently, the last line of defense in treating invasive fungal infection is a family of antimicrobial agents known as the polyene macrolides.\textsuperscript{8} To date, over 200 members of this class of natural products have been reported, and the structures of 36 of which have been elucidated. Members in this class of natural products contain 1. a polyene subunit with either 4, 5 or 7 olefins appended with an aliphatic tail; 2. a mycosamine containing subunit that is generally conserved; 3. a polyol subunit with diverse structural configurations. The polyol subunit is often what differs between members in the family, therefore represents an interesting handle for functional studies and a key challenge for synthetic access.\textsuperscript{9}

\textbf{Figure 1.1.} AmB, an archetypical example of polyene macrolide.

Isolated by Gold and coworkers in 1955 from a strain of \textit{Streptomyces nodosus} on soil collected in the Orinoco River region of Venezuela,\textsuperscript{10} AmB is an archetypical example of polyene macrolide family.\textsuperscript{11,12} It’s widespread importance as a clinical antifungal agent led to its commercialization only 3 years later.\textsuperscript{13,14} Remarkably, over the course of fifty years, only rare cases of microbial resistance of this drug have been reported.\textsuperscript{15} The discovery of AmB, as well as other members in the polyene macrolide
class, has significantly reduced the risk of blood-borne fungal infection from being a terminal disease prior to 1950.13

On the other hand, clinical application of polyene macrolides has been plagued with their excessive toxicities. Similarly, severe side effects including cardio and renal toxicity as well as hemolytic anemia are commonly accompanied with the administration of AmB.16, 17 For instance, in a study comparing AmB to another antifungal agent caspofungin for treating invasive candidiasis, proportions of patients experienced significantly increased nephrotoxic effects and/or hypokalemia in the AmB group than the caspofungin group.18 Due to extensive toxicity, sometimes discontinuation of AmB therapy is required despite a life-threatening systemic fungal infection. In order to improve the therapeutic index of this drug, liposomal formulations have been introduced19 and many studies have been devoted to target less toxic AmB derivatives from chemical modifications of the natural product.16 However, these efforts are crippled by a lack of understanding of the mechanism of action of AmB as well as other polyene macrolides.

1.1.2 Classic “barrel-stave” channel formation model of amphotericin B’s mechanism of action

For the past fifty years, the leading model of AmB’s mechanism of action involves binding to the fungal cell membrane component, ergosterol, followed by self-assembly into an octomeric ion-permeable channel.20, 21, 22 In this way, these channels cause depolarization of the membrane therefore disrupting the transmembrane electrochemical gradient and causing cell death.21,23
Figure 1.2. (A) The barrel stave model for AmB with the polyol pointing in to form a hydrophilic pore and the polyene pointing out towards the hydrophobic lipid bilayer. (B) The proposed C41 carboxylate/C3’ amine salt bridge and C8 alcohol/C9 alcohol hydrogen bonding interaction. (C) The tail-to-tail dimer of AmB pores stabilized by C35 hydroxyl group hydrogen bonding.

In this postulated mode of action, AmB molecules assemble through the stabilization of a salt bridge between the C41 carboxylate and the C3’ amine of neighboring AmB molecules, as well as a hydrogen bond between the C8 and C9 hydroxyls of neighboring AmB molecules to form an ion channel with an interior diameter of approximately 8 Å. Additionally, AmB molecules are aligned in such a way that the hydrophobic polyene units are in contact with the hydrophobic chains of the phospholipids while the hydrophilic polyol units line the water-filled interior of the pore. Despite the existence of this model for over 35 years, experimental data supporting this hypothesis is scarce. Evidence regarding the binding interaction is largely based on computational studies and the exact nature of this self-assembled complex is still poorly understood.

This mechanism of action by binding to sterols and self-assembly into an ion channel complex puts AmB outside the modern paradigm of pharmacology which operates via the inhibition of protein targets. This hypothesis has been explored to explain AmB’s low microbial resistance that has been observed.

AmB and all other polyene macrolides are produced by a common modular type I polyketide synthase (PKS) machinery found in their respective producing organisms. For AmB, C19 Mycosamine, C41 carboxylate and C8 hydroxyl are installed after the construction of the macrolide by tailoring enzyme modifications. Interestingly, all three functional groups have been proposed to be critical in stabilizing the AmB ion channels. Therefore, access to AmB derivatives with lacking each of these post-PKS installed functional groups may pave the way to probe the “barrel-stove” mechanism of AmB.
1.1.3 Sterol binding model of AmB’s mechanism of action

Our laboratory proposed that AmB’s primary mode of action is alternatively simply sterol binding, while ion channel formation only serves as a complementary mode of action thus enhancing its antifungal activity. To test the hypothesis our group applies the strategy that was described in previous section, and targeted and synthesized a series of AmB derivatives lacking functional groups that have been hypothesized to be important for channel formation.32

Presented in Figure 1.3, synthesis of amphoteronolide (AmdeB) and C41 decarboxylate AmB (C41MeAmB) was accomplished by my colleagues Palacios and Anderson.33 Synthesis of C35 deoxy AmB (C35deOAmB) was executed by a team lead by Gray and Palacios.34 Surprisingly, studies on these derivatives have revealed that while mycosamine and C35 hydroxy are indispensable to form channels, C41 carboxylate only plays a minor, if any role in such a mechanism. Furthermore, although channel formation was not observed for C35deOAmB, it still retained antifungal activity. Collectively, biophysical and biological studies of these and other derivatives have led to the conclusion that sterol binding is the primary mechanism of action of AmB. Guided by these findings, C2' deoxy derivative of AmB (C2'deOAmB) was synthesized by my
colleagues Wilcock, Endo and Uno and was examined to have an improved therapeutic index.\textsuperscript{35}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure13.png}
\caption{Biological studies of AmB and AmB derivatives. Units for MIC, MHC and MTC are in \(\mu\text{M}\).}
\end{figure}

Access to functional group deficient AmB derivatives has been pivotal in our understanding of AmB. However, the synthetic overhead has been the rate-limiting step towards further studies of AmB. Meanwhile, the current derivatives were synthesized from a top-down or hybrid approach that the natural product was used as the starting material. Preparation of most other AmB derivatives such as the C8 deoxy AmB (C8deOAmB) or C\textsuperscript{13} labeled derivative for both mechanistic and pharmacological studies can only stem from a modular total synthesis of AmB.
1.2 An iterative cross-coupling (ICC) strategy for small molecule synthesis

Organic synthesis has played an important role in modern drug discovery by allowing access to small molecules with functional properties. For instance, 91% of small molecule new chemical entities (NCE) discovered from 1981-2006 are synthesized natural products or natural products derivatives. More recently, development of molecular targets based high-throughput screens had led to an increasing demand for the generation of large libraries of derivatives by modification of active natural product skeletons as leads.

However, the remarkable complexity and variety of molecular structures found in nature made small molecule synthesis a relatively complex, unsystematized, and labor-intensive process. To date, target-oriented synthesis still represents the bottleneck in the efforts to study, understand, and harness the vast functional capacity of small molecules.

In contrast, many peptides, oligosaccharides, and oligonucleotides can now be readily prepared via general and automated synthesis platforms. In these systems common sets of building blocks, having all of the required functional groups pre-installed in the correct oxidation states and with the desired stereochemical relationships are assembled via the recursive application of a single reaction. The development of these modular synthesis platforms has dramatically increased the throughput with which these compounds can be prepared. As a result, the rate-limiting step in these areas has shifted from synthesis to the study of structure-function relationships, which in turn has had a transformational impact on many areas of science, medicine, and technology.
Inspired by the automated synthesis platforms, our group has been pursuing a more systematized approach towards complex small molecule construction, *e.g.* a synthesis strategy based upon the concept of iterative cross-coupling (ICC).\(^{41}\) In this platform, complex small molecules are assembled from bifunctional boron-protected haloboronic acid building blocks via the recursive application of the Suzuki-Miyaura cross-coupling reaction. This strategy is enabled by a protecting group for boronic acids known as *N*-methyliminodiacetic acid (MIDA) that was discovered in group in 2007.\(^{42}\)

Complexing a boronic acid with MIDA rehybridizes the boron center from \(\text{sp}^2\) to \(\text{sp}^3\) and thereby removes its p-orbital, which renders the resulting boron center inert to Suzuki-Miyaura cross-coupling conditions, thus allowing a chemoselective cross-
coupling with another boronic acid or other reactive boronic ester. On the other hand, MIDA boronates can be deprotected with mild aqueous base to give free boronic acids or transligated to boronic esters, both of which can then undergo subsequent cross-coupling with another bifunctional building block and thereby iterate the C-C bond formation process. Applying this strategy, a number of polyaryl and polyene natural products including ratanhine, retinal, parinaric acid, crocacin C, peridinin, and synechoxanthin, have been synthesized in our group.

Highlighting the ICC strategy is the synthesis of C35deOAmB presented in Scheme 1.3 which took advantage of the modular nature of this approach and established the key framework to target other AmB derivatives. Starting from the C1-C23 building block, which was prepared from an ozonolysis-based degradation sequence of AmB, deprotection of MIDA boronate was followed by the chemoselective cross-linked with bifunctional halo MIDA boronate. The deprotection/cross-coupling sequence was repeated with dienyl iodide to afford the all carbon skeleton of C35deOAmB.

Despite the success, it is evident that the synthesis of building block was originated from the degradation of the natural product, therefore making functionalization of C1-C23 challenging. In order to access functional group deficient and/or C13 labeled derivatives from C1-C23, development of an AmB total synthesis including a bottom-up synthesis of C1-C23 building block in the ICC platform is needed. However, expanding the ICC strategy to the synthesis of molecules beyond those possessing many Csp2-Csp2 connections is at present challenging. This is attributed to the challenges associated with Csp3 based cross-couplings with either alkyl boronic acids or alkyl halides.
Scheme 1.3. An ICC-based retrosynthetic strategy to the synthesis of C35deOAmB.

In the case of Csp³ boronic acid, the major challenges are: 1. much lower reactivity during both transmetallation and reductive elimination of Csp³ boronic acids compared to their Csp² counterparts; 2. various potential side reactions as a result of competitive β-hydride elimination. Furthermore, in the case of cross-coupling of
unactivated chiral secondary Csp³ boronic acids, the absolute stereochemistry of the products is unknown. Therefore, establishment of a facile method for cross-coupling of Csp³ organoboron building blocks is critical in our proposed total synthesis of AmB. In addition, successful development of such methodology stands to substantially expand the scope of the ICC platform by offering Csp³-Csp² disconnections.

1.3 Synthesis of the C1-C23 and the total synthesis of amphotericin B

To date, the only accomplished total synthesis of AmB was reported by Nicolaou in the late 1980s. Nicolaou’s retrosynthesis begins with the disconnection of the mycosamine to get back to amphoteronolide 1.10 (Scheme 1.4). The aglycone was further disconnected into two equal-sized building blocks 1.11 and 1.12 via an esterification and a ring-closing Horner-Wadsworth-Emmons reaction. Polyenone 1.11 was synthesized from another Horner-Wadsworth-Emmons reaction between aldehyde 1.13 and phosphonate 1.14, while C1-C20 Building block 1.12 was assembled from 1.15, 1.16 and 1.17. One of the highlights in this synthesis is that both building blocks 1.13 and 1.17 were prepared from (+)-diethyltartrate applying similar chemistry. Nonetheless, the Nicolaou synthesis required over 120 total steps and 58 steps in the longest linear sequence. The length of this synthesis makes access of many derivatives of interest impractical. A more efficient and modular total synthesis of AmB is needed and we propose this can now be achieved via the ICC platform.
The goal for our total synthesis of AmB is to establish a modular route to target any derivative of interest by simply preparing and assembling modified building blocks. Building on the C35deOAmB synthesis that was developed in our group, we propose a retrosynthetic strategy by disconnecting into 4 bifunctional building blocks. In the forward direction, these building blocks will be stitched together iteratively via only Suzuki-Miyaura cross-coupling. One of the key challenges in this proposal is the Csp\(^3\) organoboron cross-coupling between \textbf{1.19} and \textbf{1.20}. Our approaches, discoveries and a final solution to address this problem will be discussed in this thesis.
Scheme 1.5. ICC-based retrosynthetic strategy to the synthesis of AmB.
1.4 References


(12) Solution state NMR studies later showed that the conformation of AmB in solution was identical to that found by x-ray analysis: Sowiński, P.; Pawlak, J.; Borowski, E. *Magn. Reson. Chem.* **1992**, *30*, 275-279.


Chapter 1 Introduction


(35) Wilcock, B. C.; Endo, M. M.; Uno, B. E.; Burke, M. D. J. Am. Chem. Soc. 2013, ASAP.


Chapter 2

First generation synthesis of amphotericin B polyol subunit BB1

AmB is a polyene natural product with remarkable pharmacological activity; however it’s toxicity to humans has stymied its efficacy. Since the 1980s, more than a dozen synthetic groups including Masamune,1, 2 Nicolaou,3, 4 McGarvey,5 Carreira6, 7 and Solladié8, 9 have worked on the total synthesis of this natural product. Nevertheless, to date, the only accomplished total synthesis of this molecule was reported by Nicolaou and coworkers in a series of publications in late 1980s.3, 4 To summarize the challenges of this synthesis, Carreira states in a 2006 review on the chemistry of AmB: “In
reviewing the state of the art in macrolide synthesis in those years, both Masamune and Nicolaou noted two major problems: 1. formation of the macrocyclic ring; and 2. assembly of the polyol subunits.10 This quote is supported by a great deal of interest in the synthesis of the AmB polyol subunits received from the synthetic community. Indeed, synthesis and manipulation of the stereochemically-congested C1-C12 polyol building block of AmB has been reported by over 10 research groups and has produced enduring and widely applicable synthetic methodologies in the areas of enantio- and diastereoselective polyol synthesis and carbon-carbon bond formation.

Figure 2.1 Further disconnection of AmB polyol building block is at either C6-C7, including Masamune,1 Kinoshita,11 Nicolaou12 and Furstner,13 or at C7-C8, including Hanessian,14 Carreira,15 Solladie,9 Fraser-Reid,16 McGarvey,5 Bonini17 and Cossy.18

The synthesis of this building block involves multiple C-C bond formation reactions from simpler starting materials. Most reported syntheses in the literature employ a further disconnection at either C6-C7 or C7-C8 to give two roughly equal sized building blocks. This is a strategy we also adopted in our synthesis of this fragment. Among these existing syntheses, our final synthesis has the fewest steps and highest overall yield.
2.1 Reported synthesis of amphotericin B polyol subunit in the literature

One of the earliest efforts to tackle the total synthesis of AmB was reported by Masamune and coworkers (Scheme 2.1).19 In his synthesis of the polyol subunit, C1-C6 fragment 2.2 and C7-C12 fragment 2.3 were prepared from a common enantiomerically-enriched epoxide 2.1. Lithiation of C7-C12 sulfoxide 2.3 followed by alkylation afforded the C1-C12 framework 2.4 in a relatively low 30% yield. This intermediate was then converted to triflate 2.5 and coupled with lithiated sulfone building block 2.6 to yield C1-C19 subunit in 92% yield. 20

Just to highlight one of the many interesting challenges in this synthesis of AmB is that if the stereochemistry of the carbon labeled with blue on the orthoester 2.6 is inverted, no product for this coupling was observed. Post coupling modification arrived phosphate 2.8 which was then subjected a two-step sequence consisted with esterification and macro Horner-Wadsworth-Emmons cyclization to furnish the aglycone 2.10.

One of the drawbacks of this classic synthesis is that 17 steps are required after the coupling of 2.5 and 2.6. The linearity of this route makes targeting AmB derivative via building block modification inefficient. A similar macrocyclic ring-closing strategy is used in both Nicolaou’s total synthesis of AmB and Carreira’s synthesis of the C35 deoxy- methyl ester AmB derivative 2.17.
Scheme 2.1. Masamune’s synthesis and coupling of AmB polyol subunit.

Carreira developed a more efficient second generation synthesis of this building block that involves a novel chelate-based diastereoselective alkynylation to tie the C7-C8 bond and afforded 2.13 in excellent yield and good d.r.. After a few steps of functional group manipulation, a nitrile oxide 1,3-dipolar cycloaddition prepared the C1-C19 intermediate 2.16 in excellent yield. Thereafter, 7 more steps would give the
Masamune phosphate 2.8, *en route* to the doubly modified AmB derivative 2.17 (Scheme 2.2).

Scheme 2.2. Carreira’s synthesis and cross-coupling of AmB polyol subunit.

The examples described above demonstrate the two general schemes of AmB polyol subunit synthesis: 1. alkylation or olefination between C6-C7 such as the Masamune synthesis; 2. nucleophilic attack to C8 aldehyde to form C7-C8 bond as represented by the Carreira synthesis. Another approach, which was reported by BouzBouz and Cossy took advantage of a new method for the formation of syn-1,3,-diol from β-hydroxy aldehydes that was developed in the Cossy group (Scheme 2.3).18 Key steps in their synthesis of the AmB C1-C14 polyol fragment 2.23 are an interesting
enantioselective allyltitanation reaction that was applied twice with allylating reagents of the opposite enantiomeric configurations \((R,R)\text{-}2.19\) and \((S,S)\text{-}2.19\) and yielded products with corresponding desired stereo-configurations. Despite being an interesting approach, no reports of the synthesis being taken forward to furnish the natural product or close derivatives are published to date.

**Scheme 2.3.** BouzBouz and Cossy’s synthesis of AmB polyol subunit.

The three examples for synthesis of this intriguing building block discussed here are a representation of over ten syntheses.\(^\text{10}\) Our route to the polyol subunit of AmB, which will be discussed in the next three chapters, is in fact the shortest and highest overall yielding one. In addition, our building block is uniquely applicable to the ICC platform, making practical synthesis of many AmB derivatives accessible.
2.2 Development of a novel one-pot diastereoselective hydroboration/cross-coupling strategy

Our ICC-based strategy for the synthesis of AmB involves initial retrosynthetic fragmentation of the Csp²-rich polyene motif to generate building blocks BB3 (2.26), BB4 (2.27) and a C1-C23 containing intermediate 2.25. We have previously demonstrated that derivatives of intermediate 2.25, differing only in the identity of some protective groups, can be transformed via ICC to both AmB²² and C35-deoxyAmB.²³

Depicted in Scheme 2.4, to further disconnect the C1-C21 region of this natural product, we considered the fragmentation of 2.25 at the C12-C13 bond into Csp³ alkyl borane BB1 (2.28) and Csp² cyclic ketene acetal phosphate BB2 (2.29). Importantly, the C11-C17 motif is strictly conserved in every known mycosamine-bearing polyene macrolide natural product.²⁴,²⁵ Hence, the successful development of such a cross-coupling would help enable the ICC based synthesis of any member of this family. Thus, once developed, such a method could be widely applicable to the cross-coupling based synthesis of many other natural products and/or their derivatives.

Realizing this potential solution required three important developments: 1. a method for the diastereoselective synthesis of the unprecedented C9-C12 motif of BB1: an alkylborane flanked by a stereodefined 1,3-diol motif at the beta-delta carbons, 2. an efficient, stereo-controlled, and scalable route to BB1, 3. cross-coupling the Csp³ borane terminus of BB1 with a ketene acetal phosphate BB2 under conditions compatible with MIDA boronates.
We first targeted a method for preparing the C8-C12 motif of BB1 in a stereocontrolled fashion. Specifically, inspired by Leighton’s diastereoselective hyrdorhodation of methylene 1,3-dioxanes, we proposed an analogous substrate-controlled diastereoselective hydroboration to synthesize BB1 stereoselectively. In Leighton’s model, a half-chair ground state of prior to the hydorhodation was
proposed. Re face approach of rhodium-hydride via a favorable chair-like transition state leads to the syn-1,3-dioxane 2.32; while the anti-1,3-dioxane product requires a Si face attack via a high energy twist-boat like transition state (Scheme 2.5).

Scheme 2.5. Leighton's model for diastereoselective hydorhodation.

To validate the stereo-outcome of the hydroboration followed by the resulting cross-coupling primary Csp³ borane BB₁, a model study was performed. The route to prepare BB₁ analog 2.37 is summarized in Scheme 2.6. Starting from known mono TBS protected ethylene glycol 2.33, Swern oxidation followed by Grignard addition gave homoallylic alcohol 2.34 in 82% yield over 2 steps. Dimethyldioxirane oxidation of the resulting olefin afforded epoxide 2.35 in 50% yield (83% based on recovery of starting
material. The epoxide was then opened by LiBr. Subsequent ketalization and elimination yielded methylene 1,3-dioxane \( \text{2.37 (Scheme 2.6)} \).

With this intermediate in hand, hydroboration with 9-BBN proceeded very smoothly to generate alkyl borane intermediate \( \text{2.38} \). After oxidative work-up, the resulting protected tetraol \( \text{2.39} \) was isolated in 57% yield, the diastereoselectivity was confirmed via the Rychnovsky method (Scheme 2.7). Encouraged by this result, we then moved on to the synthesis of BB1.

![Scheme 2.7. Study of the stereo-outcome of the hydroboration.](Image)

### 2.3 Unsuccessful synthesis of BB1 based on a cross-metathesis strategy

In our first attempted synthesis, we envisioned an olefin metathesis strategy to further dissect BB1 into two easily accessible building blocks. Guided by Grubbs’ general model for selectivity in olefin cross metathesis,\(^{30}\) we anticipated a high selectivity of cross metathesis (over homo metathesis) between type III olefin \( \text{2.41} \) and type II olefin \( \text{2.42} \).
Conveniently, building block 2.41 can be prepared in 1 step from known compound 2.44\textsuperscript{31, 32} which was synthesized in 5 steps in non-racemic form from commercial starting material (Scheme 2.9). The proposed synthesis of 2.42 is depicted in Scheme 2.10. Starting with 4-pentenoic acid, loading with Evan's auxiliary is followed by oxygenation to set up the stereocenter at C9. Amide formation, silylation and vinylation afforded diene 2.48. Site selective epoxidation, ring opening and desilylation yielded diol intermediate 2.49 that is 1 step away from 2.42. However, attempts to ketalize diol 2.49 were hampered by competing intramolecular cyclization as evidenced by a fast conversion to the tricyclic byproduct 2.51. A thorough screen of Lewis acid catalysts and ketalization reagents were carried out but turned out to be fruitless (Scheme 2.10).
Scheme 2.9. Synthesis of type III olefin 2.41.

Since it is evident that ketalization in the presence of C8 carbonyl is difficult, we revised our synthetic plan by reducing the ketone before exposing the diol to ketalization condition. In this vein, cross metathesis between 2.41 and benzylated
enone \( \text{2.53} \) was tested. However, a screen of Grubbs catalysts and optimization resulted in a best yield of only 17\%, making this approach impractical (Scheme 2.11).\(^{30, 33} \)

![Scheme 2.11. Low-yielding olefin cross-metathesis to 2.54.](image)

2.4 **Successful first generation synthesis of BB1 in the form of 9-BBN alkyl borane and challenges within**

In order to bypass this low-yielding cross-metathesis reaction, inspired by a similar strategy Nicolaou used in his synthesis, we next examined a Horner–Wadsworth–Emmons coupling reaction to target the crucial enone intermediate. Aldehyde coupling partner \( \text{2.55} \) can be prepared in 1 step from ozonalysis of olefinic intermediate \( \text{2.41} \) (Scheme 2.12). Synthesis of phosphate coupling partner \( \text{2.58} \), which is depicted in Scheme 2.13, requires only 4 steps from readily accessible starting material.
Starting from commercially available, enantiomerically-enriched (\(R\))-malic acid, selective esterification followed by ketalization afforded dioxanone \(2.57\) in 89\% yield over 2 steps. Site-selective vinylation and subsequent phosphonation gave forth coupling partner \(2.58\). It needs to be noted that reagent selection played an important role in this sequence. For instance, ketalization of intermediate \(2.59\) with dimethyl ketal \(2.61\) proceeded with low conversion. The yield was boosted to 92\% by simply switching to methoxy cyclopentene \(2.60\) (Scheme 2.14). In a second case, chemoselectivity of vinylation of \(2.57\) with the Petasis reagent improved significantly when ethyl ester was in place of methyl ester, as demonstrated by the increase in yield (Scheme 2.15).
With both coupling partners in hand, the Horner-Wadsworth-Emmons reaction proceeded smoothly to afford enone intermediate which was immediately subjected to the Stryker’s reduction to yield ketone 2.62 in 51% over two steps. Substrate controlled diastereoselective reduction with L-selectride followed by silylation afforded BB1 precursor 2.63. The yield for the last step drops significantly on larger scale and ranges from 35-71% (Scheme 2.16).

With 2.63 in hand, BB1 2.64 was prepared by diastereoselective hydroboration with 9-BBN, which was not isolated and subjected directly to couple with a BB2 analog 2.65 derived valerolactone in a model study. Gratifyingly, the coupling furnished the desired product 2.66 under Buchwald’s anhydrous condition: a system that has been
tested to be compatible with other functional groups that will be present on the actual BB2 (Scheme 2.17).34, 35

Scheme 2.16. Synthesis of BB1 precursor 2.63.

Scheme 2.17. Model cross-coupling of BB1-BB2.
Despite the success in establishing a synthesis and cross-coupling of the polyol subunit BB1, the low yielding and capricious nature of the silylation to furnish 2.63 and substantial stabilities of these intermediates has made this route difficult to scale. Moreover, this route lacks a stable intermediate suitable for storage which is important for the building block based ICC synthetic strategy. A thorough analysis of this reaction revealed that the observed challenge was due to the highly sensitive nature of the methylene dioxane moiety (labeled in blue) on 2.63 (Scheme 2.18). Isomerization to the internal olefin was frequently observed upon work up and/or chromatographic purification which yielded byproduct 2.64 that is very difficult to be separated. After numerous attempts, this drawback remains and makes this route impractical to target an efficient and modular synthesis. We thereby moved on to a second generation synthesis.

2.5 Experimental section

Materials. Commercial reagents were purchased from Sigma-Aldrich, Fisher Scientific, Alfa Aesar, TCI America, or Frontier Scientific, and were used without further purification unless otherwise noted.
Solvents were purified via passage through packed columns as described by Pangborn and coworkers\(^1\) (THF, Et\(_2\)O, CH\(_3\)CN, CH\(_2\)Cl\(_2\): dry neutral alumina; hexane, benzene, and toluene, dry neutral alumina and Q5 reactant; DMSO, DMF: activated molecular sieves). All water was deionized prior to use. Diisopropylethylamine was freshly distilled under an atmosphere of nitrogen from CaH\(_2\).

**General experimental procedures.** Unless noted, all reactions were performed in flame-dried round bottom or modified Schlenk flasks fitted with rubber septa under a positive pressure of argon or nitrogen. Organic solutions were concentrated via rotary evaporation under reduced pressure with a bath temperature of 23°C unless otherwise noted. Reactions were monitored by analytical thin layer chromatography (TLC) performed using the indicated solvent on E. Merck silica gel 60 F254 plates (0.25mm). Compounds were visualized by exposure to a UV lamp (\(\lambda = 254\) nm), and/or a solution of KMnO\(_4\) and/or a solution of p-anisaldehyde, followed by brief heating using a Varitemp heat gun. Column chromatography was performed using Merck silica gel grade 9385 60Å (230-400 mesh).

**Structural analysis.** \(^1\)H NMR and \(^{13}\)C NMR spectra were recorded at 20 °C on Varian Unity 500, Varian Unity Inova 500NB or Varian Unity 500 instruments. Chemical shifts (\(\delta\)) are reported in parts per million (ppm) downfield from tetramethylsilane and referenced to residual protium in the NMR solvent (benzene, \(\delta = 7.16\); CHCl\(_3\), \(\delta = 7.26\); acetone, \(\delta = 2.05\), center line; DMSO \(\delta = 2.50\), center line) or to added tetramethyldisilane (\(\delta = 0.00\)). Data are reported as follows: chemical shift,
multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sept = septet, m = multiplet, b = broad, app = apparent), coupling constant (J) in Hertz (Hz), and integration. Chemical shifts ($\delta$) for $^{13}$C NMR are reported in ppm downfield from tetramethylsilane and referenced to carbon resonances in the NMR solvent (benzene-d$_6$, $\delta$ = 128.06, center line; CDCl$_3$, $\delta$ = 77.0, center line; acetone-d$_6$, $\delta$ = 39.5, center line; DMSO-d$_6$ $\delta$ = 39.52, center line). Carbons bearing boron substituents were not observed (quadrupolar relaxation). High resolution mass spectra (HRMS) were performed by Furong Sun, Dr. Steve Mullen and Dr. Haijun Yao at the University of Illinois School of Chemical Sciences Mass Spectrometry Laboratory.

**Epoxide 2.35.** To a solution of 2.34 (1.08 g, 5 mmol) in 20 mL CH$_3$CN and 20 mL 0.4 mM Na$_2$EDTA at 4 °C, was added cold 0.3 mL 1,1,1-trifluoroacetone with a pasteur pipette. A mixture of oxone and sodium bicarbonate was then added portionwise over 2 h. (Oxone:Sodium bicarbonate = 15:37 g:4.3 g) The resulting white suspension was stirred for 5 h at 4 °C. The solids were then removed by filtration and washed with ether. The two layers of filtrate were separated and the organic phase was washed with saturated aqueous NaHCO$_3$ and brine, then dried over MgSO$_4$, the solvent was removed under reduced pressure. Flash chromatography (SiO$_2$, hex:EtOAc = 5:1) yielded 0.58 g (50%) product 2.35 as a mixture of two diastereomers, with recovered starting material (0.43 g). Yield based on recovered starting material was 83%.
TLC (hex:EtOAc 5:1)
Rf = 0.10, stained by p-anisaldehyde

$^1$H NMR (500 MHz, CDCl$_3$) δ 3.88 (m, 1H), 3.68 (dd, $J = 10$, 4 Hz, 0.6H), 3.63 (dd, $J = 10$, 3.5 Hz, 0.4H), 3.54 (dd, $J = 10$, 7 Hz, 0.4H), 3.45 (dd, $J = 10$, 7.5 Hz, 0.6H), 3.12 (m, 1H), 2.82 (t, $J = 4.5$ Hz, 0.6H), 2.79 (t, $J = 4.5$ Hz, 0.4H), 2.55 (m, 1H), 1.84 (m, 0.6H), 1.75 (m, 0.4H), 1.67 (m, 0.4H) 1.48 (m, 0.6H), 0.90 (s, 9H), 0.08 (s, 6H).

HRMS (ESI+)
Calculated for C$_{11}$H$_{24}$O$_3$SiNa: 255.1392
Found: 255.1394

**Diol 2.68.** To a stirred solution of 2.35 (670 mg, 2.89 mmol) and acetic acid (0.82 mL, 8.66 mmol) in THF (30 mL) under argon at 23 °C was added lithium bromide (501 mg, 5.77 mmol). The solution was allowed to stir for 6 h and white precipitation was observed. Upon stopping the reaction, the solution was diluted with 1:1 H$_2$O: brine (30 mL) and ether (30 mL) and separated. The aqueous phase was extracted with 3X 50ml ether and the combined organic layers were washed with sat. NaHCO$_3$ (200 mL), and dried over MgSO$_4$. The solvent was removed in vacuo and the crude product 2.68 was used without further purification in the next reaction.
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$^1$H NMR (500MHz, CDCl$_3$) δ 4.10 (m, 1H), 3.94 (m, 1H), 3.66-3.45 (m, 4H), 1.80-1.58 (m, 2H), 0.90 (s, 9H), 0.08 (s, 6H)

Ketal 2.36. To a stirred solution of crude diol 2.68 (901.9 mg, 2.89 mmol) in 2,2-dimethoxy propane (22.74 mL, 184.96 mmol) was added PPTS (80.42 mg, 0.32 mmol). The reaction was allowed to stir for overnight. Upon stopping the reaction, the mixture was diluted with 10mL 1:1 sat. aq. NH$_4$Cl:H$_2$O and the aqueous phase was extracted with 3x diethyl ether. The combined organic layer were dried over MgSO$_4$, filtered and concentrated. Flash chromatography (SiO$_2$, 5:1 = hex:EtOAc) yielded the desired product as a colorless oil. (878.7 mg, 90% over two steps)

TLC (hex:EtOAc 5:1)
Rf = 0.48, stained by p-anisaldehyde

$^1$H NMR (500 MHz, CDCl$_3$) δ 4.03 (m, 1H), 3.92 (m, 1H), 3.67 (m), 3.57 (dd, $J = 10.5$, 5 Hz), 3.50 (dd, $J = 10.5$, 6 Hz), 3.49 (m), 3.38 (m), 2.79 (dd, $J = 10$, 6 Hz), 3.57-2.79 (4H) 1.83 (t, $J = 2.5$ Hz), 1.81 (t, $J = 2.5$ Hz), 1.77 (m), 1.66 (m), 1.83-1.66 (2H) 1.41 (m, 6H), 0.89 (s, 9H), 0.06 (m, 6H).
Methylene dioxane 2.37. To a stirred solution of ketal 2.36 (1.01 g, 3.0 mmol) in toluene (6 mL) was added 1,8-diazobicyclo[5,4,0] (4.49 mL, 30 mmol), and the mixture was heated to 100 °C and stirred for 5 h. After cooling to 23 °C, the resulting solution was filtered, and the solid was washed with hexane. The ethereal layer was washed with water (10 mL) and dried over \( \text{Na}_2\text{SO}_4 \) and concentrated under reduced pressure. Flash chromatography (florisil, 2% triethylamine, 30:1 = hex:EtOAc) yielded the desired product as a colorless oil. (0.49 g, 60%)

TLC (hex:EtOAc 10:1)

Rf = 0.33, stained by p-anisaldehyde

\(^1\text{H} \text{NMR} (500 \text{ MHz, CDCl}_3) \delta \; 4.40 \; (d, \; J = 2 \; \text{Hz, 1H}), \; 4.22 \; (d, \; J = 2 \; \text{Hz, 1H}), \; 3.96 \; (m, \; 1H), \; 3.68 \; (dd, \; J = 10, 5 \; \text{Hz, 1H}), \; 3.53 \; (dd, \; J = 10, 5 \; \text{Hz, 1H}), \; 2.22 \; (m, \; 1H), \; 2.14 \; (m, \; 1H), \; 1.47 \; (s, \; 3H), \; 1.43 \; (s, \; 1H), \; 0.90 \; (s, \; 9H), \; 0.07 \; (d, \; J = 3.5 \; \text{Hz, 6H}).
**Coupling product 2.69.** Olefin 2.37 (36.9 mg, 0.14 mmol) was treated with a 9-BBN 0.5 M solution in THF (0.4 mL, 0.20 mmol, 1.5 equiv.) under argon and the resultant solution was stirred at r.t. for 3 h. The reaction mixture was treated with 1 M aqueous NaHCO₃ (0.4 mL, 3.0 equiv.). After stirring for 15 min, Pd(PPh₃)₄ (16 mg, 0.1 equiv.) followed by a solution of cyclic ketene acetal phosphate 2.65 (67.5 mg, 1.5 equiv.) in DMF (0.17 mL) were successively added, and the resulting mixture was stirred at 50 °C for 20 h. After cooling, the reaction mixture was diluted with ether (diethyl ether:DMF = 10:1, 20 mL), washed with brine (10 mL), dried over Na₂SO₄, filtered and evaporated. The residue was dissolved in THF (5 mL) and cooled to 0 °C. The reaction was treated with 3 M NaOH (0.5 mL) followed by 30% H₂O₂ (0.2 mL). The resulting mixture was stirred at 23 °C for 30 min, diluted with ethyl acetate (20 mL), washed with saturated aqueous Na₂SO₃ and brine, dried over Na₂SO₄, filtered, and evaporated. Flash chromatography (SiO₂, 8% ethyl acetate-hexane, 2% triethylamine) yielded the desired product. (44.7 mg, 92%)

TLC (hex:EtOAc 10:1)
Rf = 0.37, stained by p-anisaldehyde

\[ ^1H \text{ NMR (400 MHz, CDCl}_3\] \(\delta\) 4.54 (t, \(J = 3.6\) Hz, 1H), 4.04 (m, 1H), 3.95 (m, 3H), 3.67 (m, 1H), 3.47 (m, 1H), 2.35 (dd, 1H), 1.98 (m, 3H), 1.77 (m, 2H), 1.67 (dt, 1H), 1.44 (s, 3H), 1.25 (s, 3H), 0.89 (s, 9H) 0.06 (d, \(J = 2.4\) Hz, 6H).

\[ ^13C \text{ NMR(100 MHz, CDCl}_3\] \(\delta\) 150.8, 98.8, 98.2, 70.1, 67.2, 67.1, 66.4, 41.9, 33.7, 30.3, 29.9, 26.1, 22.6, 20.5, 20.1.
HRMS (ESI+)

Calculated for $C_{19}H_{36}O_4Si Na$: 379.2281

Found: 379.2288

**Oxazolidinone 2.70.** To a stirred solution of 4-pentenoic acid (570 mg, 5.70 mmol, 1.0 equiv.) and triethylamine (0.63 mL, 5.98 mmol, 1.1 equiv.) in diethyl ether 31 mL (vol. 2% of TEA) at -78 °C under nitrogen was added trimethylacetal chloride (520 mg, 5.70 mmol, 1.0 equiv.). After 5 min, the bath was replaced by an ice-water bath and white precipitate was formed. The heterogeneous mixture was stirred at 0 °C for 1 h. In a separate flask, a solution of 4(R)benzyl-oxazolidin-2-one (1000 mg, 5.64 mmol, 1 equiv.) in THF 6.8 mL (0.83 M of oxazolidinone) was cooled to -78 °C and nBuLi (1.6 M in hexane, 3.6 mL, 1.01 equiv.) was added slowly. After the second reaction mixture was stirred for 10 min at -78 °C, it was cannulaed over to the cooled down flask containing the anhydride at -78 °C. After stirring at this temperature for 15 min, the reaction mixture was warmed to 0 °C and stirred for an additional 30 min. After the reaction was quenched with water, the layers were separated and the aqueous layer was extracted 3 times with diethyl ether. The combined organic layers were washed with brine, dried over $Na_2SO_4$, filtered and concentrated in vacuo. The residue was purified with flash chromatography ($SiO_2$, hex:EtOAc = 3:1) and give product 2.70 a yield as a colorless oil which freezes as colorless crystals at -20 °C. (600 mg, 82%)
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TLC (hex:EtOAc 3:1)

Rf = 0.30, stained by KMnO₄

¹H NMR (500 MHz, CDCl₃) δ 7.34-7.20 (m, 5H), 5.87 (m, 1H), 5.11 (m, 1H), 5.04 (m, 1H), 4.67 (m, 1H), 4.18 (m, 2H), 3.30 (dd, J = 13.5, 3 Hz, 1H), 3.04 (m, 2H), 2.76 (dd, J = 13.5, 10 Hz, 1H), 2.47 (m, 2H), 1.25 (s, 3H), 0.89 (s, 9H) 0.06 (d, J = 2.4 Hz, 6H).

**Alcohol 2.46.** To a solution of NaHMDS (11 mL, 1 M in THF, 1.2 equiv.) and THF (18 mL) at -78 °C was added dropwise a solution of 2.70 (2.2 g, 1 equiv.) in THF (22.5 mL) at a rate that the internal temperature was kept below -70 °C. The resulting solution was stirred for 30 min at -78 °C before being cooled down to -95 °C. A precooled to -78 °C solution of Davis’ oxaziridine (3.34 g, 1.4 equiv.) in THF (15 mL) was added to the flask in a course of half an hour. After stirring for additional half an hour, the reaction was quenched with acetic acid (2.9 mL) in THF (60 mL). The reaction mixture was poured onto water and the organic layer was separated. The aqueous layer was extracted three times with EtOAc and the combined organic layers were successively washed with sat. aq. NaHCO₃ and brine. The product was dried over Na₂SO₄ and concentrated in vacuo. After flash chromatography (SiO₂, hex:EtOAc:toluene = 4:1:2) the product 2.46 was afforded in ~90% yield.
TLC (hex:EtOAc 3:1)
Rf = 0.21, stained by KMnO₄

$^1$H NMR (500 MHz, CDCl₃) δ 7.30 (m, 5H), 5.87 (m, 1H), 5.13 (m, 2H), 4.67 (dm, $J = 3$ Hz, 1H), 4.27 (m, 2H), 3.55 (d, $J = 8$ Hz, 1H), 3.32 (dd, $J = 13.5$, 3.5 Hz, 3H), 2.84 (dd, $J = 13.5$, 9.5 Hz, 2H), 2.62 (m, 1H), 2.46 (m, 1H), 1.25 (s, 3H), 0.89 (s, 9H) 0.06 (d, $J = 2.4$ Hz, 6H).

Amide 2.71 A suspension of (MeO)NHMe HCl (289 mg, 5.25 equiv.) in THF (3.5 mL) at 0 °C was treated with a solution of AlMe₃ (2 M in toluene, 1.44 mL, 5.1 equiv.) dropwise and the resulting clear solution was stirred at 23 °C for 30 min. This clear solution was added to a cooled to 0 °C solution of 2.46 (155 mg, 1 equiv.) in THF (7 mL). The resulting mixture was warmed to 23 °C and stirred for 12 h. The reaction mixture was cooled to 0 °C, quenched by very slowly addition of 1 N. aq. tartaric acid and stirred at r.t. for 25 min. The layers were separated and the aqueous layer was extracted three times with EtOAc. The combined organic layer was dried over MgSO₄ and concentrated in vacuo. Flash chromatography (SiO₂, DCM:THF = 15:1) afforded the product 2.71. (85 mg, with benzylloxazolidin-2-one impurity present)
Chapter 2 First generation synthesis of amphotericin B polyol subunit BB1

TLC (hex:EtOAc 1:1)

Rf = 0.30, stained by KMnO₄

¹H NMR (500 MHz, CDCl₃) δ 5.85 (m, 1H), 5.10 (m, 2H), 4.45 (b, 1H), 3.70 (s, 3H), 3.33 (d, 1H), 3.22 (s, 1H), 2.49 (m, 1H), 2.33 (m, 1H).

HRMS (ESI+)

Calculated for C₇H₁₄O₃N: 160.0974

Found: 160.0974

Vinyl magnesium bromide. 25 mL of 1 M vinyl bromide solution in THF was vigorously stirred with 7.0 g magnesium turning under nitrogen at 23 °C in a round bottom flask attached to a reflux condenser. The reaction mixture started refluxing in about 5 min. Continued to stir for one additional hour and a dark brown heterogeneous solution was formed. The solution is titrated by NoD ¹H NMR technique described by Hoye¹, giving a concentration of 0.74 M vinyl magnesium bromide.

**Bisolefin 2.48.** To a stirred solution of 2.47 (260 mg, 0.95 mmol) in THF (10 mL) at 0 °C was added vinyl magnesium bromide (2.6 mL, 1.9 mmol, 2 equiv.). After stirring at 0 °C for 15 min, to the reaction was added acetic anhydride (1.00 mL) followed by methanol (1.00 mL). The solution was reduced to one quarter the volume under reduced pressure then diluted to 50 mL with diethyl ether. The solution was washed with dilute aqueous ammonium chloride solution (5 mL sat. aq. NH₄Cl and 2.5mL water x 2) and dried over NaSO₄. The solution was filtered and concentrated under reduced pressure at ambient temperature. Flash chromatography (SiO₂, hex:EtOAc = 7:1) yielded 2.48 as a colorless oil (187 mg, 82%)

TLC (hex:EtOAc 3:1)
Rf = 0.72, stained by p-anisaldehyde

^1H NMR (500 MHz, CDCl₃) δ 6.84 (dd, J = 17.5, 11 Hz, 1H), 6.38 (dd, J = 17.5, 2 Hz, 1H), 5.77 (m, 2H), 5.08 (m, 2H), 4.21 (m, 1H), 2.40 (m, 2H), 0.94 (t, J = 8 Hz, 9H), 0.60 (q, J = 8 Hz, 6H).

HRMS (ESI+)
Calculated for C₁₅H₃₂O₃N: 302.2151
Found: 302.2145
Ester 2.72. To a flask equipped with a stir bar and 24.67 g D-\((R)\)-malic acid under nitrogen was added trifluoroacetic anhydride 62 mL at 0 °C. The ice bath was removed and the reaction was allowed to stir at r.t. for 2 h. The volatiles were evaporated under rotovap. Anhydrous ethanol alcohol (123 mL) was added to the white solid residue and the resulting solution was allowed to stir and 23 °C overnight. Concentration of the solution gave the pure malic monoester 2.72 in quantitative yield (29.7 g) that can be used in the next step without further purification. Recrystallization with hexanes/ethyl acetate gave the product as white crystals.

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 4.50 (dd, \(J = 6, 4\) Hz, 1H), 4.28 (m, 2H), 2.89 (m, 3H), 1.31 (t, \(J = 7.5\) Hz 2H).

\(^{13}\)C NMR(125 MHz, CDCl\(_3\)) \(\delta\) 174.4, 173.2, 67.1, 62.5, 38.3, 14.2.

HRMS (ESI+)
Calculated for C\(_6\)H\(_{10}\)O\(_5\)Na: 185.0426
Found: 185.0430

Dioxanone 2.57. To a stirred solution of monoester 2.72 (8.9 g, 54.96 mmol) in 1370 mL anhydrous CH\(_2\)Cl\(_2\) (0.04 M) under nitrogen, was added 1-
methoxycyclopentene (16.2 g, 18.0 mL, 164.88 mmol) and PPTS (414.4 mg, 1.65 mmol) at 23 °C, and the reaction was allowed to stir at this temperature for 16h, before an aqueous solution of (1:1 H₂O : sat. aq. NaHCO₃) total of 733 mL was added to quench the reaction. The layers were separated and the aqueous layer was extracted three times with 366 mL of CH₂Cl₂. The combined organic layer was dried over 133 g Na₂SO₄ and filtered. Concentration of the solution gave the dioxanone 2.57 (11.6 g, 93%) that is used in the next reaction without further purification.

TLC (hex:EtOAc 1:1)
Rf = 0.24, stained by p-anisaldehyde

\(^1\)H NMR (500 MHz, CDCl₃) \(\delta\) 4.60 (dd, \(J = 10, 5\) Hz, 1H), 4.27 (q, \(J = 7\) Hz, 2H), 2.85 (m, 2H), 2.03 (m, 4H), 1.81 (m, 4H), 1.32 (t, \(J = 7\) Hz, 3H).

HRMS (ESI+)
Calculated for C₁₁H₁₆O₅Na: 251.0895
Found: 251.0904

**Dimethyl titanocene.** To a solution of titanocene dichloride (13.34 g, 53.6 mmol) in 146 mL toluene in a 500 mL flask was dropwise added MeMgCl (3 M in THF,
150 mmol) at 0 °C. The reaction was allowed to stir in dark at 0 °C for 1 h, and 37 mL 6% NH₄Cl aqueous solution was added. The layers were separated and the organic layer was washed with 37 mL water three times and once 37 mL brine. The organic solution was dried with 37 g Na₂SO₄ and concentrated to a smaller volume. The resulting orange solution was titrated with 1H NMR. The ideal concentration should be around 0.63 mol/g solution, and this solution can be stored in dark under argon at -20 °C for up to two weeks.

**Methylene dioxane 2.73.** Dioxanone 2.57 (1.0 g, 4.39 mmol), titanocene dichloride (65.5 mg, 0.26 mmol) and dimethyltitanocene toluene solution (0.63 mmol/g solution, 11.8 g) was stirred in a 40 mL sealed vial filled with argon. The solution was allowed to react in dark at strict 70 °C for 4 h. After the reaction was cooled to 23 °C, 1 mL sat. aq. NaHCO₃ and 2 mL EtOH was added and the mixture was allowed to stir at 40 °C for 12 h open to air. The mixture was passed through a plug of florisil and flushed with CH₂Cl₂ before concentration *in vacuo*. Flash chromatography gave 2.73 (644 mg, 65%) as a light yellow oil.

TLC (hex:EtOAc 5:1)

Rf = 0.35, stained by p-anisaldehyde

¹H NMR (500 MHz, CDCl₃) δ 4.48 (s, 1H), 4.39 (dd, J = 11, 5 Hz, 1H), 4.31 (s, 1H), 4.24 (q, J = 7 Hz, 2H), 2.51 (m, 2H), 2.04 (m, 3H), 1.71 (m, 5H), 1.30 (t, J = 7 Hz, 3H).
HRMS (EI+)

Calculated for C\textsubscript{11}H\textsubscript{16}O\textsubscript{4}: 226.1205

Found: 226.1206

**Phosphonate 36.** To a stirred solution of dimethyl methylphosphonate (1.74 g, 14.1 mmol) in 5.5 mL THF cooled to -78 °C under nitrogen was added n-BuLi (1.6 M, 8.8 mL, 14.1 mmol) dropwise. After stirring the same temperature for 1 h, ethyl ester 45 (1.06 g, 4.69 mmol) was added and the resulting solution was stirred at -78 °C for 1 h. The reaction was warmed to 0 °C and stirred for another 1 h before quenched with 2.5 mL sat. aq. NaHCO\textsubscript{3}. The mixture was passed through a pad of celite and flushed with EtOAc. Flash chromatography gave the product (1.01 g, 71%) as a colorless oil.

TLC (hex:EtOAc 1:2)

Rf = 0.26, stained by p-anisaldehyde

\(^1\)H NMR (500 MHz, CDCl\textsubscript{3})

δ 4.49 (d, J = 2 Hz, 1H), 4.34 (m, 1H), 4.33 (d, J = 2 Hz, 2H), 3.80 (dd, J = 11, 5 Hz, 6H), 3.55 (m, 1H), 3.16 (m, 1H), 2.46 (m, 1H), 2.35 (m, 1H), 2.10 (m, 1H), 2.01 (m, 1H), 1.73 (m, 6H).
HRMS (ES+)

Calculated for C\textsubscript{11}H\textsubscript{19}O\textsubscript{6}PNa: 301.0817

Found: 301.0813

**Enone 2.73.** To a solution of 2.58 (405.7 mg, 1.33 mmol) in 13.3 mL CH\textsubscript{3}CN under nitrogen was added LiCl (112.8 mg, 2.66 mmol, 120°C over dried overnight). After stirred at 23 °C for 10 min, DIPEA (343.8 mg, 2.66 mmol) was added dropwise and the mixture was allowed to stir for another 25 min. The mixture was then cooled to 0 °C and 2.55 (322.7 mg, 1.33 mmol) in 2.5 mL CH\textsubscript{3}CN was added. The reaction was stirred at 23 °C for 4 h before it was quenched with 5 mL brine. The layers were separated and the aqueous layer was extracted three times with CH\textsubscript{2}Cl\textsubscript{2}. The combined organic layer was dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated *in vacuo*. Flash chromatography furnished 2.73 (376.2 mg, 67%).

TLC (hex:EtOAc 2:1)

Rf = 0.51, stained by p-anisaldehyde

\[^1\text{H} \text{NMR} (500 \text{ MHz, CDCl}_3) \delta 6.93 \text{ (dd, } J = 15.5, 4 \text{ Hz, } 1\text{H}), \ 6.72 \text{ (dd, } J = 16, 1.5 \text{ Hz, } 2\text{H}), \ 4.51 \text{ (m, } 1\text{H}), \ 4.48 \text{ (d, } J = 1.5 \text{ Hz, } 1\text{H}), \ 4.38 \text{ (dd, } J = 12, 4 \text{ Hz, } 1\text{H}), \ 4.32 \text{ (d, } J =}
1.5 Hz, 1H), 4.29 (m, 1H), 3.70 (s, 3H), 2.59 (m, 1H), 2.42 (m, 1H), 2.39 (m, 2H), 2.13 (m, 1H), 1.97 (m, 7H), 1.71 (m, 11H).

HRMS (ES+)

Calculated for $\text{C}_{23}\text{H}_{33}\text{O}_7$: 421.2226

Found: 421.2230

Stryker’s reagent

2.73

Ketone 2.62. Stryker’s reagent ($[(\text{Ph}_3\text{P})\text{CuH}]_6$, 1.76 g, 0.90 mmol) was added to a solution of enone 2.73 (344.2 mg, 0.82 mmol) in 40 mL toluene in the glove box. The mixture was allowed to stir at 23 °C for 1 h. 13 mL hexanes was added to the reaction flask and the reaction was exposed to air. It was allowed to stir for another 1 h at 23 °C before concentration under reduced pressure. Flash chromatography afforded 2.62 (253.2 mg, 74%).

TLC (hex:EtOAc 2:1)

$\text{Rf} = 0.57$, stained by p-anisaldehyde
Chapter 2 First generation synthesis of amphotericin B polyol subunit BB1

\[ ^1H \text{NMR (500 MHz, CDCl}_3 \] 4.47 (s, 1H), 4.31 (s, 1H), 4.21 (m, 3H), 3.75 (m, 1H), 3.68 (s, 3H), 2.69 (m, 2H), 2.57 (m, 1H), 2.41 (m, 2H), 2.29 (m, 1H), 2.09 (m, 1H), 2.01 (m, 1H), 1.93 (m, 1H), 1.68 (m, 15H).

HRMS (ES+)

Calculated for C\textsubscript{23}H\textsubscript{34}O\textsubscript{7}Si Na: 445.2202

Found: 445.2203

Alcohol 2.74. L-selectride (1 M in THF, 264 \textmu L, 0.264 mmol) was added to a solution of ketone 2.62 (106.2 mg, 0.252 mmol) in 5.5 mL THF under nitrogen at -110 °C. The bath temperature was raised to -78 °C in the course of 15 min, before finally warmed to 0 °C. 0.44 mL 6 M NaOH and 0.37 mL 30% H\textsubscript{2}O\textsubscript{2} was added to the reaction. After 30 min, 7.4 mL of Et\textsubscript{2}O was added the layers were separated. The organic layer was washed with 0.74 mL 10% sat. aq. Na\textsubscript{2}S\textsubscript{2}O\textsubscript{3}, two times 0.74 mL sat. aq. NaHCO\textsubscript{3}, and 0.74 mL brine. The combined organic layer was dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated in vacuo to give the alcohol 2.74 (106 mg, 100%). The crude material was directly used in the next reaction without further purification.

TLC (hex:EtOAc 2:1)

Rf = 0.34, stained by p-anisaldehyde
\[^1\text{H NMR (500 MHz, CDCl}\_3\text{)}\] 4.43 (d, \(J = 2\) Hz, 1H), 4.25 (d, \(J = 1.5\) Hz, 1H), 4.21 (m, 2H), 3.77 (m, 1H), 3.69 (s, 3H), 3.47 (m, 1H), 2.56 (m, 2H), 2.40 (m, 1H), 2.27 (m, 1H), 2.10 (m, 2H), 1.80 (m, 20H).

\text{HRMS (ESI+)}

\text{Calculated for C}_{23}\text{H}_{36}\text{O}_7\text{Na: 447.2341}

\text{Found: 447.2359}

\text{Silyl ether 2.63.} \text{ To a stirred solution of 2.74 (85.1 mg, 0.2 mmol) and 2,6-lutidine (322.6 mg, 30.0 mmol) in 4 mL hexanes under nitrogen at -78 °C was added TBSOTf (159 mg, 0.6 mmol) slowly. After 3 h, additional TBSOTf (26.6 mg, 0.1 mmol) was added and after 0.5 h, the reaction was quenched with 2 mL of sat. aq. NaHCO}_3. \text{ The reaction was allowed to warmed to 23 °C while maintaining stirring. Layers were separated and the aqueous layer was extracted with three times of Et}_2\text{O. The combined organic layer was dried over Na}_2\text{SO}_4 \text{ and concentrated in vacuo. Flash chromatography afforded silyl ether 2.63 (75 mg, 71%).}

\text{TLC (hex:EtOAc 5:1)}

\text{Rf = 0.24, stained by p-anisaldehyde}
\(^{1}\)H NMR (500 MHz, CDCl\(_3\)) 4.47 (s, 1H), 4.31 (s, 1H), 4.21 (m, 3H), 3.75 (m, 1H), 3.68 (s, 3H), 2.69 (m, 2H), 2.57 (m, 1H), 2.41 (m, 2H), 2.29 (m, 1H), 2.09 (m, 1H), 2.01 (m, 1H), 1.93 (m, 1H), 1.68 (m, 15H).

HRMS (ESI+)

Calculated for C\(_{29}\)H\(_{51}\)O\(_7\)SiNa: 539.3404

Found: 539.3389

“northern” AmB \textbf{2.66}. \textbf{2.63} (20 mg, 0.037 mmol) was stirred with 9-BBN (0.5 M in THF, 89 uL, 0.045 mmol) and 0.27 mL additional THF in the glove box at 23 °C for 1.5 h. A premixed solution of SPhos (4%, 0.61mg) and Pd(OAc)\(_2\) (2%, 0.17 mg) in 50 uL THF was added to the first flask. K\(_3\)PO\(_4\) (23.7 mg, 0.112 mmol) and a solution of \textbf{2.65} (18.5 mg, 0.056 mmol) in 0.9 mL DMF was also added to the first flask. The heterogeneous mixture was allowed to stir at 50 °C for 24 h. The reaction mixture was allowed to pass through a pad of florisil and the solvent was removed under reduced pressure. The yield of the product was not determined at this point.

HRMS (ESI+)

Calculated for C\(_{34}\)H\(_{59}\)O\(_8\)Si: 623.3979

Found: 623.4005
2.6 References


Chapter 2 First generation synthesis of amphotericin B polyol subunit BB1


(33) Waetzig, J. D.; Hanson, P. R. Chemtracts 2007, 19, 157-167.


Chapter 3

Second generation synthesis of BB1

As discussed in chapter 2, in the first generation synthesis, late stage intermediate 2.63, as well as several of its exo-methylene dioxane moiety containing precursors readily undergo an undesired isomerization. In addition, BB1 2.64 is an air sensitive 9-BBN alkyl borane which has to be prepared in situ from 2.63 prior to the coupling. None of these intermediates are good candidates for a storage “check point” that is crucial for constructing an efficient and modular ICC-based synthesis.¹
In sharp contrast to most organoboron compounds such as 2.63, MIDA boronates-containing substrates have demonstrated extraordinary bench-top stability and reagent compatibility. Meanwhile, MIDA boronates, which are often crystalline solids, can be readily hydrolyzed with mild aqueous base to the corresponding boronic acids for subsequent cross-couplings. Thus, in our second generation synthesis, we planned to convert the sensitive exo-methylene dioxane moiety early in the route to the primary Csp³ MIDA boronate and carry it through multiple steps to access building block BB1.

![Scheme 3.1. Proposed hydrolysis of BB1-MIDA to BB1-boronic acid.](image)

To enable this proposal, three challenges has to be solved: 1. establishing a new synthesis of MIDA boronates (a route to the targeted Csp³ MIDA boronate was unknown); 2. carrying MIDA boronate through a multiple-step synthetic route to BB1; 3. hydrolyzing Csp³ primary BB₁-MIDA boronate to BB₁-boronic acid and cross-couple it to BB₂ under a Csp³-Csp² Suzuki-Miyaura condition. Successful development of this approach stood not only to provide an efficient route to a building block, but also to provide a venue to build the ubiquitous Csp³-Csp² bond and enable the development of methods to target molecules beyond the scope of this synthesis.
3.1 Cross-coupling of primary Csp\(^3\) boronic acids

With the advancement of new catalysts, cross-couplings of Csp\(^2\) hybridized aryl, vinyl, and heteroaryl boronic acids with a variety of substitution patterns can now be routinely performed. In contrast, the scope of Csp\(^3\) boronic acid cross-couplings is practically very limited due to the inherently slower transmetalation and reductive elimination. In addition, notoriously poor stability of Csp\(^3\) boronic acids has made handling and storage of these compounds difficult. Early examples of cross-coupling Csp\(^3\) boronic acids and boronic esters are limited to unbranched primary substrates.\(^4\)\(^-\)\(^7\)

\[
\begin{align*}
R & \quad B \quad OH & + & \quad X \quad Ar & \xrightarrow{\text{PdCl}_2(dppf), \ K_2CO_3, \ Ag_2O, \ THF, 70^\circ C} & R \quad B \quad Ar \\
\text{BocHN} & \quad \text{BocHN} & & & & \\
\end{align*}
\]

**Scheme 3.2.** Cross-coupling of \(\beta\)-substituted Csp\(^3\) primary boronic acids.

In 2005, Taylor reported that by applying silver oxide as an additive, cross-coupling of primary boronic acids with increased structural complexity can also be achieved (*Scheme 3.2*).\(^4\) Under his optimized condition, \(\beta\)-nitrogen containing primary Csp\(^3\) boronic acids were successfully coupled to a series of aryl halides with...
modest yields. The Taylor system somewhat resembles the BB1-BB2 cross-coupling of β-oxygen containing primary Csp³ boronic acid BB1 3.2 in our route. Intrigued by this result, a screen of model cross-coupling with commercially available primary and secondary Csp³ boronic acids was performed (Scheme 3.3).

![Scheme 3.3](image)

Scheme 3.4. Cross-coupling of Csp³ boronic acids with bromoacetophenone.

![Scheme 3.5](image)

Scheme 3.5. Cross-coupling of octylboronic acids with halides and pseudo-halide.

Applying the silver oxide promoted condition, both primary octylboronic acid 3.3 and iso-butylboronic acid 3.4 coupled well with 4-bromoacetophenone. More interestingly, cross-coupling of unactivated secondary Csp³ cyclopentylboronic acid 3.5
also gave surprisingly good yield. Following up on this interesting observation led to the development of a novel method for site- and stereo-retentive cross-coupling of unactivated chiral secondary boronic acids, which is described in chapter 5.

We next examined different halides and pseudo-halides for this reaction (Scheme 3.5). Aryl iodide is a competent coupling partner for this reaction, while aryl chloride failed to yield the desired product. In a more important study, BB2 analog cyclic ketene phosphate 3.8 gave no detectable product under this condition. This problem was solved through a quick screen, and it was found that Buchwald’s anhydrous condition can promote the Csp3-Csp2 cross-coupling efficiently (Scheme 3.6).


3.2 Synthesis of alkyl MIDA boronates

Having established a reliable primary Csp3 boronic acid cross-coupling with ketene acetal phosphate, we next targeted to find a synthesis of Csp3 MIDA boronates. Examples of existing synthesis of MIDA boronates are demonstrated in Scheme 3.7 and can be summarized into three categories: 1. condensation of boronic acid with MIDA under Dean-Stark condition;\(^2\) 2. hydroboration with tribromoborane followed by trapping with MIDA ligand (Eqa. 3.1);\(^2\) 8 3. attack of trialkyl borate with preformed organometallic nucleophile followed by trapping with MIDA ligand (Eqa. 3.2 and
3.3) The Dean-Stark procedure requires a pre-formed C-B bond. In the latter two cases, harsh reaction conditions are needed, which presumably led to only fair to moderate yields. In addition, high boiling DMSO is the solvent of choice in the second step which makes purification of the product challenging.

\[
\begin{align*}
&\text{Scheme 3.7. Existing methods for the synthesis of MIDA boronates.}
\end{align*}
\]

\[
\begin{align*}
&\text{Scheme 3.8. Potential elimination of alkyl organometallic substrate in the presence of } \beta\text{-oxygen.}
\end{align*}
\]
In our synthesis of Csp\(^3\) primary MIDA boronate, we first ruled out the formation of organometallic nucleophiles such as \(3.10\). \(\beta\)-elimination is likely to occur in the presence of \(\beta\)-oxygen containing carbon center to yield terminal olefin \(3.11\), following the mechanism proposed in Scheme 3.8.

We then attempted hydroboration condition of intermediate \(3.12\) from the first generation synthesis with dibromoborane dimethylsulfide complex. In practice, decomposition of the substrate was observed which was presumably caused by the presence of strong electrophile dibromoborane. Upon complexation with MIDA, only less than 5% yield of \(3.13\) was isolated (Scheme 3.9).

Scheme 3.9. Low yielding synthesis of Csp\(^3\) MIDA boronate building block with HBBr\(_2\).Me\(_2\)S.

In 2003, Snieckus and coworkers reported a synthesis of alkyl boronic acids by hydroboration of the olefin with the “Snieckus borane” \(3.14\). The two alkyl ligands on the hydroborated intermediate \(3.15\) are cleaved first by water, followed by formaldehyde to give boronate \(3.17\) (Scheme 3.10). Corresponding boronic acid can be prepared from hydrolysis of \(3.17\).
Building on this procedure, we were able to synthesize boronate 3.17 from 3.12. Upon complexation with MIDA, the desired MIDA boronate 3.13 was isolated in 51% yield. Furthermore, in an unoptimized experiment, we discovered that a direct transligation from the Snieckus hydroborated intermediate 3.15 to the MIDA boronate was also possible. We hypothesized that a similar 6-centered rearrangement is operative in this process (Scheme 3.11). Only the syn-diastereomer was observed.

**Scheme 3.11.** Proposed mechanism for a direct transligation from Snieckus borane to MIDA boronate.
3.3 Second generation synthesis of BB1 in the form of MIDA boronate and cross-coupling of BB1-B(OH)$_2$ with BB2

3.3.1 Synthesis of BB1-MIDA and first attempt of BB1-B(OH)$_2$ cross-coupling

With MIDA boronate 3.13 in hand, we proceeded with the BB1 synthesis via a modified route (Scheme 3.12). Reaction with alkyl lithium to form phosphonate 3.18 was accompanied with partial decomposition of the MIDA boronate and gave a moderate 47% yield. This is, however, the only time in the new route that we observed a loss of the product due to the stability of MIDA boronate moiety. Horner-Wadsworth-Emmons reaction with aldehyde 3.19 went smoothly to afford cross-coupled intermediate 3.20 in 60% yield. Finally, diastereoselective reduction with (R)-CBS, hydrogenation of the resulting olefin, and TBS silylation of C8 alcohol gave BB1-MIDA 3.1. It is noteworthy to point out that it was the first time MIDA boronate was shown to be compatible (or at least partially compatible) with reagents and reaction conditions that are labeled in blue.

Hydrolysis of 3.1 took place readily under standard aqueous NaOH condition, furnishing BB1-B(OH)$_2$ 3.2 in quantitative yield. With this building block in hand, we went on to examine the cross-coupling reaction with the valerolacton-derived BB2 analog 3.8. To our surprise, under the same condition that gave 71% cross-coupled yield (Scheme 3.6) for octylboronic acid 3.3 and valeralactone derived cyclic ketene acetal phosphate 3.8, no product was observed (Scheme 3.13).

Scheme 3.13. Failed cross-coupling of BB1-B(OH)2 (3.1) and BB2 analog (3.8).

With questionable comparison, Csp² iodide may be more reactive than Csp³ phosphates to couple with Csp³ boronic acids. In addition, triflate is considered to be an equally or more reactive functional group compared to phosphate. Thus, as part of our search for a practical coupling, we also included triflate 3.21 and vinyl iodide 3.22 derived from glucal as well as phosphate 3.8.
Over 200 conditions were screened in an attempt to find a practical coupling between BB1 and BB2 (Table 3.1). However, no reaction showed any conversion to the desired product, analyzed by TLC, mass spectrometry and crude $^1$H NMR analysis. The only difference between this system and model reaction (Scheme 3.6) is $\beta$-substitution of the primary boronic acid. Based on this analysis, we proposed that preparation of a more active boron nucleophile might solve the problem.

![Figure 3.1.](image)

Table 3.1. An partial list of BB1-BB2 cross-coupling conditions screened. Selected combinations from different columns have been examined. Not all combinations have been screened.
3.3.2 Csp³-Csp² cross-coupling of boron ate-complex

In contrast to other palladium mediated organometallic cross-coupling reactions, addition of base is necessary to promote Suzuki-Miyaura couplings.¹² ¹³ One proposed role of the base is an activator to form the nucleophilic boron ate-complex from electrophilic boronic acid. Therefore, a faster boron ate-complex formation might increase the rate of the cross-coupling. This hypothesis could be employed to explain the fact that alkyl boranes (such as first generation BB1-9-BBN 2.64) that is easier to form the ate-complex is much more reactive than their boronic acid counterparts (BB1-B(OH)₂ 3.1) under cross-coupling conditions.¹⁴ To take advantage of this phenomenon, Miyaura was able to cross-couple the preformed boronate ate-complex without the addition of any base (Scheme 3.14).¹⁵ In addition, except for a handful of cases where Johnphos ligand was used, the Miyaura triolborate is very active that high-yielding cross-coupling can be achieved even without addition of a ligand at room temperature. Inspired by this report, we prepared a series of boron ate-complexes with different electronic and steric characteristics using Miyaura’s complexation condition and tested them in a simple aryl-aryl cross-coupling, in hope to find a candidate that is more active than the boronic acid to promote the BB1-BB2 coupling. For the purpose of this screen, we used a Pd(OAc)₂ and Johnphos combination, one of the standard conditions from Miyaura’s report.

Depicted in Scheme 3.15, both boronic acid with K₃PO₄ and Miyaura’s triolborate afforded full conversion under the catalyst condition. Borate 3.25 which has a more rigid cyclohexyltriol ligand gave decreased conversion while 3.26, a more electronic deficient version of the Miyaura’s borate 3.24, was inactive.

Scheme 3.15. Comparison of different boron nucleophiles under Csp²-Csp² cross-coupling conditions.

We next prepared these borates (3.27, 3.28, 3.29) from butylboronic acid and evaluated their reactivity under Csp³-Csp² cross-coupling conditions (Scheme 3.16). With the Pd(OAc)₂ plus Johnphos catalyst/ligand combination, no conversion for any of the tested boron nucleophile was observed even at elevated temperature as high as 85°C. Next, the same series of borates were subjected to the Taylor condition. As it turned out, low conversion was observed for borates 3.28 and 3.29 while coupling of the Miyaura borate 3.27 yielded a significant amount of byproduct that was identified to be the proto-dehalogenated acetophenone. Meanwhile, butylboronic acid plus Ag₂O afforded
full conversion. From these studies, it is safe to conclude that boronic acid plus base is more reactive than the other three preformed borate ate-complex.

Scheme 3.16. Comparison of different boron nucleophiles under Csp\(^3\)-Csp\(^2\) cross-coupling conditions.

Another example of preformation alkyl boronate ate-complex strategy was reported by Falck in 2001.\(^{16}\) Instead of an anionic borate, butyl pinacol borate was treated with sec-BuLi to form the active ate-complex 3.30, which was subsequently coupled with an aryl halide under a cross-coupling condition without external base (Scheme 3.17).
Following this precedent, we thereby prepared Csp$^3$ pinacol borate 3.32 by transligation from MIDA boronate 3.32 in a model system. Once again, attempt for this tricky Csp$^3$-Csp$^2$ cross-coupling reaction was not met with success (Scheme 3.18).
Building on this platform, we next synthesized a variety of borates by treating MIDA boronate 3.31 with diols listed in Figure 3.2, trying to create a variety of steric environment around coupling site. In all cases transligation proceeded well to afford 85-99% of the borate. However, the sole positive result was from cross-coupling the least steric encumbered ethylene glycol borate 3.34 with triflate 3.21 that afforded only 7% of the desired product 3.33 (Scheme 3.19).

### 3.3.3 Csp³-Csp² cross-coupling of electron deficient borates

Having been unsuccessful to couple electron-rich borate “ate-“ complex, we took a different approach by synthesizing borates that are electron poor. The logic behind our proposal is that such borate might in fact have a lower energy barrier to react with the base and better stabilize the “ate-“ complex. Guided by this principle, a series of catechol derived borates were synthesized. However, none of these showed promising results in the cross-coupling reaction. Currently, these results led us to pursue a third generation synthesis of BB1.
3.4 Experimental section

**Materials.** Commercial reagents were purchased from Sigma-Aldrich, Fisher Scientific, Alfa Aesar, TCI America, or Frontier Scientific, and were used without further purification unless otherwise noted.

Solvents were purified via passage through packed columns as described by Pangborn and coworkers¹ (THF, Et₂O, CH₃CN, CH₂Cl₂: dry neutral alumina; hexane, benzene, and toluene, dry neutral alumina and Q₅ reactant; DMSO, DMF: activated molecular sieves). All water was deionized prior to use. Diisopropylethylamine was freshly distilled under an atmosphere of nitrogen from CaH₂.

**General experimental procedures.** Unless noted, all reactions were performed in flame-dried round bottom or modified Schlenk flasks fitted with rubber septa under a positive pressure of argon or nitrogen. Organic solutions were concentrated via rotary evaporation under reduced pressure with a bath temperature of 23 °C unless otherwise noted. Reactions were monitored by analytical thin layer chromatography (TLC) performed using the indicated solvent on E. Merck silica gel 60 F254 plates (0.25mm). Compounds were visualized by exposure to a UV lamp (λ = 254 nm), and/or a solution of KMnO₄ and/or a solution of p-anisaldehyde, followed by brief

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**Figure 3.3.** Diol ligands with different electronic profiles.
heating using a Varitemp heat gun. Column chromatography was performed using Merck silica gel grade 9385 60Å (230-400 mesh).

**Structural analysis.** \(^1\)H NMR and \(^{13}\)C NMR spectra were recorded at 20 °C on Varian Unity 500, Varian Unity Inova 500NB or Varian Unity 500 instruments. Chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane and referenced to residual protium in the NMR solvent (benzene, δ = 7.16; CHCl₃, δ = 7.26; acetone, δ = 2.05, center line; DMSO δ = 2.50, center line) or to added tetramethylsilane (δ = 0.00). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sept = septet, m = multiplet, b = broad, app = apparent), coupling constant (J) in Hertz (Hz), and integration. Chemical shifts (δ) for \(^{13}\)C NMR are reported in ppm downfield from tetramethylsilane and referenced to carbon resonances in the NMR solvent (benzene-d₆, δ = 128.06, center line; CDCl₃, δ = 77.0, center line; acetone-d₆, δ = 39.5, center line; DMSO-d₆ δ = 39.52, center line). Carbons bearing boron substituents were not observed (quadrupolar relaxation). High resolution mass spectra (HRMS) were performed by Furong Sun, Elizabeth Eves and Dr. Haijun Yao at the University of Illinois School of Chemical Sciences Mass Spectrometry Laboratory.
Chapter 3 Second generation synthesis of BB1

Under argon atmosphere, a 25 mL round-bottom-flask equipped with a stir bar was charged with diene \(3.35\) (1.06 mL, 2.20 equiv.) in 1.06 mL THF was slowly added 1 M solution of \(3.47\) mL, 1.05 equiv.) BH\(_3\).THF at 0 °C. The reaction was allowed to stir at this temperature for 3h and was used in the hydroboration as a solution.

\[
\begin{align*}
3.12 & \quad (754 \text{ mg, } 3.34 \text{ mmol, } 1.0 \text{ equiv.}) \\
3.13 & \quad (53\%)
\end{align*}
\]

\(3.12\) (754 mg, 3.34 mmol, 1.0 equiv.) was added to above solution in 1.97 mL THF. The reaction was then allowed to stir at 23 °C for 3 h before slowly added 0.45 mL water. After stirring at 23 °C for another 2 h, 0.26 mL 37% formaldehyde aqueous solution was added and the mixture was allowed to stir for 24 h.

The borane mixture was diluted with 3.32 mL of EtOAc and 6.7 mL of DMSO. MIDA ligand (0.74 g, 1.5 equiv.) was then added as a solid and was connected to a short path distillation condenser. The reaction was placed in an oil bath under house vacuum. the temperature was brought up to 50 °C and the mixture was allowed to stir at for 1 h. In this way, water as well as most low-boiling organic molecules were removed. At the same temperature, DMSO was distilled under reduced pressure. The off-yellow crude mixture was purified through flash column to give 674 mg \(3.13\) (53%)
$^1$H NMR (499 MHz, Acetone) δ 4.45 (dd, J = 12.5, 3.0, 1H),  4.25 (d, J = 17.0, 1H), 4.17-4.13 (m, 3H), 4.00 (d, J = 17.5, 1H) 3.95-3.91 (m, 2H), 3.15 (s, 3H), 1.96-1.74 (m, 5H), 1.66-1.45 (m, 5H), 1.24 (t, J = 7.5, 3H), 1.05-0.95 (m, 2H).

HRMS (ESI+)

Calculated for C17H26BNNaO8: 406.1649

Found: 406.1637

To a stirred solution of 3.36 (2.21 g, 6.0 equiv.) in 40 mL THF in a 100 mL RBF under argon was dropwise added 1.6 M nBuLi (11.4 mL, 6 equiv.) at -78°C. After 0.5 h, a solution of 1.14 g 3.13 in 4 mL THF was added via cannula. In 3.5 h, 11.44 mL (v:v=3:5) acetic acid in THF was slowly added while vigorously stirring. After stirring at -78°C for 2 min, the cold bath was removed and 22.9 mL half sat. aqueous NH₄Cl was added and the mixture was extracted with EtOAc 5 times. Drying with Na₂SO₄ was followed by concentration under reduced pressure. Flash column followed by recrystallization from acetone:Et₂O:hexanes afforded 3.18 as a white crystalline spindle in 47% (643 mg).

$^1$H NMR (400 MHz, Acetone) δ 4.45-4.41, (dd, J = 12, 8, 1H), 4.25 (d, J = 17.2, 1H) 4.15 (d, J = 16.0, 1H), 4.01 (d, J = 17.2, 1H), 3.95-3.91 (m, 2H), 3.74-3.70 (m, 6H), 3.52-
3.42 (m, 1H), 3.22-3.13 (m, 1H), 3.15 (s, 3H), 2.13-1.83 (m, 4H), 1.76-1.59 (m, 5H), 1.42-1.32 (m, 1H), 1.07-0.95 (m, 2H).

HRMS (ESI+)

Calculated for C18H29BNNaO10P: 484.1520

Found: 484.1527

To a stirred solution of 3.18 (757 mg, 1.0 equiv.) in 16.4 mL MeCN in a 100 mL RBF under argon at 23°C was added 209 mg oven dried LiCl (3.0 equiv.). In 15 min, 0.86 mL DIPEA (3.0 equiv.) was added. In another 25 min, 3.19 in 8.2 mL MeCN was cannulaed over at 0°C. The reaction was let stir at 23°C for 2.5 h before being quenched with 12.8 mL sat. aqueous NH4Cl. The mixture was extracted with EtOAc 5 times. Drying over MgSO4 was followed by concentration under reduced pressure. Crude yield was 770 mg, (83%) and after column purification afforded the product as a white solid 557 mg (60%).

1H NMR (499 MHz, Acetone) δ 6.87 (dd, J = 15.5, 4, 1H) 6.70 (dd, J = 15.5, 1.5, 1H), 4.64-4.61 (m, 1H), 4.52 (dd, J = 12, 3.0, 1H), 4.33-4.31 (m, 1H), 4.25 (d, J = 17.0,
1H), 4.15 (d, J = 16.5, 1H), 4.01 (d, J = 17.5, 1H), 3.98-3.97 (m, 1H), 3.94 (d, J = 16.5, 1H), 3.63 (s, 3H), 3.17 (s, 3H), 2.49-2.46 (m, 2H), 1.99-1.58 (m, 17H), 1.41-1.20 (m, 3H), 1.60-0.50 (m, 2H).

HRMS (ESI+)
Calculated for C28H40BNNaO11: 600.2592
Found: 600.2600

In a 40 mL IChem vial equipped with a stir bar under argon, a 1 M solution (R)-CBS (0.44 mL, 1.0 equiv.) was diluted with 1.5 mL THF. The solution was cooled to -10 °C and was added 0.46 mL 2.0 M BH₃·Me₂S in toluene (2.1 equiv.). In 10 min, a solution of 3.20 in 4.3 mL THF was added and the mixture was allowed to stir at the same temperature for 1 h before 5 mL sat. aqueous NH₄Cl was added to quench the reaction. After vigorously stirring for 1 h, layers were separated and the aqueous layer was extracted with EtOAc x 5. Drying over Na₂SO₄ before filtered through a pad of celite. Concentration under reduced pressure afforded the product 3.37 which was used directly into the next reaction without further purification. Crude yield, 250 mg, 98%

¹H NMR (499 MHz, Acetone) δ 5.78-5.69 (m, 2H), 4.40-4.36 (m, 1H), 4.29-4.21 (m, 2H), 4.12 (d, J = 16, 1H), 4.00 (d, J = 17.5, 1H), 3.95-3.90 (m, 2H), 3.88-3.83 (m,
1H), 3.72-2.66 (m, 2H), 3.63 (s, 3H), 3.15 (s, 3H), 2.49-2.40 (m, 2H), 2.04-1.53 (m, 17H),
1.32-1.22 (m, 3H), 1.02-0.89 (m, 2H).

HRMS (ESI+)

Calculated for C28H42BNNaO11: 602.2749

Found: 602.2745

The substrate 3.37 (230 mg, 0.40 mmol) was azeotropically dried with toluene
under vacuum before refilled with dry nitrogen in a 40 mL I-Chem vial. 17.28 mL EtOAc
was added followed by 10wt% Pd/C (6.36 mg/63.6 mg, 15 mol%) in one portion. 2 9-
inch full balloons of hydrogen was charged to the vigorously stirred reaction at 23 °C.
Both balloons were recharged in 14.5 h, and in another 12 h the balloons were removed.
The reaction mixture was passed through a pad of celite and flushed with EtOAc before
concentration under reduced pressure. The product 3.38 which was used directly into
the next reaction without further purification afforded crude yield 225 mg, 98%.

1H NMR (499 MHz, Acetone) δ 4.25-4.18 (m, 2H), 4.12 (d, J = 16, 1H), 4.00 (d, J
= 17.5, 1H), 3.93 (d, J = 16.5, 1H), 3.90-3.81 (m, 2H), 3.71-2.67 (m, 1H), 3.42-3.36 (m,
1H), 3.62 (s, 3H), 3.15 (s, 3H), 1.92-1.91 (m, 2H), 1.82-1.71 (m, 6H), 1.66-1.49 (m, 14H),
1.21-1.14 (m, 2H), 1.04-0.91 (m, 2H).
HRMS (ESI+)
Calculated for C\textsubscript{28}H\textsubscript{44}BNNaO\textsubscript{11}: 604.2905
Found: 604.2915

**General procedure to** prepare with primary C\textsuperscript{sp3} boronates

![Diagram of chemical reaction]

2-mL I-Chem vial was charged with primary C\textsuperscript{sp3} MIDA boronate \textit{3.31} (0.145 mmol, 1.0 equiv.), was added a solution of diol (0.434 mmol, 3.0 equiv.) in 1 mL MeOH. Solid NaHCO\textsubscript{3} (0.061 g, 0.723 mmol, 5.0 equiv.) was then added.

The reaction was stirred at 23 °C for 3 hours and then was concentrated in vacuo and finely ground anhydrous CaCl\textsubscript{2} (0.064 g, 0.579 mmol, 4 eq), solid NaHCO\textsubscript{3} (0.024 g, 0.289 mmol, 2 equiv.), and toluene (4.3 mL) were added to the resulting residue. The mixture was stirred at 23 °C for 45 minutes, filtered through a pad of celite with toluene (50 mL) and concentrated to yield the boronate. The product was used directly in the next reaction without further purification.

### 3.5 References


Chapter 4

Third generation synthesis of BB1

In Chapter 2, we discussed a successful one pot hydroboration/cross-coupling strategy to make the BB1-BB2 bond in a model study. This first generation synthesis was however hampered with the accessibility of BB1 precursor 2.63 as a consequence of the very sensitive nature of 2.63.
Chapter 4 Third generation synthesis of BB1

To address this problem, discussed in chapter 3, a very stable BB1-MIDA 3.1 was prepared and was readily hydrolyzed to boronic acid 3.2 for the cross-coupling. After a thorough screen of reaction conditions, however, a catalyst system to promote such a transformation was not found.

Therefore, these studies revealed that 2.63 is unstable but reactive, while 3.1 is very stable yet unreactive. We hence sought for a solution that combines the merits of the first two syntheses. This chapter describes the successful development of a solution to this problem and the subsequent total synthesis of a protected form of doubly C13 labeled AmB.
4.1 Third generation synthesis of BB1

In the first generation synthesis of BB1, a route to AmB polyol subunit BB1 2.64 in the form of 9-BBN alkyl borane was achieved and a cross-coupling of BB1 and BB2 analog 2.65 was successfully established. Nonetheless, this approach was severely hampered by the instability of its intermediates such as 2.63, making a scalable synthesis impractical. In contrast, the second generation synthesis where BB1 was prepared in the form of an alkyl boronic acid employed relative stable intermediates, mostly in the form of MIDA boronates. However, we failed to find a high-yielding condition to cross-couple BB1 3.2 which was an alkyl boronic acid that is known to be less reactive than its alkyl borane counterpart. Thus, in the third generation synthesis we need to address both the stability and reactivity problems.

Scheme 4.1.

In the first generation synthesis, we discovered that ketone 2.62 is a crystalline white solid which proved to be more stable than most other methylene dioxane containing intermediates in the route. We attributed this increased stability to the electron withdrawing effect of the C8 ketone which reduces the nucleophilicity of the terminal olefin. This hypothesis also explains the physical reasons that intermediate 2.63 which has C8 alcohol protected as electron rich TBS silyl ether, being the least stable compound in the route. Based on this hypothesis, we thereby prepared electron
deficient C8-acylated BB1 precursor 4.1. To our delight, acylation with acetic anhydride smoothly afforded 4.1, an intermediate which turned out to be much more stable than 2.63. Specifically, isomerization of the terminal olefin that plagued the isolation of 2.63 is negligible in 4.1. A highly reproducible yield for the protection was thus boosted from a capricious 35-71% to 82%. (Scheme 4.2)

Scheme 4.2. Synthesis of acylated BB1 precursor 4.1.

With a robust and scalable synthesis of C8-acylated BB1 precursor 4.1 in hand, we turned our attention to developing a set of conditions that would promote the boron-selective cross-coupling of C8-acylated BB1 precursor 4.1 with the MIDA boronate
containing cyclic ketene acetal phosphate \textbf{BB2}. I was joined by fellow graduate student Stephen Davis for the screen of the final cross-coupling. We first attempted the model \textbf{BB1-BB2} coupling with the same analog \textbf{4.3} that was used in our first and second generation syntheses. This required finding mild conditions for this cross-coupling that would not hydrolyze the MIDA boronate motif.\textsuperscript{2, 3} While several anhydrous basic conditions led to little or no product and the inclusion of bulk water led to MIDA boronate hydrolysis, we ultimately determined that the addition of 3 equivalents of water to a THF suspension of K\textsubscript{3}PO\textsubscript{4} in the presence of the second generation SPhos palladacycle led to a very smooth coupling of \textbf{BB1 4.1} and \textbf{BB2} analog \textbf{4.3} (\textbf{Scheme 4.3}).

Concerned about potential undesired hydrolysis of \textbf{BB2} MIDA boronate, fellow student Stephen Davis studied the rate of hydrolysis of simple MIDA boronate at different concentration of water and temperature. Greater than 90% of MIDA boronate survived with the addition of three equivalents of water at 50°C in 6 hours, which was enough to promote \textbf{BB1-BB2} analog cross-coupling.

Doubly C\textsubscript{13} labeled (at C\textsubscript{13} and C\textsubscript{19}) bifunctional building block \textbf{BB2 4.5} was prepared by a team of my colleagues Ian Daily, Justin Struble, David Knapp, Nagarjuna Palyam and Jim Tucker. With both \textbf{BB1} and \textbf{BB2} in hand, our synthesis unfortunately hit another road block that cross-coupling condition from \textbf{BB1-BB2} model system gave no product in this real \textbf{BB1-BB2} coupling. Fortunately, this time only after a short exploration, I was able to solve the problem by running the reaction using a stoichiometric amount of catalyst and an elevated temperature at 70°C (\textbf{Scheme 4.4}).
Collectively, these advances represent an ICC-inspired total synthesis of the C1-C23 portion of AmB, setting the stage for ICC-based total synthesis of AmB derivatives having modifications in this otherwise very challenging to access portion of the natural product. More broadly, the success of this approach towards AmB argues very favorably for the effectiveness of a similar approach to other members of this family of natural products. Finally, the tactics and methods developed herein that proved viable in this very complex application, stand ready to further accelerate the development of ICC with
MIDA boronates as an increasingly general approach for complex small molecule synthesis.

**4.2 progress towards an ICC-based total synthesis of AmB-^{13}C_{2}**

Establishing the key cross-coupling between **BB1-BB2** enabled the first step of our ICC-based total synthesis of AmB. Applying this platform, rapid access to the macrocycle was anticipated by two more cycles of deprotection/cross-coupling.

![Scheme 4.5](image)

**Scheme 4.5.** Transligation from MIDA boronate to pinacol boronate.
First step of the deprotection is a transligation from MIDA boronate to pinacol boronate 4.7, a procedure that was established by Eric Woerly and Kaitlyn Gray in our group (Scheme 4.5). Interestingly, in practice instead of formation of the pinacol boronate, proto-deborolation to the diene was constantly observed. After lengthy optimization, it was discovered that this decomposition pathway was promoted residual palladium undetectable by 1H NMR and HPLC that was carried over from last cross-coupling reaction. To address this drawback, two equally-effective solutions were developed: 1. after normal-phase column purification, treating the product with palladium scavenger (propylamine functionalized silica); 2. after normal-phase column purification, running a second reverse-phase chromatographic purification.

Having solved this problem, collaborating with Dr. Justin Struble, we smoothly cross-coupled pinacol BB1-2 4.7 with bifunctional BB3 4.8 to yield the C1-C29 core of AmB. Upon purification, another round of deprotection-coupling followed by hydrolysis and macrolactonization was performed by Struble to achieve the AmB macrocycle 4.10 with all carbon connections established (Scheme 4.6). To finish the synthesis, global deprotection conditions are being actively pursued in our laboratory.
Scheme 4.6. ICC-based synthesis of the AmB macrocycle.
4.3 Experimental section

Materials. Commercial reagents were purchased from Sigma-Aldrich, Fisher Scientific, Alfa Aesar, TCI America, or Frontier Scientific, and were used without further purification unless otherwise noted.

Solvents were purified via passage through packed columns as described by Pangborn and coworkers (THF, Et₂O, CH₃CN, CH₂Cl₂: dry neutral alumina; hexane, benzene, and toluene, dry neutral alumina and Q₅ reactant; DMSO, DMF: activated molecular sieves). All water was deionized prior to use. Diisopropylethylamine was freshly distilled under an atmosphere of nitrogen from CaH₂.

General experimental procedures. Unless noted, all reactions were performed in flame-dried round bottom or modified Schlenk flasks fitted with rubber septa under a positive pressure of argon or nitrogen. Organic solutions were concentrated via rotary evaporation under reduced pressure with a bath temperature of 23 °C unless otherwise noted. Reactions were monitored by analytical thin layer chromatography (TLC) performed using the indicated solvent on E. Merck silica gel 60 F254 plates (0.25mm). Compounds were visualized by exposure to a UV lamp (λ = 254 nm), and/or a solution of KMnO₄ and/or a solution of p-anisaldehyde, followed by brief heating using a Varitemp heat gun. Column chromatography was performed using Merck silica gel grade 9385 60Å (230-400 mesh).

Structural analysis. ¹H NMR and ¹³C NMR spectra were recorded at 20 °C on Varian Unity 500, Varian Unity Inova 500NB or Varian Unity 500 instruments. Chemical shifts (δ) are reported in parts per million (ppm) downfield from
Chapter 4 Third generation synthesis of BB1

tetramethylsilane and referenced to residual protium in the NMR solvent (benzene, \( \delta = 7.16 \); CHCl\(_3\), \( \delta = 7.26 \); acetone, \( \delta = 2.05 \), center line; DMSO \( \delta = 2.50 \), center line) or to added tetramethylsilane (\( \delta = 0.00 \)). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sept = septet, m = multiplet, b = broad, app = apparent), coupling constant (\( J \)) in Hertz (Hz), and integration. Chemical shifts (\( \delta \)) for \( ^{13} \text{C} \) NMR are reported in ppm downfield from tetramethylsilane and referenced to carbon resonances in the NMR solvent (benzene-d\(_6\), \( \delta = 128.06 \), center line; CDCl\(_3\), \( \delta = 77.0 \), center line; acetone-d\(_6\), \( \delta = 39.5 \), center line; DMSO-d\(_6\) \( \delta = 39.52 \), center line). Carbons bearing boron substituents were not observed (quadrupolar relaxation). High resolution mass spectra (HRMS) were performed by Furong Sun, Elizabeth Eves and Dr. Haijun Yao at the University of Illinois School of Chemical Sciences Mass Spectrometry Laboratory.

A freshly mixed solution of DMAP (136 mg, 1.02 equiv.), TEA (0.85 mL, 5.60 equiv.) and Ac\(_2\)O (0.41 mL, 4.00 equiv.) in DCM (20 mL) was added to a solution of substrate (463 mg) in 5 mL DCM in a 100 mL RBF. After stirring at 23 °C for 5 h, or when TLC indicated full conversion, saturated aqueous NaHCO\(_3\) 15 mL was added and layers were separated. The aqueous layer was extracted with DCM x 3. The combined organic layer was washed with CuSO\(_4\) twice. The CuSO\(_4\) wash was then back extracted with DCM. The combined organic layer was washed with NaHCO\(_3\), brine. Drying with
Na$_2$SO$_4$ was followed with concentration in vacuo. Reverse phase MPLC afforded product 4.1 (431 mg, 81%) as an off-white solid.

$^1$H NMR (500 MHz, Benzene) $\delta$ 5.11 (m, 1H), 4.59 (d, J = 2, 1H), 4.20-4.13 (m, 1H), 4.16 (d, J = 2, 1H), 3.81-3.78 (m, 1H), 3.54 (m, 1H), 3.33 (s, 3H), 2.52 (dd, J = 15.5, 7.5, 1H), 2.37-2.32 (m, 1H), 2.17 (dd, 15.5, 5, 1H), 2.11-2.01 (m, 5H), 1.93-1.73 (m, 5H), 1.69 (s, 3H), 1.64-1.47 (m, 11H), 1.18-1.11 (m, 2H).

$^{13}$C NMR (126 MHz, Benzene) $\delta$ 170.8, 170.0, 155.1, 128.1, 112.9, 110.9, 94.1, 74.3, 72.1, 70.3, 67.9, 51.0, 41.5, 40.8, 39.5, 37.0, 33.2, 32.4, 31.7, 30.8, 25.8, 24.8, 24.4, 23.1, 22.8, 20.5, 0.1.

HRMS (ESI+)

Calculated for C$_{25}$H$_{39}$O$_8$: 467.2645

Found: 467.2638
To a stirred 0.25 M solution of substrate \(4.1\) (34 mg, 73.7 µmol) in 0.3 mL THF was added 0.15 mL 9-BBN in THF at 23 °C. The mixture was allowed to stir for 2.5 h before the next step.

In the glove box, to the solid phosphate \(BB2 \ 4.5\) (50 mg, 36.8 µmol) was added the palladium catalyst (26.5 mg, 36.8 µmol) followed by solid K₃PO₄ (23.5 mg, 111 µmol), 0.2 mL THF and then above BB1-BBN \(4.2\) solution (approx. 0.45 mL). A 1 v% solution of H₂O in THF (0.2 mL, 3 equiv. of H₂O) was then added. The reaction was allowed to react for 5 h at 70 °C.

After cooling down to 23 °C, the reaction mixture was passed through a short pad of florisil and flushed with EtOAc before concentration. The mixture was then loaded on
a florisil column with pentane. The column was then flushed with \( \text{Et}_2\text{O} \) to elute the greasy byproduct, and the product was eluted with hex:EtOAc = 1:2.

The product was collected as a light yellow solid, and was likely contaminated with leftover undetectable Pd. The solid was treated with 3 equiv. Pd scavenger (1 mmol/g) = 2.5 x mass equiv., and dilute with hexane (50 mg/mL), after stirring at 23 °C for 30 min, the mixture was filtered over a pad of florisil, and flushed with EtOAc. Concentration gave an off-white solid.

The solid was then treated with 3 equiv. Pd scavenger (propylamino SiO2, 2.5 mass equiv.) in hexane, and let stir for 30 min before passing through a pad of florisil, flushed with EtOAc, concentration afforded pure \( \text{BB1-BB2 4,6} \) in 67% yield (36 mg).

\[
\begin{align*}
\text{1H NMR (500 MHz, Benzene) } & \delta 6.86 (\text{dd, } J = 21, 10.5, 1\text{H}), 6.64 (\text{m, } 1\text{H}), 6.00-5.96 (\text{m, } 1\text{H}), 5.62 (\text{d, } J = 17.5, 1\text{H}), 5.20 (\text{m, } 1\text{H}), 5.01 (\text{m, } 1\text{H}), 4.86 (\text{m, } 1\text{H}), 4.85-4.54 (\text{m, } 1\text{H}), 4.44-4.28 (\text{m, } 3\text{H}), 4.25-4.24 (\text{m, } 2\text{H}), 3.95 (\text{m, } 1\text{H}), 3.89-3.86 (\text{m, } 1\text{H}), 3.78 (\text{d, } J = 2.5, 1\text{H}), 3.69-3.65 (\text{m, } 2\text{H}), 3.35 (\text{s, } 3\text{H}), 3.09 (\text{m, } 1\text{H}), 3.00 (\text{m, } 1\text{H}), 2.91 (\text{dd, } J = 9.5, 2.5, 1\text{H}), 2.57 (\text{dd, } J = 15.5, 7.5, 1\text{H}), 2.44-2.23 (\text{m, } 6\text{H}), 2.13-2.03 (\text{m, } 4\text{H}), 1.99-1.84 (\text{m, } 5\text{H}), 1.83 (\text{s, } 3\text{H}), 1.73-1.64 (\text{m, } 4\text{H}), 1.60-1.53 (\text{m, } 4\text{H}), 1.42-1.32 (\text{m, } 5\text{H}), 1.30 (\text{s, } 3\text{H}), 1.12 (\text{s, } 9\text{H}), 1.07 (\text{m, } 1\text{H}), 1.02 (\text{s, } 9\text{H}), 1.00 (\text{s, } 9\text{H}), 0.32 (\text{s, } 3\text{H}), 0.31 (\text{s, } 3\text{H}), 0.30 (\text{s, } 3\text{H}), 0.16 (\text{s, } 3\text{H}), 0.15 (\text{s, } 3\text{H}), 0.02 (\text{s, } 9\text{H}).
\end{align*}
\]
A 40 mL vial was charged with dienyl MIDA boronate 4.6 (0.145 mmol, 1.0 equiv.), pinacol (0.052 g, 0.434 mmol, 3.0 equiv.), solid NaHCO₃ (0.061 g, 0.723 mmol, 5.0 equiv.). anhydrous MeOH (3 mL) was then added. The reaction was stirred at 45 °C for 3 hours and then was concentrated in vacuo and finely ground anhydrous CaCl₂ (0.064 g, 0.579 mmol, 4.0 equiv.), solid NaHCO₃ (0.024 g, 0.289 mmol, 2.0 equiv.), and pentane (4.3 mL) were added to the resulting residue. The mixture was stirred at 23 °C for 45 minutes, filtered through a pad of celite with pentane (50 mL) and concentrated to yield 4.7 (0.143 mmol, >95%) as a white solid. The product was used directly in the next reaction without further purification. Note that proto-deborolation to the terminal diene is likely to occur is 4.6 is contaminated with ¹H NMR undetectable Pd.
To a vial containing a stir bar and 6 mg pin ester 4.7, in the glove box was added I-BB3 4.8 (4.5 mg, 3.0 equiv.), Cs2CO3 (3.5 mg, 4.0 equiv.), catalyst (6.5 mg, 20%) and DMSO (0.2 mL). The reaction was capped and removed from the glove box and placed in a 35 °C heating block with stirring. In 13 h the reaction was cooled to 23 °C and dilute with EtOAc and 1:1 brine:water. Layers were separated and the aqueous layer was extracted with EtOAc. The combined ethereal layer was washed with 1:1 brine:water. The solution was then dried over Na2SO4 before concentration. Chromatographic purification afforded the product 4.9 as a solid.
Chapter 4 Third generation synthesis of **BB1**

HRMS (ESI+)

Calculated for C\textsubscript{75}H\textsubscript{130}BNN\textsubscript{4}O\textsubscript{20}Si\textsubscript{4}: 1555.8516

Found: 1555.8512

### 4.4 References


Chapter 5

Development of a site- and stereoreten-
tive cross-coupling of unactivated chiral secondary organo-boronic acids

The ICC strategy for small molecule synthesis was inspired by the facile manner by which polypeptides are assembled from bifunctional building blocks with pre-
formed stereochemistry and oxidation state using a single coupling reaction.\textsuperscript{1, 2} Applying this strategy, a number of natural products that can be retrosynthetically fragmented through Csp\textsuperscript{2}-Csp\textsuperscript{2} connection including ratanhine,\textsuperscript{1} retinal,\textsuperscript{3} parinaric acid,\textsuperscript{3} crocacin C,\textsuperscript{4} peridinin,\textsuperscript{5} and synechoxanthin,\textsuperscript{6} have been synthesized in our group.
As discussed in chapters 2-4, the ICC approach can be extended for Csp3-Csp2 disconnections showcased in the BB1-BB2 cross-coupling in our total synthesis of the AmB macrocycle. However, the system is far from general. It is evident from our unsuccessful second generation BB1-BB2 connection that cross-coupling of unactivated Csp3 organoboronic acid still remains an unsolved challenge.

During the synthesis of BB1, I also took on the challenge of trying to find a solution to this “sp3 problem”. The inspiration of this project is the lead of a highly efficient secondary Csp3 boronic acid cross-coupling we discovered in Scheme 3.4. Successful development of a general solution to this problem would substantially increase the scope of Suzuki-Miyaura reaction, and in turn expand the scope of target molecules for the ICC strategy.
5.1 ICC strategy for small molecule synthesis

In contrast to the synthesis of peptides,7 oligonucleotides,8 and increasingly oligosacharides,9 which can be rapidly and flexibly assembled in a systematic fashion from pre-fabricated building blocks, the synthesis of small molecules has remained a relatively slow, complex, and unsystematized process. With the potential of addressing these limitations, an analogous building block-based approach for making small molecules e.g. iterative cross-coupling (ICC) strategy has started to emerge. In the idealized limit, a collection of off-the-shelf boronic acid-based building blocks having all of the required functional groups pre-installed in the correct oxidation states and with the desired stereochemical relationships are readily assembled using only Suzuki-Miyaura cross-coupling reaction in an iterative manner.1

Figure 5.1. ICC strategy for small molecule synthesis.
5.2 Problems in cross-couplings of secondary Csp\textsuperscript{3} boron center

5.2.1 Three problems

Iterative cross-coupling (ICC) based synthesis of a wide range of Csp\textsuperscript{2}-containing natural products, pharmaceuticals, and organic materials has demonstrated substantial promise of this approach. However, at present, Csp\textsuperscript{3} boronates cannot be cross-coupled with the same levels of efficiency, site-, and stereoretention that is now routinely achieved with their Csp\textsuperscript{2} hybridized counterparts. Solving this problem stands to enable a wide range of stereochemically complex natural products and Csp\textsuperscript{3}-rich pharmaceuticals to be efficiently and flexibly prepared via the simple assembly of off-the-shelf chiral organoboronate building blocks.

Scheme 5.1. site- and stereoretentive cross-coupling of unactivated secondary Csp\textsuperscript{3} boronic acid.

Achieving site- and stereoretentive cross-coupling of unactivated chiral secondary organoboronic acids, e.g., 5.1, required concomitantly solving several major problems (Scheme 1), including: 1. reactivity - unactivated Csp\textsuperscript{3} boronic acids are less
reactive than their Csp² and activated Csp³ counterparts, 2. site-retention - a competing sequence of β-hydride elimination followed by hydropalladation and reductive elimination from the less sterically hindered primary carbon-palladium bond typically generates undesired linear product 5.4 as a major byproduct, and 3. stereoretention – a competing sequence of β-hydride elimination followed by hydropalladation and reductive elimination from the more sterically hindered secondary carbon-palladium bond results in loss of stereochemical information pre-installed in the boronic acid.

\[
\text{Scheme 5.2. cross-coupling of unactivated secondary Csp}^3 \text{ boronic acid or trifluoroborate salt.}
\]
There have been important advances in cross-coupling secondary alkyl halides. There have recently also been several important breakthroughs in the site- and/or stereo-controlled cross-coupling of a range of *activated* chiral secondary alkylboranes. However, to our knowledge, there is not a single reported example of stereo-controlled cross-coupling with an unactivated chiral non-racemic secondary boronic acid, *e.g.*, [equation 5.1](equa. 5.1) – the simplest possible version of such a substrate.

Examples of unactivated secondary boronic acid cross-coupling are either with cyclic substrate, where isomerization is impossible (*equation 5.1*, Scheme 5.2), or suffer from isomerization to the linear product (*equation 5.2* and *equation 5.3*). In addition, when substituted cyclic trifluoroborate was subjected to the cross-coupling, a mixture of isomers through a mechanism of repeating $\beta$-hydride elimination/reinsertion were observed (*equation 5.4*). These problems have limited the application of the otherwise powerful transformation of secondary Csp$^3$ boronic acid cross-coupling. In fact, examples in Scheme 5.2 include all published Suzuki-Miyaura coupling of unactivated secondary Csp$^3$ boronic acid or boronate to the best of my knowledge.

Comparing to other organo-metal nucl

Isomerization to the linear product is in fact commonly observed in the cross-coupling of secondary Csp$^3$ organo-metal other than boronic acids.

### 5.2.2 Cross-coupling of activated secondary Csp$^3$ boronic acids or boronates

Methods have been developed to activate secondary Csp$^3$ boron centers. These systems operate either by removing $\beta$-hydrogen on the substrate, making it impossible
Chapter 5 Development of a site- and stereoretentive cross-coupling of unactivated chiral secondary organo-boronic acids

for \( \beta \)-hydride elimination, or through a back donation to stabilize the organopalladium intermediate prior to reductive elimination.

Scheme 5.3. cross-coupling of activated secondary Csp\(^3\) boronic acid or boronate.

An interesting phenomenon in the cross-coupling of activated secondary Csp\(^3\) organoboronic is the absolute stereo-outcome of the product. For instance, while cross-coupling of enantiomerically enriched allylic pinacol borate gave product with high level of stereo-retention (equa 5.5, Scheme 5.3), Suzuki-Miyaura reaction of \( \beta \)-amide
non-racemic trifluoroborate salt afforded stereo-inverted product (equa. 5.6\textsuperscript{16,17}). More interestingly, when a doubly activated allylic alpha-amide secondary Csp\textsuperscript{3} pinacol borate was subjected to the cross-coupling condition, the back donation of the amide would override the effect of the aryl group and gave stereo-inversion (equa 5.7\textsuperscript{16,18}). Meanwhile, under otherwise identical condition, addition of an alcohol can break the amide-boron chelate, and provide the cross-coupled product with stereo-retention (equa 5.8\textsuperscript{18}).

These studies on cross-coupling of activated secondary Csp\textsuperscript{3} boronic acid or boronate have made the first step to expand Suzuki-Miyaura reaction into a prolific area and to reveal the mechanistic insight for this transformation. Nonetheless, currently synthetic applications from these researches are limited due to functional group requirements for the substrate. Development of a general condition for the cross-coupling of unactivated secondary Csp\textsuperscript{3} boronic acid would substantially improve the applicability of this reaction, and offer an answer to the intriguing question of the product stereo-outcome of cross-coupling of unactivated secondary boronic acid coupling.

5.2.3 Catalyst screening for a solution to the reactivity and site-retention problems

Developing a solution to this problem required that three challenges be solved simultaneously by one catalyst system, \textit{i.e.}, high levels of reactivity, site-retention, and stereoretention. To address the first two of these problems, we pursued the cross-coupling (±)-5.1 with an aryl halide (Table 5.1). Consistent with the poor reactivity of secondary boronic acids, a series of standard conditions yielded no product (Table 5.1,
entries 1-3). Silver(I) oxide has been shown to be effective in promoting Suzuki-Miyaura reactions with primary alkyl boronic acids and activated secondary boronic esters.\textsuperscript{14, 19-22}

Building on this precedent, we found that the very simple combination of Pd(PPh\textsubscript{3})\textsubscript{4} and Ag\textsubscript{2}O in THF promoted the cross-coupling of $\text{5.1}$ with $\text{5.5}$ to generate an 81% yield of cross-coupling products, albeit as a 1:1 ratio of branched and linear isomers $\text{5.6}$ and $\text{5.7}$ (entry 4).

\begin{table}[h]
\centering
\begin{tabular}{llllll}
\hline
entry & catalyst & ligand & base & combined yield (%) & $\text{5.6}:\text{5.7}$ \\
\hline
1 & Pd(PPh\textsubscript{3})\textsubscript{4} & - & K\textsubscript{2}CO\textsubscript{3} & 0 & - \\
2 & Pd(PPh\textsubscript{3})\textsubscript{4} & - & K\textsubscript{3}PO\textsubscript{4} & 0 & - \\
3 & Pd(PPh\textsubscript{3})\textsubscript{4} & - & NaOH & 0 & - \\
4 & Pd(PPh\textsubscript{3})\textsubscript{4} & - & Ag\textsubscript{2}O & 81 & 1:1 \\
5 & Pd(dCyPh)Cl\textsubscript{2} & - & Ag\textsubscript{2}O & 0 & - \\
6 & Pd(dt-Bupf)Cl\textsubscript{2} & - & Ag\textsubscript{2}O & 16 & 1:1 \\
7 & Pd(dppf)Cl\textsubscript{2} & - & Ag\textsubscript{2}O & 65 & 1:1 \\
8 & Pd(OAc)\textsubscript{2} & Cy\textsubscript{3}P & Ag\textsubscript{2}O & 0 & - \\
9 & Pd(OAc)\textsubscript{2} & tBu\textsubscript{3}P & Ag\textsubscript{2}O & 0 & - \\
10 & Pd(OAc)\textsubscript{2} & Bu\textsubscript{2}MeP & Ag\textsubscript{2}O & 0 & - \\
11 & Pd(OAc)\textsubscript{2} & SPhos & Ag\textsubscript{2}O & <5 & - \\
12 & Pd(OAc)\textsubscript{2} & XPhos & Ag\textsubscript{2}O & <5 & - \\
13 & Pd(OAc)\textsubscript{2} & Ruphos & Ag\textsubscript{2}O & 0 & - \\
14 & Pd(OAc)\textsubscript{2} & P(o-tol)\textsubscript{3} & Ag\textsubscript{2}O & 47 & >20:1 \\
15 & Pd(P(o-tol)\textsubscript{3})\textsubscript{2} & - & Ag\textsubscript{2}O & 81 & >20:1 \\
\hline
\end{tabular}
\caption{Coupling of chiral unactivated secondary boronic acid and aryl halides.}
\end{table}
Turning our attention to the problem of site-retention, we first tested ligand/Pd systems with the potential to accelerate the desired reductive elimination pathway. However, bidentate phosphine ligands resulted in decreased yields and/or no improvement in site-selectivity (Table 5.1, entries 5-7), and bulky trialkylphosphine ligands did not yield any detectable product (entries 8-10). We also sought to disfavor the undesired β-hydride elimination pathway by employing ligands that might block the required agostic interaction between Pd and a β-hydrogen on the alkyl ligand (Scheme 5.1). Buchwald-type dialkyl biaryl phosphine ligands, which possess an ipso-interaction between the Pd center and the biaryl moiety on the ligand and thus could theoretically achieve this goal, are ineffective in promoting the desired cross-coupling (entries 11-13). Along these same lines, we noted that a mechanistically analogous β-hydride elimination pathway that competes during C-N cross-coupling with primary alkyl amines was disfavored by the use of Pd(P(o-tol)₃)₂, in which the ortho-methyl groups on the ligand are proposed to sterically block the required open coordination site on Pd. Enouragingly, the addition of Pd(OAc)₂ and P(o-tol)₃ provided a 20:1 ratio of 5.6:5.7, albeit in modest yield. Alternative employment of preformed Pd(P(o-tol)₃)₂, an air-stable and commercially available catalyst, afforded both excellent reactivity and virtually complete site-retention, yielding the product 3a in 81% (entry 15).

5.3 Synthesis of chiral non-racemic secondary Csp³ boronates

In order to examine the stereo-outcome of the cross-coupling reaction, the starting material chiral secondary Csp³ boronic acids need to be accessed in non-racemic forms. The synthesis of enantiomerically-enriched 2-butyl boronic acid 5.1 has
been reported by Brown through a 4-step process. However, like other secondary Csp\textsuperscript{3} boronic acid, 2-butyl boronic acid is not stable to bench-top storage. To address the absolute stereo-purity and stability issue at the same time, we complexed the racemic boronic acid with chiral N-alkyl iminodiacidic acid ligands that were recently reported in our group, with the hope to provide a venue to separate the two diastereomers through column chromatography while forming a crystalline building block with excellent bench-top stability.

In this vein, we tested three different chiral ligands and were lucky to find that the two diastereomers from complexation of 2-butyl boronic acid with N-benzyl-cyclopentyl iminodiacidic acid (BIDA) can be easily separated by flash chromatography to give up to 97/3 d.r.. This d.r. can be improved to 98.5/1.5 upon a single recrystallization. In addition, the 2-butyl BIDA boronate is stable on bench-top, open to air for at least 200 days; while 2-butyl boronic acid fully decomposes with 24 hours. Moreover, highly enantiomerically enriched (S)-\textit{5.1} can be readily prepared as the pure boronic acid via a simple hydrolysis of \textit{5.8} immediately prior to a cross-coupling reaction.

**Scheme 5.4.** Synthesis of chiral non-racemic 2-butyl boronic acid \textit{5.1}. 

\[ \text{Me} \begin{array}{c} \text{H} \\ \text{O} \\ \text{B(OH)}_2 \\ \text{Me} \end{array} \] (\(\text{S}\)-\textit{5.1})
5.4 First site- and stereoretentive cross-coupling of unactivated chiral secondary boronic acid strategy and scope

With robust and practical access to (S)-5.1 in hand, we subjected this unactivated chiral non-racemic boronic acid to our optimized cross-coupling conditions and determined the stereochemical outcome via chiral GC (Scheme 3). The desired product 3a was formed with 88% stereoretention.

Finally, with a high yielding, site- and stereoretentive cross-coupling method in hand, we performed a preliminary survey of the reaction scope (Table 2). We found that (S)-5.1 can also couple to activated aryl iodides (entry 1) as well as a series of non-activated aryl bromides and iodides (entries 2-5), with good to excellent branched:linear ratios, and stereoretention. The reaction can be sensitive to steric hinderance on the organohalide, as no productive coupling was observed with 2-phenyl bromo- and 2-phenyl-iodobenzene (entries 6,7). Alternatively, some electronic deactivation of the aryl halide is tolerable, as cross-coupling was achieved with para-\(t\)-Bu-bromobenzene (entry 8) and even more effectively with the corresponding iodide (entry 9). A range of cyclic secondary boronic acids are also excellent substrates (entries 10-13). There also appears to be tolerance to some increased steric bulk on the boronic acid, with \(anti\)-1-methyl-2cyclohexylboronic acid reacting with activated, unactivated, and deactivated halides 2a, 2d, and 2i to yield the corresponding cross-coupling products with excellent site-selectivity and as single diastereoisomers (entries 14-15).
Chapter 5 Development of a site- and stereoretentive cross-coupling of unactivated chiral secondary organo-boronic acids

![Chemical structure](image)

Table 5.2. Coupling of chiral unactivated secondary boronic acid and aryl halides. The branch: linear ratio was determined by $^1$H NMR and HPLC analysis. Absolute stereochemistry of entry 1 and 2 were assigned by comparison with the optical rotation of known compound, others were assigned by analogy.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Secondary boronic acid</th>
<th>Halide (X)</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Branch: linear</th>
<th>Stereo-retention</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(S)-5.1</td>
<td>I</td>
<td>![Product Image]</td>
<td>69</td>
<td>&gt;20:1</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>(S)-5.1</td>
<td>Br</td>
<td>![Product Image]</td>
<td>84</td>
<td>&gt;20:1</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>(S)-5.1</td>
<td>Br</td>
<td>![Product Image]</td>
<td>81</td>
<td>&gt;20:1</td>
<td>94</td>
</tr>
<tr>
<td>4</td>
<td>(S)-5.1</td>
<td>I</td>
<td>![Product Image]</td>
<td>83</td>
<td>&gt;20:1</td>
<td>94</td>
</tr>
<tr>
<td>5</td>
<td>(S)-5.1</td>
<td>Br</td>
<td>![Product Image]</td>
<td>82</td>
<td>&gt;20:1</td>
<td>96</td>
</tr>
<tr>
<td>6</td>
<td>(S)-5.1</td>
<td>Br</td>
<td>![Product Image]</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>(S)-5.1</td>
<td>I</td>
<td>![Product Image]</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>(S)-5.1</td>
<td>Br</td>
<td>![Product Image]</td>
<td>31</td>
<td>&gt;20:1</td>
<td>nd</td>
</tr>
<tr>
<td>9</td>
<td>(S)-5.1</td>
<td>I</td>
<td>![Product Image]</td>
<td>61</td>
<td>&gt;20:1</td>
<td>nd</td>
</tr>
<tr>
<td>10</td>
<td>![B(OH)2]</td>
<td>Br</td>
<td>![Product Image]</td>
<td>95</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Table 5.2 (cont’d). Coupling of chiral unactivated secondary boronic acid and aryl halides.

In summary, we developed the first site- and stereoretentive cross-couplings of unactivated secondary boronic acids inspired from an interesting lead we discovered from the total synthesis of AmB. This advance represents an important step towards
adding chiral secondary carbon-containing fragments to the growing list of substructures compatible with a general, building block-based approach for small molecule synthesis.

5.5 Experimental section

Materials. Commercial reagents were purchased from Sigma-Aldrich, Fisher Scientific, Alfa Aesar, TCI America, or Frontier Scientific, and were used without further purification unless otherwise noted.

Pd(P(o-tol)$_3$)$_2$, and Ag$_2$O were purchased from Sigma-Aldrich. A gift of Pd(P(o-tol)$_3$)$_2$ was donated by Johnson Matthey. Solvents were purified via passage through packed columns as described by Pangborn and coworkers$^1$ (THF, Et$_2$O, CH$_3$CN, CH$_2$Cl$_2$: dry neutral alumina; hexane, benzene, and toluene, dry neutral alumina and Q$_5$ reactant; DMSO, DMF: activated molecular sieves). All water was deionized prior to use. Diisopropylethylamine was freshly distilled under an atmosphere of nitrogen from CaH$_2$.

General experimental procedures. Unless noted, all reactions were performed in flame-dried round bottom or modified Schlenk flasks fitted with rubber septa under a positive pressure of argon or nitrogen. Organic solutions were concentrated via rotary evaporation under reduced pressure with a bath temperature of 23 °C unless otherwise noted. Reactions were monitored by analytical thin layer chromatography (TLC) performed using the indicated solvent on E. Merck silica gel 60 F254 plates (0.25mm). Compounds were visualized by exposure to a UV lamp ($\lambda = 254$ nm), and/or a solution of KMnO$_4$ and/or a solution of p-anisaldehyde, followed by brief
Chapter 5 Development of a site- and stereoretentive cross-coupling of unactivated chiral secondary organo-boronic acids

heating using a Varitemp heat gun. Column chromatography was performed using Merck silica gel grade 9385 60Å (230-400 mesh).

**Structural analysis.** $^1$H NMR and $^{13}$C NMR spectra were recorded at 20 °C on Varian Unity 500, Varian Unity Inova 500NB or Varian Unity 500 instruments. Chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane and referenced to residual protium in the NMR solvent (benzene, δ = 7.16; CHCl$_3$, δ = 7.26; acetone, δ = 2.05, center line; DMSO δ = 2.50, center line) or to added tetramethylsilane (δ = 0.00). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sept = septet, m = multiplet, b = broad, app = apparent), coupling constant (J) in Hertz (Hz), and integration. Chemical shifts (δ) for $^{13}$C NMR are reported in ppm downfield from tetramethylsilane and referenced to carbon resonances in the NMR solvent (benzene-d$_6$, δ = 128.06, center line; CDCl$_3$, δ = 77.0, center line; acetone-d$_6$, δ = 39.5, center line; DMSO-d$_6$ δ = 39.52, center line). Carbons bearing boron substituents were not observed (quadrupolar relaxation). High resolution mass spectra (HRMS) were performed by Furong Sun, Elizabeth Eves and Dr. Haijun Yao at the University of Illinois School of Chemical Sciences Mass Spectrometry Laboratory.
a. Synthesis of chiral racemic MIDA boronates and boronic acids

To a 40-mL sealed I-Chem vial under nitrogen was added racemic 2-butyl boronic acid (710 mg, 5 mmol), N-methyliminodiacetic acid (MIDA) (2200 g, 15 mmol), pyridinium p-toluenesulfonate (126 mg, 0.5 mmol) followed by acetonitrile (16.7 mL, 0.3 M for the borate). The reaction was sealed and allowed to stir at 80 °C for 12 hours. After cooling down, the mixture was passed through a pad of silica gel before concentration. The light brown solid mixture was then loaded onto a silica gel column and flushed with copious amount of Et₂O, the product was then eluted by straight EtOAc. Upon concentration, the product was obtained as a crystalline white solid (949 mg, 89%).

\[ \text{1H NMR (500 MHz, DMSO)} \delta 4.18 (d, J = 17.0, 1H), 4.16 (d, J = 17.0, 1H), 3.98 (d, J = 17.0, 2H), 2.87 (s, 3H), 1.47 (m, 1H), 1.03 (m, 1H), 0.88 (t, J = 7.5, 3H), 0.81 (d, J = 7.0, 3H), 0.67 (s, 1H). \]

\[ \text{13C NMR (126 MHz, DMSO)} \delta 169.1, 169.0, 62.3, 62.1, 45.4, 24.5, 13.8, 12.7. \]

HRMS (ESI+)

Calculated for C₉H₁₇BNO₄: 214.1251

Found: 214.1252
To a 40-mL sealed I-Chem vial under nitrogen was added racemic potassium trans-2-methylcyclohexyltrifluoro borate (1.02 g, 5 mmol), N-methyliminodiacetic acid (MIDA) (2.20 g, 15 mmol), pyridinium p-toluenesulfonate (126 mg, 0.5 mmol) and silica gel (900 mg) followed by acetonitrile (16.7 mL, 0.3 M for the borate). The reaction was sealed and allowed to stir at 80 °C for 12 hours. After cooling down, the mixture was passed through a pad of silica gel before concentration. The light brown solid mixture was then loaded onto a silica gel column and flushed with copious amount of Et₂O, the product was then eluted by straight EtOAc. Upon concentration, the product was obtained as a crystalline white solid (1.17 g, 93%).

¹H NMR (499 MHz, DMSO) δ 4.17 (d, J = 17.0, 1H), 4.10 (d, J = 17.0, 1H), 3.98 (d, J = 17.0, 1H), 3.93 (d, J = 17.0, 1H), 2.89 (s, 3H), 1.66-1.56 (m, 4H), 1.44 (m, 1H) 1.24 (m, 1H), 1.15 (m, 1H), 1.09-0.96 (m, 2H), 0.95 (d, J = 6.5, 3H), 0.47 (m, 1H).


HRMS (ESI+)
Calculated for C₁₂H₂₁BNO₄: 254.1564
Found: 254.1554
General procedure of hydrolysis of MIDA boronate

![Chemical structure of MIDA boronate](image)

To a stirred solution of MIDA boronate (0.25 mmol) in 2 mL THF under argon was added 2 mL 1M solution of NaOH. The reaction was allowed to stir at 23 °C for 0.5 h before 4 mL saturated aqueous NH₄Cl was added. Layers were separated and the aqueous layer was extracted with Et₂O three times. The combined ethereal layers were concentrated to near dry (complete dryness might lead to decomposition) and was re-extracted (a small portion of brine could be added if necessary) with Et₂O three times before drying over Na₂SO₄ and concentrating to around 200 µL under reduced pressure. The solution was diluted with THF and dried with Na₂SO₄ again before concentration to a waxy solid to afford the boronic acid in quantitative yield (0.25 mmol).

b. Synthesis of enantiomerically-enriched boronic acid (S)-1

![Chemical structure of S-1](image)

The preparation of benzylcyclopentyl iminodiacetic acid (BIDA) followed the procedure developed previously in our group.²⁷
To a 40-mL sealed I-Chem vial under nitrogen was added racemic 2-butyl boronic acid (+/-)-5.1 (6 mmol), BIDA 5 (4 mmol), pyridinium p-toluenesulfonate (0.4 mmol) followed by acetonitrile (27 mL, 0.15 M for 5). The reaction was allowed to stir at 80 °C for 24 hours. After cooling down, the mixture was passed through a pad of florisil before concentration. The light brown solid mixture was then dissolved in Et₂O to make a heterogeneous mixture and filtered; the filtrate was washed with copious amount of Et₂O. The Et₂O solution contains residual boronic acid and a ~4:1 diastereomeric ratio of (R)-5.8:5.8 determined for the by HPLC. The white solid was recrystalized with acetone:Et₂O twice to give a >97% d.r. 6 (463 mg, 31%).
Chapter 5 Development of a site- and stereoretentive cross-coupling of unactivated chiral secondary organo-boronic acids

TLC: (hexanes:EtOAc = 1:1, KMnO₄)

Rf = 0.41, (S) isomer 5.8; Rf = 0.16, (R) isomer (R)-5.8

¹H NMR (500 MHz, DMSO-d6) δ 7.35 (m, 4H), 7.30 (m, 1H), 4.52 (d, J = 11, 1H), 4.46 (d, J = 11, 1H), 4.13 (m, 4H), 3.93 (d, J = 17, 1H), 3.51 (q, J = 6, 1H), 2.05 (m, 1H), 1.99 (m, 1H), 1.65 (m, 3H), 1.50 (m, 1H), 1.42 (m, 1H), 1.06 (m, 1H), 0.85 (t, J = , 3H), 0.77 (m, 3H).

¹³C NMR (125 MHz, DMSO-d6) δ 169.8, 168.3, 137.9, 128.3, 127.8, 127.6, 79.8, 72.1, 70.9, 59.3, 56.4, 39.5, 29.4, 26.2, 24.9, 21.0, 14.2, 12.6.

HRMS (ESI+)

Calculated for C20H29BNO5: 374.2139

Found: 374.2119

To a stirred solution of 5.8 (93 mg, 0.25 mmol) in 2 mL THF under argon was added 2 mL 1M solution of NaOH, the reaction was allowed to stir at 23 °C for 0.5 h before 4 mL saturated aqueous NH₄Cl was added. Layers were separated and the aqueous layer was extracted with Et₂O three times. The combined ethereal layers were
concentrated to near dry (complete dryness might lead to decomposition) and was re-extracted (a small portion of brine could be added if necessary) with Et₂O three times before drying over Na₂SO₄ and concentrating to around 200 µL under reduced pressure. The solution was diluted with THF and dried with Na₂SO₄ again before concentration to a waxy solid to afford \((S)\)-5.1 (25 mg, 100%).

c. General procedure of coupling reactions of aryl halides with alkyl boronic acids

\[
\begin{align*}
&\text{Me} \quad \text{B(OH)₂} \\
5.1 &\quad \text{Me} \\
&\quad \text{X} \quad \text{Ar} \\
\underset{\text{Pd(P(o-tol)₃)₂, Ag₂O}}{\text{THF}} &\quad \text{Me} \quad \text{Ar} \\
&\quad \text{Me}
\end{align*}
\]

In the glove box under argon atmosphere, aryl halide (0.10 mmol), boronic acid (0.20 mmol), Ag₂O (70 mg, 0.30 mmol) and Pd(P(o-tol)₃)₂ (7.15 mg, 0.010 mmol) were taken up in THF (220 µL) in a 7 mL vial. The reaction was sealed, and stirred at 85 °C for 24 h. The mixture was then passed through a pad of silica gel and flushed with diethyl ether before concentration \textit{in vacuo}. The desired product was isolated by column chromatography and/or preparative reverse-phase HPLC.

Cross coupling reactions of aryl halides with alkyl boronic acids

\[
\begin{align*}
&\text{Me} \quad \text{OMe} \\
5.10 &\quad \text{Me} \\
\end{align*}
\]

Product was isolated as a colorless oil (Br-, 71%; I-, 69%)
Enantiomeric ratio (Br-, 85:15, a 88% retention of e.r.; I-, 89:11, a 91% retention of e.r.) was determined by chiral-GC (CP chirasil-DEX CB Column)

\[ \text{\textsuperscript{1}H NMR (500 MHz, Benzene)} \delta 8.15 (d, J = 8.5, 2H), 6.96 (d, J = 8.0, 2H), 3.522 (s, 3H), 2.33 (m, 1H), 1.37 (m, 1H), 1.02 (d, J = 7.0, 3H), 0.68 (t, J = 7.5, 3H). \]

\[ \text{\textsuperscript{13}C NMR (126 MHz, Benzene-d6)} \delta 166.8, 153.0, 130.2, 127.4, 51.5, 41.9, 31.1, 21.7, 12.3. \]

HRMS (EI+)

Calculated for C12H16O2: 192.1150

Found: 192.1141
Product was isolated as a colorless oil (Br-, 84%) 

Enantiomeric ratio (Br-, 85:15, a 88% retention of e.r.) was determined by SFC analysis (OD-H Column)

\[ \text{\^{1}H NMR (499 MHz, Benzene)} \delta 7.67 (m, 3H), 7.52 (s, 1H), 7.28 (m, 2H), 7.21 (dd, J = 8.0, 1.5, 1H), 2.595 (m, 1H), 1.60 (m, 1H), 1.54 (m, 1H), 1.23 (d, J = 7.0, 3H), 0.80 (t, J = 7.5, 3H). \]

\[ \text{\^{13}C NMR (126 MHz, Benzene)} \delta 145.1, 134.4, 132.9, 126.1, 126.0, 125.8, 125.4, 42.2, 31.3, 22.1, 12.5. \]
Chapter 5 Development of a site- and stereoretentive cross-coupling of unactivated chiral secondary organo-boronic acids

HRMS (EI+)

Calculated for C_{14}H_{16}: 184.1250

Found: 184.1249

Product was isolated as a brown solid (Br-, 75%; I-, 81%)

Enantiomeric ratio (Br-, 73:27, a 75% retention of e.r.; I-, 75:25, a 77% retention of e.r.) was determined by chiral-GC (CP chiral-DEX CB Column)

^{1}H NMR (500 MHz, Benzene-d6) δ 7.85 (d, J = 8.8, 2H), 6.62 (d, J = 8.6, 2H), 2.17 (m, 1H), 1.24 (m, 2H), 0.89 (d, J = 7.0, 3H), 0.59 (t, J = 7.5, 3H).

^{13}C NMR (125 MHz, Benzene-d6) δ 216.3, 154.6, 123.7, 41.6, 30.8, 21.4, 12.1.

HRMS (ESI+)

Calculated for C_{10}H_{13}NO_{2}Na: 210.1409

Found: 210.1410
Product was isolated as a colorless oil (Br-, 81%; I-, 83%)

Enantiomeric ratio (Br-, 92:8, a 94% retention of e.r.; I-, 92:8, a 94% retention of e.r.) was determined by SFC analysis (OD-H Column)

\[ \text{1H NMR (500 MHz, Benzene-d6) } \delta 7.53 (d, J = 7.0, 2H), 7.49 (d, J = 8.0, 2H), 7.24 (t, J = 8.2, 2H), 7.12 (d, J = 8.0, 2H), 2.48 (m, 1H), 1.53 (m, 2H), 1.19 (d, J = 7.0, 3H), 0.81 (t, J = 7.5, 3H). \]

\[ \text{13C NMR (125 MHz, Benzene-d6) } \delta 146.8, 141.8, 139.4, 129.0, 127.5, 127.4, 127.2, 41.7, 31.5, 22.1, 12.5. \]
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HRMS (EI+)

Calculated for C16H18: 210.1409

Found: 210.1414

Product was isolated as a colorless oil (Br-, 82%)

Enantiomeric ratio (Br-, 93:7, a 96% retention of e.r.) was determined by SFC analysis (OD-H Column)

$^1$H NMR (499 MHz, Benzene) $\delta$ 7.54 (M, 2H), 7.43 (t, J = 2.0, 1H), 7.38 (m, 1H), 7.24 (t, J = 15.5, 3H), 7.06 (m, 1H), 2.50 (m, 1H), 1.55 (m, 1H), 1.49 (m, 1H), 1.19 (d, J = 7.0, 3H), 0.80 (t, J = 7.5, 3H).
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$^{13}$C NMR (126 MHz, Benzene) $\delta$ 148.3, 142.2, 141.9, 129.2, 129.0, 127.7, 127.4, 126.5, 126.3, 125.3, 42.2, 31.5, 22.2, 12.5.

HRMS (EI+)
Calculated for C16H18: 210.1409
Found: 210.1410

Product was isolated as a colorless oil (Br-, 31%; I-, 61%)

$^1$H NMR (499 MHz, Benzene) $\delta$ 7.31 (d, J = 8.5, 2H), 7.11 (d, J = 8.5, 2H), 2.49 (m, 1H), 2.47 (m, 1H), 1.50 (m, 1H), 1.26 (s, 9H), 1.20 (d, J = 7.0, 3H), 0.81 (t, J = 7.5, 3H).

$^{13}$C NMR (126 MHz, Benzene) $\delta$ 148.6, 144.7, 127.1, 125.5, 41.6, 34.4, 31.6, 31.6, 22.3, 12.5.

HRMS (EI+)
Calculated for C12H16O2: 192.1150
Found: 192.1141
Product was isolated as a colorless oil (I-, 52%)

Enantiomeric ratio (I-, 60:40, a 62% retention of e.r.;) was determined by chiral-GC (CP chiral-DEX CB Column)

$^1$H NMR (500 MHz, Benzene) $\delta$ 8.04 (d, $J = 5.0$, 1H), 6.85 (s, 1H), 6.35 (dd $J = 5.0$, 1.5, 1H), 1.97 (m, 1H), 1.12 (m, 2H), 0.77 (d, $J = 7.0$, 3H), 0.53 (t, $J = 7.0$, 3H).

$^{13}$C NMR (126 MHz, Benzene) $\delta$ 150.0, 123.1, 121.2, 40.9, 30.2, 20.6, 11.9.

HRMS (EI+)

Calculated for C$_9$H$_{12}$NCl: 169.0658

Found: 169.0656

Product was isolated as a colorless oil (Br-, 65%)
Chapter 5 Development of a site- and stereoretentive cross-coupling of unactivated chiral secondary organo-boronic acids

$^{1}$H NMR (500 MHz, Benzene) $\delta$ 8.16 (d, $J = 8.5$, 2H), 6.97 (d, $J = 8.5$, 2H), 3.53 (s, 3H), 1.88 (td, $J = 11.0$, 3.0, 1H), 1.68-1.61 (m, 4H), 1.38-1.30 (m, 1H), 1.28-1.12 (m, 3H), 0.97-0.88 (m, 1H), 0.61 (d, $J = 6.5$, 3H).

$^{13}$C NMR (126 MHz, Benzene) $\delta$ 166.8, 152.3, 130.2, 128.8, 128.1, 52.7, 51.4, 37.6, 35.9, 35.5, 27.1, 26.9, 20.9.

HRMS (EI+)

Calculated for C$_{15}$H$_{20}$O$_{2}$: 232.1463

Found: 232.1466

Product was isolated as a colorless oil (I-, 62%)

$^{1}$H NMR (499 MHz, Benzene) $\delta$ 7.55 (m, 1H), 7.53 (m, 1H), 7.51 (d, $J = 8.5$, 2H), 7.240 (tm, $J = 7.5$, 2H), 7.13 (m, 3H), 2.01 (td, $J = 11.0$, 3.5, 1H), 1.83 (dm, $J = 13.5$, 1H), 1.76-1.69 (m, 3H), 1.54-1.45 (m, 1H), 1.44-1.22 (m, 3H), 1.06-0.97(m, 1H), 0.76 (d, $J = 6.5$, 3H).

$^{13}$C NMR (126 MHz, Benzene) $\delta$ 146.2, 141.8, 139.4, 129.0, 127.5, 127.4, 127.2, 52.5, 38.0, 36.1, 36.0, 27.3, 27.1, 21.1.
HRMS (EI+)

Calculated for C$_{19}$H$_{22}$: 250.1721

Found: 250.1724

d. **Determination of the absolute stereochemistry of 3a-3c**

The absolute stereochemistry of compounds 3a-3c was determined by comparison of the optical rotation to the literature value.\textsuperscript{28-30} All products correspond to net retention in the cross-coupling reaction.

![Schema 5.10](image)

(S)-3a, $[\alpha]_{D}^{23}$ +21.0 (EtOH, e.e. = 78% based on chiral GC)

lit: (R)-3a, $[\alpha]_{D}^{25}$ -19.02 (EtOH, e.e. = 65%)(ref. 28)

![Schema 5.11](image)

(S)-3b, $[\alpha]_{D}^{23}$ +24.5 (benzene, e.e. = 70% based on SFC)

lit: (R)-3b, $[\alpha]_{D}^{23}$ +33.3 (neat, e.e. = 94%)(ref. 28,29)

![Schema 5.12](image)

(S)-3c, $[\alpha]_{D}^{23}$ +16.8 (benzene, e.e. = 50% based chiral GC)

lit: (S)-3c, $[\alpha]_{D}^{23}$ +35.4 (benzene)(ref. 30)
III. Determination of benchtop stability of boronic acids and MIDA boronates

The stability of 2-butyl boronic acid and 2-butyl BIDA boronates to storage as solids under air at 23 °C was quantified using the following general procedure: Two 7-mL vials were charged with 10 mg of freshly prepared boronic acid or BIDA boronate at 23 °C under ambient atmosphere. The vials containing these solid samples were then sealed with PTFE-lined screwcaps under ambient atmosphere and placed on the benchtop at 23 ºC. The solid sample present in one of the vials was then immediately analyzed by 1H-NMR to verify the purity and quantity of boronic acid present at time zero (the NMR assay is described below). After 1 day (boronic acid) or 60 days (BIDA boronates), the solid sample in the second vial was analyzed by 1H NMR, again by the method described below, to determine the quantity of boronic acid remaining at the indicated time.

NMR assay: An NMR stock solution was prepared as follows: To a 25 mL volumetric flask was added bromoacetophenone (0.336 g, 1.69 mmol, internal standard for quantification of the boronic acid), tetramethylsilane (1 mL, internal standard for the NMR shifts), and DMSO-d6:D2O 95:5 to a final solution volume of 25.0 mL. To a vial containing solid boronic acid or solid BIDA boronate (see above) was added 1.00 mL of this NMR stock solution, and the resulting solution was analyzed by 1H-NMR. The mmol of boronic acid or MIDA boronate present in the sample was determined by comparing the ratio of the integrated 4-bromoacetophenone aryl C–H doublets (7.90 ppm relative to TMS) to that of the boronic acid or MIDA boronate C–H signals.
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5.6 References


(2) Gillis, E. P.; Burke, M. D. *Aldrichimica Acta* 2009, 42, 17-27.


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