ITERATIVE CROSS-COUPLING WITH MIDA BORONATES

BY

ERIC PAUL GILLIS

DISSERTATION

Submitted in partial fulfillment of the requirements
for the degree of Doctor of Philosophy in Chemistry
in the Graduate College of the
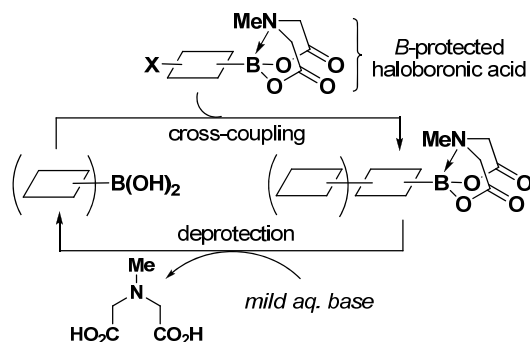University of Illinois at Urbana-Champaign, 2010

Urbana, Illinois

Doctoral Committee:

    Assistant Professor Martin D. Burke, Chair
    Professor Scott E. Denmark
    Professor John F. Hartwig
    Professor Paul J. Hergenrother

ABSTRACT

Many small molecules targeted for synthesis in the laboratory are inherently modular in their construction. Harnessing this modularity towards a unified strategy for the synthesis of these compounds, this dissertation describes an approach to small molecule making based on the iterative cross-coupling (ICC) of bifunctional haloboronic acid building blocks. Realizing a general ICC approach in the context of small molecule synthesis required the discovery of a ligand with the capacity to attenuate the reactivity of boronic acids under Suzuki-Miyaura cross-coupling (SMC) conditions and then liberate this masked reactivity under mild conditions. Towards this end, *N*-methyliminodiacetic acid (MIDA) was discovered to be such a ligand, enabling an approach by which the reactivity of boronic acids is modulated via rehybridization of the boron center. Further, MIDA boronates, which result from the condensation of MIDA with boronic acids, were found to possess a number of enabling properties. Specifically, MIDA boronates are uniformly stable to SiO_2 chromatography and to storage under ambient air at room temperature. MIDA boronates were also found to be compatible with a broad range of common reagents and reaction conditions, enabling an approach by which relatively simple MIDA boronates can be elaborated through multiple-step organic synthesis en route to structurally complex boronate building blocks. Through a process of rate-controlled in situ release of boronic acids from the corresponding MIDA boronates, MIDA boronates were found to serve as generally effective surrogates for otherwise unstable boronic acids in high-yielding Suzuki-Miyaura cross-coupling reactions with deactivated aryl chlorides. Enabled by these collective discoveries, and towards the goal of a simple and accessible approach to small molecule synthesis, a machine with the capacity to perform fully automated ICC syntheses was developed and was employed in the syntheses of several natural products.

To Elly

ABBREVIATIONS

Ac	acetate	
Boc	*t*-butoxycarbonyl	
CuTC	Copper(I) thiophene-2-carboxylate	
Cy	cyclohexyl	
Cy-John-Phos	(2-Biphenyl)dicyclohexylphosphine	
dba	dibenzylideneacetone	
DMF	dimethylformamide	
DMP	Dess-Martin periodane	
DMSO	dimethylsulfoxide	
dppf	1,1-*bis*(diphenylphosphino)ferrocene	
GC	capillary gas chromatography	
HPLC	high pressure liquid chromatography	
ICC	iterative cross-coupling	
John-Phos	(2-Biphenyl)di-*tert*-butylphosphine	
Mes	mesityl	

MIDA	N-methyliminodiacetic acid	
MOM	methoxymethyl	
MPLC	medium-pressure chromatography	
NMR	nuclear magnetic resonance	
NMO	*N*-methylmorpholine oxide	
PDC	pyridinium dichromate	
PMB	*p*-methoxybenzyl	
pyr	pyridyl	
SMC	Suzuki-Miyaura cross-coupling	
S-Phos	2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl	
SRCC	"slow-release" cross-coupling	
TBAF	tetra-*n*-butylammonium fluoride	
TBS	*t*-butyldimethylsilyl	
Tf	trifluoromethanesulfonyl	
THF	tetrahydrofuran	
TMEDA	N,N,N',N'-tetramethylethylenediamine	
TMS	trimethylsilyl	
TPAP	tetra-*n*-propylammonium perruthenate	
X-Phos	2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl	

TABLE OF CONTENTS

CHAPTER 1

INTRODUCTION

Eric P. Gillis and Martin D. Burke

In contrast to the efficiency with which peptides and oligonucleotides can be prepared in the laboratory, the process of small molecule synthesis remains a relatively complex, un-systematized, and inflexible process that is practiced almost exclusively by highly trained specialists. However, like peptides and oligonucleotides, most small molecules are modular in their construction. This dissertation began with the hypothesis that the inherent modularity in small molecules remains largely underutilized, and that a unified strategy for the construction of these compounds through the iterative coupling of bifunctional building blocks might be possible. As a basis for this idea, this chapter introduces pioneering studies that have expanded the use of iterative coupling in organic synthesis. Attention is focused on the use of palladium-catalyzed cross-coupling in these iterative processes, with a specific interest in the use of the Suzuki-Miyaura cross-coupling (SMC) as the primary C-C bond forming reaction. Further, a mechanistic framework is discussed for the proposal that sp^3-hybridized boronates might serve as protected-boronic acid equivalents in the SMC reaction.

Iterative peptide coupling   **Iterative cross-coupling**
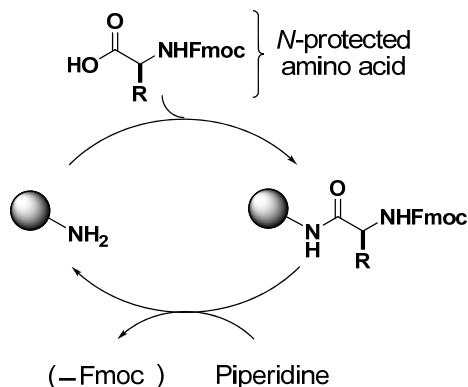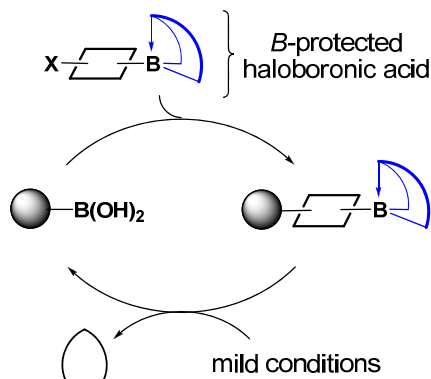
Adapted from Gillis, E. P.; Burke, M. D. *Aldrichimica Acta* **2009**, *42*, 17-27.

1-1 THE PROSPECT OF A GENERAL APPROACH TO SMALL MOLECULE SYNTHESIS

Many organic molecules are inherently modular in their constitution. With respect to the molecules found in living systems, this modularity is a direct consequence of the fact that nearly all biosynthetic systems are based on the iterative coupling of bifunctional building blocks. For example, polypeptides are built from amino acids, oligonucleotides are derived from nucleotide monomers, and oligosaccharides are stitched together from individual sugar units. Interestingly, most small-molecule natural products are similarly constructed by the iterative coupling of bifunctional building blocks: e.g., polyketides from malonyl-CoA or methylmalonyl-CoA units, nonribosomal peptides from amino acids, polyterpenes from isopentenyl pyrophosphate or dimethylallyl pyrophosphate, and fatty acids from malonyl-CoA. Similarly, many synthetic pharmaceuticals are also highly modular because they are constructed by using different reactions to assemble collections of small building blocks, typically cyclic and heterocyclic fragments and their associated appendages. Thus, modularity is a remarkably general feature of many of the molecules that are targeted for synthesis in the laboratory.

Automated solid-phase peptide synthesis

Despite the common modularity inherent to small molecules, the strategies utilized for making polypeptides, oligonucleotides, and oligosaccharides are very different from those typically used to prepare small molecules. Specifically, all of the former classes of compounds are almost always constructed via iterative coupling of suitably protected forms of their constituent monomers.[1] In this regard, solid-phase peptide synthesis (SPPS) represents a pinnacle in synthetic strategy in terms of efficiency, simplicity and modularity.

Shown in Scheme 1.1 is the general, modern approach to peptide synthesis. A key principal of this approach is the use of a bifunctional building block (an amino acid) in which, crucial to avoiding unwanted oligomerization, one of the functional groups is masked with a protecting group. Although the first peptide, glycyl-glycine, was synthesized in 1901 by Emil Fischer,[2] it was not until 1932 that the first protecting group with the capacity to reversibly attenuate the reactivity of nitrogen, the carbobenzoxy

group, was introduced by Max Bergmann.[3] With a suitably protected building block, the peptide bond-forming reaction can proceed with high selectivity. Following the bond-forming step, the protecting group is removed to expose the reactive amine terminus which is available to undergo a subsequent round of peptide coupling. In each iteration a different amino acid can be introduced, thus the process is highly flexible and modular. In 1963 Bruce Merrifield introduced the concept of solid-phase synthesis, whereby one of the termini of a peptide would be bound to a solid resin particle.[4] This advance introduced a simple, robust and importantly, *general* method for the purification of peptides. In fact, only two years after this report the first automated SPPS instrument was disclosed.[5] Certainly the simplicity of the approach and the generality of the coupling, deprotection and purification conditions contributed to the rapid translation of SPPS to an automated platform. In fact, the first automated synthesis of a peptide, the nine-amino acid peptide bradykinin, was executed using only 80 steps encoded onto a stepping-drum.[5a,6] The development of an automated, iterative approach to peptide synthesis has had a dramatic impact on the use of peptides in science.[1a] Similar automated iterative strategies have also been developed for oligonucleotides, and to a lesser extent oligosaccharides.[1b,1c] Importantly, the advanced development of such automation has made it possible for even non-chemists to routinely prepare these types of compounds for a wide range of applications.
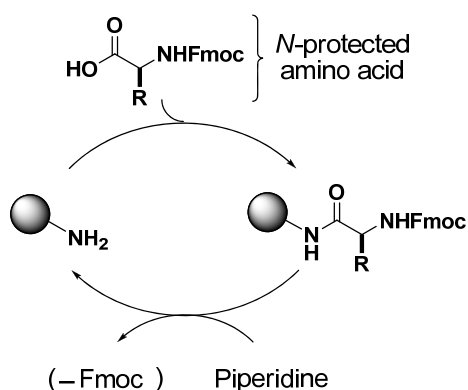
Scheme 1.1. The paradigm of modern peptide synthesis is based on the coupling of bifunctional building blocks (amino acids) in which the required functional groups are preinstalled in the correct oxidation state and with the desired stereochemical relationships. In order to avoid undesired oligomerization, one of the functionalities must be chemically masked during the coupling step. Following the coupling, the masking group is removed and the cycle can be repeated, in theory, a limitless number of times. In each iteration a different amino acid can be introduced, thus the process is highly flexible and modular.

Automated solid-phase synthesis of organic polymers via iterative cross-coupling

In stark contrast to the efficiency with which peptides and oligonucleotides can be prepared in the laboratory, in small molecule synthesis it is typical for a synthetic chemist to develop a unique, customized strategy for each small molecule that is targeted for preparation. As a result, the synthesis of small molecules remains a relatively complex, un-systematized, and inflexible process that is practiced almost exclusively by highly trained specialists. In terms of conceptualizing a more direct approach to small molecule synthesis, the pioneering work of Moore and co-workers on the development of the first automated, iterative cross-coupling (ICC) approach towards polymer synthesis represents a very important advance.[7,8]

The first iterative protocol for Pd-mediated cross-coupling was reported by Moore and co-workers in 1992,[7] and two years later this methodology was transferred to an automated platform.[8] The methodology described by these authors was based on an iterative cycle of Sonogashira cross-coupling reactions[9] utilizing bifunctional building blocks containing both an acetylene and an aryl iodide functionality (in either reactive or masked forms). Two distinct protecting-group strategies were employed in complementary approaches, such that either the acetylene (Scheme 1.2A) or the aryl iodide (Scheme 1.2B) functionalities could be masked. Because of the complementarities of these two approaches the products could be utilized in a converging synthesis.[7] In one case, a trimethylsilyl moiety bound to the acetylene unit prevented the alkyne from undergoing transmetallation to Pd (Scheme 1.2A).[10a] Following a selective coupling with the free acetylene of another compound, the silyl group was removed under the action of K_2CO_3 in methanol allowing the iterative cycle to be repeated.[10] Alternatively, the diethyltriazene group was used as a masking group, serving as a latent aryl iodide.[11] In this approach, following a selective coupling the aryl iodide functionality was introduced by treating the diethyltriazene group with MeI in a pressurized bomb at 110 °C (Scheme 1.2B).

A

B
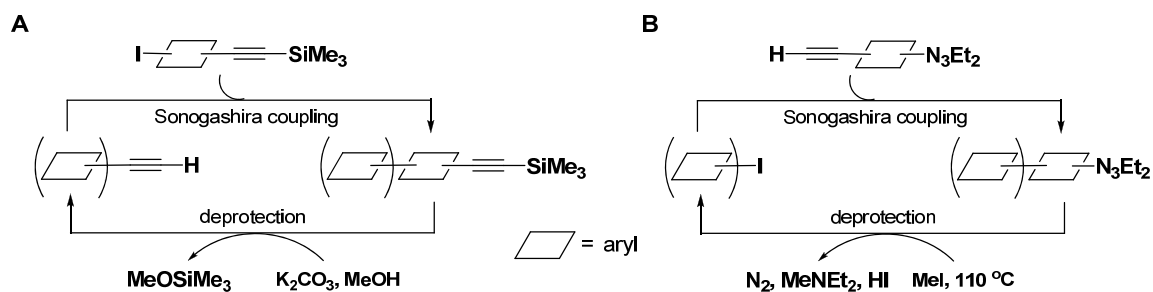
Scheme 1.2. Moore and co-workers reported two complementary approaches to the iterative synthesis of organic polymers. Both approaches utilize a bifunctional building block in iterative Sonogashira coupling, and differ in which functionality is masked: the terminal acetylene (A) or the aryl iodide (B).

To enable an automated approach similar to that employed by Merrifield,[1a] Moore and co-workers devised a chemical linker by which the coupled product would be bound to the solid-phase through a triazene linkage (Scheme 1.3).[8] Cleavage of the desired product from the solid support was accomplished by treating the resin with MeI at 110 °C to generate the corresponding aryl iodide, similar to the method described for the solution-phase approach. Through this approach a polymer 32 units in length was synthesized. This methodology has played a major role in promoting the synthesis and study of a wide range of phenylacetylyne oligomers that possess interesting functions.
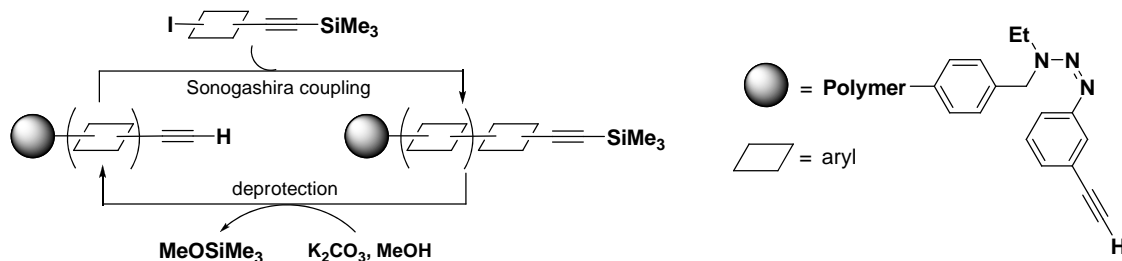
Scheme 1.3. Automated iterative Sonogashira coupling was made possible through the development of a triazene-based linker for the solid-phase. Through this automated approach a polymer 32 units in length was synthesized.

Other iterative cross-coupling approaches

An ICC approach to the synthesis of polyenes has been developed by Zeng and Negishi (Scheme 1.4).[12] In this approach a bromo enyne is employed as a bifunctional building block, where the alkyne serves as a latent *E*-alkenyl zirconacene group.[13] Alkenyl zirconacenes can be utilized as cross-coupling partners in a multi-metal catalyzed process in which the organic group appended to Zr is transmetallated to Al,

then Zn, and finally Pd.[13,14] In the iterative cycle, following selective cross-coupling the trimethylsilyl group is removed under the action of K_2CO_3 in methanol to expose the terminal alkyne,[10a] which is then utilized in a subsequent hydrozirconation reaction with Schwartz's reagent[15] to introduce the *E*-alkenyl zirconacene group. As a demonstration of the utility of this approach Zeng and Negishi applied this ICC method to the synthesis of four polyene fragments which constitute portions of the natural products mycoticin A and B, roseofungin, surgumycin, RK-397, roflamycoin, dermostatin A and B and amphotericin B.[12] Although this approach was successful in the synthesis of several all-*trans* polyenes, the scope of this ICC method is limited to certain classes of polyenes and substrates that are compatible with the required hydrozirconation reaction.
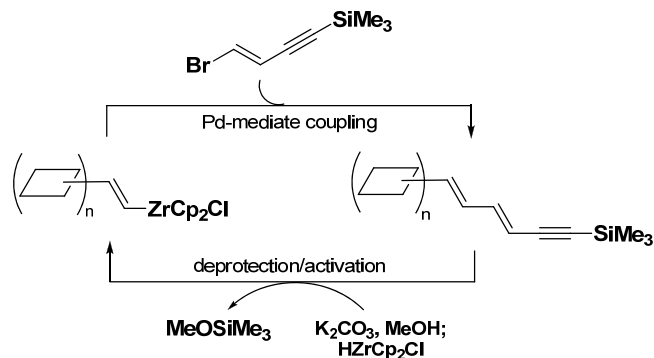
Scheme 1.4. Zeng and Negishi reported an ICC approach in which bromo enynes serve as bifunctional building blocks. The alkyne functionality serves as a latent *E*-alkenyl zirconacene group. Through multi-metal catalysis the organozirconacene group undergoes cross-coupling with alkenyl bromides. Following the coupling reaction the trimethylsilyl group is removed under the action of K_2CO_3 in methanol and the resulting terminal alkyne is utilized in a hydrozirconation reaction with Schwartz's reagent to install the *E*-alkenyl zirconacene group.

Lynchpin systems

A compound containing two functional groups, both of which could react under the same reaction manifold, but which can be distinguished with a high degree of chemical selectivity, can be referred to as a "lynchpin" reagent. The boron-tin reagents developed by Coleman for polyene synthesis[16] are good examples of these types of reagents (Scheme 1.5). While either terminus of linchpin **1.1** could cross-coupling with **1.2** under palladium catalysis, the absence of base in the first coupling step allows complete differentiation of the boron and tin functionalities, and ensures that only the stannane terminus of **1.1** undergoes transmetallation. Since both **1.2** and **1.3** react under

the same reaction manifold (oxidative addition to palladium), an efficient reaction sequence could still be expected if, alternatively, **1.3** was employed in the first coupling and **1.1** was used the second coupling. In a related example, the organic group transferred by lynchpin **1.4** is asymmetric (Scheme 1.6).[17] If halide **1.6** was used in the first coupling and halide **1.5** was used in the second coupling, a different product would be expected. Thus, this approach is well suited towards the synthesis of libraries of compounds since multiple products can be obtained simply by reordering the steps in which the same reagents are used.
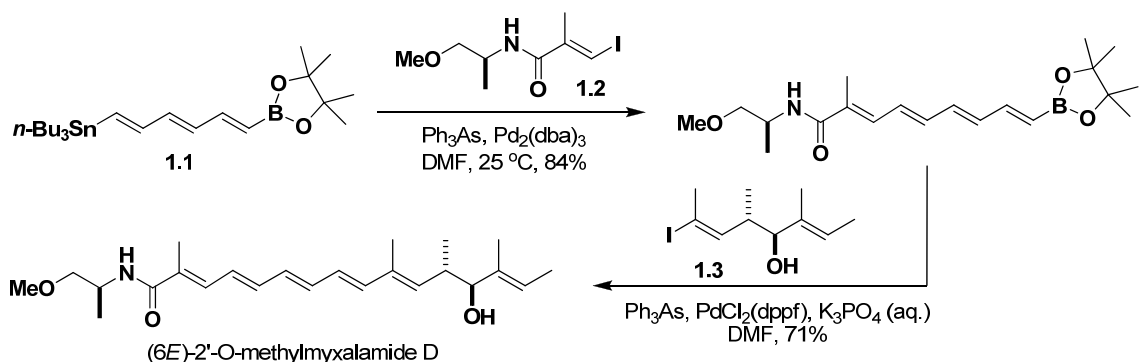
Scheme 1.5. Reagent **1.1** is an example of a lynchpin reagent because both the stannane and borane functionalities are reactive under the same manifold (Pd-catalyzed cross-coupling) but their reactivity can be differentiated with a high degree of selectivity.
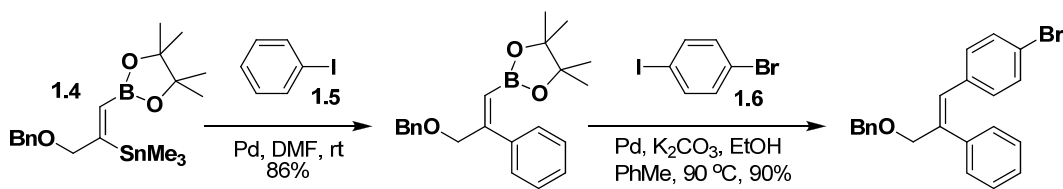
Scheme 1.6. Asymmetric lynchpin reagents such as **1.4** are versatile building blocks since a simple reordering of the coupling steps with **1.5** and **1.6** can be expected to afford a different final product.

Lynchpins with termini containing the *same* metal can be differentiated by selective activation.[18] In an approach demonstrated by Denmark and co-workers[19] (Scheme 1.7), treatment of lynchpin **1.7** with TMSOK results in the selective activation of the silanol moiety,[20] allowing the first coupling to proceed with high selectivity. A second coupling follows in which the dimethylheterocyclic silane[21] is activated by fluoride.[22]
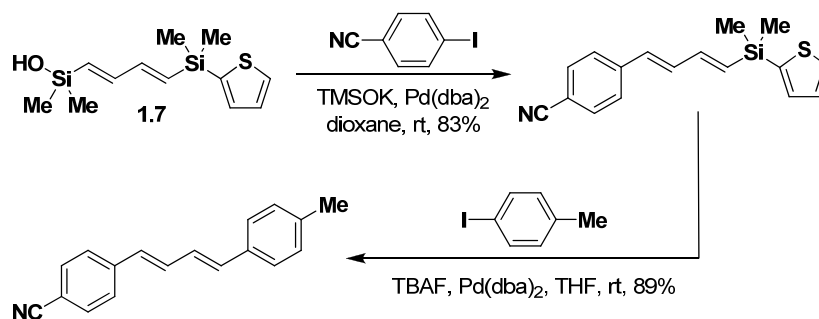
Scheme 1.7. The cross-coupling of **1.7** demonstrates the use of a lynchpin in which the termini are differentiated via selective activation.

Lynchpin reagents can also exploit the difference in rates of oxidative addition between halides/pseudo-halides. Aryl iodides, bromides and triflates can be engaged in Suzuki-Miyaura cross-coupling (SMC) reactions under standard conditions using traditional palladium catalysts such as $Pd(PPh_3)_4$, Pd_2dba_3, $Pd(OAc)_2$ and $PdCl_2(dppf)$. On the other hand, aryl chlorides are typically unreactive under these conditions but can be cross-coupled using palladium catalysts supported by sterically bulky and/or electron-rich phosphine or N-heterocyclic carbene ligands.[23, 24] This difference in reactivity allowed Hii and coworkers to employ chlorobromoarenes as lynchpin reagents in the synthesis of many triaryl compounds (Scheme 1.8).[25] Recently the first cross-coupling reactions involving oxidative addition to an aryl acetate C-O bond were reported.[26,27] Critical to this advance was the identification of nickel catalysts capable of undergoing selective oxidative addition into this C-O bond; palladium catalysts capable of this reactivity have not yet been discovered. Capitalizing on the difference in capabilities of palladium and nickel catalysts to insert into aryl acetate C-O bonds, Garg and co-workers demonstrated that bromopivalate **1.10** can serve as a lynchpin reagent where the first and second couplings are differentiated by the identity of the catalytic metal (Scheme 1.9).[26] Although many important molecules lend themselves to a synthesis approach based on lynchpin reagents, the lynchpin approach cannot be used as an iterative coupling strategy that can be turned over a theoretically limitless number of times.
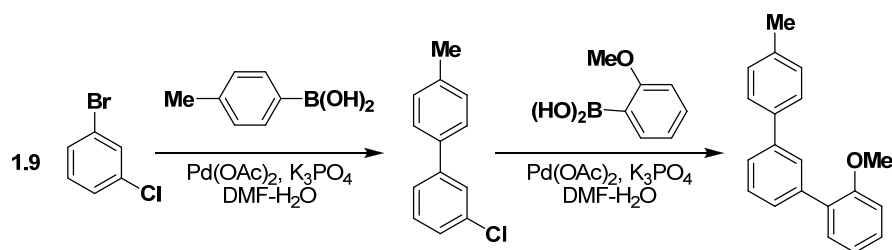
Scheme 1.8. The difference in reactivity of a C-Br and C-Cl bond towards oxidative addition was exploited by Hii and coworkers in the synthesis of several triaryl compounds.
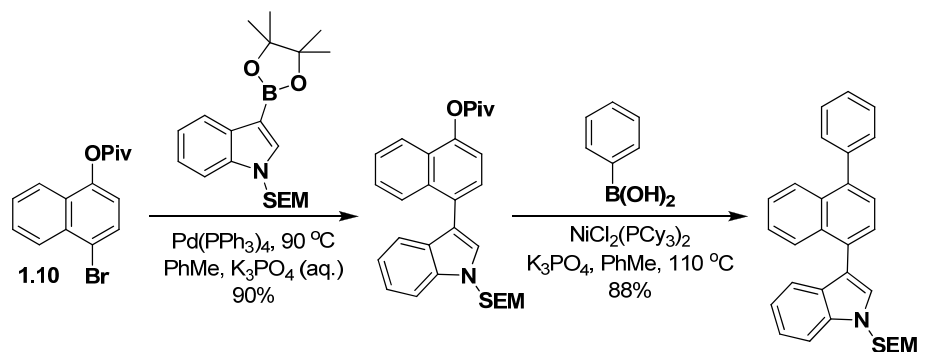
Scheme 1.9. Garg and coworkers demonstrated that the identity of the catalytic metal (Pd or Ni) used in a SMC reaction can be used to differentiate the functionality of a lynchpin reagent.

Iterative coupling is herein distinguished from the use of lynchpin reagents in the fact that with this approach, in theory, a limitless number of iterations are possible. Instead of employing an approach in which the termini of a building block are differentiated by selective activation, in iterative coupling the termini of a bifunctional building block are differentiated by chemically masking one of the two functionalities in order to render it unreactive. When the proper masking group is employed the differentiation potential can be expected to remain very high regardless of the identity of the building block. Following the coupling of the building blocks, in a separate chemical step the masking group is removed to expose the otherwise latent functionality. Because the conditions of the unmasking step are orthogonal to the conditions of the coupling step, in theory the reaction conditions used in the first coupling step will remain applicable to any of the following coupling steps. That is, unlike coupling reactions which employ lynchpin reagents, in iterative coupling the conditions used to promote the coupling of each new building block can, in theory, be identical. The scope of substrates which are amenable to an iterative synthesis approach is determined by the generality of the

coupling reaction, the availability of building blocks, the mildness of the coupling and deprotection steps, and the stability of the chemical intermediates and products.

The potential for a general approach to small molecule synthesis

This dissertation began with the hypothesis that the inherent modularity in small molecules remains largely underutilized, and that a unified strategy for the construction of these compounds through the iterative coupling of bifunctional building blocks might be possible. In the idealized form of this "iterative cross-coupling" (ICC) approach, building blocks having all of the required functional groups preinstalled in the correct oxidation states and with the desired stereochemical relationships would be iteratively united using only stereospecific cross-coupling reactions (Scheme 1.10). Towards this end, the Suzuki-Miyaura cross-coupling (SMC) reaction[28] between an organohalide and a boronic acid represents an efficient, functional group tolerant, stereospecific, and increasingly general method for C–C bond formation in complex molecule synthesis,[29] and thus was selected as the principal reaction on which to base the ICC platform. Our envisioned ICC approach was based on the use of bifunctional building blocks containing both of the functionalities that are reactive under SMC conditions: a halide and a boronic acid. In order to avoid undesired random oligomerization, realizing this ICC approach required the discovery of a means to reversibly attenuate the reactivity of either the halide or the boronic acid under SMC conditions.
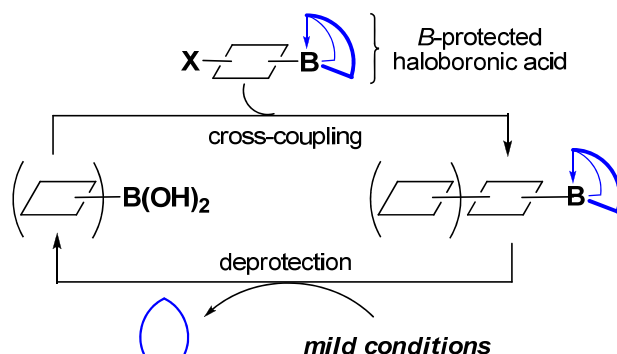
Scheme 1.10. Similar to the approach used in the iterative synthesis of peptides, we envisioned an iterative strategy for the synthesis of small molecules. This strategy would be based on the iterative cross-coupling (ICC) of bifunctional haloboronic acids via the Suzuki-Miyaura reaction. Realizing this approach required the discovery of a ligand with the capacity to reversibly attenuate the reactivity of a boronic acid.

In order to realize the ICC approach in the context of complex small molecule synthesis, it was critical to achieve boronic acid or halide unmasking under mild conditions that would be compatible with sensitive building blocks. Although there are methods for generating halides and pseudo-halides from functional groups that are inert to SMC conditions, this approach was less preferred because the conditions used in these transformations are relatively harsh and/or the reactions are limited in generality.[30] Alternatively, the reactivity of a boronic acid can be modulated by exchanging the OH groups on boron for other chemical moieties.[31] Further, the reactivity of boron towards ligand substitution is a general and well studied phenomenon.[32] However, at the onset of our work there were no reports of a ligand for boronic acids with the capacity to attenuate reactivity under SMC conditions *and* be cleaved to liberate a reactive boronic acid under conditions mild enough to be generally compatible with complex molecule synthesis.

Boronic acids and boronic esters are preferred reagents for cross-coupling reactions due to the low toxicity of boranes and their associated byproducts,[31] the relatively good stability of boronic acids/esters versus organomagnesium[33] and organozinc reagents[34] and the relatively mild conditions required to activate boranes towards cross-coupling.[22] However, some boronic acids/esters are inherently unstable to storage and/or the conditions of the SMC reaction. With the goal of maximizing the generality of the ICC approach, it would be desirable that even these unstable reagents could be utilized efficiently in a SMC reaction. A ligand with the capacity to attenuate the reactivity of boron under SMC conditions might also possess the capacity to attenuate the reactivity of the borane towards oxidation and protodeboronation processes. In this case, these "protected" boranes might serve as easily stored and handled surrogates for otherwise unstable boronic acids.[35] Achieving this surrogate therefore constituted a second goal.

Another important factor in the generality of the ICC approach is the efficiency with which complex building blocks can be accessed. The synthesis of complex boronic acids is generally limited by the incompatibility of common reagents with this functional group[35] and/or the problematic isolation of complex boranes in multistep synthesis.[31,36] Further, many of the methods used for installing boron suffer from limited functional

group compatibility.[31] Therefore, a third goal in the development of ICC would be to discover a more efficient approach to accessing complex boronic acids.

As our ultimate objective, we hoped that discoveries made in the development of the ICC approach might allow this process to be translated to an automated platform. Realizing the goal of automated iterative cross-coupling would be more readily achieved if the chemical steps involved in the ICC approach remained general and technically simple. Additionally, realizing an automated ICC approach would require the development of an automated synthesis machine which might require additional chemical, engineering and software development.

1-2 THE TRANSMETALLATION STEP OF THE SUZUKI-MIYAURA CROSS-COUPLING REACTION

To enable our vision of a general ICC approach to small molecule synthesis we would need to discover a ligand for boronic acids with the capacity to reversibly attenuate the reactivity of boron under SMC reaction conditions. As a framework for developing a hypothesis on how such a ligand might function, it is instructive to consider the mechanism of the SMC reaction,[28] and specifically the mechanism of the transmetallation step. The catalytic cycle of the SMC reaction can most simply be understood as a series of three general steps: oxidative addition, transmetallation and reductive elimination (Scheme 1.11). In the first step, a Pd(0) species undergoes oxidative addition with the C-X bond of an organo-halide or organo-pseudo-halide (OTf, OMs, OTs)[37] to furnish a Pd(II) intermediate containing as anionic ligands the halide/pseudo-halide and the organic group originally appended to the halide/pseudo-halide. The rate of oxidative addition is affected by the identity of the halide/pseudo-halide, and follows the general trend: I > OTf > Br >> Cl and OTf > OTs ~ OMs, although there are exceptions to this trend.[38] Additionally, the rate of oxidative addition is generally faster for electron-deficient organo-halides/pseudo-halides than for electron-rich organo-halide/pseudo-halides.

Following oxidative addition, an activated organoborane species undergoes transmetallation with the Pd(II) species. There are several mechanistic pathways that are possible for the transmetallation step, and the specifics of these mechanisms will be discussed below. Regardless of the details of this step, the overall effect is that the halide

on Pd(II) is replaced by the organic group originally bonded to boron. In the final step the two organic ligands on Pd(II), in *cis*-relationship, undergo a reductive elimination process in which the product is formed and a Pd(0) species is regenerated, thereby allowing the catalytic cycle to turnover. Oxidative addition, transmetallation and reductive elimination, are typically faster for aryl and vinyl organic groups (containing terminal sp^2-hybridized carbons) than for alkyl groups (containing terminal sp^3-hybridized carbons), and this phenomenon has an effect on the substrate scope of the SMC reaction and in cross-coupling reactions in general. Byproducts from the SMC catalytic cycle are a halide/pseudo-halide salt and a borane, typically boric acid, both of which are generally non-toxic.
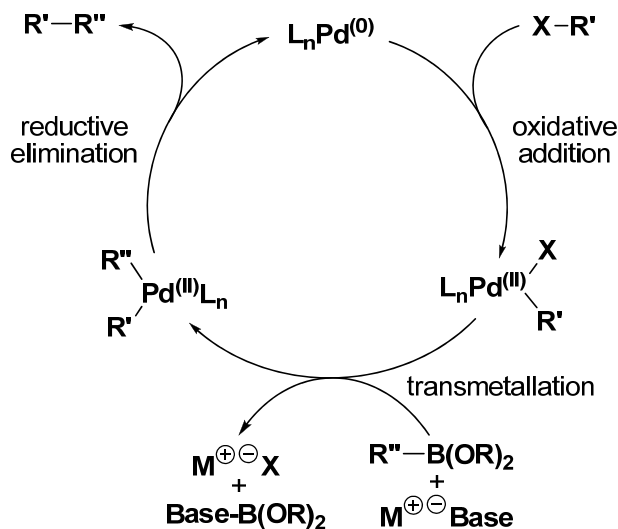
Scheme 1.11 The catalytic cycle of the SMC reaction involves three steps: oxidative addition, transmetallation, and reductive elimination.

The transmetallation step of the SMC mechanism is complex and, relative to oxidative addition and reductive elimination, remains poorly understood. Current data suggest that transmetallation between Pd(II) and a boronic acid/ester proceeds via either of two mechanistic pathways (Scheme 1.12).[28, 39,40,41,42] As an exception, it is known that tetraphenylborate salts undergo transmetallation without added base.[28a] Additionally, anionic triol-complexed boronates undergo transmetallation with Pd(II) without added base.[43,44] In pathway A (Scheme 1.12), an electronically activated boron "ate" complex is formed via the coordination of hydroxide or alkoxide with a neutral boronic acid.[28]

Displacement of the halide of the Pd(II) intermediate is proposed to occur via an S_E2 mechanism leading to transition state C (Scheme 1.12).[45] Although the formation of a boron "ate" complex is supported by numerous experimental observations,[28] and most recently by the isolation and characterization of discrete boron "ate" complexes,[46] direct experimental evidence for this mechanism has remained elusive.
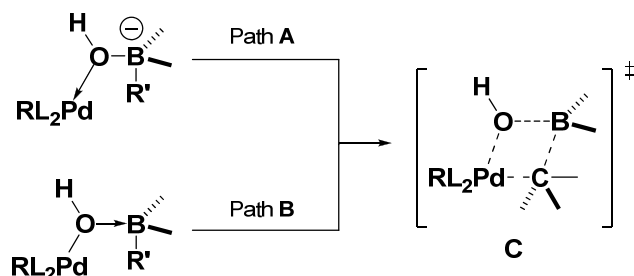
Scheme 1.12. Transmetallation between Pd(II) and a boronic acid is proposed to proceed via either of two mechanistic pathways.

In pathway B (Scheme 1.12), an oxygen atom on a ligand bound to Pd(II) is proposed to coordinate to a neutral boron species via donation of oxygen lone pair electron density into the boron p-orbital. In support of this mechanism, boronic esters have been demonstrated to undergo transmetalation to an (alkoxo)palladium(II) intermediate without added base, whereas transmetalation to a (chloro)palladium(II) intermediate under the same conditions did not occur (Scheme 1.13).[47] Further, a boronic acid has been shown to undergo transmetalation with a (hydroxo)palladium(II) intermediate in the absence of base (Scheme 1.14).[40] Recent DFT calculations support a mechanistic pathway from a (hydroxo)palladium(II) intermediate to transition state **C** (Scheme 1.12).[45] In this study a pathway from a (bromo)palladium(II) intermediate to a (hydroxo)palladium(II) intermediate was not located. However, the formation of a (hydroxo)palladium(II) intermediate under mock catalytic conditions (Pd(PPh$_3$)$_4$:PhBr 1:49) has been observed by Matos and Soderquist.[39] With regard to our goal of attenuating boronic acid reactivity, the most important lesson derived from these studies is that both pathways A and B necessitate a vacant and Lewis-acidic p-orbital on boron (Scheme 1.12).

14
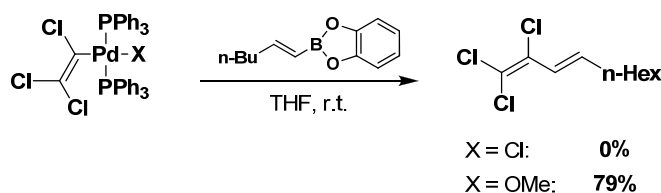
Scheme 1.13. Transmetalation of a boronic ester to a (chloro)palladium(II) intermediate does not proceed, while transmetalation of a boronic ester to an (alkoxo)palladium(II) intermediate occurs without added base.[47]
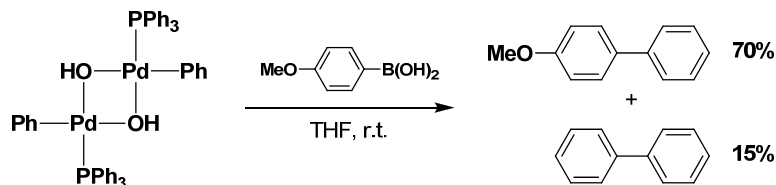
Scheme 1.14. Transmetalation of a boronic acid to a (hydroxo)palladium(II) intermediate occurs in the absence of base.[40]

1-3 ATTENUATING THE REACTIVITY OF BORONIC ACIDS VIA REDUCTION OF THE LEWIS ACIDITY OF THE BORON P-ORBITAL

Bidentate ligands that contain strongly electron-donating heteroatoms bonded to boron are known to attenuate the cross-coupling of organoboron compounds.[39,40] This is presumably due to conjugation of the lone pair electron density on the heteroatoms of these ligands to the empty p-orbital on boron, which in turn reduces the Lewis acidity of the boron center. In the first example that harnesses this effect, Soderquist and co-workers demonstrated a large difference in reactivity between a 9-BBN borane and an oxo-9-BBN borane, with the latter possessing an electron-donating heteroatom (Scheme 1.15).[39] Also harnessing this effect, a few examples of selective cross-coupling of bifunctional building blocks possessing both a halide and a boron-containing functional group have been reported. Deng, Mayeux, and Cai achieved the selective cross-coupling of an aryl iodide with an aryl boronic acid in the presence of an aryl pinacol boronic ester (Scheme 1.16),[48] and Hohn and Pietruszka reported the selective coupling of a cyclopropyl iodide with a boronic acid in the presence of a boronic ester (Scheme 1.17.).[49] Contemporaneous with our studies, Suginome and co-workers introduced the 1,8-diaminonapthalene (dan) ligand as a protecting group for boronic acids[50] and demonstrated its use in the iterative synthesis of a collection of polyarene compounds

(Scheme 1.8).[50a] Similar to the ICC approach discussed herein, the Suginome approach utilizes bifunctional haloboronic acid building blocks in which the reactivity of the boron functionality is masked via complexation with a ligand, in this case 1,8-diaminonapthalene. However, due to the strong boron-heteroatom bonds of these and related boronic esters, hydrolysis these bonds typically requires relatively harsh conditions which may be incompatible with complex small molecule synthesis. For example, the 1,8-diaminonapthalene ligand is typically cleaved upon treating at room temperature with aqueous 5 M HCl for 5 hours or aqueous 2 M H_2SO_4 for 10-27 hours.[50a-b] Cleavage of the pinacol ligand typically requires acid and/or an oxidant such as $NaIO_4$.[51,52]
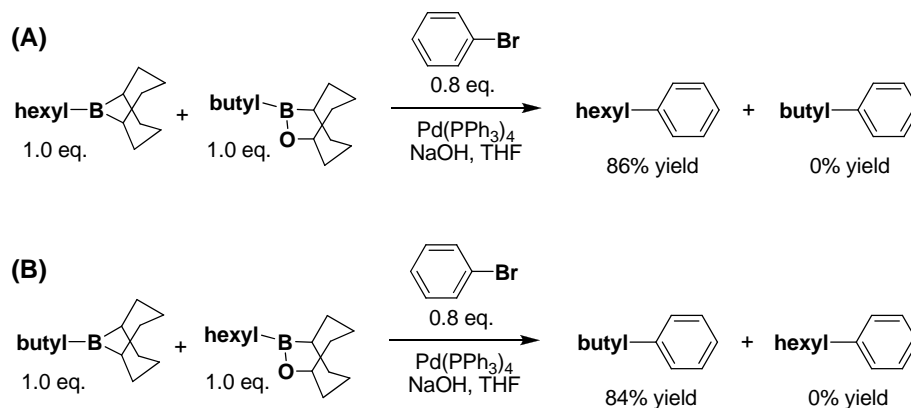
Scheme 1.15. (A) A 9-BBN borane was found to be much more reactive than a related oxo-9-BBN borane under SMC conditions. (B) It was demonstrated that difference in the organic group on boron does not account for this difference in reactivity.
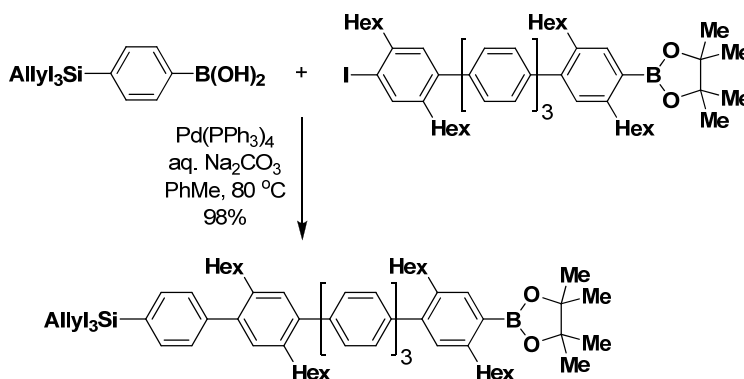
Scheme 1.16. Deng and co-workers have described a selective SMC reaction between an aryl boronic acid and an aryl iodide in the presence of a pinacol boronic.
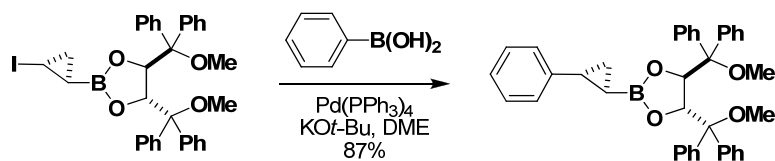
Scheme 1.17. Hohn and Pietruszka have reported a selective SMC reaction between a cyclopropyl iodide and a boronic acid that occurs selectively in the presence of a sterically encumbered boronic ester.
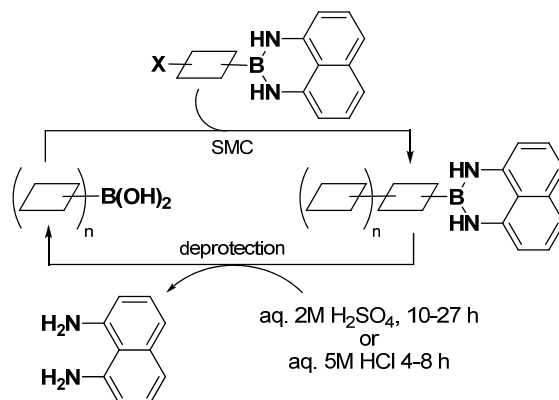
Scheme 1.18. Contemporaneous with our studies, Suginome and co-workers reported an ICC approach utilizing bifunctional haloboronic acids in which the reactivity of the boron functionality is reversibly attenuated via complexation with 1,8-diaminonapthalene (dan). The conditions required to remove the dan ligand from boron are relatively harsh and to date this methodology has only been applied in the synthesis of robust polyarene and polystyrene products.

1-4 ATTENUATING THE REACTIVITY OF BORONIC ACIDS VIA PYRAMIDALIZATION AT THE BORON CENTER

The work described herein was based on the hypothesis that boronic acid reactivity could alternatively be attenuated by rehybridization of a boron center from sp^2 to sp^3 via complexation with a heteroatomic, tridentate ligand. In theory, an sp^3-hybridized boronate complex lacking a p-orbital on boron would be unreactive under SMC conditions. Importantly, it was known that the boron-heteroatom bonds in such complexes are weaker that those found in their sp^2-hybridized counterparts. For example, the E(B-O) of the complex $NH_3 \cdot Me_2BOH$ is estimated to be 11 kcal/mol weaker than in that of Me_2BOH.[53] Thus, we reasoned that it might be possible to cleave the ligand to regenerate the boronic acid under mild conditions.

In order to test our hypothesis, we would need to be able to access a stable, sp^3-hybridized boronate. Fortunately, the synthesis and characterization of sp^3-hybridized

17

organoboronates has been a rich area of study[32] and there was a significant amount of precedent to inform our endeavors in the synthesis of boronate complexes. A particularly intriguing report by Mancilla, Contreras and Wrackmeyer described boronates derived from the condensation of boronic acids with the ligand N-methyliminodiacetic acid (MIDA) (Scheme 1.19).[54] In this report ^{1}H-NMR studies were performed that indicated that these complexes are sp^3 hybridized and quite stable.[54] To us, this unique structure raised intriguing questions as to its potential lack of reactivity under SMC conditions. However, reports on the reactivity of these interesting boronate compounds were limited to descriptions detailing the derivatization of the ligand itself.[55] Most studies in this area had been directed towards the synthesis and characterization of new derivatives of these boronates for potential applications in boron-neutron capture therapy to treat brain tumors and melanomas.[55,56] Therefore, the chemistry of this class of stable, neutral boronate species remained largely unexplored.
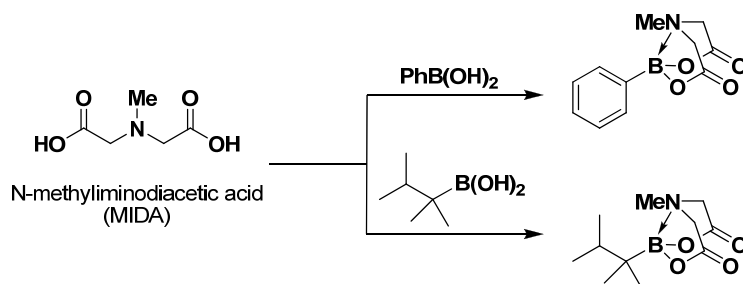
Scheme 1.19. Studies by Mancilla, Contreras and Wrackmeyer demonstrated that condensation of boronic acids with N-methyliminodiacetic acid (MIDA) affords isolable boronate complexes that are sp^3-hybridized at the boron center.

1-5 REFERENCES

1   (a) Merrifield, R. B. *Angew Chem. Int. Ed.* **1985**, *24*, 799. (b) Caruthers, M. H. *Science* **1985**, *230*, 281. (c) Plante, O. J.; Palmacci, M. R.; Seeberger, P. H. *Science* **2001**, *291*, 1523.

2   Fisher, E. ; Fourneau, E. *Ber. Dtsch. Chern. Ges.* **1901**, *34*, 2868-2877.

3   Bergmann, M.; Zervas, L. *Ber. Dfsch. Chem. Ges.* **1932**, *65*, 1192-1201.

[4] Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2149.

[5] (a) Merrifield, R. B.; Stewart, J. M. *Nature* **1965**, *207*, 522-523. (b) Merrifield, R. B.; Stewart, J. M.; Jernberg, N. *Anal. Chem.* **1966**, *38*, 1905-1914.

[6] A stepping drum is mechanically similar to a classic music box. A metal cylinder is encoded with elevations that press triggers in periodic intervals as the drum rotates.

[7] Zhang, J.; Moore, J. S.; Zu, Z.; Aguirre, R. A. *J. Am. Chem. Soc.* **1992**, *114*, 2273-2274.

[8] Young, J. K.; Nelson, J. C.; Moore, J. S. *J. Am. Chem. Soc.* **1994**, *116*, 10841-10842.

[9] (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *4467.* (b) Cassar, L. *J. Organomet. Chem.* **1975**, *93*, 253-257. (c) Dieck, H. A.; Heck, R. F. *J. Organomet. Chem.* **1975**, *93*, 259-263.

[10] (a) Eastmond, R.; Walton, D. R. M. *Tetrahedron* **1972**, *28*, 4601-4616. (b) Eaborn, C.; Walton, D. R. M. *J. Organomet. Chem.* **1965**, *4*, 217-228.

[11] Moore, J. S.; Weinstein, E. J.; Wu, Z. *Tetrahedron Lett.* **1991**, *32*, 2465-2466.

[12] Zeng, F.; Negishi, E. *Org. Lett.* **2002**, *4*, 703-706.

[13] Zeng, F.; Negishi, E. *Org. Lett.* **2001**, *3*, 719-722.

[14] Negishi, E.; Okukado, N.; King, A. O.; Van Horn, D. E.; Spiegel, B. I. *J. Am. Chem. Soc.* **1978**, *100*, 2254-2256

[15] Hart, D. W.; Schwartz, J. *J. Am. Chem. Soc.* **1974**, *96*, 8115-8116.

[16] (a) Coleman, R. S.; Walczak, M. C.; Campbell, E. L. *J. Am. Chem. Soc.* **2005**, *127*, 16038-16039 (b) Coleman, R. S.; Xiaoling, L.; Modolo, I. *J. Am. Chem. Soc.* **2007**, *129*, 3826-3827 (c) Other bis-metallated polyene lynchpins have been reported. For an example of a tin-silicon lynchpin see: Murakami, M.; Matsuda, T.; Itami, K.; Ashida, S.; Terayama, M.; *Synthesis* **2004**, *9*, 1522-1526 (d) For an example of a boron-silicon lynchpin see: Babudri, F.; Farinola, G. M; Fiandanese, V.; Mazzone, L.; Francesco, N. *Tetrahedron* **1998**, *54*, 1085-1094.

[17] Singidi, R. R.; RajanBabu, T. V.; *Org. Lett.* **2010**, *12*, 2622-2625.

[18] Following our original report on ICC, an iterative cross-coupling approach based on selective activation of silicon was reported: Nakao, Y.; Chen, J.; Tanaka, M.; Hiyama, T. *J. Am. Chem. Soc.* **2007**, *129*, 11694-11695.

[19] Denmark, S. E.; Tymonko, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 8004-8005.

[20] Denmark, S. E.; Sweis, R. F.; *J. Am. Chem. Soc.* **2001**, *123*, 6439-6440.

[21] Itami, K.; Nokami, T; Yoshida, J. *J. Am. Chem. Soc.* **2001**, *123*, 5600-5601.

[22] Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 918-920

[23] Littke, A. F.; Fu, G. C. *Angew. Chem. Int. Ed.* **2002**, *41*, 4176-4211.

[24] For other examples of *bis*-halogenated lynchpin building blocks see: (a) Organ, M. G.; Ghasemi, H. *J. Org. Chem.* **2004**, *69*, 695-700. (b) Organ, M. G.; Ghasemi, H.; Valente, C. *Tetrahedron* **2004**, *60*, 9453-9461. (c) Qian, M.; Huang, Z.; Negishi, E. *Org. Lett.* **2004**, *6*, 1531-1534. (d) reference 13.

[25] Miguez, J. M. A.; Adrio, L. A.; Sousa-Pedrares, A.; Vila, J. M.; Hii, K. K. *J. Org. Chem.* **2007**, *72*, 7771-7774.

[26] Quasdorf, K. W.; Tian, X.; Garg, N. K. *J. Am. Chem. Soc.* **2008**, *130*, 14422-14423

[27] Guan, B-T.; Wang, Y.; Li, B-J.; Yu, D-G.; Shi, Z-J. *J. Am. Chem. Soc.* **2008** *130*, 14468-14470

[28] (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457-2483. (b) Miyaura, N. *Top. Cur. Chem.* **2002**, *219*, 11-59.

[29] Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4442-4489

[30] (a) Liess, P.; Hensel, V.; Schlüter, A. D. *Liebigs Ann.* **1996**, 1037-1040. (b) Blake, A. J.; Cooke, P. A.; Doyle, K. J.; Gair, S.; Simpkins, N. S. *Tetrahedron Lett.* **1998**, *39*, 9093-9096. (c) Malenfant, P. R. L.; Groenendaal, L.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1998**, *120*, 10990-10991. (d) Kirschbaum, T.; Azumi, R.; Mena-Osteritz, E.; Baüerle, P. *New J. Chem.* **1999**, 241-250. (e) Read, M. W.; Escobedo, J. O.; Willis, D. M.; Beck, P. A.; Strongin, R. M. *Org. Lett.* **2000**, *2*, 3201-3204. (f) Yoo, Y-S.; Choi, J-H.; Song, J-H.; Oh, N-K.; Zin, W-C.; Park, S.; Chang, T.; Lee, M. *J. Am. Chem. Soc.* **2004**, *126*, 6294-6300. (g) Kanibolotsky, A. L.; Berridge, R.; Skabara, P. J.; Perepichka, I. F.; Bradley, D. D. C.; Koeberg, M. *J. Am. Chem. Soc.* **2004**, *126*, 13695-13702.

[31] Hall, D. G. *Boronic Acids*; Wiley-VCH: Weinheim, Germany, 2005; chapter 1.

[32] For a review of boronate esters see: Höpfl, H. *J. Organomet. Chem.* **1999**, *581*, 129-149.

[33] (a) Corriu, R. J. P.; Masse, J. P. *J. Chem. Soc., Chem. Commun.* **1972**, 144. (b) Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374-4376. (c) Tamao, K.; Kiso, Y.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 9268-9269.

[34] Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340-348.

[35] For leading studies with trifluoroborate salts as boronic acid surrogates, see: (a) Molander, G. A.; Figueroa, R.; *Aldrichimica Acta* **2005**, *38*, 49-56. (b) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275-286. (c) Darses, S.; Genet, J.-P. *Chem. Rev.* **2008**, *108*, 288–325

[36] Matteson, D. S. *J. Organomet. Chem.* **1999**, *581*, 51-56.

[37] Recently oxidative addition of the C-O bond of aryl acetates with Ni catalysts was reported. See references 26 and 27.

[38] (a) Littke, A.; Dai, C.; Fu, G. *J. Am. Chem. Soc.* **2000**, *122*, 4020-4028. (b) Barrios-Landeros, F.; Carrow, B. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2009**, *131*, 8141-8154.

[39] Matos, K.; Soderquist, J. A. *J. Org. Chem.* **1998**, *63*, 461-470.

[40] Miyaura, N. *J. Organomet. Chem.* **2002**, *653*, 54-57.

[41] Interestingly, evidence for a third mechanistic pathway was recently reported: Ochmura, T.; Awano, T.; Suginome, M. *J. Am. Chem. Soc.* **2010**, *ASAP*.

[42] A recent study indicates that organo trifluoroborate salts undergo transmetallation as the corresponding boronic acid, and thus may be engaged in these same pathways: Butters, M.; Harvey, J. N.; Jover, J.; Lennox, A. J. J.; Lloyd-Jones, G.; Murray, P. M. *Angew. Chem. Int. Ed.* **2010**, *49*, 1-6.

[43] Yamamoto, Y.; Takizawa, M.; Yu, X-Q.; Miyaura, N. *Angew. Chem. Int. Ed.* **2008**, *47*, 928-931.

[44] Prior to the report by Miyaura, we observed that anionic cyclohexyltriol-complexed boronates undergo transmetallation without added base (chapter 2 of this dissertation).

[45] Braga, A. A. C.; Morgon, N. H.; Ujaque, G.; Maseras, F. *J. Am. Chem. Soc.* **2005**, *127*, 9298-9307.

[46] Cammidge, A. N; Goddard, V. H. M.; Gopee, H.; Harrison, N. L.; Hughes, D. L.; Schubert, C. J.; Sutton, B. M.; Watts, G. L.; Whitehead, A. J. *Org. Lett.* **2006**, *8*, 4071-4074.

[47] Miyaura, N.; Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 972-980.

[48] Deng, X.; Mayeux, A.; Cai, C. *J. Org. Chem.* **2002**, *67*, 5279-5283.

[49] Hohn, E.; Pietruszka, J. *Adv. Synth. Catal.* **2004**, *346*, 863-866.

[50] (a) Noguchi, H.; Hojo, K.; Suginome, M. *J. Am. Chem. Soc.* **2007**, *129*, 758-759. (b) Noguchi, H.; Shioda, T.; Chou, C-M. Suginome, M. *Org. Lett.* **2008**, *10*, 377-380. (c) Iwadate, N.; Suginome, M. *Org. Lett.* **2009**, *11*, 1899-1902. (d) Iwadate, N.; Suginome, M. *J. Organomet. Chem.* **2009**, *694*, 1713-1717. (e) Iwadate, N.; Suginome, M. *J. Am. Chem. Soc.* **2010**, *132*, 2548-2549.

[51] Murphy, J. M.; Tzschuck, C. C.; Hartwig, J. F. *Org. Lett.* **2007**, *9*, 757-760.

[52] Alternatively, pinacol and related diol boronic esters can be hydrolyzed via the intermediacy of an insoluble diethanolamine boronate complex: (a) Wang, Y-C.; Georghiou, P. E. *Org. Lett.* **2002**, *4*, 2675-2678. (b) Matteson, D. S.; Man, H-W. *J. Org. Chem.* **1996**, *61*, 6047-6051. (c) Brown, H. C.; Prasad, J. V. N. V. *J. Org. Chem.* **1986**, *51*, 4526-4530. (d) Roy, C. D.; Brown, H. C. *Monatshefte für Chemie* **2007**, *138*, 879-887.

[53] Matteson, D. S. S*tereodirected Synthesis with Organoboranes*; Springer: Berlin, 1995; pp 1-20.

[54] Mancilla, T.; Contreras, R.; Wrackmeyer, B. *J. Organomet. Chem.* **1986**, *307*, 1-6.

[55] (a) Mancilla, T.; Carrillo, L.; Reducindo, M. D. P. *Polyhedron* **1996**, *15*, 3777-3785. (b) Mancilla, T.; Alarcón, M. L.; Carrillo, L. *Heteroatom Chem.* **1994**, *5*, 455-462. (c) Mancilla, T.; Romo, M. A. C.; Delgado, L. A. *Polyhedron* **2007**, *26*, 1023-1028.

[56] (a) Mancilla, T.; Hopfl, H.; Bravo, G.; Carrillo, L. *Main Group Metal Chem.* **1997**, *20*, 31-36. (b) Beltrán, H. I.; Alas, S. J.; Santillan, R.; Farfán, N. *Can. J. Chem.* **2002**, *80*, 801-812. (c) Beltrán, H. I.; Zamudio-Rivera, L. S.; Mancilla, T.; Santillan, R.; Farfán, N. *J. Organomet. Chem.* **2002**, *657*, 194-204. (d) Mancilla, T.; Zamudio-Rivera, L. S.; Beltrán, H. I.; Santillan, R.; Farfán, N. *ARKIVOC* **2005**, 366-376.

CHAPTER 2

ITERATIVE CROSS-COUPLING WITH B-PROTECTED HALOBORONIC ACID BUILDING BLOCKS

Eric P. Gillis, Steven G. Ballmer, and Martin D. Burke

Realizing a general iterative cross-coupling (ICC) approach to the synthesis of complex small molecules required the discovery of a ligand with the capacity to attenuate the reactivity of boronic acids under Suzuki-Miyaura cross-coupling (SMC) conditions and then liberate this masked reactivity under mild conditions. This chapter describes the study and selection of a ligand with such a capacity, *N*-methyliminodiacetic acid (MIDA). It was found that condensation of MIDA with boronic acids affords sp^3-hybridized MIDA boronate esters which are crystalline solids that are generally stable to SiO$_2$ chromatography and storage under ambient air at room temperature. Further, and irrespective of the organic group appended to boron, it was found that MIDA boronates are inert to the conditions of anhydrous SMC reactions, yet are converted to the corresponding boronic acid using mild aqueous base. The applicability of ICC to complex molecule synthesis was tested in the first total synthesis of the natural product ratanhine. Subsequent studies indicate that the ICC methodology is applicable to multi-gram scale synthesis. Steven G. Ballmer contributed to the work presented in this chapter by performing the experiments described in Scheme 2.11.
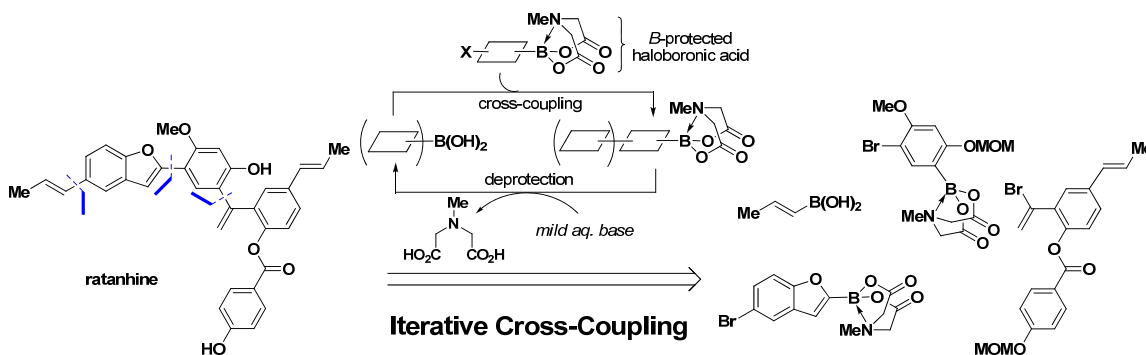
2-1 BACKGROUND

When I joined Professor Martin Burke's research group during my first year at the University of Illinois, Champaign-Urbana in August 2005, he suggested that I investigate the potential of using the ligand *N*-methyliminodiacetic acid (MIDA) (**2.1a**, Figure 2.1) to attenuate the reactivity of boronic acids under Suzuki-Miyaura cross-coupling (SMC) conditions. Pioneering studies by Mancilla, Contreras and Wrackmeyer [1] had demonstrated that this ligand, when condensed with boronic acids under Dean-Stark dehydration conditions, forms an isolable boron-containing complex (Figure 2.1). [2] Further, it was shown through variable-temperature ^{1}H-NMR studies that these complexes are sp^3 hybridized with a B-N bond strength of >20 kcal/mol. [1] Despite numerous reports on the synthesis of derivatives of these boronates, [3] the reactivity of this class of borane remained unknown. In fact, very little was known about the reactivity of neutral sp^3-hybridized boronates in general other than reactions involved in the formation and solvolysis of these compounds. [2] Therefore, boronates based on the MIDA ligand and its derivatives appeared to present a foundation on which to test our two hypotheses: that neutral sp^3-hybridized boronates will not undergo transmetallation with Pd(II), and that regenerating the boronic acid from an sp^3-hybridized boronate will be possible under mild conditions.
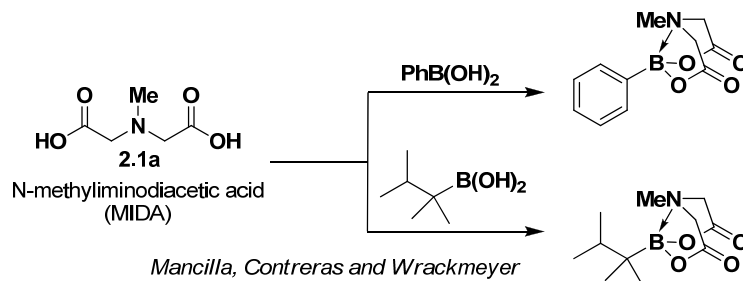
Figure 2.1. Studies by Mancilla, Contreras and Wrackmeyer demonstrated that condensation of boronic acids with N-methyliminodiacetic acid (MIDA) affords isolable boronate complexes that are sp^3-hybridized at the boron center.

2-2 DISCOVERY THAT MIDA ATTENUATES THE REACTIVITY OF BORONIC ACIDS

To test the hypothesis that sp³-hybridized boronate esters would be inert to cross-coupling we prepared a collection of boronate esters and evaluated their reactivity under SMC conditions. As a first step towards accessing a diverse collection of boronate esters, a collection of tridentate ligands representing a variety of structural motifs was gathered (Figure 2.2). Ligands **2.1a**, **2.1b**, **2.1f**, and **2.1g** were purchased from commercial sources, ligands **2.1c**, **2.1d**, **2.1e**, and **2.1h** were prepared by the general route shown in Scheme 2.1,[4] and ligand **2.1i**[5] was prepared in three steps from 2-chloroanisole (Scheme 2.2). Next, ligands **2.1a**–**2.1i** were condensed under Dean-Stark conditions with *p*-tolylboronic acid (**2.2**) to afford boronates **2.3a**–**2.3i** (Scheme 2.3).[1,5] Remarkably, boronates **2.3a**, **2.3c**, **2.3d** and **2.3h** were *all completely stable to standard SiO₂ chromatography*. To the best of our knowledge, the stability of this class of boronate to SiO₂ was previously unknown.[1,3] Complexation of **2.2** with **2.1e** was not successful, likely due to the weak Lewis-basic character of the aniline nitrogen. All of the boronates accessed in Scheme 2.3 were found to have good solubility in THF with the exceptions of **2.3b**, which did not fully dissolve even in DMF at a 0.05 M concentration.
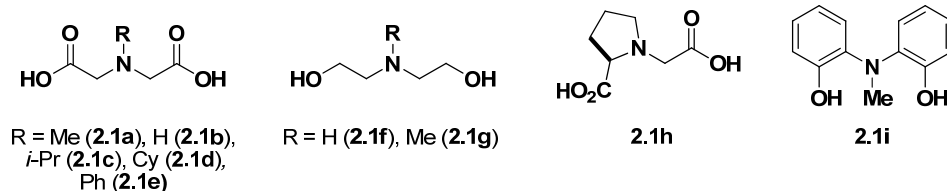
Figure 2.2. A collection of trivalent ligands for boron.
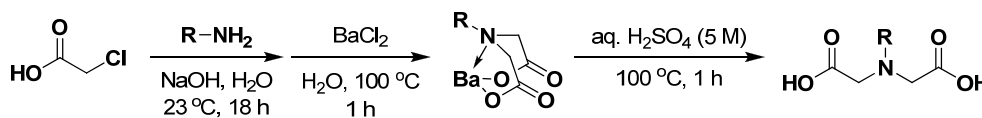
Scheme 2.1. A general route to iminodiacetic acid derivatives. Treatment with BaCl₂ results in the selective precipitation of the tridentate ligand as the barium chelate. Hydrolysis of the chelate with H₂SO₄ affords the water soluble product which is readily separated from the water-insoluble BaSO₄ byproduct.
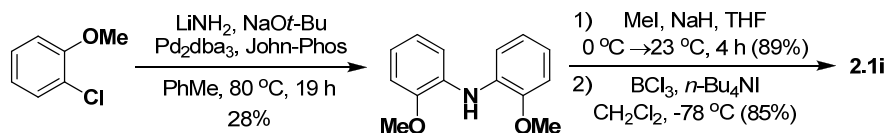
Scheme 2.2. Synthesis of a diphenolamine ligand for boron.
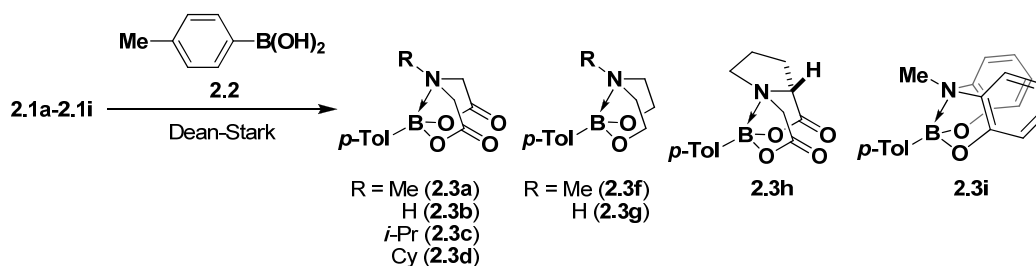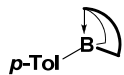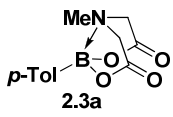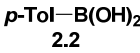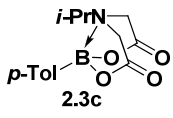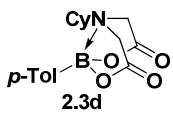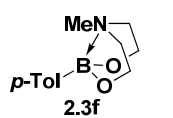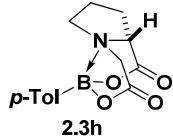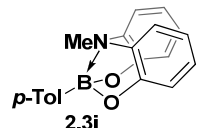
Scheme 2.3. sp³-hybridized boronates were prepared via Dean-Stark condensation of *p*-tolylboronic acid with ligands **2.1a–2.1i**.

To test the hypothesis that boron pyramidalization will inhibit cross-coupling, one equivalent of boronate **2.3a** and one equivalent of boronic acid **2.4** were allowed to react with a limiting quantity of *p*-bromobenzaldehyde (**2.5**) under anhydrous [6] SMC conditions[7] (Table 2.1). In this experiment a 24:1.0 ratio of biaryls **2.6** and **2.7** was observed, consistent with strong preferential reactivity with the sp²-hybridized boronic acid **2.4** (entry 1). The control experiment with **2.2** yielded a 1.0:1.0 mixture of products (entry 2). Sterically bulky *N*-alkyl substitution was tolerated but not significantly advantageous (entries 3 and 4). Interestingly, diethanolamine adduct **2.3f**, for which related structures have been shown to be sp³-hybridized but also less conformationally rigid than their iminodiacetic acid counterparts,[8] demonstrated no selectivity (entry 5). When the SMC experiment was repeated employing **2.3f** and **2.4**, but in the absence of **2.5**, ¹H-NMR analysis of the final reaction solution demonstrated no change in composition of **2.3f**, indicating that the reactivity of **2.3f** is not due to cleavage of the diethanolamine ligand under SMC conditions. Proline-derived boronate **2.3h** demonstrated similar reactivity to **2.3a** (entry 6). Boronate **2.3i** showed low selectivity possibly due to the low basicity of the aniline nitrogen (entry 7). In a related study, 1-butenyl boronic acid was complexed with ligands **2.1a–2.1g**, and the resulting boronates were evaluated in a SMC competition experiment similar to that described in Table 2.1.

Specifically, in each case one equivalent of the boronate and one equivalent of *E*-propenyl boronic acid were allowed to react with a limiting one equivalent of β-bromostyrene under SMC conditions employing $Pd(OAc)_2$:John-Phos and K_3PO_4 in THF at room temperature for 12 hours. In all cases the results obtained in this study were similar to those described in Table 2.1. Prior to these studies, to the best of our knowledge, this type of reactivity attenuation with neutral, sp^3-hybridized boronate esters was unknown. Owing to the structural simplicity and commercial availability of MIDA, the attractive physical properties of MIDA boronates, and the effectiveness of the ligand to attenuate the reactivity of boronic acids, the MIDA ligand was selected for further studies.[9,10]

Table 2.1

Entry	(p-Tol–B structure)	2.6 : 2.7[*]
1	p-Tol, MeN **2.3a**	24 : 1.0
2	p-Tol—B(OH)$_2$ **2.2**	1.0 : 1.0
3	p-Tol, i-PrN **2.3c**	26 : 1.0
4	p-Tol, CyN **2.3d**	11 : 1.0
5	p-Tol, MeN **2.3f**	1.0 : 1.0
6	p-Tol, N–H **2.3h**	21 : 1.0
7	p-Tol, MeN **2.3i**	8.2 : 1.0
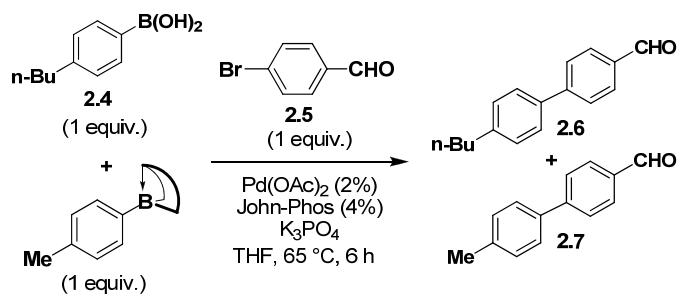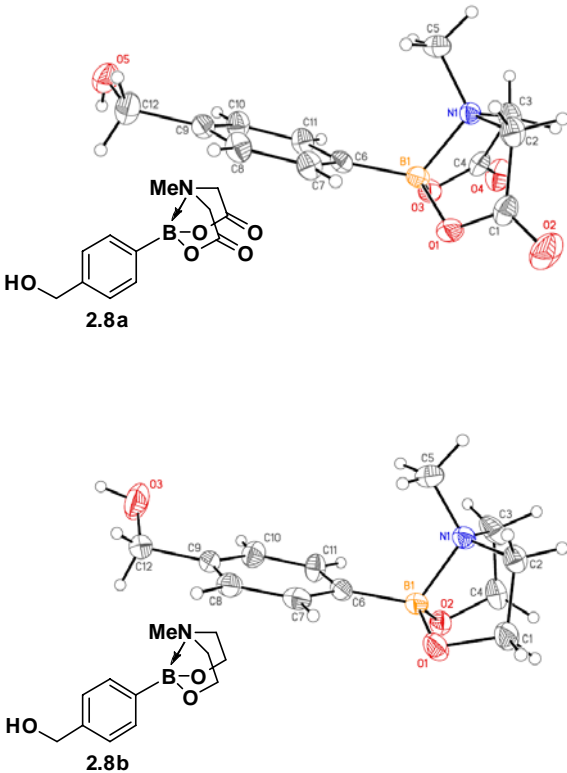
[*]HPLC, average of three single runs

n-Bu—C$_6$H$_4$—B(OH)$_2$ **2.4** (1 equiv.)

Br—C$_6$H$_4$—CHO **2.5** (1 equiv.)

+

Me—C$_6$H$_4$—B (1 equiv.)

→

Pd(OAc)$_2$ (2%)
John-Phos (4%)
K$_3$PO$_4$
THF, 65 °C, 6 h

n-Bu—C$_6$H$_4$—C$_6$H$_4$—CHO **2.6**

+

Me—C$_6$H$_4$—C$_6$H$_4$—CHO **2.7**

28

2-3 MECHANISTIC UNDERPINNINGS OF MIDA BORONATE REACTIVITY

To gain understanding on the dramatic difference in reactivity for the structurally related MIDA (**2.3a**) and *N*-methyldiethanolamine (**2.3f**) adducts, we carried out single crystal X-ray analysis on the related boronates **2.8a** and **2.8b**[11] which revealed no major differences in bond lengths, bond angles, or tetrahedral character[12] at the boron centers (Table 2.2). In contrast, and consistent with studies of related complexes,[1,8,13] variable temperature ^{1}H-NMR analysis of a solution of **2.8b** in d_6-DSMO revealed coalescence of the diastereotopic methylene protons of the diethanolamine backbone upon heating from 23 °C to 60 °C (Figure 2.3A); the same experiment with MIDA boronate **2.8a** indicated no coalescence, even upon heating to 150 °C (Figure 2.3B). These data are consistent with the conclusion that the N→B bond in **2.8b** is dynamic which renders the boron p-orbital and nitrogen lone-pair susceptible to reactivity, whereas for boronate **2.3a** these potentially reactive sites are kinetically inaccessible even at high temperature.

Table 2.2.

Bond distance (Å)	2.8a	2.8b
B1-N1	1.667	1.688
B1-O1	1.476	1.442
B1-O2	1.475	1.467
B1-C6	1.578	1.590
Bond angle (°)	2.8a	2.8b
C6-B1-N1	114.7	115.0
C6-B1-O1	115.1	112.4
C6-B1-O2	113.4	112.4
N1-B1-O1	100.8	101.1
N1-B1-O2	101.9	100.1
O1-B1-O2	109.5	114.9
THC (%)[12]	**65.6**	**61.7**
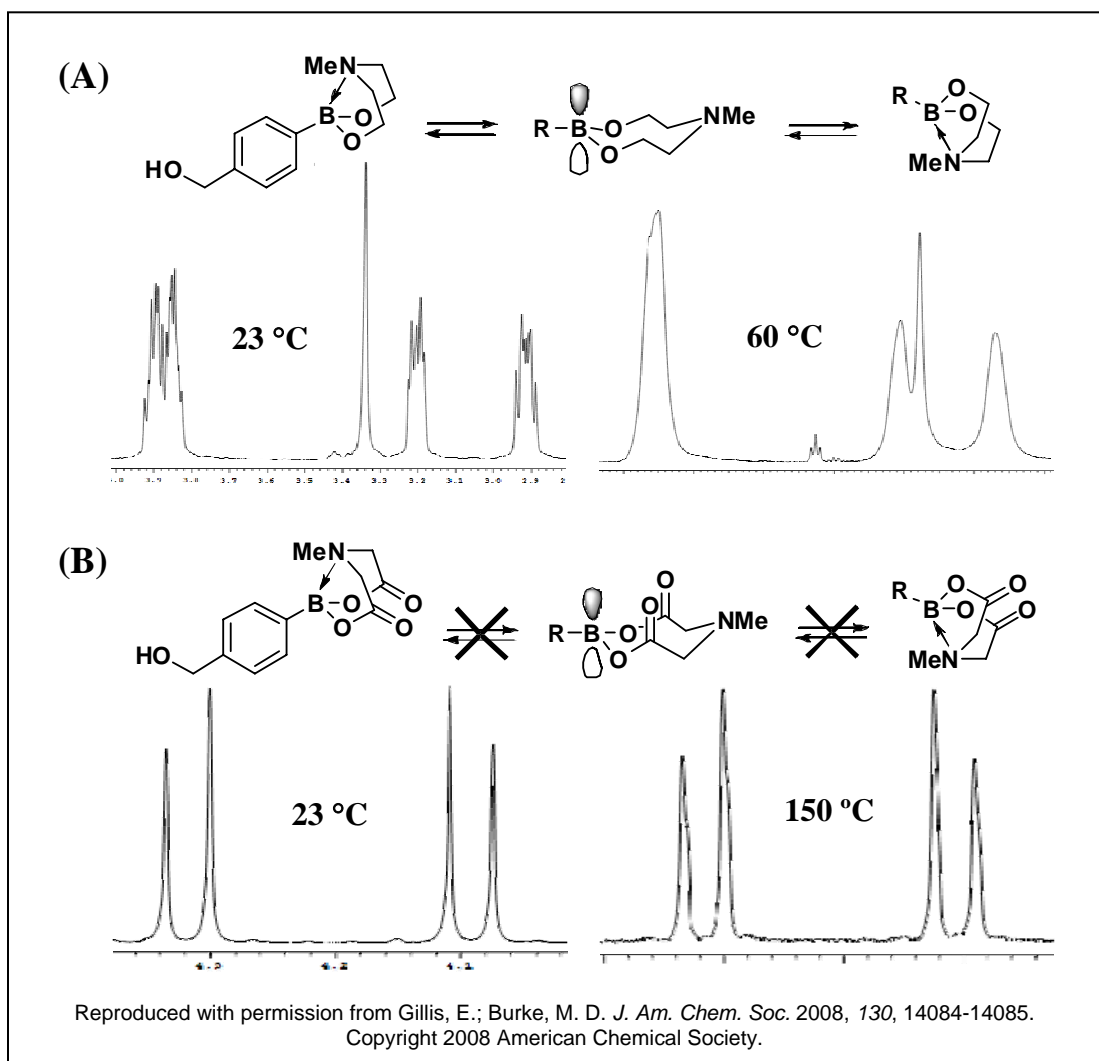
Figure 2.3. (A) The ^{1}H-NMR spectrum of diethanolamine adduct **2.8b** at 60 °C demonstrates full coalescence of the methylene proton resonances indicating that the boronate is fluxional at this temperature. (B) The ^{1}H-NMR spectra of MIDA boronate **2.8a** at 23 °C and 150 °C are the same, indicating that the MIDA boronate is conformationally rigid even at high temperature.

To probe the physical organic underpinnings which contribute to the observed difference in conformational rigidity of **2.8a** and **2.8b** (and as a corollary, **2.3a** and **2.3f**), we collaborated with Professor Kendall Houk and Dr. Paul Cheong to study these compounds using computer modeling.[14] In some regards, the difficulty in modeling the N→B dative bond[15] restricted the nature of these studies. However, preliminary studies shed light on an important interaction: the lone pair electrons of the oxygen atoms of the diethanolamine ligand have a strong interaction with the B–N σ* orbital of the boronate

(Figure 2.4). This interaction should lead to a weakening of the N→B bond. This interaction is substantially reduced in the case of the MIDA boronate due to the electron withdrawing capacity of the adjacent carbonyl functionality. Interestingly, computational studies also suggest that the magnitude of the resonance contribution of the MIDA boronate N→B dative bond to adjacent unsaturated systems is greater than hyperconjugation of a σ-bond but is weaker than the resonance contribution of a π-bond. Collectively, these studies and literature precedents[1,8] indicate that the difference in reactivity of MIDA boronates and diethanolamine adducts is due to a difference in the conformational rigidity of these boronates. These results also have implications for the chemistry described in chapter 4.
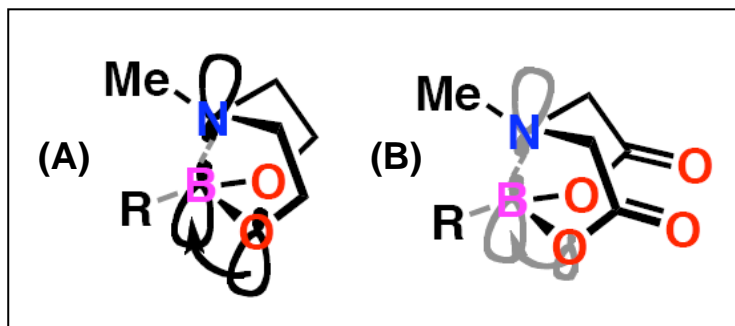
Figure 2.4. (A) Computer modeling suggests that lone pair electron density of the oxygen atoms of the diethanolamine ligand strongly interacts with the B–N σ* orbital. (B) This interaction is substantially reduced in the case of the MIDA boronate.

2-4 DEPROTECTION OF MIDA BORONATES UNDER MILD CONDITIONS

The generality of an ICC strategy depends critically on the ability to transform the latent functional group of a bifunctional building block into a reactive form under *mild* conditions. Because boron-heteroatom bonds in sp³-hybridized complexes are predicted to be approximately 11 kcal/mol weaker than those in the corresponding sp² species,[16] we hypothesized that it might be possible to remove the ligand on boron under relatively mild conditions; this in fact was a principal consideration in our approach towards attenuating the reactivity of a boronic acid via a hybridization state change. To test this hypothesis, in a preliminary study a number of bases were screened in the conversion of MIDA boronate **2.9** to boronic acid **2.10** (Table 2.3). Weak bases were moderately effective (entries 1, 2, 3, and 5) but in the absence of bulk water or alcohol little

conversion was observed (entries 4 and 5). On the other hand, the use of strong bases led to full conversion within one hour (entries 7, 8, 9, 10). Interestingly, the observation of slow hydrolysis with weak bases would become important in developing the slow-release protocol (chapter 3). The stability of MIDA boronates to anhydrous conditions, as was indicated in earlier sections, was also determined through this initial screen.

Table 2.3

Entry	Base	ROH	% **2.10**, t = 1 h[a]	% **2.10**, t = 24 h[a]
1	$NaHCO_3$	H_2O	< 5%	~ 25%
2	Na_2CO_3	H_2O	< 5%	~ 25%
3	K_2CO_3	H_2O	< 5%	~ 25%
4	K_2CO_3	None	< 5%	< 5%
5	K_3PO_4	H_2O	< 5%	~ 25%
6	K_3PO_4	None	< 5%	< 5%
7	NaOH	H_2O	100%	100%
8	KOH	H_2O	100%	100%
9	NaOEt	EtOH	100%	100%
10	KO*t*-Bu	*t*-BuOH	100%	100%

[a] Estimated based on TLC

Based on these initial qualitative results, a series of follow-up experiments on the hydrolysis of MIDA boronates were performed. From these studies two mild and effective deprotection conditions were identified (Scheme 2.4). Specifically, it was discovered that treatment of a THF solution of **2.3a** with aqueous NaOH (1 M) led to complete conversion to boronic acid **2.2** *in just 10 minutes at room temperature*. Further, it was determined that **2.3a** could be efficiently converted to **2.2** at room temperature in six hours by employing the mild conditions of aq. NaHCO₃/MeOH. In this second transformation the use of MeOH was critical, presumably because a significant amount of aqueous base is dissolved in the organic phase, but also possibly because the alcohol catalyses the process through a methyl boronic ester intermediate. On the other hand,

when MIDA boronates are dissolved in EtOAc, acetone:EtOAc, THF, dioxane, CH_2Cl_2 or other similar solvents, the rate of aq. $NaHCO_3$-promoted hydrolysis at room temperature is negligible over the course of one hour to the point that these systems can be generally used for aqueous workups of MIDA boronate products (chapter 4).

Bulk water or alcoholic solvents, even in the absence of base, appear to *slowly* hydrolyze MIDA boronates to the corresponding boronic acid over the course of 24 hours, although studies on these processes are limited. Under normal handling and storage practices atmospheric moisture does not lead to any observable hydrolysis of MIDA boronates. This phenomenon was studied quantitatively in the context of slow-release cross-coupling (chapter 3). Further, at least one equivalent of water appears to be tolerated by the MIDA boronate functional group even under SMC conditions in the presence of K_3PO_4 at 60 °C for 18 h.[17]
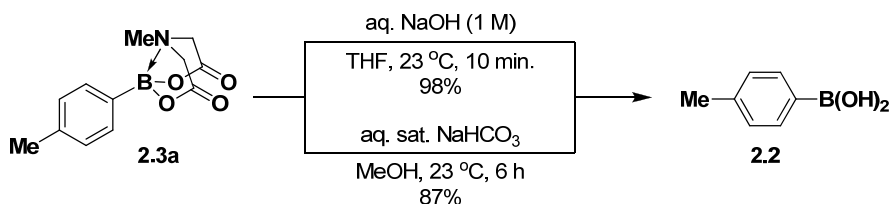
Scheme 2.4. Complimentary mild conditions for the hydrolysis of MIDA boronates to the corresponding boronic acid.

2-5 BORON-PROTECTED HALOBORONIC ACID BUILDING BLOCKS

Building on the promising results of the early studies, we next sought to prepare a collection of Boron-protected haloboronic acid bifunctional building blocks in order to test these reagents in the context of ICC. The MIDA ligand was selected for this purpose due to its commercial availability, the ease with which MIDA boronates can be accessed, and the favorable properties of the resulting MIDA boronate esters: highly attenuated reactivity under SMC reaction conditions, mild conversion of the boronate to the boronic acid, stability to SiO_2 chromatography, and stability to storage under ambient atmosphere at room temperature. Towards this end, a variety of haloboronic acids were complexed with MIDA to yield a series of B-protected bifunctional building blocks (Scheme 2.5). All three positional isomers of bromophenyl boronic acid as well as the heteroaromatic 5-

bromothiopheneboronic acid reacted cleanly to generate **2.12a–2.12d** in excellent yields. The same complexation conditions yielded vinyl and alkyl boronate esters **2.12e** and **2.12f** in high yields. Further, boronates **2.12a**, **2.12b**, **2.12c**, **2.12d**, and **2.12f** were isolated as analytically pure, colorless, crystalline solids after a single SiO$_2$ chromatographic step. MIDA boronates **2.12a–2.12f** and were also found to be completely stable to storage at room temperature under ambient atmosphere. The stability of MIDA boronates to SiO$_2$ chromatography and storage has since proved to be a general phenomenon and should be assumed for all MIDA boronates discussed in this dissertation unless explicitly stated otherwise.
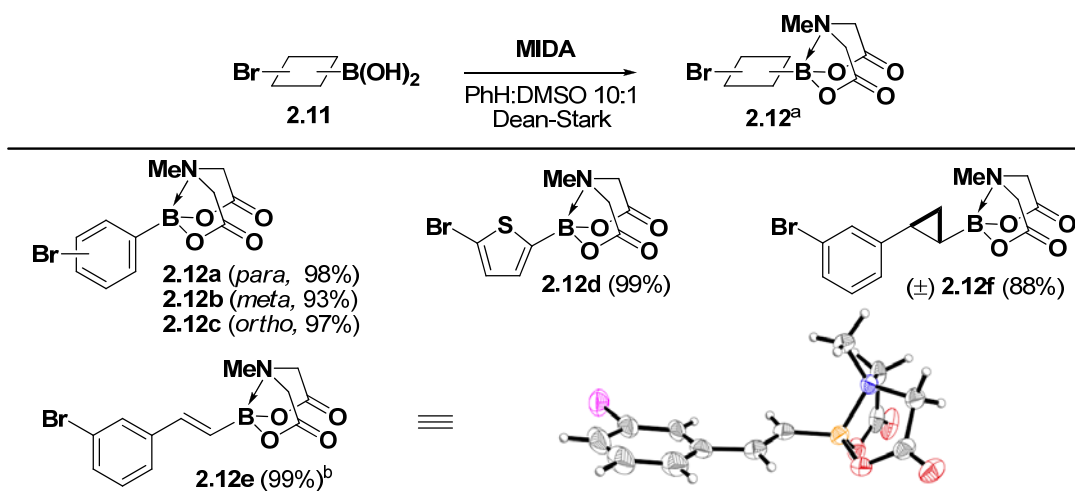
[a]Isolated yields after silica gel chromatography refer to analytically pure materials. [b]Crystallized from THF.

Reproduced with permission from Gillis, E. P.; Burke, M. D. J. Am. Chem. Soc. 2007, 129, 6716-6717. Copyright 2007 American Chemical Society.

Scheme 2.5. A collection of aryl, heteroaryl, vinyl and alkyl boronates was prepared by condensing the corresponding boronic acid with the MIDA ligand under Dean-Stark conditions.

The potential of the MIDA ligand to enable selective cross-couplings was probed by allowing each of **2.12a–2.12f** to react with *p*-tolylboronic acid (Table 2.4). Although the reactivity of aryl, heteroaryl, vinyl, and alkyl boronic acids can vary dramatically,[18] the MIDA ligand was effective for all four classes of nucleophiles, yielding selective cross-coupling products **2.13a–2.13f**. All four classes of nucleophiles were also efficiently deprotected under the standard aqueous basic conditions (1 M aqueous NaOH:THF, 23 °C, 10 min). The pure boronic acids **2.14a–2.14f** were isolated simply by neutralizing the aqueous phase with pH 7.0 phosphate buffer, partitioning the phases, and

then concentrating the organic phase *in vacuo*. Aqueous NaHCO$_3$:MeOH was also effective (entry 3). The generally effective cross-coupling of **2.12a–2.12f** and subsequent deprotection of **2.13a–2.13f** represents a realization of the two steps of an ICC sequence. At this point we sought to investigate whether ICC could be used in the synthesis of a small molecule natural product.

Table 2.4

Entry	2.12	Protected product	% Yield	Deprotected product	% Yield
1	**2.12a**	**2.13a** (*para*)	87[a]	**2.14a** (*para*)	86
2	**2.12b**	**2.13b** (*meta*)	85	**2.14b** (*meta*)	92
3	**2.12c**	**2.13c** (*ortho*)	80	**2.14c** (*ortho*)	97[b]
4[c]	**2.12d**	**2.13d**	81	**2.14d**	88
5	**2.12e**	**2.13e**	82	**2.14e**	83
6	**2.12f**	(±) **2.13f**	94	(±) **2.14f**	91

[a] The same yield was observed whether this reaction was set up in the glovebox or under air.
[b] *B*-Deprotection was achieved via treatment with saturated aq. NaHCO$_3$/MeOH, 23 °C, 6 h, (85%).
[c] S-Phos was used instead of Cy-JohnPhos.

Reproduced with permission from Gillis, E. P.; Burke, M. D. J. Am. Chem. Soc. 2007, 129, 6716-6717. Copyright 2007 American Chemical Society.

2-6 ITERATIVE CROSS-COUPLING IN THE SYNTHESIS OF RATANHINE

To test the hypothesis that ICC could be used as the basis for the synthesis of a small molecule natural product, we targeted the first total synthesis of the natural product ratanhine (**2.15**) (Scheme 2.6), the most complex member of a large family of neolignans isolated from *Ratanhiae* radix.[19] Retrosynthetic fragmentation of **2.15** into four simpler building blocks (**2.16–2.19**) was achieved via recursive application of three SMC

transforms (Scheme 2.6). There were several challenges associated with this plan that were anticipated to provide rigorous tests for the new methodology. First, the initial SMC reaction would require the selective coupling of vinyl boronic acid **2.16** in the presence of aryl boronate **2.17**. The cross-coupling of aryl boronic acids tends to be more facile than the that of their vinyl counterparts,[18] making this coupling unsecured. In addition, heteroaryl boronic acids such as the deprotected analogue of **2.17** are known to be very sensitive to proto-deboronation.[20] Moreover, cross-coupling with the highly electron-rich and sterically encumbered aryl bromide **2.18** was expected to require elevated temperatures and/or prolonged reaction times that would test the limits of stability for the MIDA ligand.
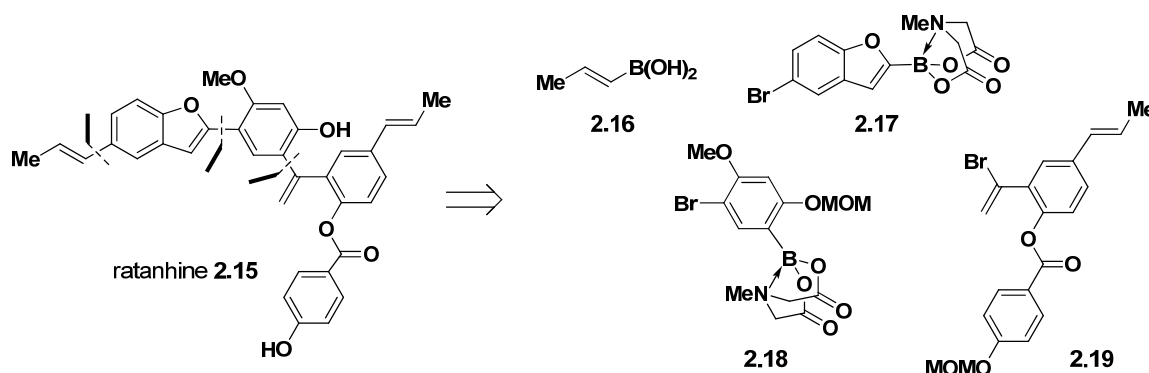
Scheme 2.6. The natural product ratanhine was retrosynthetically fragmented via recursive SMC transforms to identify four building blocks, two of which are bifunctional building blocks (**2.17** and **2.18**).

Before the ICC synthesis of **2.15** could be attempted, access to building blocks **2.16–2.19** needed to be secured. Propenylboronic acid (**2.16**) was purchased from Sigma Aldrich, but can now be efficiently accessed from propenylmagnesium bromide via the corresponding MIDA boronate (chapter 4). The synthesis of **2.17** was accomplished according to the synthetic route outlined in Scheme 2.7. Through modifications of a related Rap-Stoermer condensation,[21] benzofuran **2.22** was synthesized in 77% overall yield from **2.20** and **2.21** and was then converted to boronic acid **2.23** following the literature procedure.[22] Condensation of **2.23** with MIDA under Dean-Stark conditions afforded **2.17** in 90% yield as a colorless, crystalline solid that was stable to storage under ambient air at room temperature for at least eight months.
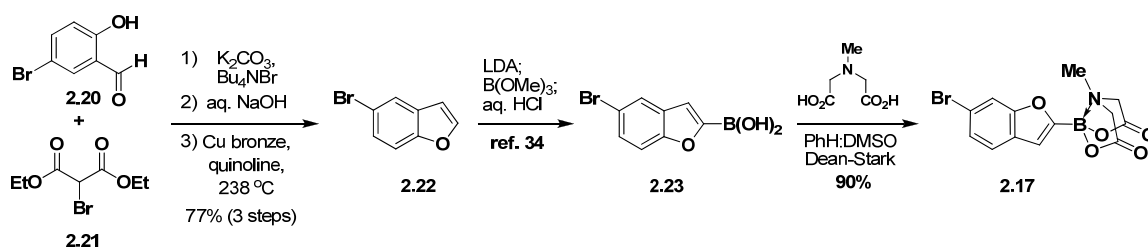
Scheme 2.7. Synthesis of building block **2.17**.

The synthesis of **2.18** was realized according to the route outlined in Scheme 2.8. The synthesis commenced with bromination of 3-methoxyphenol according to the literature procedure[23] that afforded a mixture of isomers[24] from which **2.24** was isolated in early runs via silica gel chromatography and later more efficiently via C_{18} reverse-phase chromatography. Protection of phenol **2.24** as the corresponding MOM ether **2.25**, followed by lithium-halogen exchange and trapping with iodine afforded aryl iodide **2.26**. A more direct route to **2.26** via iodination of 3-methoxyphenol was not successful. Bromination of **2.26** with *N*-bromosuccinimide (NBS) in the presence of catalytic SiO_2 afforded **2.27**. Selective Miyaura borylation[25] of **2.27** followed by hydrolysis of the resulting boronic ester under aqueous basic conditions provided boronic acid **2.28**. The related bis(pinacolato)diboron reagent was also effective in this transformation but hydrolysis of the pinacol ester to afford **2.28** was significantly more challenging. Silica gel chromatography of **2.28** proved problematic due to the partial instability of the boronic acid to SiO_2. However, this problem was obviated by carrying **2.28** forward in crude form into a subsequent Dean-Stark condensation with MIDA. The resulting product was readily purified by silica gel chromatography to afford bifunctional building **2.18** as a colorless, crystalline solid. Concurrently, the synthesis of bromide **2.19** was achieved by Professor Martin Burke via the route outlined in Scheme 2.9. Halide **2.19** is stable to storage at -4 °C for at least one year.
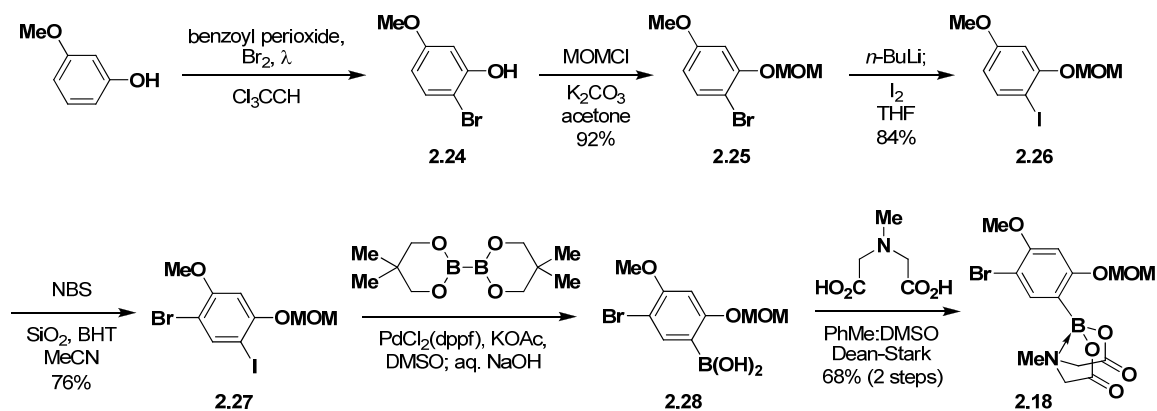
Scheme 2.8. Synthesis of building block **2.18**.
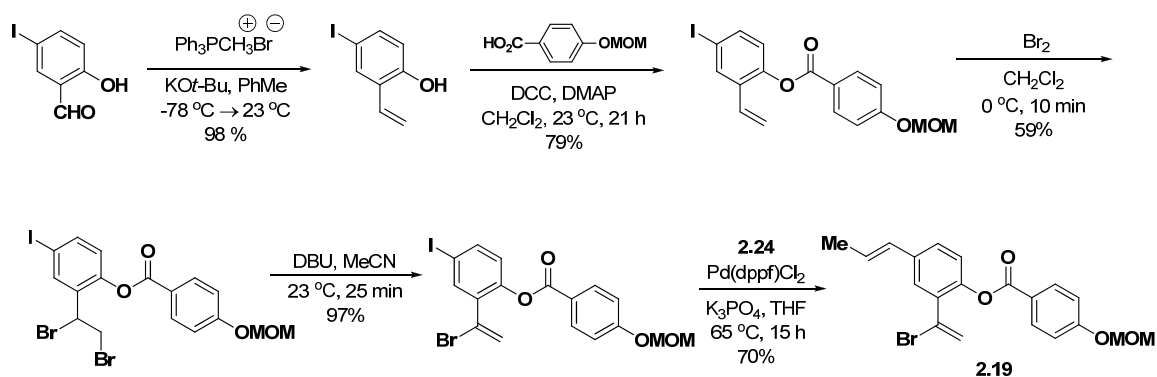
Scheme 2.9. Synthesis of halide **2.19**.

With building blocks **2.16**–**2.19** in hand, the synthesis of ratanhine commenced with the selective SMC reaction between propenyl boronic acid **2.16** and haloboronate **2.17** under anhydrous conditions to afford boronate **2.29** (Scheme 2.10). Applying the standard aqueous NaOH deprotection conditions afforded boronic acid **2.30** in 93% yield and excellent purity which was then carried forward into an anhydrous SMC reaction with the electronically rich and sterically encumbered aryl bromide **2.18**. Focused screening of reaction conditions for this coupling indicated that high temperature (80 °C) and a prolonged reaction time (28 h) were ideal. Even under these relatively more forcing conditions the MIDA boronate functional group was found to be stable, allowing boronate **2.31** to be isolated in 73% yield. Treatment of **2.31** with aqueous NaOH under the standard conditions afforded boronic **2.32**. However, boronic acid **2.32** proved to be especially unstable to isolation and decomposed immediately if concentrated *in vacuo*

38

from an acetonitrile solution at temperatures greater than 30 °C. Alternatively, the boronic acid was isolated free of solvent in 99% yield by performing at < 30 °C cycles of coevaporation with toluene, then acetonitrile, and finally dichloromethane. Storage of **2.32**, and to a lesser degree **2.30**, was found to be problematic, but could be conveniently avoided by generating **2.32** and **2.30** from the corresponding MIDA boronates immediately prior to use. A SMC reaction between **2.32** and **2.19** proceeded to only 60% conversion of the halide when 2% Pd loading was used due to significant deboronation of **2.32** as a side reaction. Alternatively, when the Pd loading was increased to 4% full conversion of the halide and an 81% isolated yield of **2.33** was obtained.

Treatment of **2.33** with concentrated aqueous hydrochloric acid in methanol at 65 °C for 1 hour followed by C_{18} HPLC purification afforded the natural product **2.15** as an iridescent oil in 41% yield. The modest yield realized in the deprotection of **2.33** is consistent with the observation by HPLC of a considerable quantity of an unknown byproduct. Performing the deprotection step at room temperature instead of 65 °C led to a slower reaction rate but did not change the ratio of product to byproduct. Additionally, no improvement in the yield was found when the deprotection was performed with anhydrous HCl, camphorsulfonic acid (CSA), pyridinium *p*-toluenesulfonic acid (PPTS), trifluoroacetic acid (TFA), or trimethylsilyl iodide. Additionally, **2.15** was discovered to be unstable to chromatography with SiO_2 or Florisil. At this point a lack of material prevented any further attempts at improving the yield of **2.33** to **2.15**. The spectral properties of **2.15** as analyzed by ^{1}H NMR, ^{13}C NMR, HRMS, and IR were in agreement with the literature characterization for ratanhine, confirming the original structure proposed by Arnone and coworkers,[19] and thus completing the first total synthesis of this natural product. More importantly, this synthesis represents, to the best of our knowledge, the first synthesis of a small molecule natural product in which only a single type of reaction is used to unite a pre-assembled collection of bifunctional building blocks. The inherent efficiency and flexibility of this approach has important implications for potential automation of small molecule synthesis.
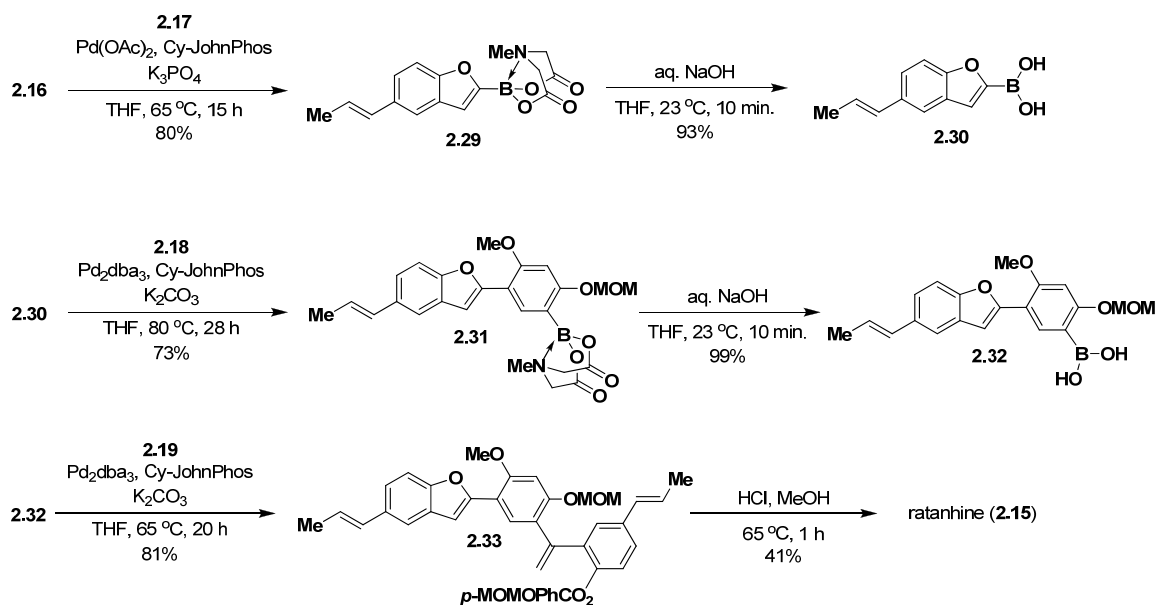
Scheme 2.10. The synthesis of the neolignan natural product ratanhine was accomplished by employing an iterative cycle of SMC reactions to unit a collection of four building blocks.

2-7 MULTI-GRAM SCALE APPLICATION OF ICC WITH MIDA BORONATES

MIDA boronates appear well suited to large scale synthetic applications due to the numerous favorable properties of these compounds. Unlike boronic acids which readily dehydrate to form waxy oligomeric boroxines,[26] MIDA boronates are monomeric and therefore allow precise control of the stoichiometry of a reaction. MIDA boronates in general are highly crystalline solids, regardless of the organic group appended to the MIDA boronate functional group.[27] Although not routinely practiced in our early development of the MIDA boronate platform, we predicted that this property should allow MIDA boronates to be purified on a multi-gram scale simply via recrystallization, and further, should simplify their handling. Additionally, the stability of MIDA boronates to storage under ambient atmosphere at room temperature should facilitate the storage and transport of MIDA boronates on a multi-gram to kilo-gram scale.

To test the efficiency of each step in the ICC process upon scale-up, a complexation step, a selective SMC step, and a deprotection step were performed on a multi-gram scale (Scheme 2.11). First, 4-bromophenylboronic acid (**2.11a**, 25.0 g) was exposed to MIDA under Dean-Stark dehydration conditions (step A). Toluene was used in place of benzene to mitigate concerns with the toxicity of the solvent. Additionally, the

40

amount of DMSO used in the reaction was greatly reduced from the precedent ratios and thus allowed the product to be directly crystallized from the crude reaction solution to afford 4-bromophenyl MIDA boronate (**2.12a**) as an analytically pure material in 94% yield.[28] By avoiding SiO_2 purification, this procedure represents a process by which very large amounts of a MIDA boronate can be synthesized from the corresponding boronic acid.[29] The bifunctional building block (25.0 g) was then engaged in an anhydrous SMC reaction with *p*-tolylboronic acid where the experiment was set up and executed with the avoidance of glove box manipulations (step B). The crude product was purified by aqueous workup followed by recrystallization from acetone:Et_2O to provide MIDA boronate **2.13a** in 77% yield. This product was then treated with aqueous NaOH following the standard procedure which, after simple partitioning of the aqueous and organic phases, afforded 4-(*p*-tolyl)-phenylboronic acid (**2.14a**) in 94% yield and in good purity[30] (step C). These experiments indicate that all of the steps of an ICC sequence are amenable to multi-gram scale synthesis. All purifications were achieved through recrystallization or simple aqueous extraction, only standard manipulations following Schlenk technique were used, and no physical or chemical properties were observed that would indicate that these reactions could not be scaled further.
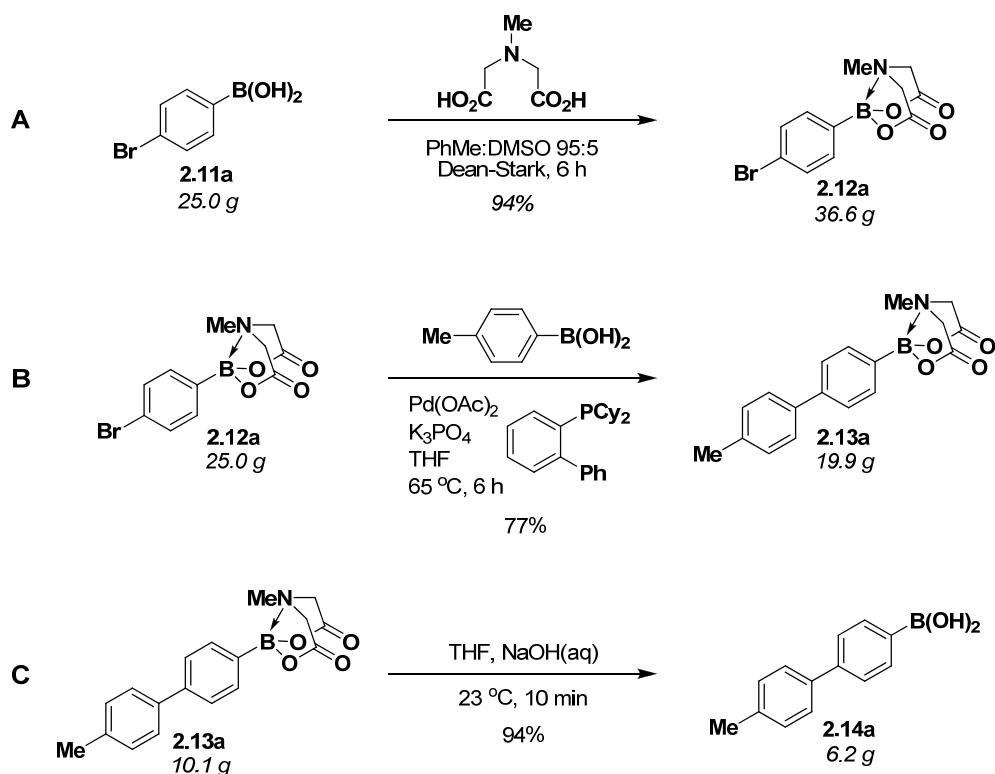
Scheme 2.11. Each step of the ICC cycle was evaluated in a multi-gram scale experiment. In all cases it was determined that the scale of the reaction does not impact the outcome of the step. Further, purification procedures were developed which avoided the use of SiO$_2$ chromatography to allow the efficient purification of large amounts of material.

To further enable the development and use of MIDA boronates, we developed an improved synthesis of MIDA to provide practical access to this material in mulit-gram to kilo-gram quantities at a low cost. The original procedure as practiced in our laboratories was later improved upon with contributions from Steve Ballmer, Brice Uno, and Jenna Klubnick. Specifically, the optimized route to MIDA was based on methylation of the commodity chemical iminodiacetic acid using Eschweiler-Clarke conditions (formaldehyde/formic acid) (Scheme 2.12).[31] Tens of thousands of metric tons of iminodiacetic acid are produced each year as a starting material for herbicides, surfactants, and environmental chelating reagents,[32] thus this starting material is very inexpensive. Additionally, all of the components of this reaction, including the MIDA ligand, are environmentally benign.[33] From a technical standpoint the reaction is very efficient. The reaction is complete within two hours and is run at a very high concentration (3 M). The product is isolated and purified simply by diluting the aqueous

reaction solution with approximately six volume equivalents of acetone and filtering the resulting mixture. It was discovered that a colorless product is reliably obtained if the *formalin* is added to the reaction solution rather than if the formic acid is added to the reaction solution. Further, the highest quality material is obtained if the isolated solids are dried in a vacuum oven at 110 ºC overnight. This route has been performed on a kilogram scale to provide MIDA at a cost, including all chemicals and solvents, of $0.05/g to $0.10/g. It has been estimated by commercial suppliers that the cost of MIDA could be as low as $0.017/g if synthesized on a kilo-ton scale.
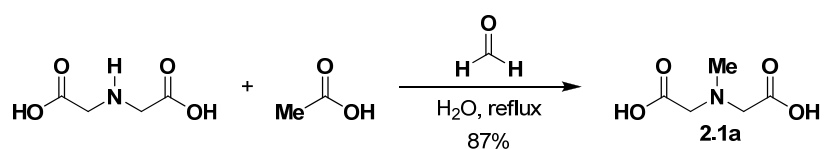
Scheme 2.12. MIDA can be accessed on a large scale and at a low cost from the commodity chemical iminodiacetic acid. All components of this reaction are environmentally benign and the process is fast and technically simple.

2-8 AN ACID-CLEAVED LIGAND THAT ATTENUATES THE REACTIVITY OF BORONIC ACIDS UNDER SMC CONDITIONS

During the development of the ICC platform a triol-based ligand with distinctly different properties from MIDA was discovered to effectively attenuate the reactivity of a boronic acid. Targeting a boronate hybridized through a B→O interaction rather than a B→N interaction, boronate **2.3j** was synthesized in two steps from commercially available *cis-cis*-1,3,5-cyclohexanetriol dihydrate as shown in Scheme 2.13. The triol was mixed with boronic acid **2.2** and sodium hydroxide to afford sodium borate **2.34**,[34] which was then alkylated with MeI to afford **2.3j**. Interestingly, borate **2.34** participated in a SMC reaction with *p*-bromoacetophenone *without added base* to generate a significant amount of the biaryl product,[35] a finding later mirrored by methodology reported by Miyaura and co-workers.[36] Boronate **2.3j** was found to be stable to Florisil but not to SiO_2 chromatography. Also, **2.3j** was fully converted to boronic acid **2.2** upon mixing with one equivalent acetic acid in $MeOH:H_2O$ (2:1) at room temperature for 35 minutes. In a competition experiment similar to that of Table 2.1, one equivalent of boronate **2.3j** and one equivalent of boronic acid **2.4** were allowed to react with a limiting quantity of

p-bromobenzaldehyde (**2.5**) under anhydrous SMC conditions (Scheme 2.14). In this experiment a 101:1.0 ratio of biaryls **2.6** and **2.7** was observed, consistent with strong preferential reactivity with the sp²-hybridized boronic acid **2.4**. Combined with the discovery that **2.3j** can be converted to **2.2** under mild acidic conditions, the high selectivity found in experiment suggests that this ligand or its derivatives could serve as a complementary protecting group to MIDA. However, **2.3i** was more difficult to synthesize and isolate than **2.3a** and further studies on **2.3j** were not pursued.
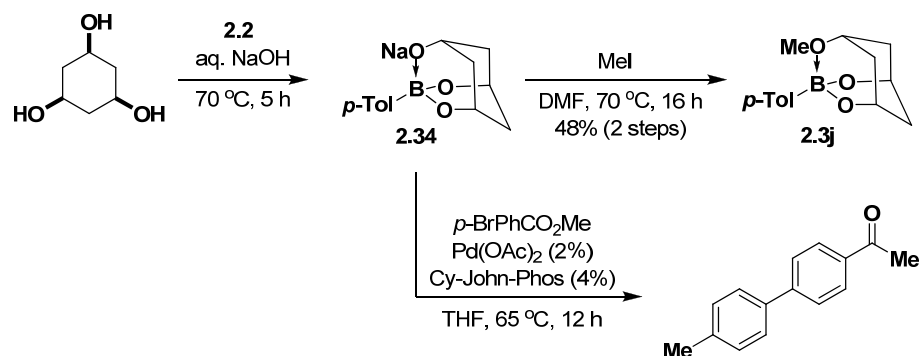
Scheme 2.13. Synthesis of a boronate that is hybridized through a B→O interaction rather than a B→N interaction.
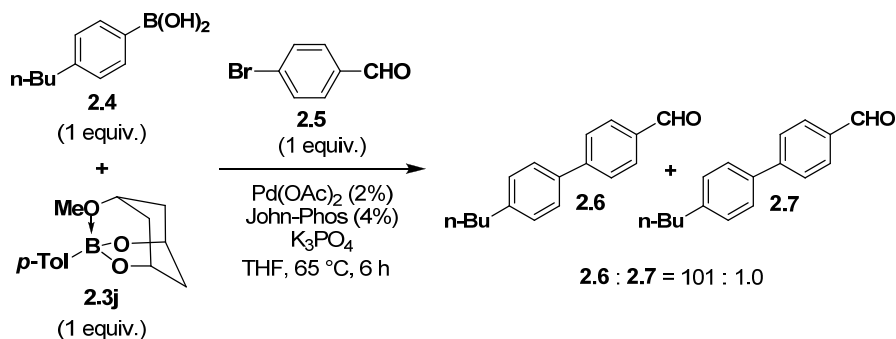
Scheme 2.14. In a competition experiment between **2.4** and **2.3j**, boronate **2.3j** was found to be substantially less reactive than boronic acid **2.4**. The product ratio of **2.6** : **2.7** was determined by HPLC (average of three runs).

2-9 SUMMARY

In summary, the realization of an iterative cross-coupling strategy based on the Suzuki-Miyaura cross-coupling reaction required the discovery of a ligand with the capacity to reversibly attenuate the reactivity of boronic acids. *N*-methyliminodiacetic acid (MIDA) was discovered to be such a ligand, transforming boronic acids into MIDA boronate esters which are inert to Suzuki-Miyaura cross-coupling under anhydrous conditions. It was found that the boronic acid can be regenerated under very mild conditions by exposing the MIDA boronate functional group to mild aqueous base at room temperature. The favorable properties of MIDA boronates were found to be general across aryl, heteroaryl, alkenyl and alkyl substrates. These properties include high crystallinity, and stability to both SiO_2 chromatography and to storage under ambient atmosphere at room temperature. The applicability of ICC to the synthesis of natural products was confirmed through in the first total synthesis of ratanhine. Additional studies have indicated that the MIDA boronate methodology, while initially developed on a small laboratory scale, is applicable on a multi-gram scale. Access to large quantities of MIDA at low cost was achieved through the optimized methylation of the commodity chemical iminodiacetic acid.

2-10 REFERENCES

[1] Mancilla, T.; Contreras, R.; Wrackmeyer, B. *J. Organomet. Chem.* **1986**, *307*, 1-6.

[2] For a review of boronate esters see: Höpfl, H. *J. Organomet. Chem.* **1999**, *581*, 129-149.

[3] (a) Mancilla, T.; Carrillo, L.; Reducindo, M. D. P. *Polyhedron* **1996**, *15*, 3777-3785. (b) Mancilla, T.; Alarcón, M. L.; Carrillo, L. *Heteroatom Chem.* **1994**, *5*, 455-462. (c) Mancilla, T.; Romo, M. A. C.; Delgado, L. A. *Polyhedron* **2007**, *26*, 1023-1028. (d) Mancilla, T.; Hopfl, H.; Bravo, G.; Carrillo, L. *Main Group Metal Chem.* **1997**, *20*, 31-36. (e) Beltrán, H. I.; Alas, S. J.; Santillan, R.; Farfán, N. *Can. J. Chem.* **2002**, *80*, 801-812. (f) Beltrán, H. I.; Zamudio-Rivera, L. S.; Mancilla, T.; Santillan, R.; Farfán,

N. *J. Organomet. Chem.* **2002**, *657*, 194-204. (g) Mancilla, T.; Zamudio-Rivera, L. S.; Beltrán, H. I.; Santillan, R.; Farfán, N. *ARKIVOC* **2005**, 366-376.

4 (a) Dubé, E. C.; Mukhopadhyay, S.; Bonitatebus, P. J.; Staples, R. J.; Armstrong, W. H. *Inorg. Chem.* **2005**, *44*, 5161-5175. (b) Rojas-González, P. X.; Lazarte-Choquesillo, D.; González-Pérez, J. M.; Ruíz-García, S. A.; Carballo, R.; Castiñeiras, A.; Niclós-Gutiérrez, J. *Polyhedron* **2003**, *22*, 1027-1037.

5 (a) Farfán, N.; Joseph-Nathan, P.; Chiquete, L. M.; Contreras, R. C. *J. Organomet. Chem.* **1988**, *348*, 149-156. (b) Mancilla, T.; Castillo, D.; Carrillo, L.; Farfán, N. *Heteroatom. Chem.* **1999**, *10*, 133-139. (c) Abreu, A.; Alas, S. J.; Beltrán, H. I.; Santillan, R.; Farfán, N. *J. Organomet. Chem.* **2006**, *691*, 337-348.

6 The stability of MIDA boronates to anhydrous base was determined in preliminary studies; see Table 2.3.

7 Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685-4696.

8 Contreras, R.; García, C.; Mancilla, T.; Wrackmeyer, B. *J. Organomet. Chem.* **1983**, *246*, 213-217.

9 These results also served as the starting point for my colleague Suk Joong Lee to study the synthesis of polyenes through ICC with MIDA boronates. He was later assisted in this work by Kaitlyn Gray and was supported with starting material by James Paek. See reference 10.

10 Lee, S. J.; Gray, K. C.; Paek, J. S.; Burke, M. D. *J. Am. Chem. Soc.* **2008**, *130*, 466-468.

11 Boronates **2.8a** and **2.8b** were used instead of **2.3a** and **2.3f** because this study was performed later in the context chapter 3. The results are included in chapter 2 for continuity.

12 As defined by Höpfl (see reference 2):

$$\text{tetrahedral character (THC)} = \left[1 - \frac{\sum_{n=1-6} \left| 109.5 - \theta_n \right|^\circ}{90^\circ} \right] \times 100$$

13 Psarras, T.G.; Zimmerman, H.K.; Rasiel, Y.; Weidman, H. *Liebigs Ann. Chem.* **1962**, *655*, 48-54.

[14] The results of these computational studies are unpublished.

[15] Plumley, J. A.; Evanseck, J. D. *J. Phys. Chem. A* **2007**, *111*, 13472-13483.

[16] The E(B-O) in NH_3 complexes of R_2B-OR is estimated to be 11 kcal/mol weaker than that in R_2B-OR: Matteson, D. S. *Stereodirected Synthesis with Organoboranes*; Springer: Berlin, 1995; pp 1-20.

[17] As judged by ^{1}H-NMR; Klubnick, J. A. *Unpublished data.*

[18] (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457-2483. (b) Miyaura, N. *Top. Cur. Chem.* **2002**, *219*, 11-59.

[19] Arnone, A.; Dimodugno, V.; Nasini, G.; Depava, O. *Gazz. Chim. Ital.* **1990**, *120*, 397-401.

[20] Tyrrell, E.; Brookes, P. *Synthesis* **2003**, *4*, 469-483.

[21] Plé, P. A.; Green, T. P.; Hennequin, L. F.; Curwen, J.; Fennell, M.; Allen, J.; Labert-van der Brempt, C.; Costello, G. *J. Med. Chem.* **2004**, *47*, 871-887.

[22] Friedman, M. R.; Toyne, K. J.; Goodby, J. W.; Hird, M. *J. Mater. Chem.* **2001**, *11*, 2759-2772.

[23] Albert, J. S.; Aharony, D.; Andisik, D.; Barthlow, H.; Bernstein, P. R.; Bialecki, R. A.; Dedinas, R.; Dembofsky, B. T.; Hill, D.; Kirkland, K.; Koether, G. M.; Kosmider, B. J.; Ohnmacht, C.; Palmer, W.; Potts, W.; Rumsey, W.; Shen, L.; Shenvi, A.; Sherwood, S.; Warwick, P. J.; Russell, K. *J. Med. Chem.* **2002**, *45*, 3972-3983.

[24] Side-products of the reaction are:
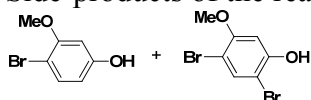
[25] Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508-7510.

[26] Hall, D.G. *Boronic Acids*, Wiley-VCH, Germany, **2005**, pg 15.

[27] An exception to this general trend is the ethenylstannane MIDA boronate shown below. This compound is soluble even in hexanes, rendering crystallization difficult, and when crystals are obtained they are small and amorphous. However, *n*-dodecyl MIDA boronate which is similarly non-polar can be readily isolated via crystallization:

cannot be isolated via crystallization   *can* be isolated via crystallization

[28] This modification serves to prolong the reaction time since only a small portion of the total quantity of MIDA is dissolved at any point during the reaction. Although the reduction in DMSO is greatly simplifying, this approach is not recommended for sensitive substrates such as 2-heterocyclic boronic acids since the extended reaction times result in decomposition of the boronic acid.

[29] This and related studies helped enable the commercialization of a large number of MIDA boronates: http://www.aldrich.com/MIDA

[30] The boronic acid was judged by ^{1}H-NMR to be 82-87%. Checkers of the *Org. Syn.* procedure found 91-93% purity of the boronic acid.

[31] Our synthesis is based on modifications to the reported literature procedure: Chase, B. H.; Downes, A. M. *J. Chem. Soc.* **1953**, 3874-3877.

[32] Yangong, Z. *China Chemical Reporter* **2005**, *16*, 16.

[33] Iminodiacetic acid and MIDA have been found to be biodegradable: Warren, C. B.; Malec, E. J. *Science* **1972**, *176*, 277-279.

[34] Reany, O.; Blair, S.; Kataky, R.; Parker, D. *J. Chem. Soc., Perkin Trans.* **2000**, *2*, 623-630.

[35] The yield of this reaction was not determined. This result has been repeated by David Knapp in related couplings (unpublished results).

[36] Yamamoto, Y.; Takizawa, M.; Yu, X.-Q.; Miyaura, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 928-931.

CHAPTER 2: EXPERIMENTAL SECTION

Materials. Commercial reagents were purchased from Sigma-Aldrich, Fisher Scientific, Alfa Aesar, Lancaster Synthesis, or Frontier Scientific, and were used without further purification unless otherwise noted. N-Bromosuccinimide and 4-butylphenylboronic acid were recrystallized from hot water prior to use. Solvents were purified via passage through packed columns as described by Pangborn and coworkers[1] (THF, Et_2O, CH_3CN, CH_2Cl_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. Triethylamine, diisopropylamine, diethylamine, pyridine, 2,6-lutidine, and ethanol were freshly distilled under an atmosphere of nitrogen from CaH_2. The following compounds were prepared according to literature precedent: N-isopropyliminodiacetic acid,[2] (*E*)-3-bromostyrenylboronic acid,[3] 5-bromo-2-benzofuranylboronic acid,[4] 2-bromo-5-methoxyphenol,[5] 4-(methoxymethoxy)benzoic acid.[6] Building block **2.19** was prepared by Martin Burke.[7] The multi-gram scale synthesis of **2.12a**, **2.13a**, and **2.14a** was performed by Steven Ballmer.[8] Solutions of *n*-butyllithium were titrated according to the method of Hoye and coworkers.[9]

General Experimental Procedures. Suzuki-Miyaura cross-coupling reactions were typically performed under an atmosphere of argon in oven- or flame-dried I-Chem or Wheaton vials sealed with PTFE-lined plastic caps. All other reactions were performed in oven- or flame-dried round-bottom or modified Schlenk flasks fitted with rubber septa under a positive pressure of argon or nitrogen unless otherwise indicated. Organic solutions were concentrated via rotary evaporation under reduced pressure. 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), a glass chamber containing iodine, and/or a solution of $KMnO_4$, an acidic solution of p-anisaldehyde, or a solution of ceric

ammonium molybdate (CAM) followed by brief heating using a Varitemp heat gun. Flash column chromatography was performed as described by Still and coworkers[10] using EM Merck silica gel 60 (230-400 mesh).

Structural analysis. ^{1}H NMR spectra were recorded at 23 °C on one of the following instruments: Varian Unity 400, Varian Unity 500 or Varian Unity Inova 500NB spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane and referenced to residual protium in the NMR solvent (CHCl$_3$, δ = 7.26; CD$_2$HCN, δ = 1.93, center line; acetone-d$_6$ δ = 2.05, 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. ^{13}C NMR spectra were recorded at 23 °C on a Varian Unity 400 or Varian Unity 500 spectrometer. Chemical shifts (δ) are reported in ppm downfield from tetramethylsilane and referenced to carbon resonances in the NMR solvent (CDCl$_3$, δ = 77.0, center line; **CD$_3$CN**, δ = 1.30, center line, acetone-d$_6$ δ = 29.80, center line) or to added tetramethylsilane (δ = 0.00). Carbons bearing boron substituents were not observed (quadrupolar relaxation). ^{11}B NMR were recorded using a General Electric GN300WB or Varian Unity 400 spectrometer and referenced to an external standard of (BF$_3$•Et$_2$O). High resolution mass spectra (HRMS) were performed by Furong Sun and Dr. Steve Mullen at the University of Illinois School of Chemical Sciences Mass Spectrometry Laboratory. Infrared spectra were collected from a thin film on NaCl plates on a Perkin-Elmer Spectrum BX FT-IR spectrometer. Absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}). X-ray crystallographic analyses of **2.8a** and **2.8b** were carried out by Dr. Scott Wilson at the University of Illinois George L. Clark X-Ray facility.

Synthesis of boronates (Scheme 2.3)
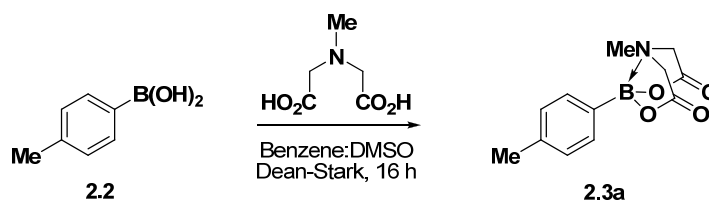
Boronate ester 2.3a

A 500 mL flask was charged with *p*-tolylboronic acid (3.00 g, 22.1 mmol, 1 equiv.), N-methyliminodiacetic acid (3.25 g, 22.1 mmol, 1 equiv.), benzene (360 mL) and DMSO (40 mL). The flask was fitted with a Dean-Stark trap and a reflux condenser, and the mixture was refluxed with stirring for 16 h followed by concentration *in vacuo*. The resulting crude product was adsorbed onto Florisil gel from a MeCN solution. The resulting powder was dry-loaded on top of a silica gel column slurry-packed with EtOAc. The product was eluted using a gradient (EtOAc → EtOAc:MeCN 2:1) to yield boronate ester **2.3a** as a colorless, crystalline solid (5.05 g, 93%).

TLC (EtOAc)

$R_f = 0.40$, stained by $KMnO_4$

^{1}H-NMR (500 MHz, CD_3CN)

δ 7.37 (d, *J* = 8 Hz, 2H), 7.20 (d, *J* = 8 Hz, 2H), 4.05 (d, *J* = 17 Hz, 2H), 3.87 (d, *J* = 17 Hz, 2H), 2.47 (s, 3H), 2.33 (s, 3H).

^{13}C-NMR (125 MHz, CD_3CN)

δ 169.6, 140.0, 133.4, 129.6, 62.7, 48.4, 21.4.

^{11}B-NMR (100 MHz, CD_3CN)

δ 12.2

HRMS (EI+)

Calculated for $C_{12}H_{14}O_4NB$ (M)[+]:   247.1016
Found: 247.1014

IR (thin film, cm^{-1})

      3046, 3023, 3003, 2958, 2917, 1746, 1612, 1454, 1424, 1397, 1335, 1257, 1243, 1188, 1150, 1038, 1012, 993, 961, 867, 807, 786, 650, 638.

The following data are consistent with the assignment of **2.3a** *as an sp^3-hybridized boronate ester.*

1. ^{1}H NMR: The diastereotopic methylene protons of **2.3a** appear as a well-resolved pair of doublets at δ 4.05 and 3.87 with a large geminal coupling constant of 17 Hz. This is consistent with literature precedent for related conformationally-rigid arylboronate ester complexes.[11] One such complex has been characterized unambiguously by single crystal X-ray diffraction analysis.[12]
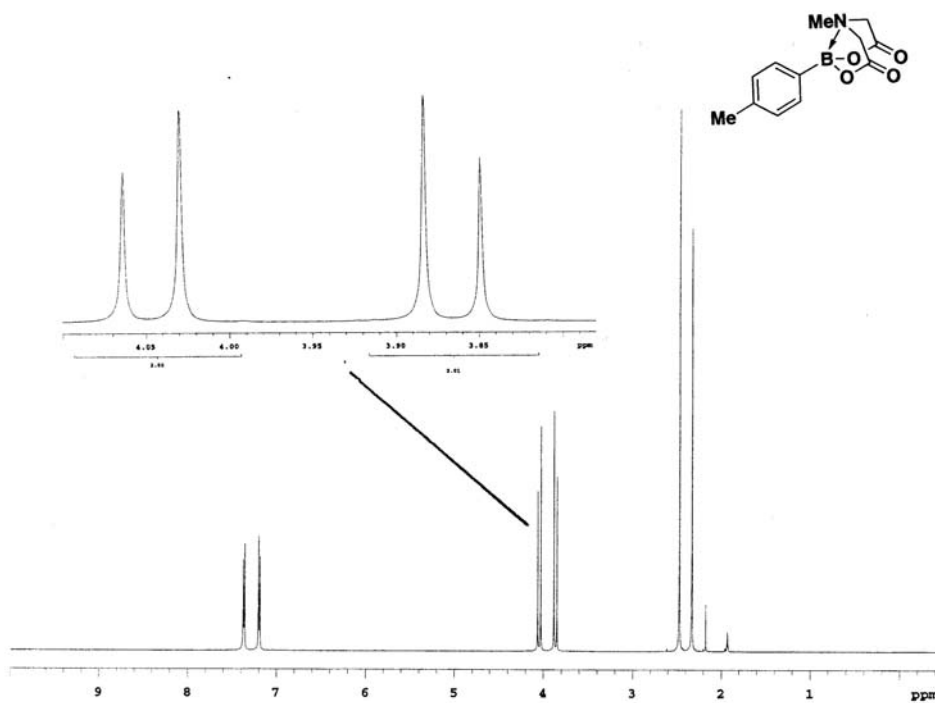
2. ^{11}B NMR: Boron NMR spectroscopy is a well-established method for probing the structure of boronic acids and boronate ester complexes.[13] The ^{11}B NMR spectra for *p*-tolyboronic acid and **2.3a** demonstrate chemical shifts of δ 29.6 and δ 12.2, respectively. These data are consistent with the assignment of **2.3a** as a pyramidalized boronate ester.

3. These same diagnostic ^{1}H and ^{11}B NMR signals are observed for the vinylic haloboronate ester **2.12e**. We have obtained an X-ray structure of this compound (Scheme 2.5) which confirmed unambiguously the sp^3-hybridization of the boron center.
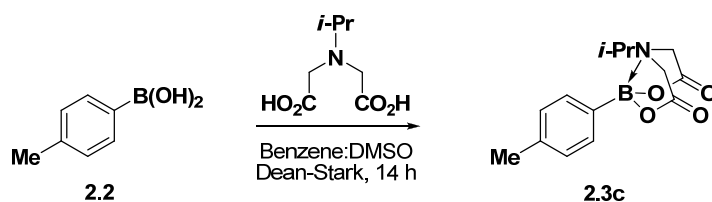
Boronate ester 2.3c

In an unoptimized procedure, a 250 mL roundbottom flask was charged with *p*-tolylboronic acid (7.36 mmol, 1.00 g), *N*-isopropyliminodiacetic acid (7.36 mmol, 1.29 g), benzene (150 mL) and DMSO (15 mL). The flask was fitted with a Dean-Stark trap and a reflux condenser, and the mixture was refluxed with stirring for 14 h and then concentrated *in vacuo*. Purification by flash chromatography (Et$_2$O → Et$_2$O:MeCN 1:2) yielded boronate ester **2.3c** as a colorless, crystalline solid (747 mg, 37%).

TLC (EtOAc)

　　R$_f$ = 0.36, stained by KMnO$_4$

^{1}H-NMR (500 MHz, CD$_3$CN)

　　δ 7.40 (d, *J* = 8 Hz, 2H), 7.19 (d, *J* = 8 Hz, 2H), 4.05 (d, *J* = 17 Hz, 2H), 3.81 (d, *J* = 17 Hz, 2H), 3.06 (sept, *J* = 6.5 Hz, 1H), 2.33 (s, 3H), 1.05 (d, *J* = 6.5 Hz, 6H).

^{13}C-NMR (125 MHz, CD$_3$CN)

　　δ 169.8, 139.9, 133.6, 129.5, 59.8, 57.2, 21.4, 17.2.

^{11}B-NMR (100 MHz, CD$_3$CN)

δ 11.96

HRMS (EI+)

Calculated for C$_{14}$H$_{18}$O$_4$NB (M)$^+$:   275.1329
Found: 275.1331

IR (thin film, cm^{-1})

3011, 2951, 1761, 1744, 1727, 1312, 1240, 1048, 1021, 982, 862, 808.
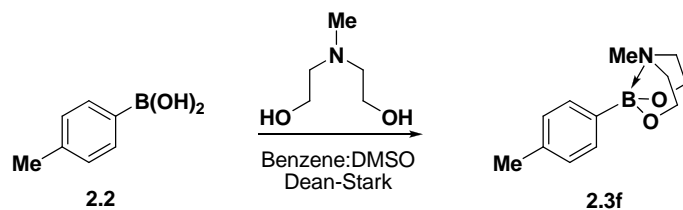
Boronate ester 2.3f

In an unoptimized procedure, a 100 mL roundbottom flask was charged with *p*-tolylboronic acid (3.68 mmol, 500 mg), *N*-methyldiethanolamine (3.68 mmol, 422 µL) and toluene (70 mL). The flask was fitted with a Dean-Stark trap and a reflux condenser, and the solution was refluxed with stirring for 8 h and then allowed to cool to 23 °C. CaCl$_2$ (app. 200 mg, a fine powder) and NaHCO$_3$ (app. 200 mg) were then added, and the resulting mixture was stirred for 15 min. and then was filtered.   The filtrate was concentrated *in vacuo* and residual solvent was removed via co-evaporation with CH$_2$Cl$_2$ to yield boronate ester **2.3f** as a colorless, crystalline solid (399 mg, 50%).

TLC

Compound is unstable to SiO$_2$

^{1}H NMR (500 MHz, CD$_3$CN)

δ 7.42 (d, *J* = 8 Hz, 2H), 7.07 (d, *J* = 8 Hz, 2H), 3.99 (ddd, *J* = 10, 8, 5 Hz, 2H), 3.93 (ddd, *J* = 10, 6, 4 Hz, 2H), 3.17 (ddd, *J* = 12, 5, 4 Hz, 2H), 2.93 (ddd, *J* = 12, 8, 6 Hz, 2H), 2.28 (s, 3H), 2.20 (s, 3H).

^{13}C NMR (125 MHz, CD$_3$CN)

δ 137.3, 134.3, 128.7, 62.9, 61.1, 48.0, 21.4.

^{11}B NMR (100 MHz, CD$_3$CN)

δ 12.7

HRMS (EI+)

Calculated for C$_{12}$H$_{18}$O$_2$NB (M)$^+$:   219.1431

Found: 219.1427

IR (thin film, cm^{-1})

2999, 2948, 2911, 2873, 2830, 1606, 1455, 1370, 1338, 1280, 1250, 1222, 1193, 1181, 1150, 1097, 1035, 994, 944, 808, 786, 735, 718.

Competition studies (Table 2.1)

Preparation of catalyst stock solution.

      In a glove box, to a vial equipped with a small stir bar and containing the 2-(di-*tert*-butylphosphino)biphenyl ligand was added a 0.02 M solution of Pd(OAc)$_2$ in THF in a volume sufficient to yield a 0.04 M solution with respect to the phosphine ligand. The vial was sealed with a PTFE-lined cap, removed from the glove box, and maintained at 65°C with stirring for 30 min.

Reaction setup

      In a glove box, a glass vial equipped with a small stir bar was charged with boronate ester **2.3** (0.06 mmol) and anhydrous K$_3$PO$_4$ as a finely ground powder (32 mg, 0.15 mmol).   To this vial was then added a 250 µL of a THF solution of 4-butylphenylboronic acid (**2.4**) (0.24 M, 0.06 mmol), 4-bromobenzaldehyde (**2.5**) (0.20 M, 0.05 mmol) and biphenyl (0.08 M, internal std. for HPLC analysis). Finally, to this same vial was added 50 uL of the catalyst stock solution described above. The vial was then sealed with a PTFE-lined cap, removed from the glove box, and maintained in a 65 °C oil bath with stirring for 12 h. The reaction solution was then allowed to cool to 23 ºC and filtered through a plug of silica gel, eluting with MeCN:THF 1:1. The filtrate was then analyzed by HPLC as described below.

Analysis

      The ratio of products **2.6** and **2.7** was determined using an HPLC system (Agilent Technologies) fitted with a Waters SunFire Prep C$_{18}$ 5µm column (10 x 250 mm, Lot No. 156-160331) with a flow rate of 4 mL/min and a gradient of MeCN:H$_2$O 5:95 → 95:5 over 23 min., with UV detection at 268 nm (4-bromobenzaldehyde, t_R = 14.66 min.; biphenyl, t_R = 21.80 min.) and 293 nm (**2.6**, t_R = 25.79 min.; **2.7**, t_R = 20.50 min.; it was determined that the absorption coefficients for **2.6** and **2.7** at 293 nm are identical within the limits of experimental error).

Table 2.1, Entry 1

The general procedure was followed using **2.3a** (0.06 mmol). The ratio of **2.6**:**2.7** was 24:1.0, average of 3 runs.

Table 2.1, Entry 2

The general procedure was followed using **2.2** (0.06 mmol). The ratio of **2.6**:**2.7** was 1.0:1.0, average of 3 runs.

Table 2.1, Entry 3

The general procedure was followed using **2.3c** (0.06 mmol). The ratio of **2.6**:**2.7** was 26:1.0, average of 3 runs.

Table 2.1, Entry 4

The general procedure was followed using **2.3d** (0.06 mmol). The ratio of **2.6**:**2.7** was 11:1.0, average of 3 runs.

Table 2.1, Entry 5

The general procedure was followed using **2.3f** (0.06 mmol). The ratio of **2.6**:**2.7** was 1.0:1.0, average of 3 runs.

Table 2.1, Entry 6

The general procedure was followed using **2.3h** (0.06 mmol). The ratio of **2.6**:**2.7** was 21:1.0, average of 3 runs.

Table 2.1, Entry 7

The general procedure was followed using **2.3i** (0.06 mmol). The ratio of **2.6**:**2.7** was 8.2:1.0, average of 3 runs.

Synthesis of haloboronate esters 2.12 (Scheme 2.5)
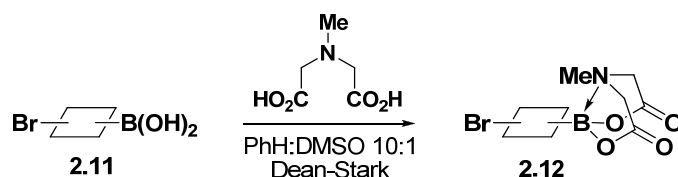
General procedure for the synthesis of haloboronate esters

A roundbottom flask equipped with a stir bar was charged with haloboronic acid (1 equiv.), *N*-methyliminodiacetic acid (1-1.5 equiv.), and benzene:DMSO (10:1). The flask was fitted with a Dean-Stark trap and a reflux condenser, and the mixture was refluxed with stirring for 12-18 hours. The reaction solution was allowed to cool to 23 $^{\circ}$C and the solvent was removed *in vacuo*. The resulting crude solid was absorbed onto Florisil gel from a MeCN solution. The resulting powder was dry-loaded on top of a silica gel column slurry-packed with Et$_2$O. The column was flushed with a copious volume of Et$_2$O; the product was then eluted with a mixture of Et$_2$O:MeCN. All products thus obtained were analytically pure, colorless, crystalline solids that were indefinitely bench stable at 23 $^{\circ}$C under air.
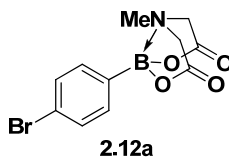
Boronate ester 2.12a

The general procedure was followed using 4-bromophenylboronic acid (1.00 g, 4.98 mmol, 1 equiv.), N-methyliminodiacetic acid (733 mg, 4.98 mmol), benzene (150 mL) and DMSO (15 mL). The mixture was refluxed for 12 h. The product was eluted using a gradient; Et$_2$O → Et$_2$O:CH$_3$CN 1:1. The title compound was isolated as an analytically pure, colorless, crystalline solid (1.53 g, 98%).

TLC (EtOAc)

$R_f = 0.36$, stained by $KMnO_4$

^{1}H-NMR (500 MHz, CD$_3$CN)

δ 7.53 (d, J = 8 Hz, 2H), 7.41 (d, J = 8 Hz, 2H), 4.07 (d, J = 17 Hz, 2H), 3.89 (d, J = 17 Hz, 2H), 2.50 (s, 3H).

^{13}C-NMR (125 MHz, CD$_3$CN)

δ 169.4, 135.5, 131.9, 124.4, 62.8, 48.5.

^{11}B NMR (100 MHz, CD$_3$CN)

δ 11.9

HRMS (EI+)

Calculated for C$_{11}$H$_{11}$O$_4$NBrB (M)$^+$: 310.9964

Found: 310.9967

Elemental Analysis

Calculated: C, 42.36   H, 3.55   N, 4.49   Br, 25.62

Found: C, 42.25   H, 3.50   N, 4.46   Br, 25.30

IR (thin film, cm^{-1})

3006, 2961, 1743, 1582, 1559, 1458, 1447, 1384, 1342, 1181, 1153, 1040, 1018, 997, 981, 865, 811.
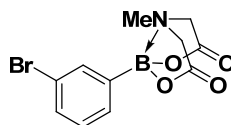
2.12b

MIDA boronate 2.12b

The general procedure was followed using 3-bromophenylboronic acid (2.00 g, 9.96 mmol), N-methyliminodiacetic acid (1.47 g, 9.96 mmol), benzene (300 mL) and DMSO (30 mL). The mixture was refluxed for 18 h. The product was eluted with

Et$_2$O:CH$_3$CN 1:1. The title compound was isolated as an analytically pure, colorless, crystalline solid (2.89 g, 93%).

TLC (EtOAc)

R_f = 0.57, stained by KMnO$_4$

^{1}H-NMR (500 MHz, CD$_3$CN)

δ 7.63 (m, 1H), 7.56 (m, 1H), 7.46 (m, 1H), 7.30 (m, 1H), 4.07 (d, J = 17 Hz, 2H), 3.90 (d, J = 17 Hz, 2H), 2.52 (s, 3H).

^{13}C-NMR (125 MHz, CD$_3$CN)

δ 169.3, 136.1, 133.1, 132.3, 131.0, 123.3, 62.9, 48.6.

^{11}B-NMR (100 MHz, CD$_3$CN)

δ 11.5

HRMS (EI+)

Calculated for C$_{11}$H$_{11}$O$_4$NBrB (M)$^+$: 310.9964
Found: 310.9966

Elemental Analysis

Calculated: C, 42.36   H, 3.55   N, 4.49
Found: C, 42.83,   H, 3.42   N, 4.51

IR (thin film, cm^{-1})

3012, 2959, 1766, 1468, 1454, 1395, 1335, 1286, 1235, 1211, 1096, 1075, 1038, 1001, 892, 860, 787, 693.
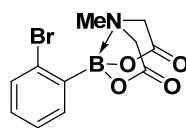
2.12c

MIDA boronate 2.12c

The general procedure was followed using 2-bromophenylboronic acid (2.00 g, 9.96 mmol), N-methyliminodiacetic acid (1.47 g, 9.96 mmol), benzene (300 mL) and DMSO (30 mL). The mixture was refluxed for 13 h. The product was eluted with Et$_2$O:MeCN 1:1. The title compound was isolated as an analytically pure, colorless, crystalline solid (3.01 g, 97%).

TLC (EtOAc)

R_f = 0.44, stained by KMnO$_4$

^{1}H-NMR (500 MHz, CD$_3$CN)

δ 7.66 (dd, *J* = 7.5, 2 Hz, 1H), 7.60 (dd, *J* = 8, 1 Hz, 1H), 7.38 (app dt, *J* = 7.5, 1 Hz, 1H), 7.29 (app dt, *J* = 8, 2 Hz, 1H), 4.13 (d, *J* = 17 Hz, 2H), 4.02 (d, *J* = 17 Hz, 2H), 2.70 (s, 3H).

^{13}C-NMR (125 MHz, CD$_3$CN)

δ 169.6, 137.4, 134.6, 132.4, 128.7, 128.0, 65.2, 49.5.

^{11}B-NMR (100 MHz, CD$_3$CN)

δ 12.1

HRMS (EI+)

Calculated for C$_{11}$H$_{11}$O$_4$NBrB (M)$^+$:310.9964

Found: 310.9967

Elemental Analysis

Calculated: C, 42.36   H, 3.55   N, 4.49   Br, 25.62

Found: C, 42.41   H, 3.53   N, 4.50   Br, 25.21

IR (thin film, cm^{-1})

3011, 2963, 1767, 1709, 1485, 1556, 1453, 1418, 1338, 1299, 1276, 1198, 1119, 1060, 1036, 1002, 879, 858, 759.
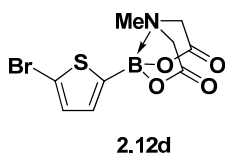
2.12d

MIDA boronate 2.12d

The general procedure was followed using 4-bromothiophene-2-boronic acid (281 mg, 1.36 mmol), N-methyliminodiacetic acid (240 mg, 1.63 mmol), benzene (50 mL) and DMSO (5 mL). The mixture was refluxed for 13 h. The product was eluted with Et$_2$O:MeCN 3:1. The title compound was isolated as an analytically pure, colorless, crystalline solid (429 mg, 99%).

TLC (Et$_2$O:MeCN 3:1)

R$_f$ = 0.56, stained by KMnO$_4$

^{1}H-NMR (500 MHz, CD$_3$CN)

δ 7.17 (d, J = 3.5 Hz, 1H), 7.06 (d, J = 3.5 Hz, 1H), 4.06 (d, J = 17 Hz, 2H), 3.90 (d, J = 17 Hz, 2H), 2.64 (s, 3H).

^{13}C-NMR (100 MHz, CD$_3$CN)

δ 168.9, 135.1, 132.8, 116.2, 62.5, 48.4

^{11}B-NMR (100 MHz, CD$_3$CN)

δ 10.6

HRMS (EI+)

Calculated for $C_9H_9O_4NBrBS$ (M)$^+$: 316.9529

Found: 316.9526

Elemental Analysis

Calculated: C, 34.00　H, 2.85　N, 4.41

Found:　　C, 34.12　H, 2.45　N, 4.34

IR (thin film, cm^{-1})

3003, 1771, 1519, 1452, 1422, 1337, 1293, 1284, 1210, 1166, 1031, 981, 966, 870, 824, 790.
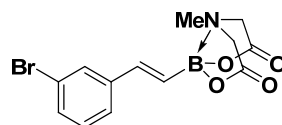
2.12e

MIDA boronate 2.12e

The general procedure was followed 2-(3-bromophenyl)ethenylboronic acid (227 mg, 1.0 mmol), N-methyliminodiacetic acid (147 mg, 1.0 mmol), benzene (50 mL) and DMSO (5 mL). The mixture was refluxed for 11 h. The product was eluted with Et$_2$O:MeCN 5:1. The title compound was isolated as an analytically pure, colorless, crystalline solid (334 mg, 99%).

TLC (EtOAc)

R_f = 0.27, stained by KMnO$_4$

^{1}H-NMR (500 MHz, CD$_3$CN)

δ 7.70 (m, 1H), 7.47 (m, 1H), 7.42 (m, 1H), 7.26 (m, 1H), 6.89 (d, J = 18 Hz, 1H), 6.32 (d, J = 18 Hz, 1H), 3.99 (d, J = 17 Hz, 2H), 3.83 (d, J = 17 Hz, 2H), 2.80 (s, 3H).

^{13}C-NMR (125 MHz, CD$_3$CN)

δ 169.3, 141.6, 141.5, 131.6, 131.4, 130.2, 126.6, 123.2, 62.4, 47.7.

^{11}B-NMR (100 MHz, CD$_3$CN)

δ 11.3

HRMS (EI+)

Calculated for C$_{13}$H$_{13}$O$_4$NBrB (M)$^+$:337.0121

Found: 337.0123

Elemental Analysis

Calculated: C, 46.20   H, 3.88   N, 4.14

Found: C, 46.22   H, 3.51   N, 4.12

IR (thin film, cm^{-1})

3010, 2958, 1759, 1627, 1588, 1560, 1469, 1424, 1337, 1291, 1233, 1198, 1154, 1114, 1088, 1071, 1029, 994, 956, 875, 826, 778, 729, 679, 661, 593.
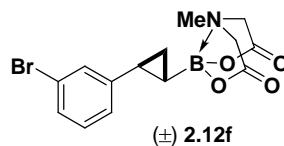
(±) **2.12f**

MIDA boronate 2.12f

The general procedure was followed using 2-(3-bromophenyl)cyclopropylboronic acid (**2.11f**, see below for the preparation of this material) (316 mg, 1.31 mmol), N-methyliminodiacetic acid (232 mg, 1.58 mmol), benzene (50 mL) and DMSO (5 mL). The mixture was refluxed for 6 h. The product was eluted with MeCN:Et$_2$O 5:1. The title compound was isolated as an analytically pure, colorless solid (408 mg, 88%).

TLC (EtOAc)

R$_f$ = 0.27, stained by KMnO$_4$

^{1}H-NMR (500 MHz, CD$_3$CN)

δ 7.28-7.26 (m, 2H), 7.15 (m, 1H), 7.09 (m, 1H), 3.96 (app dd, J = 17, 3 Hz, 2H), 3.84 (app dd, J = 17, 9.5 Hz, 2H), 1.77 (ddd, J = 8, 5.5, 5 Hz, 1H), 0.96-0.87 (m, 2H), 0.19 (ddd, J = 10, 7, 5.5 Hz, 1H).

^{13}C-NMR (125 MHz, CD$_3$CN)

δ 169.3, 169.1, 148.3, 131.1, 129.1, 129.1, 125.4, 123.0, 63.1, 63.0, 47.4, 19.6, 13.8.

^{11}B-NMR (100 MHz, CD$_3$CN)

δ 12.6

HRMS (EI+)

Calculated for C$_{14}$H$_{15}$O$_4$NBrB (M)$^+$: 351.0277

Found: 351.0274

Elemental Analysis

Calculated: C, 47.77   H, 4.30   N, 3.98

Found: C, 47.89   H, 4.35   N, 3.95

IR (thin film, cm^{-1})

3004, 2968, 2922, 1749, 1716, 1422, 1363, 1222, 1092, 900, 736.
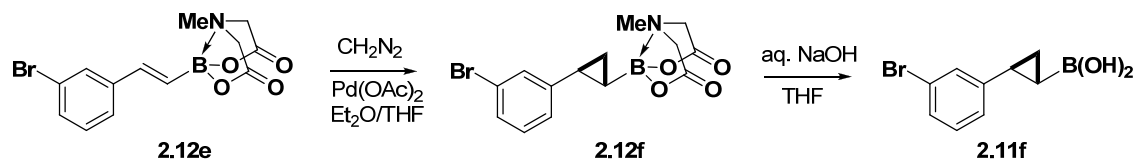
2-(3-bromophenyl)cyclopropylboronic acid (2.11f)

To a stirred solution of **2.12e** (1.21 g, 3.59 mmol) and Pd(OAc)$_2$ (0.0239 g, 0.11 mmol) in THF (24 mL) at 0 ^{o}C in a 250 mL Schlenk flask was added a freshly prepared

ethereal solution of diazomethane (35 mL of a 0.25 M solution, 8.8 mmol) dropwise over 20 minutes. Additional Pd(OAc)$_2$ was then added (0.0239 g, 0.11 mmol) as a solution in THF (1 mL) followed by the dropwise addition over 20 min of an additional 35 mL of 0.25 M ethereal diazomethane (8.8 mmol). The reaction was then allowed to warm to 23 °C and the excess diazomethane was removed under a stream of N$_2$. The crude reaction mixture was then poured into 120 mL of 0.5 M pH 7 sodium phosphate buffer and extracted with THF:Et$_2$O 1:1 (3 x 120 mL). The combined organic fractions were then washed with brine, dried over Na$_2$SO$_4$, and concentrated *in vacuo*. Purification by flash chromatography (SiO$_2$, Et$_2$O → Et$_2$O:CH$_3$CN 1:1) yielded **2.12f** (1.21 g, 96%) (See above for characterization of **2.12f**.) To a stirred solution of **2.12f** (0.513 g, 1.46 mmol) in THF (20 mL) was added 1M aq. NaOH (4.37 mL, 4.37 mmol) and the resulting mixture was stirred at 23 °C for 20 minutes. The reaction was then quenched with the addition of 0.5 M pH 7 phosphate buffer (20 mL) and diluted with Et$_2$O (20 mL). The layers were separated and the aq. layer was extracted with THF:Et$_2$O 1:1 (40 mL). The combined organic fractions were dried over MgSO$_4$ and concentrated *in vacuo* to yield the desired cyclopropylboronic acid **2.11f** as a colorless solid (0.339 g, 97%).

TLC (Et$_2$O:CH$_3$CN 3:1)

      R$_f$ = 0.64, visualized by UV

^{1}H-NMR (500 MHz, d_6-DMSO:D$_2$O 95:5)

      δ 7.30 (d, J = 8 Hz, 1H), 7.23 (s, 1H), 7.19 (app t, J = 8 Hz, 1H), 7.07 (d, J = 8 Hz, 1H), 1.95 (m, 1H), 1.06 (m, 1H), 0.96 (m, 1H), 0.07 (m, 1H).

^{13}C-NMR (125 MHz, CD$_3$CN)

      δ 147.2, 130.3, 127.9, 127.7, 124.3, 121.7, 20.8, 14.8.

HRMS (EI+)

      Calculated for C$_9$H$_{10}$O$_2$BrB (M)$^+$:   239.9957
      Found: 239.9956

Selective Suzuki-Miyaura coupling with haloboronate esters (Table 2.4)
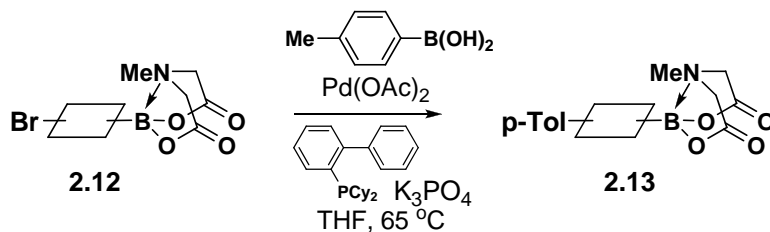
General procedures for selective Suzuki-Miyaura coupling reactions

Note: The same yield was observed for the transformation of **2.12a → 2.13a** whether this reaction was set up in the glovebox or in the air (see below).

Preparation of catalyst stock

In a glove box, to a vial equipped with a stir bar was added the phosphine ligand. To the vial was then added a 0.02 M solution of Pd(OAc)$_2$ in THF in a volume sufficient to yield a 0.04 M solution with respect to the phosphine ligand. The vial was sealed with a PTFE-lined cap, removed from the glove box, and maintained at 65°C with stirring for 30 min.

Suzuki-Miyaura Coupling

To a 40 mL vial equipped with a stir bar was added the haloboronate ester (1.0 mmol) and the boronic acid (typically 1.2-1.5 mmol). The vial was brought into the glove box. To the vial was added K$_3$PO$_4$ (3.0 mmol, 636.8 mg, a finely ground powder), THF (9.0 mL), and then the catalyst stock solution (1.0 mL). The vial was capped with a PTFE-lined cap, removed from the glove box, and placed in a 65°C oil bath with stirring for 12 h. The reaction mixture was allowed to cool to 23 °C and then filtered through a very thin pad of silica gel topped with sand and then celite, eluting with a copious volume of MeCN. To the resulting solution was added Florisil gel (app. 25 mg/mL of solution), and then solvent was removed *in vacuo*. The resulting powder was dry-loaded on top of

a silica gel column slurry-packed with Et$_2$O. The column was flushed with a copious volume of Et$_2$O; the product was then eluted with Et$_2$O:MeCN.
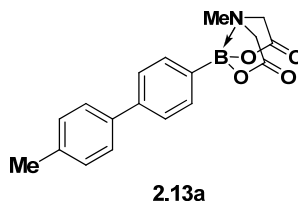
2.13a

MIDA boronate 2.13a

The general procedure was followed using **2.12a** (312 mg, 1.00 mmol), tolylboronic acid (163 mg, 1.20 mmol), and 2-(dicyclohexylphosphino)biphenyl. The product was eluted with Et$_2$O:MeCN 1:1. The title compound was isolated as a colorless solid (280 mg, 87%).

This same reaction was also set up using standard Schlenk techniques without the use of a glove box. A flame-dried 25 mL Schlenk flask equipped with a stir bar was evacuated and purged with argon 3 times.   This flask was charged with 2-(dicyclohexylphosphino)biphenyl (14.1 mg, 0.04 mmol) Pd(OAc)$_2$ (4.4 mg, 0.02 mmol), and THF (10 mL). The flask was then fitted with a reflux condensor and the yellow solution was heated to reflux for 5 minutes resulting in discoloration. A separate flame-dried 25 mL Schlenk flask equipped with a stir bar was evacuated and purged with argon 3 times. This flask was charged with haloboronate ester **2.12a** (312.1 mg, 1.00 mmol), tolylboronic acid (163.2 mg, 1.20 mmol), and freshly ground anhydrous K$_3$PO$_4$ (637.2 mg, 3.00 mmol). This flask was then fitted with a reflux condensor. The catalyst solution was then transferred via cannula into the flask containing the coupling partners and base. The resulting mixture was heated at reflux for 12 hours. The reaction was worked-up as described in the general procedure above. The product was eluted with Et$_2$O:MeCN 3:1 → 1:1. The title compound was isolated as a nearly colorless solid (279.6 mg, 87%).

TLC (EtOAc)

R$_f$ = 0.29, stained by KMnO$_4$

¹H-NMR (500 MHz, CD₃CN)

δ 7.64 (d, J = 8 Hz, 2H), 7.55 (app d, J = 7.5 Hz, 4H), 7.27 (d, J = 8 Hz, 2H), 4.07 (d, J = 17 Hz, 2H), 3.90 (d, J = 17 Hz, 2H), 2.54 (s, 3H), 2.37 (s, 3H).

¹³C-NMR (125 MHz, CD₃CN)

δ 169.6, 142.5, 138.6, 138.4, 134.0, 130.5, 127.7, 127.1, 62.8, 48.5, 21.1.

¹¹B-NMR (100 MHz, CD₃CN)

δ 12.0

HRMS (EI+)

Calculated for $C_{18}H_{18}O_4NB$ (M)⁺:   323.1329
Found: 323.1332

IR (thin film, cm⁻¹)

3012, 2952, 1765, 1711, 1607, 1455, 1340, 1297, 1237, 1202, 1040, 992, 891, 866, 840, 806.
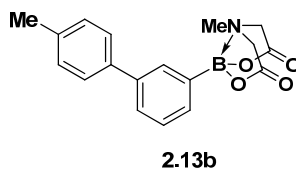
2.13b

MIDA boronate 2.13b

The general procedure was followed using **2.12b** (312 mg, 1.00 mmol), tolylboronic acid (163 mg, 1.20 mmol), and 2-(dicyclohexylphosphino)biphenyl. The product was eluted with Et₂O:MeCN 1:1. The title compound was isolated as a colorless, crystalline solid (276 mg, 85%).

TLC (EtOAc)

R_f = 0.38, stained by KMnO₄

¹H-NMR (500 MHZ, CD₃CN)

δ 7.12 (m, 1H), 7.64 (m, 1H), 7.55 (m, 2H), 7.45 (m, 2H), 7.27 (app d, J = 8 Hz, 2H), 4.07 (d, J = 17 Hz, 2H), 3.91 (d, J = 17 Hz, 2H), 2.53 (s, 3H), 2.36 (s, 3H).

¹³C-NMR (100 MHz, CD₃CN)

δ 169.6, 141.2, 139.2, 138.2, 132.3, 131.7, 130.5, 129.4, 128.7, 127.8, 62.9, 48.6, 21.1.

¹¹B-NMR (100 MHZ, CD₃CN)

δ 12.2

HRMS (EI+)

Calculated for $C_{18}H_{18}O_4NB$ (M)⁺:   323.1329
Found: 323.1326

IR (thin film, cm⁻¹)

3050, 3017, 2959, 2920, 1765, 1515, 1456, 1420, 1389, 1336, 1295, 1238, 1220, 1203, 1097, 1058, 1035, 965, 891, 861, 794, 730, 710, 652.
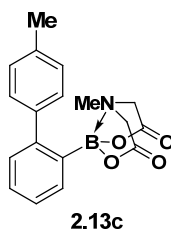
2.13c

MIDA boronate 2.13c

The general procedure was followed using **2.12c** (312 mg, 1.00 mmol), tolylboronic acid (172 mg, 2.00 mmol) and 2-(dicyclohexylphosphino)biphenyl. The product was eluted with a gradient of Et₂O:MeCN 5:1 → 1:1. The title compound was isolated as a pale yellow solid (257 mg, 80%).

TLC (EtOAc)

   $R_f = 0.40$, stained by KMnO$_4$

^{1}H-NMR (500 MHz, CD$_3$CN)

   δ 7.72 (dd, J = 7.25, 1 Hz, 1H), 7.43-7.34 (m, 2H), 7.18-7.08 (m, 5H), 3.73 (d, J = 17 Hz, 2H), 3.27 (d, J = 17 Hz, 2H), 2.42 (s, 3H), 2.34 (s, 3H).

^{13}C-NMR (125 MHz, CD$_3$CN)

   δ 168.9, 148.8, 141.8, 137.4, 135.2, 132.0, 130.5, 129.9, 129.4, 127.6, 63.5, 48.5, 21.1.

^{11}B-NMR (100 MHz, CD$_3$CN)

   δ 12.5

HRMS (EI+):

   Calculated for C$_{18}$H$_{18}$O$_4$NB (M)$^+$:   323.1329
   Found: 323.1332

IR (thin film, cm^{-1})

   3051, 3013, 2956, 2923, 2869, 1770, 1592, 1515, 1452, 1431, 1336, 1299, 1279, 1197, 1112, 1030, 1005, 887, 857, 824, 770, 755, 706, 639.
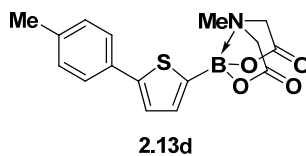
2.13d

MIDA boronate 2.13d

   The general procedure was followed using **2.12d** (318 mg, 1.00 mmol), tolylboronic acid (204 mg, 1.50 mmol), K$_2$CO$_3$ (415 mg, 3.00 mmol,) and 2-(dicyclohexylphosphino)-2',4',6'-tri-isopropyl-1,1'-biphenyl. The product was eluted

using a gradient of Et$_2$O:MeCN 5:1 → 3:1. The title compound was isolated as a pale yellow solid (266 mg, 81%).

TLC (EtOAc)

R_f = 0.52, stained by KMnO$_4$

^{1}H-NMR (400 MHz, CD$_3$CN)

δ 7.56 (d, J = 8 Hz, 2H), 7.41 (d, J = 3.2 Hz, 1H), 7.23 (d, J = 3.2 Hz, 1H), 7.21 (d, J = 8 Hz, 2H), 4.08 (d, J = 17 Hz, 2H), 3.92 (d, J = 17 Hz, 2H), 2.66 (s, 3H), 2.33 (s, 3H).

^{13}C-NMR (125 MHz, CD$_3$CN)

δ 169.0, 149.4, 138.8, 135.4, 132.4, 130.6, 126.6, 125.2, 62.4, 48.4, 21.1.

^{11}B-NMR (100 MHz, CD$_3$CN)

δ 11.2

HRMS (TOF ES+)

Calculated for C$_{16}$H$_{16}$O$_4$BNNaS (M+Na)$^+$:   352.0791
Found: 352.0800

IR (thin film, cm^{-1})

2999, 2948, 1755, 1453, 1337, 1284, 1248, 1169, 1031, 978, 894, 869, 802.
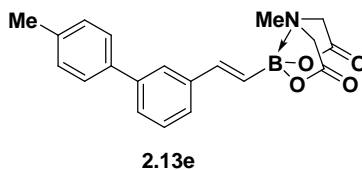
2.13e

MIDA boroante 2.13e

The general procedure was followed using **2.12e** (338 mg, 1.00 mmol), tolylboronic acid (163 mg, 1.20 mmol), and 2-(dicyclohexylphosphino)biphenyl. The

product was eluted with Et_2O:MeCN 5:1. The title compound was isolated as an off-white solid (282 mg, 82%).

TLC (EtOAc)

> $R_f = 0.29$, stained by $KMnO_4$

^{1}H-NMR (500 MHz, CD_3CN)

> δ 7.76 (app t, $J = 1.5$ Hz, 1H), 7.55 (m, 2H), 7.50 (m, 2H), 7.40 (app t, $J = 8$ Hz, 1H), 7.27 (app d, $J = 8$ Hz, 2H), 7.01 (d, $J = 18.5$ Hz, 1H), 6.37 (d, $J = 18.5$ Hz, 1H), 4.00 (d, $J = 17$ Hz, 2H), 3.84 (d, $J = 17$ Hz, 2H), 2.81 (s, 3H), 2.36 (s, 3H).

^{13}C-NMR (125 MHz, CD_3CN)

> δ 169.5, 143.3, 142.2, 139.8, 138.8, 138.5, 130.6, 130.1, 127.9, 127.5, 126.4, 126.2, 62.5, 47.8, 21.2.

^{11}B-NMR (100 MHz, CD_3CN)

> δ 11.9

HRMS (EI+)

> Calculated for $C_{20}H_{20}O_4NB$ (M)$^+$: 349.1485
> Found: 349.1480

IR (thin film, cm^{-1})

> 3005, 2952, 2922, 2868, 1764, 1628, 1598, 1582, 1517, 1427, 1396, 1337, 1289, 1233, 1192, 1153, 1114, 1086, 1028, 995, 956, 878, 823, 785, 697.
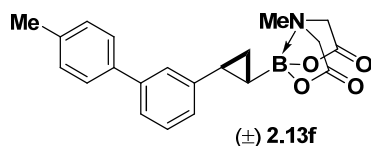
(±) 2.13f

MIDA boronate 2.13f

The general procedure was followed using **2.12f** (237 mg, 0.674 mmol), tolylboronic acid (109 mg, 0.808 mmol), K_3PO_4 (429 mg, 2.02 mmol), catalyst stock solution containing 2-(dicyclohexylphosphino)biphenyl (674 µL), and THF 6.06 mL. The product was eluted with Et_2O:MeCN (1:1). The title compound was isolated as an off-white crystalline solid (229 mg, 94%).

TLC (EtOAc)

$R_f = 0.33$, stained by $KMnO_4$

^{1}H-NMR (500 MHz, CD_3CN)

δ 7.51 (app d, $J = 8$ Hz, 2H), 7.35 (m, 2H), 7.29 (app t, $J = 8$ Hz, 1H), 7.07 (app d, $J = 8$ Hz, 1H), 3.96 (app dd, $J = 17, 4$ Hz, 2H), 3.84 (app dd, $J = 17, 12$ Hz, 2H), 1.84 (ddd, $J = 8, 5.5, 5$ Hz, 1H), 0.99 (ddd, $J = 10, 5, 4$ Hz, 1H), 0.91 (ddd, $J = 8,7,4$ Hz, 1H), 0.25 (ddd, $J = 10, 7, 5.5$ Hz, 1H).

^{13}C-NMR (125 MHz, CD_3CN)

δ 168.0, 167.9, 144.6, 140.5, 137.8, 136.9, 129.1, 128.5, 126.5, 123.7, 123.5, 123.4, 61.8, 61.7, 46.1, 19.8, 18.7, 12.2.

^{11}B-NMR (100 MHz, CD_3CN)

δ 13.1

HRMS (EI+)

Calculated for $C_{21}H_{22}O_4NB$ $(M)^+$: 363.1642

Found: 363.1645

IR (thin film, cm^{-1})

3014, 2963, 2921, 1762, 1603, 1517, 1485, 1458, 1379, 1338, 1292, 1246, 1153, 1115, 1084, 1030, 960, 891, 861, 825, 792, 707.

Deprotection of MIDA boronate esters (Table 2.4)
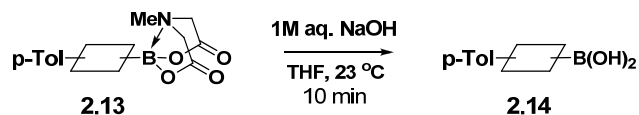
General procedure for NaOH-mediated hydrolysis of boronate esters

A round bottom flask equipped with a stir bar was charged with the boronate ester (1 equiv.), THF (10 mL), and 1M aq. NaOH (3 equiv.) and the resulting mixture was vigorously stirred at 23 °C for 10 minutes. The reaction mixture was then diluted with aq. sodium phosphate buffer (0.5 M, pH 7.0, 10 mL) and Et$_2$O (10 mL), the layers were separated, and the aq. phase was extracted once with THF:Et$_2$O 1:1 (20 mL). (On some occasions phosphate salts precipated and during the extraction process and were redissolved by the addition of water. The combined organic fractions were then dried over MgSO$_4$ and concentrated *in vacuo*. Residual solvent was co-evaporated with MeCN.
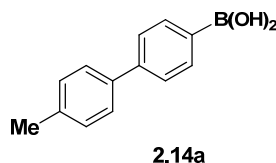
Boronic acid 2.14a

The general procedure was followed using **2.13a** (261 mg, 0.806 mmol) and 1 M aq. NaOH (2.42 mL, 2.42 mmol). The title compound was isolated as a white solid (147.4 mg, 86%)

TLC (EtOAc)

Rf = 0.55, stained by KMnO$_4$

^{1}H-NMR (500 MHz, d_6-DMSO:D$_2$O 95:5)

δ 7.87 (d, *J* = 8 Hz, 2H), 7.62 (d, *J* = 8 Hz, 2H), 7.59 (d, *J* = 8 Hz, 2H), 7.28 (d, *J* = 8 Hz, 2H), 2.35 (s, 3H).

^{13}C-NMR (125 MHz, d_6-DMSO:D$_2$O 95:5)

δ 141.5, 137.1, 136.9, 134.7, 129.5, 126.4, 125.3, 20.6.

HRMS (EI+)

Calculated for C$_{13}$H$_{13}$O$_2$B (M)$^+$:   212.1009

Found: 212.1011
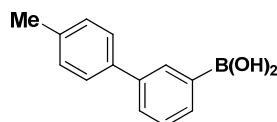
2.14b

Boronic acid 2.14b

The general procedure was followed using **2.13b** (268 mg, 0.830 mmol) and 1 M aq. NaOH (2.49 mL, 2.49 mmol). The title compound was isolated as a white solid (161 mg, 92%).

TLC (EtOAc)

R$_f$ = 0.59, stained by KMnO$_4$

^{1}H-NMR (500 MHz, d_6-DMSO:D$_2$O 95:5)

δ 8.09 (s, 1H), 7.75 (d, J = 7 Hz, 1H), 7.68 (d, J = 8 Hz, 2H), 7.57 (d, J = 8 Hz, 2H), 7.43 (app t, J = 7.5 Hz, 1H), 7.29 (d, J = 8 Hz, 2H), 2.35 (s, 3H).

^{13}C-NMR (125 MHz, d_6-DMSO:D$_2$O 95:5)

δ 139.0, 137.5, 136.5, 132.8, 132.1, 129.4, 128.1, 128.0, 126.4, 20.6.

HRMS (EI+)

Calculated for C$_{13}$H$_{13}$O$_2$B (M)$^+$:   212.1009

Found: 212.1008
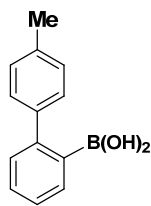
2.14c

Boronic acid 2.14c

Hydrolysis with NaOH. The general procedure was followed using **2.13c** (236 mg, 0.729 mmol) and 1M aq. NaOH (2.19 mL, 2.19 mmol). The title compound was isolated as a white solid (150 mg, 97%).

Hydrolysis with NaHCO₃. To a 40 mL I-Chem vial equipped with a stir bar and containing **2.13c** (0.672 mmol, 217 mg) was added MeOH (7 mL) and sat. aq. NaHCO$_3$ (3.5 mL). The mixture was vigorously stirred for 6 h at 23 °C. The mixture was then diluted with saturated aq. NH$_4$Cl (7 mL) and Et$_2$O (14 mL), and the phases were separated. The aqueous phase was twice extracted with Et$_2$O (14 mL), and the combined organics were dried over MgSO$_4$ and concentrated *in vacuo*. The residue was twice suspended in MeCN followed by concentration *in vacuo* and then dissolved in CH$_2$Cl$_2$ and concentrated *in vacuo* to yield **2.14c** as a colorless, crystalline solid (121 mg, 85%).

TLC (EtOAc)

R_f = 0.84, stained by KMnO$_4$

^{1}H-NMR (500 MHz, d_6-DMSO:D$_2$O 95:5)

δ 7.45-7.27 (m, 6H), 7.21 (d, *J* = 8 Hz, 2H), 2.34 (s, 3H).

^{13}C-NMR (125 MHz, d_6-DMSO:D$_2$O 95:5)

δ 144.0, 140.2, 135.8, 132.1, 128.7, 128.2, 128.0, 127.9, 125.7, 20.5.

HRMS (EI+)

Calculated for C$_{13}$H$_{13}$O$_2$B (M)$^+$:   212.1009

Found: 212.1005
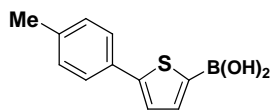
2.14d

Boronic acid 2.14d

The general procedure was followed using **2.13d** (226 mg, 0.686 mmol) and 1 M aq. NaOH (2.06 mL, 2.06 mmol). The title compound was isolated as a pale green solid (131 mg, 88%).

TLC (Et$_2$O:CH$_3$CN 3:1)

R_f = 0.57, visualized by UV

^{1}H-NMR (500 MHz, d_6-DMSO:D$_2$O 95:5)

δ 7.64 (d, J = 3.5 Hz, 1H), 7.57 (d, J = 8 Hz, 2H), 7.47 (d, J = 3.5 Hz, 1H), 7.24 (d, J = 8Hz, 2H), 2.32 (s, 3H).

^{13}C-NMR (125 MHz, d_6-DMSO:D$_2$O 95:5)

δ 148.9, 137.2, 137.2, 131.0, 129.6, 125.4, 124.1, 20.6.

HRMS (TOF ES+)

Calculated for C$_{11}$H$_{12}$O$_2$BS (M+H)$^+$: 219.0651
Found: 219.0659
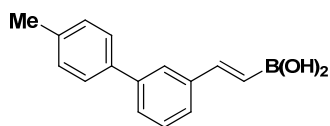
2.14e

Boronic acid 2.14e

The general procedure was followed using **2.13e** (243 mg, 0.696 mmol) and 1 M aq. NaOH (2.09 mL, 2.09 mmol). The title compound was isolated as an off-white solid (138 mg, 83%).

78

TLC (EtOAc)

  R_f = 0.40, stained by KMnO$_4$

^{1}H-NMR (500 MHz, d_6-DMSO:D$_2$O 95:5)

  δ 7.79-7.26 (m, 9H), 6.24 (d, J = 18.5 Hz, 1H), 2.35 (s, 3H).

^{13}C-NMR (125 MHz, d_6-DMSO:D$_2$O 95:5)

  δ 145.8, 140.4, 138.1, 136.9, 136.9, 129.5, 129.3, 126.5, 126.5, 125.2, 124.7, 20.6.

HRMS (CI+)

  Calculated for C$_{15}$H$_{16}$O$_2$B (M+H)$^+$:   239.1243
  Found: 239.1244
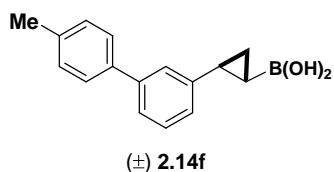
(±) **2.14f**

Boronic acid 2.14f

  The general procedure was followed using **2.13f** (202 mg, 0.56 mmol) and 1M aq. NaOH (1.67 mL, 1.67 mmol). The title compound was isolated as an off-white solid (127 mg, 91%).

TLC (EtOAc)

  R_f = 0.41, visualized by UV

^{1}H-NMR (500 MHz, CDCl$_3$)

  δ 7.49 (d, J = 8 Hz, 2H), 7.40-7.22 (m, 5H), 7.07 (m, 1H), 2.40 (s, 3H), 2.29 (m, 1H), 1.33 (m, 1H), 1.22 (m, 1H), 0.44 (m, 1H).

^{13}C-NMR (125 MHz, CDCl$_3$)

  δ 145.2, 143.2, 141.3, 138.4, 137.0, 129.4, 128.7, 127.0, 124.6, 124.3.

79

HRMS (FAB+)

      Calculated for $C_{16}H_{18}O_2B$ (M+H)$^+$: 253.1400

      Found: 253.1401

Total synthesis of ratanhine (Schemes 2.7, 2.8 and 2.10)
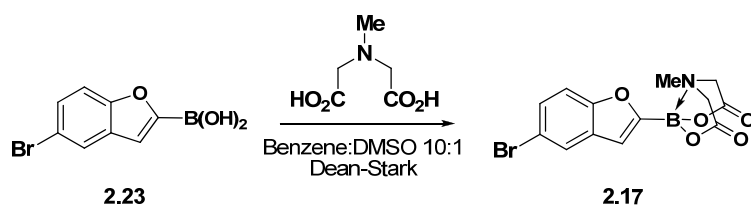
MIDA boronate 2.17

      The general procedure for the synthesis of haloboronate esters **2.13** (see above) was followed using 5-bromo-2-benzofuranylboronic acid (**2.23**)[4] (1.33 g, 5.50 mmol), N-methyliminodiacetic acid (970 mg, 6.60 mmol), benzene (80 mL) and DMSO (8 mL). The mixture was refluxed for 13 h. The product was eluted using a gradient of Et$_2$O:MeCN 1:1 → 1:2. The title compound was isolated as an analytically pure, off-white, crystalline solid (1.73 g, 90%).

TLC (EtOAc)

      R_f = 0.31, stained by KMnO$_4$

^{1}H-NMR (500 MHz, CD$_3$CN)

      δ 7.55 (d, J = 1.5 Hz, 1H), 7.42 (d, J = 8.5 Hz, 1H), 7.34 (dd, J = 8.5, 1.5 Hz, 1H), 7.05 (d, J = 1.5 Hz, 1H), 6.50 (dd, J = 16, 1.5 Hz, 1H), 6.24 (dq, J = 16, 6.5 Hz, 1H), 4.11 (d, J = 17 Hz, 2H), 3.96 (d, J = 17 Hz, 2H), 2.69 (s, 3H), 1.85 (dd, J = 6.5, 1.5 Hz, 3H).

^{13}C-NMR (125 MHz, CD$_3$CN)

  δ 169.0, 157.1, 131.3, 128.3, 124.8, 116.0, 115.2, 114.0, 62.6, 48.2.

^{11}B-NMR (100 MHz, CD$_3$CN)

  δ 9.3

HRMS (EI+)

  Calculated for C$_{13}$H$_{11}$O$_5$NBrB (M)$^+$: 350.9914

  Found: 350.9913

Elemental Analysis

  Calculated: C, 44.36   H, 3.15   N, 3.98   Br, 22.70

  Found: C, 44.43   H, 2.81   N, 3.98   Br, 22.96

IR (thin film, cm^{-1})

  3012, 2964, 1754, 1467, 1446, 1282, 1233, 1199, 1140, 1078, 1047, 1002, 989,

  802.

Synthesis of MIDA boronate 2.18
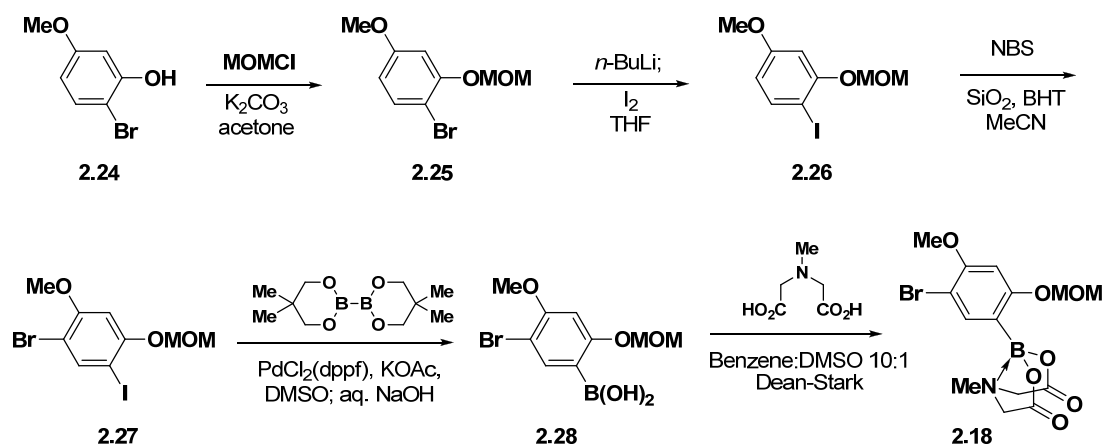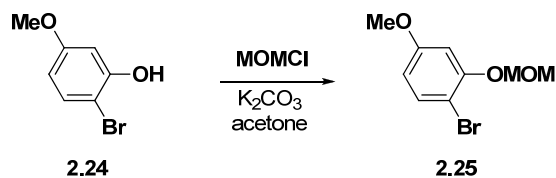
Methoxymethylether 2.34

To a stirred mixture of 2-bromo-5-methoxyphenol (**2.24**)[5] (2.19 g, 10.8 mmol) and K_2CO_3 (4.46 g, 32.3 mmol) in acetone (55 mL) was added chloromethyl methyl ether (1.63 mL, 21.5 mmol). The mixture was refluxed for 3 h and then allowed to cool to 23 ^{o}C. The mixture was filtered and the filtrate was concentrated *in vacuo*. The crude product was then purified by flash chromatography (SiO_2, hexanes:EtOAc 95:5) to provide **2.25** as colorless liquid (2.43 g, 92%).

TLC (hexanes:EtOAc 95:5)

   R_f = 0.17, stained by anisaldehyde (red)

^{1}H-NMR (500 MHz, CDCl$_3$)

   δ 7.40 (d, J = 9 Hz, 1H), 6.77 (d, J = 3 Hz, 1H), 6.46 (dd, J = 9, 3 Hz, 1H), 5.22 (s, 2H), 3.77 (s, 3H), 3.51 (s, 3H).

^{13}C-NMR (125 MHz, CDCl$_3$)

   δ 160.0, 154.4, 133.1, 108.1, 103.4, 103.2, 95.1, 56.3, 55.5.

HRMS (EI+)

   Calculated for $C_9H_{11}O_3Br$ (M)$^+$:   245.9892

   Found: 245.9891

IR (thin film, cm^{-1})

   3087, 2998, 2959, 2938, 2907, 2835, 1587, 1483, 1426, 1393, 1307, 1281, 1253, 1219, 1155, 1086, 1056, 1023, 991, 841, 792.

MeO / OMOM / Br **2.25** → (n-BuLi; I₂, THF) → MeO / OMOM / I **2.26**
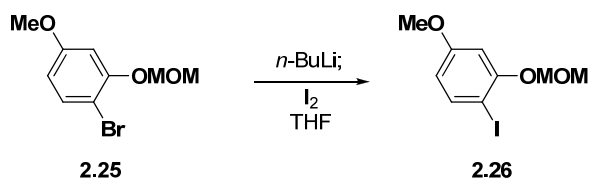
Aryliodide 2.26[14]

To a stirred solution of **2.25** (1.04 g, 4.23 mmol) in THF (13 mL) at -95 °C (hexanes/N_2) was added n-BuLi (1.6 M in hexanes, 2.91 mL, 4.65 mmol) and the resulting solution was stirred for 5 min. To this solution was then added by syringe a solution of I_2 (1.28 g, 5.07 mmol) in THF (8.5 mL) until a yellow color persisted. The solution was then permitted to warm to 23 °C and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, petroleum ether:Et_2O 8:1) to provide **2.26** as a pale-orange oil (1.04 g, 84%).

TLC (petroleum ether:Et_2O 8:1)

R_f = 0.16, stained by anisaldehyde (red)

^{1}H-NMR (500 MHz, CDCl$_3$)

δ 7.62 (d, J = 8.5 Hz, 1H), 6.70 (d, J = 3 Hz, 1H), 6.39 (dd, J = 8.5, 3 Hz, 1H), 5.22 (s, 2H), 3.78 (s, 3H), 3.51 (s, 3H).

^{13}C-NMR (125 MHz, CDCl$_3$)

δ 161.2, 156.8, 139.1, 109.0, 102.3, 95.0, 75.8, 56.4, 55.5.

HRMS (EI+):

Calculated for $C_9H_{11}O_3I$ (M)$^+$:   293.9753

Found: 293.9758

IR (thin film, cm^{-1})

2999, 2959, 2936, 2904, 2835, 1580, 1477, 1424, 1392, 1304, 1279, 1253, 1218, 1162, 1085, 1052, 991, 924, 840, 791.
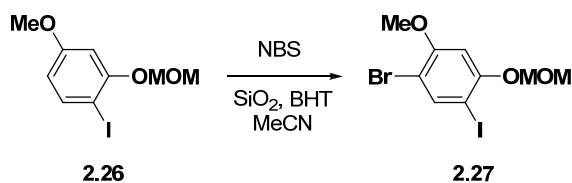
Aryl bromide 2.27

To a stirred solution of **2.26** (5.24 g, 17.8 mmol) in MeCN (55 mL) was added silica gel (1.32 g), 2,6-di-*tert*-butyl-4-hydroxytoluene (60 mg), and then *N*-bromosuccinimide (3.17 g, 17.8 mmol). The mixture was stirred at 23 °C for 1 hour and then filtered. The filtrate was concentrated *in vacuo* and the residue was dissolved in CH_2Cl_2 (100 mL). To this solution was added water (100 mL) and the resulting mixture was vigorously stirred for 5 min. The layers were then separated and the aq. phase was extracted with CH_2Cl_2 (2 x 100 mL). The combined organics were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash-column chromatography (SiO_2, petroleum ether:Et_2O 8:1) to provide **2.27** as a yellow oil (5.05 g, 76%).

TLC (petroleum ether:Et_2O 8:1)

R_f = 0.17, stained by anisaldehyde (red)

^{1}H-NMR (500 MHz, CDCl$_3$)

δ 7.85 (s, 1H), 6.73 (s, 1H), 5.23 (s, 2H), 3.87 (s, 3H), 3.52 (s, 3H).

^{13}C-NMR (CD$_3$CN)

δ 157.0, 156.6, 141.3, 104.7, 100.1, 95.4, 75.5, 56.5, 56.4.

HRMS (EI+):

Calculated for $C_9H_{10}O_3BrI$ (M)$^+$:   371.8858
Found: 371.8859

IR (thin film, cm^{-1})

2999, 2963, 2937, 2906, 2853, 2826, 1575, 1470, 1439, 1408, 1358, 1283, 1268, 1217, 1151, 1086, 1056, 994, 993, 878, 818.
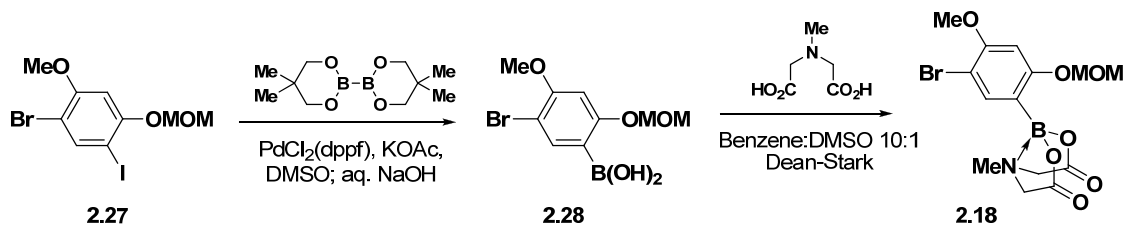
MIDA boronate 2.18

In a glove box, to a 40 mL I-Chem vial equipped with a stir bar and containing **2.27** (500 mg, 1.34 mmol) was added potassium acetate (395 mg, 4.02 mmol), bis(neopentylglycolato)diboron (363 mg, 1.61 mmol) and PdCl$_2$(dppf) (33 mg, 0.040 mmol). The vial was sealed with a septum cap and then removed from the glove box. To the vial was then added DMSO (11 mL) and the resulting mixture was sealed under an atmosphere of argon and stirred at 80 °C for 13 h. The mixture was then allowed to cool to 23 °C and 1 M aq. NaOH was added (0.9 mL, 0.9 mmol). The mixture was stirred at 23°C for 10 minutes and then diluted with saturated aq. NH$_4$Cl (50 mL), water (50 mL), and Et$_2$O (100 mL). The layers were separated and the organic phase was washed with water (3 x 100 mL), dried over MgSO$_4$, and concentrated *in vacuo*. The residue was thrice dissolved in MeCN and concentrated *in vacuo* to afford a crude sample of boronic acid **2.28** as a light brown solid (343 mg): TLC (EtOAc) R$_f$ = 0.50, stained by KMnO$_4$; ^{1}H-NMR (400 MHz, CDCl$_3$) δ 7.97 (s, 1H), 6.75 (s, 1H), 5.97 (s, 2H), 5.29 (s, 2H), 3.91 (s, 3H), 3.52 (s, 3H). To this crude boronic acid dissolved in benzene:DMSO (10:1) was added *N*-methyliminodiacetic acid (210 mg, 1.43 mmol). The flask was fitted with a Dean-Stark trap and a reflux condenser and the mixture was refluxed with stirring for 11 h followed by concentration *in vacuo*. The resulting crude product was adsorbed onto Florisil gel from a MeCN solution. The resulting powder was dry-loaded on top of a silica gel column slurry-packed with Et$_2$O. The column was flushed with a copious volume of Et$_2$O and then the product was eluted with Et$_2$O:MeCN 1:1 to yield MIDA boronate **2.18** as an off-white solid (365 mg, 68% yield over two steps).

TLC (Et$_2$O:CH$_3$CN 3:1)

R$_f$ = 0.44, stained by KMnO$_4$

¹H-NMR (500 MHz, CD₃CN)

^{1}H-NMR (500 MHz, CD$_3$CN)

δ 7.62 (s, 1H), 6.76 (s, 1H), 5.18 (s, 2H), 4.06 (d, J = 17 Hz, 2H), 3.94 (d, J = 17 Hz, 2H), 3.85 (s, 3H), 3.39 (s, 3H), 2.64 (s, 3H).

^{13}C-NMR (125 MHz, CD$_3$CN)

δ 169.5, 161.6, 158.6, 139.0, 103.6, 100.1, 95.1, 64.4, 64.2, 56.9, 48.4.

^{11}B-NMR (100 MHz, CD$_3$CN)

δ 11.9

HRMS (EI+)

Calculated for C$_{14}$H$_{17}$O$_7$NBrB (M)$^+$: 401.0281

Found: 401.0281

IR (thin film, cm^{-1})

3008, 2963, 2944, 2904, 1768, 1596, 1558, 1488, 1446, 1367, 1337, 1276, 1198, 1164, 1147, 1048, 1035, 1006, 951, 858.

Iterative Suzuki-Miyaura coupling of building blocks 2.16–2.19
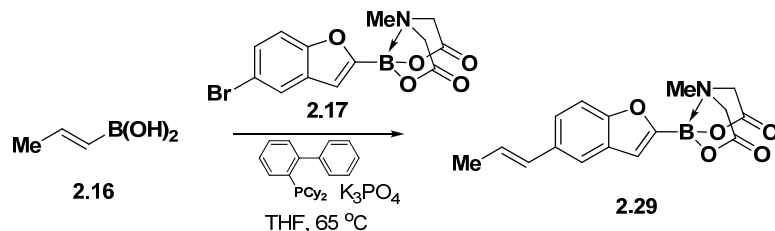
MIDA boronate 2.29

The general procedure for Suzuki-Miyaura coupling reactions (see above) was followed using **2.17** (352 mg, 1.00 mmol) and (*E*)-1-propenylboronic acid (144 mg, 2.00 mmol). The product was eluted using a gradient of Et$_2$O:MeCN 10:1 → 1:1. The desired product **2.29** was isolated as a colorless crystalline solid (251 mg, 80%).

TLC (EtOAc)

  R$_f$ = 0.34, stained by KMnO$_4$

^{1}H-NMR (500 MHz, CD$_3$CN)

  δ 7.55 (m, 1H), 7.42 (d, *J* = 8.5 Hz, 1H), 7.34 (dd, *J* = 8.5 Hz, 1H), 7.05 (d, *J* = 1 Hz, 1H), 6.51 (m, 1H), 6.25 (dq, *J* = 16, 7 Hz, 1H), 4.11 (d, *J* = 17 Hz, 2H), 3.96 (d, *J* = 17 Hz, 2H), 2.69 (s, 3H), 1.85 (dd, *J* = 7, 2 Hz, 3H).

^{13}C-NMR (125 MHz, CD$_3$CN)

  δ 169.1, 157.6, 134.0, 131.8, 129.5, 125.5, 123.7, 119.4, 115.8, 112.2, 62.6, 48.1, 18.6.

^{11}B-NMR (100 MHz, CD$_3$CN)

  δ 9.8

HRMS (EI+):

  Calculated for C$_{16}$H$_{16}$O$_5$NB (M)$^+$:   313.1122
  Found: 313.1123

IR (thin film, cm^{-1})

3008, 2958, 1767, 1711, 1563, 1453, 1336, 1283, 1253, 1175, 1053, 1006, 963, 855.
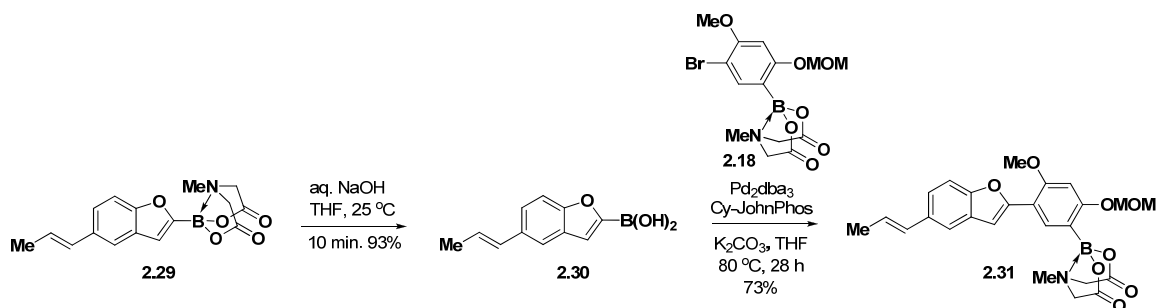
Boronate ester 2.31

The general procedure for deprotection of boronate esters (see above) was followed using **2.29** (313 mg, 1.00 mmol), and 1 M aq. NaOH (3.0 mL, 3.0 mmol) to afford boronic acid **2.30** as an off-white solid (188 mg, 93%); TLC: (EtOAc) R$_f$ = 0.2, visualized by UV; HRMS (EI+): Calculated for C$_{11}$H$_{11}$O$_3$B (M)$^+$ 202.0801, Found 202.0805. Boronic acid **2.30** was found to be very sensitive to decomposition upon storage and was therefore used immediately in the next reaction. In a glove box, to a 40 mL I-Chem vial containing **2.18** (141 mg, 0.351 mmol) was added boronic acid **2.30** (106 mg, 0.526 mmol) as a solution in THF (3.15 mL) followed by solid K$_2$CO$_3$ (145 mg, 1.05 mmol). To the vial was then added 350 μL of a THF catalyst stock solution containing 2-(dicyclohexylphosphino)biphenyl (0.04 M) and Pd$_2$dba$_3$ (0.01 M) which was preincubated at 65 ºC for 30 min. with stirring. The vial was sealed with a PTFE-lined cap, removed from the glove box, and maintained at 80 ºC with stirring for 28 h. The reaction mixture was allowed to cool to 23 ºC, and was then passed through a thin pad of silica gel topped with Celite, eluting with a copious volume of Et$_2$O. The filtrate was concentrated *in vacuo* and the resulting crude product was adsorbed onto Florisil gel from a MeCN solution. The resulting powder was dry-loaded on top of a silica gel column slurry-packed with Et$_2$O. The column was flushed with a copious volume of Et$_2$O; the product was then eluted with Et$_2$O:MeCN 3:1 to yield boronate ester **2.31** as an off-white solid (123 mg, 73%).

TLC (Et$_2$O:CH$_3$CN 3:1)

R_f = 0.36, stained by KMnO$_4$

^{1}H-NMR (500 MHz, CD$_3$CN)

δ 8.15 (s, 1H), 7.53 (d, *J* = 2 Hz, 1H), 7.44 (d, *J* = 8.5 Hz, 1H), 7.29 (dd, *J* = 8.5, 2 Hz, 1H), 7.22 (s, 1H), 6.85 (s, 1H), 6.51 (dd, *J* = 16, 1.5 Hz, 1H), 6.26 (dq, *J* = 16, 6.5 Hz, 1H), 5.25 (s, 2H), 4.11 (d, *J* = 17 Hz, 2H), 3.99 (d, *J* = 17 Hz, 2H), 3.99 (s, 3H), 3.42 (s, 3H), 2.68 (s, 3H), 1.86 (dd, *J* = 6.5, 1.5 Hz, 3H).

^{13}C-NMR (125 MHz, CD$_3$CN)

δ 169.7, 162.5, 160.0, 154.0, 153.8, 134.2, 133.6, 131.9, 131.2, 125.3, 123.0, 118.8,

113.1, 111.4, 105.4, 98.6, 95.0, 64.5, 57.0, 56.4, 48.4, 18.6.

^{11}B-NMR (100 MHz, CD$_3$CN)

δ 12.0

HRMS (FAB+)

Calculated for C$_{25}$H$_{27}$O$_8$NB (M+H)$^+$:	480.1830
Found:	480.1828

IR (thin film, cm^{-1})

3009, 2959, 2911, 2850, 1768, 1710, 1605, 1575, 1501, 1446, 1368, 1337, 1299, 1267, 1193, 1153, 1139, 1080, 1036, 1008, 964, 859, 816.
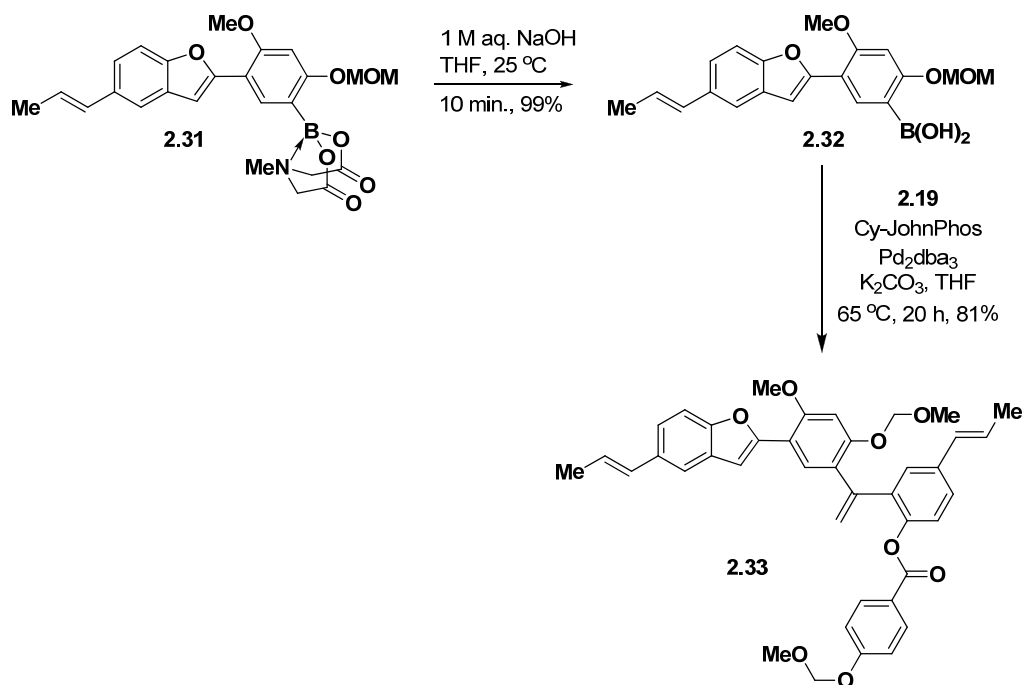
MOM-ratanhine 2.33

A 6 mL vial equipped with a stir bar was charged with boronate ester **2.31** (51 mg, 0.106 mmol), THF (1.0 mL), and 1 M aq. NaOH (0.32 mL, 0.32 mmol). The resulting mixture was vigorously stirred for 10 min., then diluted with 0.5 M pH 7 phosphate buffer (2.0 mL) and Et$_2$O (1.0 mL). The phases were separated and the aq. phase was extracted once with THF:Et$_2$O 1:1 (2.0 mL). The combined organics were dried over MgSO$_4$, filtered, and then concentrated *in vacuo*. Residual solvent was removed via coevaporation with PhMe, followed by MeCN (2X), and then CH$_2$Cl$_2$ (2X) (bath temperature maintained at < 30 °C) to yield boronic acid **2.32** as an off-white solid (39.2 mg, 99%): TLC (EtOAc) R$_f$ = 0.53, visualized by UV; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.49 (s, 1H), 7.49 (s, 1H), 7.42 (d, *J* = 8 Hz, 1H), 7.26 (m, 1H), 7.17 (s, 1H), 6.84 (s, 1H), 6.49 (d, *J* = 16 Hz, 1H), 6.20 (dq, *J* = 16, 6.4 Hz, 1H), 5.77 (s, 2H), 5.35 (s, 2H), 4.03 (s, 3H), 3.55 (s, 3H), 1.90 (d, *J* = 6.4 Hz, 3H); HRMS (TOF ES+): Calculated for C$_{20}$H$_{22}$O$_6$B (M+H)$^+$ 369.1509, Found 369.1515.

This boronic acid was then quantitatively transferred as a solution in THF to a 6 mL vial containing **2.19** (28.5 mg, 0.071 mmol) and the solvent was removed *in vacuo*. In the glove box, to this vial was added solid K$_2$CO$_3$ (39.2 mg, 0.28 mmol), and a freshly-

prepared THF solution (1.06 mL) of 2-(dicyclohexylphosphino)biphenyl (0.008 M) and Pd$_2$dba$_3$ (0.002 M). A stir bar was added and the vial was sealed with a PTFE-lined cap, removed from the glove box, and maintained at 65 °C with stirring for 20 h. The reaction mixture was then allowed to cool to 23 °C and passed through a thin pad of silica gel topped with Celite, eluting with a copious volume of EtOAc. The filtrate was concentrated *in vacuo*, and the resulting crude product was adsorbed onto Florisil gel from a CH$_2$Cl$_2$ solution. The resulting powder was dry-loaded on top of a silica gel column slurry-packed with hexanes:EtOAc 10:1. The column was eluted with hexanes:EtOAc 10:1 → 3:1 to yield **2.33** as a viscous yellow oil (37.0 mg, 81%).

TLC (Hexanes:ethyl acetate 1:1)

R_f = 0.47, visualized by UV

^{1}H-NMR (500 MHz, CDCl$_3$)

7.76 (s, 1H), 7.65 (d, J = 9 Hz, 2H), 7.49 (d, J = 2 Hz, 1H), 7.44 (d, J = 1 Hz, 1H), 7.31 (d, J = 8.5 Hz, 1H), 7.29 (dd, J = 8.5, 2 Hz, 1H), 7.24 (dd, J = 8.5, 1.5 Hz, 1H), 6.99 (s, 1H), 6.98 (d, J = 8.5 Hz, 1H), 6.64 (d, J = 9 Hz, 2H), 6.61 (s, 1H), 6.49 (dd, J = 16, 1 Hz, 1H), 6.45 (dd, J = 16, 1 Hz, 1H), 6.26 (dq, J = 16, 6.5 Hz, 1H), 6.20 (dq, J = 16, 6.5 Hz, 1H), 5.53 (d, J = 1.5 Hz, 1H), 5.51 (d, J = 1.5 Hz, 1H), 4.84 (s, 2H), 4.64 (s, 2H), 3.92 (s, 3H), 3.28 (s, 3H), 3.17 (s, 3H), 1.91 (app d, J = 6.5 Hz, 6H).

^{13}C-NMR (125 MHz, CDCl$_3$)

164.2, 160.9, 157.2, 155.2, 152.8, 152.5, 146.6, 144.4, 135.7, 135.6, 132.7, 131.8, 131.3, 130.3, 130.1, 128.8, 127.8, 125.8, 125.3, 124.1, 124.0, 122.8, 122.1, 121.8, 119.2, 117.6, 114.5, 112.9, 110.6, 104.3, 98.5, 94.4, 93.5, 55.9, 55.8, 55.6, 18.5, 18.5.

HRMS (TOF ES+)

Calculated for C$_{40}$H$_{39}$O$_8$ (M+H)$^+$:   647.2645

Found: 647.2642

IR (thin film, cm^{-1})

2961, 2928, 2913, 1732, 1606, 1574, 1508, 1448, 1379, 1264, 1243, 1197, 1168, 1151, 1080, 1065, 1002, 967,
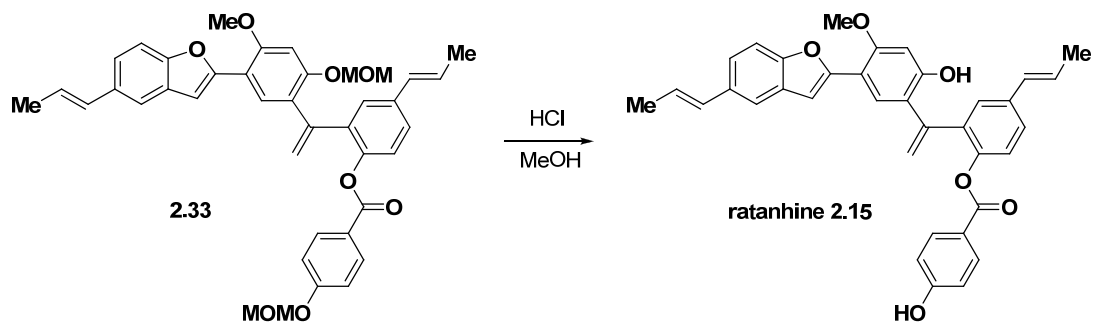
Ratanhine 2.15

A 6 mL vial equipped with a stir bar was charged with **2.33** (27 mg, 0.042 mmol), THF (0.3 mL), MeOH (0.6 mL), and concentrated HCl (12 µL). The vial was sealed with a PTFE-lined cap and maintained at 65 °C with stirring for 1 h. The solution was then allowed to cool to 23 °C and diluted with H_2O (1 mL), THF (1 mL) and Et_2O (2 mL). The phases were separated and the aq. phase was extracted repeatedly with EtOAc. The combined organics were concentrated *in vacuo* and the resulting crude product was purified by preparative HPLC (Waters SunFire Prep C_{18} OBD 30 x 150 mm column, Lot # 168I161701, 25 mL/min., H_2O:MeCN 95:5 → 5:95 over 20 min., then H_2O:MeCN 5:95 for 15 min.; t_R = 24.84 min with UV detection at 325 and 218 nm) to yield **2.15** (9.6 mg, 41%) [^{1}H NMR analysis demonstrated that this sample contained a small amount (~5-10%) of an unidentified impurity.] An optimized preparative HPLC method was subsequently developed (Waters SunFire Prep C_{18} OBD 30 x 150 mm column, Lot # 168I161701, 33 mL/min., isochratic H_2O:MeCN 20:80; t_R = 21.72 min with UV detection at 325 and 218 nm) that yielded the pure natural product. ^{1}H NMR, ^{13}C NMR, HRMS, and IR analysis of synthetic **2.15** were fully consistent with the data reported for the isolated natural product ratanhine (see below), thus confirming the original structure proposed by Arnone and coworkers.[15]

TLC (Hexanes:EtOAc, 1:1)

$R_f = 0.49$, visualized by UV

^{1}H-NMR (500 MHz, d_6-DMSO)

δ 10.25 (br s, 1H), 9.82 (br s, 1H), 7.52 (s, 1H), 7.48 (d, $J = 8.5$ Hz, 2H), 7.48 (s, 1H), 7.40 (s, 1H), 7.39 (m, 1H), 7.39 (m, 1H), 7.25 (d, $J = 8.5$ Hz, 1H), 7.07 (d, $J = 8$ Hz, 1H), 7.01 (s, 1H), 6.59 (d, $J = 8.5$ Hz, 2H), 6.47 (s, 1H), 6.47 (d, $J = 16$ Hz, 1H), 6.47 (d, $J = 16$ Hz, 1H), 6.31 (dq, $J = 16, 7$ Hz, 1H), 6.23 (dq, $J = 16, 7$ Hz, 1H), 5.51 (s, 1H), 5.44 (s, 1H), 3.86 (s, 3H), 1.86 (m, 3H), 1.86 (m, 3H).

^{13}C-NMR (125 MHz, d_6-DMSO)

δ 163.8, 162.3, 156.8, 156.4, 152.5, 152.1, 146.6, 142.8, 135.3, 135.0, 132.4, 131.7 (2C), 131.1, 130.0, 129.7, 127.7, 127.4, 125.7, 125.2, 123.7, 123.2, 121.6, 120.7, 119.0, 118.8, 117.5, 114.8 (2C), 110.4, 109.5, 103.3, 99.4, 55.5, 18.3, 18.3.

HRMS (TOF ES+)

Calculated for $C_{36}H_{31}O_6$ $(M+H)^+$: 559.2121

Found: 559.2118

IR (thin film, cm^{-1})

3344, 1700, 1608, 1591, 1502, 1447, 1267, 1197, 1163, 1101, 1076, 1031, 964, 912.

^{1}H NMR data for natural[15] and synthetic ratanhine: δ_H/ppm (integration)

Natural **2.15** (300 MHz, d_6-DMSO)	Synthetic **2.15** (500 MHz, d_6-DMSO)
10.22 (1H)	10.25 (1H)
9.78 (1H)	9.82 (1H)
7.52 (1H)	7.52 (1H)
7.51 (2H)	7.48 (2H)
7.51 (1H)	7.48 (1H)
7.41 (1H)	7.40 (1H)
7.39 (1H)	7.39 (1H)
7.38 (1H)	7.39 (1H)
7.24 (1H)	7.25 (1H)
7.07 (1H)	7.07 (1H)
7.02 (1H)	7.01 (1H)
6.62 (2H)	6.59 (2H)
6.50 (1H)	6.47 (1H)
6.47 (1H)	6.47 (1H)
6.47 (1H)	6.47 (1H)
6.31 (1H)	6.31 (1H)
6.23 (1H)	6.23 (1H)
5.53 (1H)	5.51 (1H)
5.46 (1H)	5.44 (1H)
3.87 (3H)	3.86 (3H)
1.86 (3H)	1.86 (3H)
1.86 (3H)	1.86 (3H)

^{13}C NMR data for natural[15] and synthetic ratanhine: δ_C/ppm

Natural **2.15** (69.2 MHz, d_6-DMSO)	Synthetic **2.15** (125 MHz, d_6-DMSO)
163.8	163.8
162.1	162.3
156.7	156.8
156.3	156.4
152.5	152.5
152.0	152.1
146.5	146.6
142.8	142.8
135.3	135.3
134.9	135.0
132.3	132.4
131.7 (2C)	131.7 (2C)
131.0	131.1
130.0	130.0
129.7	129.7
127.7	127.7
127.4	127.4
125.6	125.7
125.1	125.2
123.7	123.7
123.1	123.2
121.6	121.6
120.7	120.7
119.0	119.0
118.7	118.8
117.4	117.5
114.8 (2C)	114.8 (2C)
110.4	110.4
109.5	109.5
103.3	103.3
99.4	99.4
55.4	55.5
18.2	18.3
18.2	18.3

REFERENCES

[1] Pangborn, A. B.; Giardello, M. A; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518-1520.

[2] (a) Stein, A.; Gregor, H. P.; Spoerri, P. E. *J. Am. Chem. Soc.* **1955**, *77*, 191-192. (b) Dubé, C. E.; Mukhopadhyay, S.; Bonitatebus, P. J.; Staples, R. J.; Armstrong, W. H., *Inorg. Chem.*, **2005**, *44*, 5161-5175.

[3] Perner, R. J. and coworkers, *Biorg. Med. Chem. Lett.* **2005**, *15*, 2803-2807.

[4] Friedman, M. R.; Toyne, K. J.; Goodby, J. W.; Hird, M., *J. Mater. Chem.*, **2001**, *11*, 2759-2772.

[5] Albert, J. S.; Aharony, D.; Andisik, D.; Barthlow, H.; Bernstein, P. R.; Bialecki, R. A.; Dedinas, R.; Dembofsky, B. T.; Hill, D.; Kirkland, K.; Koether, G. M.; Kosmider, B. J.; Ohnmacht, C.; Palmer, W.; Potts, W.; Rumsey, W.; Shen, L.; Shenvi, A.; Sherwood, S.; Warwick, P. J.; and Russell, K., *J. Med. Chem.*, **2002**, *45*, 3972-3983.

[6] Lampe, J. W.; Bigger, C. K.; Defauw, J. M; Foglesong, R. J.; Hall, S. E.; Heerding, J. M.; Hollinshead, S. P.; Hu, H.; Hughes, P. F.; Jagdmann, E. J.; Johnson, M. G.; Yen-Shi, L.; Lowden, C. T.; Lynch, M. P.; Mendoza, J. S.; Murphy, M. M.; Wilson, J. W.; Ballas, L. M.; Carter, K.; Darges, J. W.; Davis, J. E.; Hubbard, F. R.; Stamper, M. L. *J. Med. Chem.* **2002**, *45*, 2624-2643.

[7] Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2007**, *129*, 6716-6717.

[8] Ballmer, S. G.; Gillis, E. P.; Burke, M. D. *Org. Synth.* **2009**, *86*, 344-359.

[9] Hoye, T. R.; Eklov, B. M.; Voloshin, M. *Org. Lett.*, **2004**, *6*, 2567-2570.

[10] Still, W. C.; Kahn, M.; Mitra, A.; *J. Org. Chem.* **1978**, *43*, 2923-2925.

[11] Mancilla, T.; Contreras, R. *J. Organomet. Chem.* **1986**, *307*, 1-6.

[12] Mancilla, T.; Zamudio-Rivera, L. S.; Beltrán, H. I.; Santillan, R.; Farfán, N. *ARKIVOC* **2005**, 366-376.

[13] Zhu, L.; Shabbir, S. H.; Gray, M.; Lynch, V. M.; Sorey, S.; Anslyn, E. V. *J. Am. Chem. Soc.* **2006**, *128*, 1222-1232.

[14] An alternative preparation of **2.26** has been previously described: Tsukayama, M.; Hideyuki, U.; Kunugi, A.; Nozaki, H. *Heterocycles*, **1997**, *45*, 1131-1142.

[15] Arnone, A.; Modugno, V.D.; Nasini, G.; de Pava, O.V. *Gazetta Chimica Italiana*, **1990**, *120*, 397-401.

CHAPTER 3

SLOW-RELEASE CROSS-COUPLING OF MIDA BORONATES

Eric P. Gillis, David M. Knapp, Graham R. Dick and Martin D. Burke

In order for the ICC approach to be as broadly applicable as possible, it is necessary that boronic acids representing any structural motif can be efficiently engaged in the SMC reaction. This chapter describes the development of a highly general SMC protocol based on the in situ slow-release of boronic acids from the corresponding MIDA boronates. The scope of this slow-release cross-coupling (SRCC) protocol is demonstrated in numerous high yielding couplings between otherwise unstable boronic acids and aryl chlorides, including couplings of the notoriously unstable 2-pyridyl motif. The condensation of MIDA with borate salts at high temperature was found to be an efficient route to otherwise difficult-to-access MIDA boronates. David M. Knapp contributed to the work presented in this chapter by contributing ideas used in the development of SRCC and by performing the experiments described in Table 3.2, Table 3.3, Table 3.4, Scheme 3.3, and Figure 3.2. Graham R. Dick contributed all of the results described in section 3-6.
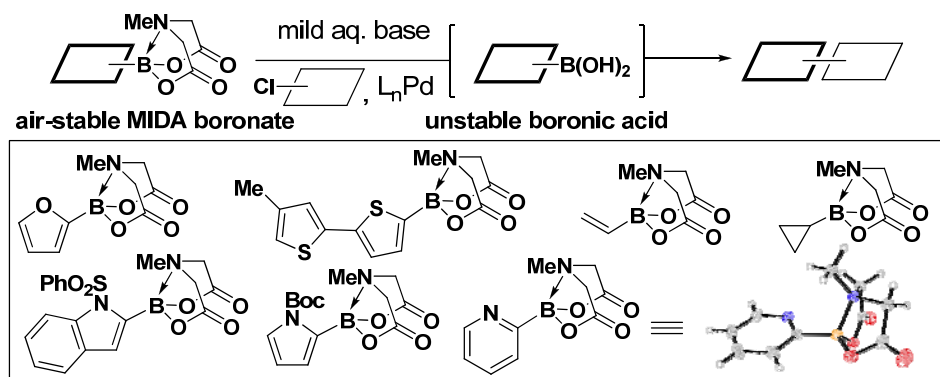
Reproduced with permission from Knapp, D. M.; Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* 2009, *131*, 6961-6963. Copyright 2009 American Chemical Society.

Adapted from Knapp, D. M.; Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2009**, *131*, 6961-6963 and Dick, G. R.; Knapp, D. M.; Gillis, E. P.; Burke, M. D. *Org. Lett.* **2010**, *12*, 2314-2317.

3-1 BACKGROUND

Traditionally efforts towards increasing the substrate scope of the SMC reaction[1] have focused on the design of more reactive catalysts for this transformation.[2] However, despite these remarkable developments certain classes of boronic acids/esters remain ineffective coupling partners in the SMC reaction, especially in reactions employing difficult halide coupling partners such as electron-rich aryl chlorides.[3,4,5] Specifically, boronic acids representing 2-heterocyclic,[3,4,5] vinyl,[6] and cyclopropyl derivatives[7] are known to be particularly sensitive to decomposition. In some cases this instability renders storage of these reagents difficult and limits the ability to input a pure form of the boronic acid to the SMC reaction. In addition, decomposition processes for boronic acids are thought to be accelerated in the presence of heat, base, and/or a Pd catalyst, causing the in situ decomposition of unstable boronic acids to compete with their cross-coupling.[3] This latter challenge is exacerbated in coupling reactions which utilize slower-reacting halides, such as unactivated aryl chlorides.[3]

To address the challenge of using unstable boronic acids in the SMC reaction, efforts have been directed towards developing surrogates for the boron coupling partner that possess more favorable properties.[8] These surrogates include trialkoxy or trihydroxyborate salts,[9,10] diethanolamine adducts,[11] sterically bulky boronic esters,[12] and boroxines.[13] As perhaps the most notable advance, trifluoroborates have emerged as powerful boron coupling partners that address a number of the shortcomings associated with boronic acids. For example, trifluoroborate salts are generally monomeric, free-flowing, crystalline solids, and many of these building blocks are stable to storage under ambient air at room temperature.[14] Trifluoroborate salts can serve as useful surrogates for otherwise unstable boronic acids,[15] and further, the use of trifluoroborate salts in the SMC reaction has also expanded the scope of organic groups which can be transferred from boron in this transformation.[16] However, despite these many advantages, limitations remain. Significantly, the general incompatibility of trifluoroborate salts with SiO_2 chromatography[17,18] limits the efficiency with which these reagents can be functionalized and purified. Further, the use of trifluoroborate salts is associated with the release of HF[19] which can damage glassware and poses a safety and environmental risk. There are a few examples of SMC reactions between 2-heterocyclic trifluoroborate salts and electron-rich

and/or sterically encumbered aryl chlorides (Table 3.1, entries 1-3);[15b] there is also a recent example of a coupling to an electron-rich aryl mesylate (entry 4).[15a] However, it has not been established that 2-heterocyclic trifluoroborates are generally effective coupling partners in reactions with electron-rich aryl chlorides. Further, the stability problems inherent to 2-pyridyl boronic acid cannot be addressed through the use of a trifluoroborate salt.[15c] The lack of a boron reagent class and a SMC protocol by which otherwise unstable boronic acids could be generally and efficiently utilized in SMC couplings with even highly challenging coupling partners such as electron rich- and/or sterically encumbered aryl chlorides prompted us to explore a possible solution to this important and unmet need.

Table 3.1

Entry	Reaction
1	75%
2	62%
3	78%
4	70%

3-2 STABILITY OF BORONIC ACIDS AND MIDA BORONATES TO STORAGE

Although the instability to storage of 2-heterocyclic, vinyl and cyclopropyl boronic acids has frequently been discussed in the literature anecdotally,[3-7] there is very little quantitative data available on this phenomenon. To ground ourselves in a quantitative understanding of the stability of these types of boronic acids, a collection of freshly prepared boronic acids were stored under ambient air at room temperature and the purity of the samples was assayed after 15 days (Table 3.2). Specifically, boronic acids **3.1a–3.1h** were prepared in > 95% purity via base-promoted hydrolysis of the corresponding MIDA boronates **3.2a–3.2h**. In many cases the yield for this transformation was high (entries 1-5). Surprisingly, even vinyl boronic acid (**3.2g**), which has been reported to be unstable to isolation,[6a] could be accessed as a pure material in 45% yield through this approach (entry 7). Multiple samples of each pure boronic acid **3.1a–3.1h** were stored at 23 °C on the benchtop in vials that were sealed under ambient atmosphere. At specific time intervals a sample of each boronic acid was uncapped, assayed via ^{1}H-NMR, and then was discarded. As Table 3.2 indicates, for every boronic acid **3.1a–3.1h** at least some decomposition was observed after 15 days of storage. For boronic acids **3.1a**, **3.1e**, and **3.1f**, the extent of decomposition was so significant that essentially no boronic acid was observed after 15 days, and for **3.1g** nearly complete decomposition (>95%) was observed after just *two days*. Interestingly, the rate of decomposition for **3.1a** was not linear, and may indicate an autocatalytic process.[20] On the other hand, when MIDA boronates were examined under the same storage conditions there was no noticeable change in the composition of the samples even after sixty days. The stability of MIDA boronates to storage is consistent with the previously observed properties of these compounds (chapter 2), and indicates that MIDA boronates might serve as bench-stable surrogates for otherwise unstable boronic acids.

Table 3.2
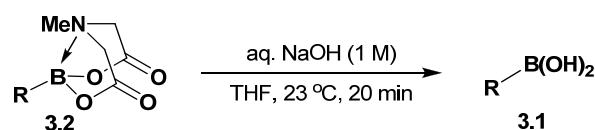
			% remaining after storage under air at 23 °C [a]	
entry	R	% yield 3.2 → 3.1	3.1 (15 days)	3.2 (60 days)
1	a	95%	7	>95[b]
2	b	89%	88	>95
3	c	99%	80	>95
4	d	91%	80	>95[b]
5	e	89%	<5	>95
6	f	65%	<5	>95
7	g	45%	5	>95[b]
8	h	53%	31	>95

[a] Freshly prepared boronic acids **3.1** and MIDA boronates **3.2** were stored as solids on the benchtop under air for 15 and 60 days, respectively. [b] Stored for 107 days.

Reproduced in part with permission from Knapp, D. M.; Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* 2009, *131*, 6961-6963. Copyright 2009 American Chemical Society.

3-3 FAST-RELEASE CROSS-COUPLING OF MIDA BORONATES

Although MIDA boronates can serve as stable surrogates for otherwise unstable boronic acids, the MIDA boronate functionality is inert under anhydrous SMC conditions and requires a separate hydrolysis step to expose the corresponding reactive boronic acid. As indicated above, for many MIDA boronates this deprotection step is straightforward and affords a pure boronic acid product which can be isolated in high yield. However, it would be more expedient if MIDA boronates could be used directly in the SMC reaction.

Further, a number of boronic acids are stable in solution but their isolation can be problematic.[21] Noting that aqueous base is used both to deprotect MIDA boronates *and* as a standard reagent in the SMC reaction, we wondered if a MIDA boronate under aqueous SMC conditions might be deprotected *in situ* to the corresponding boronic acid, and that this boronic acid might be quickly consumed in a SMC reaction. It is known that the MIDA ligand can form complexes with Pd[II] species,[22] and under the proposed aqueous SMC conditions there would likely be at least a 50-fold excess of MIDA relative to the Pd catalyst. An important question to be addressed was whether the MIDA ligand released by deprotecting a MIDA boronate would have a deleterious impact on the reactivity of the Pd catalyst. To address this question, bromoacetophenone **3.3** and biphenyl MIDA boronate **3.4** were exposed to SMC conditions utilizing K_2CO_3 as the base in the presence of bulk water (Scheme 3.1). Analysis of the reaction solution by TLC indicated that a significant amount of triaryl product **3.5** had been formed. This result suggested that the free MIDA ligand (or the diacetate salt of MIDA) did not significantly affect the reactivity of the Pd catalyst.[23]
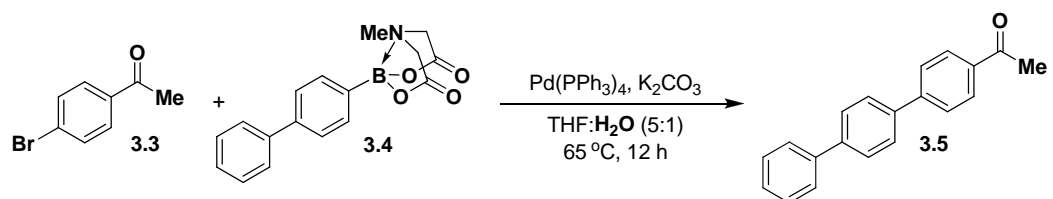
Scheme 3.1. Exposing MIDA boronate **3.4** to aqueous SMC conditions resulted in formation of a significant amount of triaryl product **3.5**. This result is attributed to the in situ deprotection of **3.4** under the action of aqueous base leading to the release of the corresponding reactive boronic acid. The presence of free MIDA ligand in the reaction mixture does not appear to have inhibited the reactivity of the Pd catalyst.

In a subsequent study, the yields obtained in aqueous "direct release" SMC reactions of MIDA boronates were compared to the yields obtained when the corresponding boronic acids were subjected to the otherwise identical reaction conditions (Table 3.3). Of note, these otherwise standard SMC reaction conditions employed an increased amount of base to account for the equivalents of this reagent which are consumed in the deprotection of the MIDA boronate. As described in Table 3.3, in all cases the yields obtained from **3.6** and **3.7** were effectively the same, with the exceptions of entries 5 and 6. In these latter cases the lower yields obtained with **3.6** are likely due to partial decomposition of the boronic acids which were used as received from the

commercial sources. These results provide further evidence that the MIDA ligand (or the diacetate salt of MIDA) does not attenuate the reactivity of the Pd catalyst under "direct release" SMC conditions.

Table 3.3

Entry[a]	3.6 or 3.7: R	aryl bromide	Product	Yield from 3.6 (%)	Yield from 3.7 (%)
1	(4-Me-C₆H₄)	3.8a		96	97
2		3.8b		96	93
3	(3-MeO-C₆H₄)	3.8a		98	98
4		3.8b		94	96
5	(Me(CH₂)₃CH=CH)	3.8a		90	96
6	(PhCH=CH)	3.8a		87	95
7	(4-pyridyl)	3.8a		96	96

[a] Reaction conditions: 1 equiv. aryl bromide, 1.5 equiv. of **3.6** or **3.7**, 7.5 equiv. NaOH, 2 mol % Pd(PPh$_3$)$_4$

MIDA boronates are fully converted to the corresponding boronic acid within 10 minutes upon treatment with aqueous NaOH at room temperature (chapter 2). It was determined that this transformation at 65 °C is also complete after 10 minutes, although it is likely that this process was complete much earlier than this time point. Assuming that the MIDA ligand acts as a spectator species, there is little distinction after the first few minutes between a SMC process performed using pure boronic acid and a "fast-release" SMC process performed using a MIDA boronate with aqueous NaOH present. In essence, both of these reactions necessarily have a similar amount of boronic acid present at any

point in time. As a consequence, although "fast-release" Suzuki-Miyaura couplings employing aqueous NaOH allow MIDA boronates to be used directly in this reaction, and by using MIDA boronates the challenge of storing unstable boronic acids is mitigated, this approach does not address the problem that is faced when the boronic acid is unstable to the conditions of the SMC reaction. For example, it was observed that both freshly-prepared furanyl boronic acid **3.1a** and MIDA boronate **3.2a** performed similarly poorly in a SMC reaction with deactivated aryl chloride **3.9a** (Scheme 3.2). Subsequent experiments (see below) indicate that **3.1a** is prone to rapid deboronation in the presence of aqueous base, which is consistent with the well recognized limitation of using unstable boronic acids in the SMC reaction.[3,4,5]
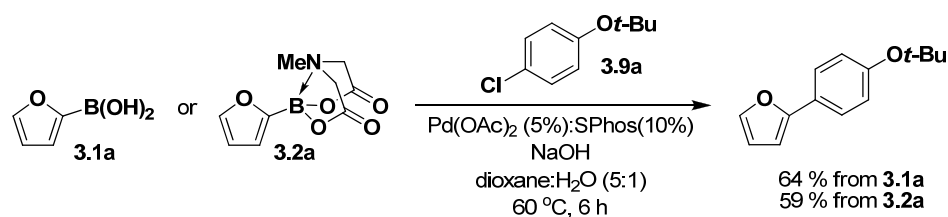
Scheme 3.2. A SMC reaction between **3.1a** and electron-rich aryl chloride **3.9a** proceeded in modest yield. The corresponding MIDA boronate performed similarly poorly under the same SMC reaction conditions. The MIDA boronate is almost certainly completely deprotected within the first few minutes of the reaction, thus both of these reactions necessarily have a similar amount of boronic acid present at any point in time.

3-4 SLOW-RELEASE CROSS-COUPLING OF MIDA BORONATES

A likely explanation for the low yields observed in the SMC reactions presented in Scheme 3.2 is that the rate of consumption of **3.1a** through a productive coupling reaction is competitive with the rate of consumption of **3.1a** through a destructive proto-deboronation reaction. The sub-stoichiometric quantity of catalyst, in this case ≤ 5% relative to the halide, represents a significant bottleneck in the reaction. For example, at the start of the reaction (t = 0) only at most 5% of the boronic acid can undergo a reaction with the palladium catalyst, leaving the remaining 95% of the boronic acid in solution and vunerable to decomposition. Since the decomposition pathways for the boronic acid likely involve water and/or base,[24] but not palladium,[25] the 95% of boronic acid that remains outside of the catalytic cycle will begin to decompose at a rate independent of the turn-over frequency (TOF) of the catalyst. Meanwhile, the productive consumption of the boronic acid *is* dependent on the TOF of the catalyst, the most dilute species in the reaction.

One approach towards increasing the efficiency of SMC reactions employing sensitive boronic acids, where the rate of decomposing of the boronic acid is competitive with the rate of productive coupling, is to increase the amount of catalyst used in the reaction. The effect of adding more catalyst to the reaction is that more catalytic sites will be available; with all reactant concentrations otherwise equal, the increased amount of catalyst will not affect the TOF of the catalyst.[26] With more catalytic sites available to the boronic acid, the bottleneck in the productive consumption of this reagent is reduced. As described in chapter 2, this type of approach was applied successfully to improve the conversion of **2.32** to **2.33**. However, this approach is not practical for highly sensitive boronic acids because the amount of Pd catalyst required to obtain a favorable yield would be prohibitive.

Alternatively, a sensitive boronic acid might be efficiently utilized in a SMC reaction if it were added to the reaction flask at a rate slower than the TOF of the catalyst.[27] The reasoning underlying this hypothesis is that the productive consumption of the boronic acid would be fastest if there was a higher stoichiometry of the catalyst than the borane. That is, the reaction would be fastest if every molecule of boronic acid had access to a free catalytic site at the start of the reaction. For example, assuming that the catalytic species had already been formed from the pre-catalyst, repeating the reaction of Scheme 3.2 with 1/10,000[th] of the original amount of boronic acid would be expected to lead to very high consumption of **3.1a** through the productive versus destructive pathway. Once the catalytic species returned to equilibrium, a second portion of the same very small amount of boronic acid could be added, with the expectation of an equally effective coupling. If in theory if this process was repeated an additional 10,000 times, almost all of the boronic acid might be consumed in a productive coupling. A more reasonable way to implement a similar concept would be to add the boronic acid to the SMC reaction at a rate that is slower than the catalyst TOF. Therefore, to test the hypothesis that slow addition of an unstable boronic acid might lead to an efficient SMC reaction, the coupling experiment of Scheme 3.2 was repeated with the difference that freshly prepared **3.1a** was added to the flask over the course of 3 hours via a syringe pump. Consistent with our hypothesis, a nearly quantitative 98% yield of the biaryl product **3.10a** was isolated (Scheme 3.3).[28] This finding is consistent with the report that slow addition of 3-

thiophenylboronic acid to a SMC reaction led to an improvement in yield relative to if the entirety of the boronic acid was added at the start of the reaction.[3] With this result, we proposed that a similar phenomenon might be observed if, instead of using a syringe-pump, the slow introduction of boronic acid resulted from slow in situ deprotection of a MIDA boronate.
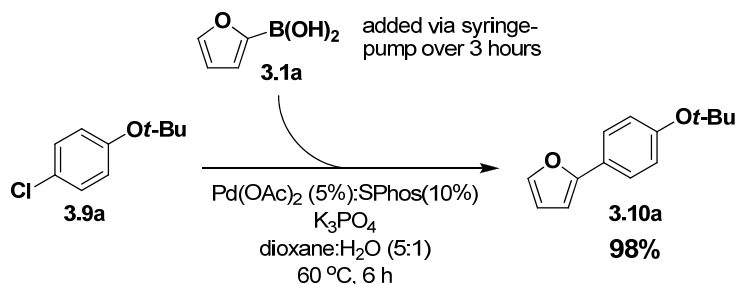
Scheme 3.3. Slow addition of furanyl boronic acid **3.1a** to the SMC to the reaction mixture resulted in nearly quantitative yield of the biaryl product 3.10a. This remarkable increase in yield is attributed to the addition rate of the boronic acid being slower than the TOF of the Pd catalyst.

Discovery of slow-release conditions for MIDA boronates

To test our hypothesis that slow release of boronic acids from MIDA boronates would lead to high yields in the SMC reaction regardless of the sensitivity of the corresponding boronic acid, we first needed to discover conditions that would effect the deprotection of a MIDA boronate at a rate slower than the TOF of the Pd catalyst. Our prior result using a syringe-pump indicated that release of the boronic acid over the course of three hours would likely lead to an efficient SMC reaction. However, to more accurately determine the rates of the processes involved, we first attempted to establish the rate of the SMC reaction between **3.1a** and aryl chloride **3.9a**. To do this, freshly-prepared boronic acid **3.1a** and aryl chloride **3.9a** were combined under the SMC conditions of Scheme 3.3 (but without syringe-pump addition) and the conversion of **3.9a** was monitored over the course of the reaction (Figure 3.1). Consistent with our previous findings described in Scheme 3.2, the reaction stalled at 62% conversion. Still, these results indicated that the SMC reaction required only 30 minutes to reach maximum conversion. To provide evidence that the poor conversion of this reaction was due to the decomposition of the boronic acid, in a subsequent experiment freshly prepared **3.1a** was

combined with aqueous K_3PO_4 and dioxane at 60 °C and the percentage of boronic acid that remained was monitored over the course of six hours (Figure 3.2). Under these conditions approximately 40% of **3.1a** had decomposed within 1 hour, and essentially all of **3.1a** had decomposed within 6 hours. To an approximation, the results presented in Figure 3.2 account for the fact that the coupling between **3.1a** and **3.9a** stalls at 62% conversion within one hour. This coupling likely cannot proceed past 62% conversion because at this point all of **3.1a** has been consumed either through a cross-coupling reaction or a decomposition process. Overall, these experiments indicated that MIDA boronates should be deprotected at 60 °C over the course of *at least 30 minutes* in order to achieve a rate of release that is slower than the TOF of the catalyst.
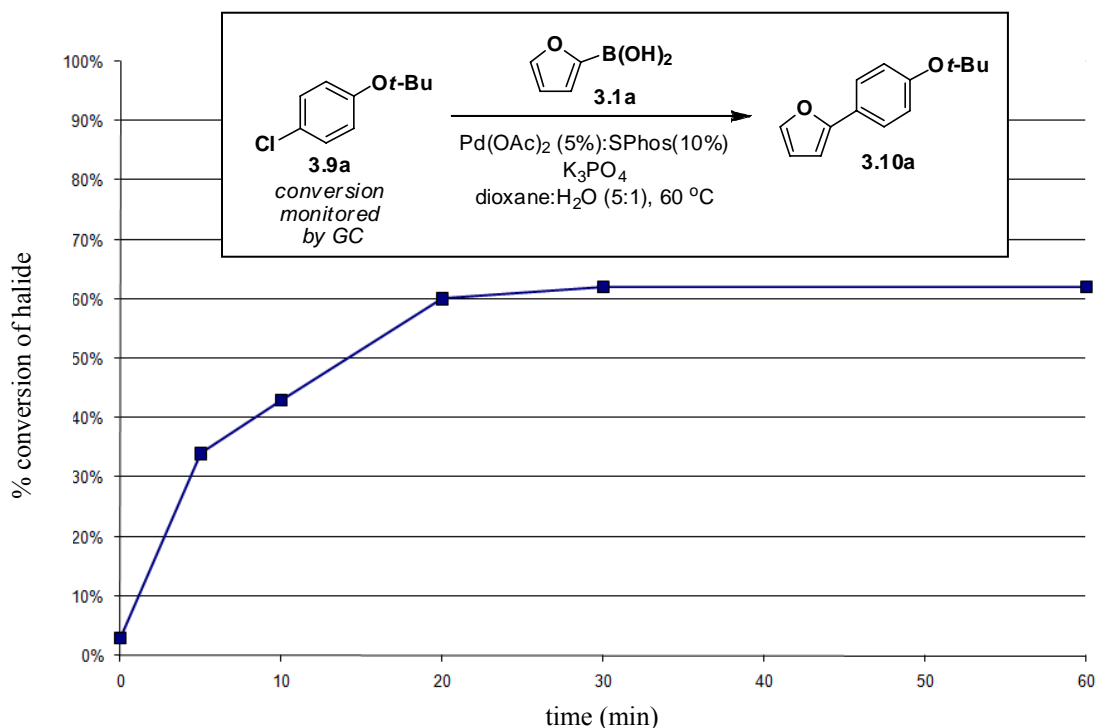
Figure 3.1. The conversion of **3.9a** in a SMC reaction with boronic acid **3.1a** was monitored by GC. These results indicate that this reaction is fast but stalls at 60% conversion. These results are consistent with the previously observation that under similar conditions this coupling affords the product in 64% yield.
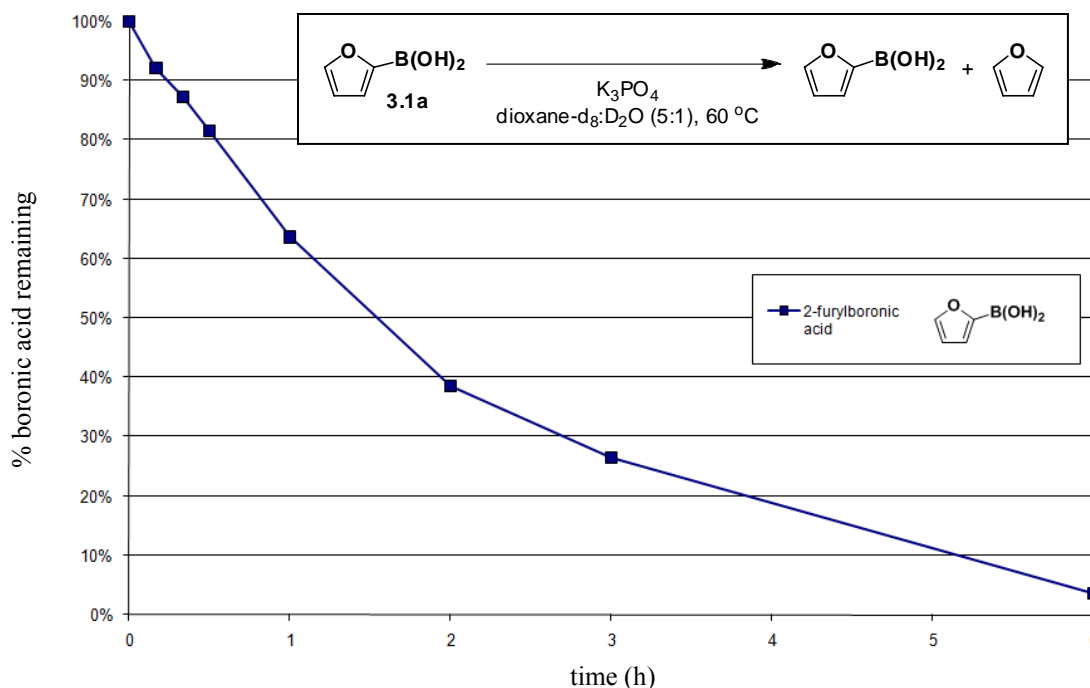
107

Figure 3.2. The rate of decomposition of boronic acid **3.1a** under mock SMC conditions (absent the Pd complex) was monitored by ^{1}H-NMR. Specifically, the amount of boronic acid remaining was determined over the course of six hours.

Early work in the context of testing the stability of MIDA boronates to base (chapter 2, table 2.5) indicated that MIDA boronates upon treatment with aqueous NaHCO$_3$, Na$_2$CO$_3$, K$_2$CO$_3$ or K$_3$PO$_4$ at room temperature hydrolyzed to the corresponding boronic acid. Importantly, it was observed that this process was much slower than when MIDA boronates were treated with NaOH, and in fact was only partially complete after 24 hours. Building on these results, we surveyed the rate of hydrolysis of a MIDA boronate when treated with aqueous K$_3$PO$_4$ at 23 °C, 40 °C and 60 °C and observed by TLC that the rate of hydrolysis increased as the temperature of the reaction increased. Specifically, the hydrolysis reaction at 60 °C was complete between 4 and 12 hours, while the reactions at 23 °C and 40 °C were incomplete after 12 hours.

To quantitatively determine the rate of deprotection of 3.2a upon treatment with aqueous K$_3$PO$_4$, a series of experiments was performed in which 3.2a was dissolved in dioxane-d$_8$ and was treated with K$_3$PO$_4$ in D$_2$O. These reactions were stirred at 60 °C or

100 °C. Every hour a sample at each temperature was diluted with CD$_3$CN, by ^{1}H-NMR the amount of 3.2a remaining was judged against an internal standard, and then the sample was discarded. The results of these experiments are summarized in Figure 3.3 and indicate that at 60 °C the deprotection of 3.2a required between three and four hours to complete. This rate of deprotection is slower than the rate of cross-coupling observed in Figure 3.1, meeting the criteria that the rate of boronic acid release must be slower than the TOF of the catalyst. Even at 100 °C the deprotection of 3.2a required between 30 and 60 minutes to complete. This result suggests that the slow-release cross-coupling approach may be applicable even at 100 °C. On the other hand, at 23 °C the deprotection of 3.2a required 24 hours to complete. Interestingly, in these experiments it was necessary to measure the *N*-CH$_3$ resonances of the MIDA boronates because the diastereotopic methylene protons were completely exchanged for deuterium atoms within the first 10 minutes of treatment with K$_3$PO$_4$ in D$_2$O, even when this reaction was performed at room temperature.
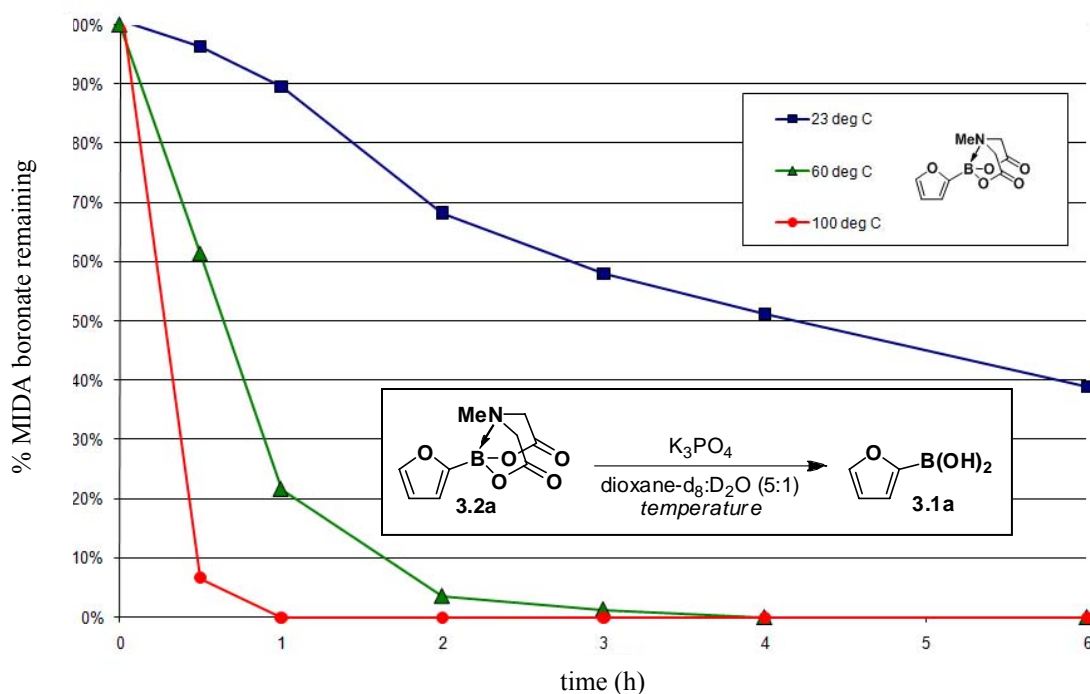
Figure 3.3. The rate of hydrolysis of **3.2a** is dependent on the temperature of the reaction. In all cases the rate of hydrolysis is much slower than the similar reaction employing NaOH. This phenomenon is referred to as "slow-release".

The organic group appended to boron may potentially influence the rate of deprotection of a MIDA boronate. To explore this possibility, a series of experiments was performed in which MIDA boronates representing aryl, heteroaryl, vinyl and alkyl (cyclopropyl) appendages were treated with K_3PO_4 in dioxane-d_8:D_2O at 60 °C and the disappearance of the MIDA boronate was monitored by ^{1}H-NMR as described above (Figure 3.4). Consistent with the growing body of evidence suggesting that the reactivity of MIDA boronates is general, all four classes of MIDA boronates underwent hydrolysis at similar rates, requiring between three and four hours to reach full conversion.
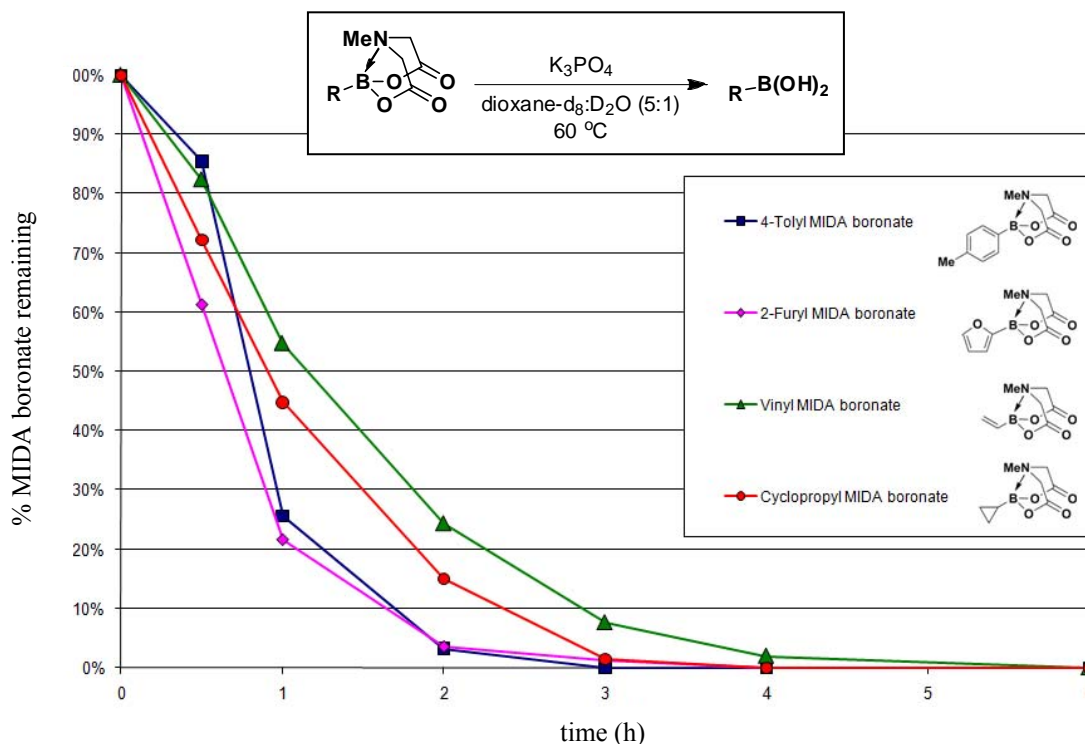
Figure 3.4. The rate of MIDA boronate hydrolysis was found to be general across aryl, heteroaryl, vinyl and alkyl substrates. In all cases the hydrolysis required between three and four hours at 60 °C.

To test our hypothesis that in situ slow-release of a boronic acid from a MIDA boronate would enable the efficient coupling of an otherwise unstable boronic acid, a SMC experiment was performed employing the conditions which were identified to provide a release rate of boronic acid that is slower than the TOF of the catalyst.[27] Specifically, 1.0 equivalent of furanyl MIDA boronate **3.2a** and 1.0 equivalent of aryl

chloride **3.9a** were exposed to aqueous K_3PO_4 under SMC reaction conditions at 60 °C (Table 3.4). In agreement with our hypothesis, the product **3.10a** was isolated in a very high 94% yield (entry 1). The efficiency of this reaction is in agreement with the results obtained through the syringe-pump mediated experiment described in Scheme 3.3. From a methodology standpoint, this result was very exciting because it demonstrated that *only a single equivalent of the MIDA boronate*, serving as stable a surrogate for an otherwise highly sensitive boronic acid, was required to obtain a high yield in a coupling reaction with a very demanding halide partner. Following this result, the efficiency of this slow-release cross-coupling (SRCC) method was compared with the standard coupling of a boronic acid. Specifically, MIDA boronates **3.2b–3.2h** were exposed to the SRCC condition and the yields obtained through this process were compared to the yields obtained through an otherwise identical process employing *freshly prepared* boronic acids **3.1b–3.1h** (Table 3.4). In all cases the SRCC reactions employing MIDA boronates (**3.2**) afforded yields of ≥ 90% using *a single equivalent* of the boron reagent. In contrast, boronic acids **3.1b–3.1g** produced substantially inferior results compared to the yields obtained from **3.2b–3.2g**. Strikingly, the cross-coupling reaction with **3.1f** afforded **3.10f** in only 14% yield while the same coupling with the corresponding MIDA boronate **3.2f** proceeded in 93% yield. Interestingly, freshly prepared boronic acid **3.1h** and MIDA boronate **3.2h** were equally effective in coupling to **3.9a** (entry 8), indicating that many of the challenges associated with the use of **3.1h**[7a] may be primarily attributable to its instability to storage (Table 3.2, entry 8).

Table 3.4

			% isolated yield from cross-coupling[a]	
entry	R	3.10	3.1	3.2
1	**a**	3.10a	68	**94**
2	**b**	3.10b	50	**92**
3	**c**	3.10c	37	**94**
4	**d**	3.10d	45	**96**
5	**e**	3.10e	61	**90**
6	**f**	3.10f	14	**93**
7[d]	**g**	3.10g	79	**98**
8[d]	**h**	3.10h	95	**96**

[a]Reaction conditions: 1.0 equiv of **3.9a** (1 mmol), 1.0 equiv of **3.1** (freshly prepared, >95% pure) or 1.0 equiv of **3.2**, 5 mol % Pd(OAc)$_2$, 10 mol % SPhos, 7.5 equi. K$_3$PO$_4$, 0.07 M in dioxane:H$_2$O 5:1, 60 °C, 6 h. [d]Cross-couplings were run at 100 °C.

The scope of SRCC reactions with aryl chlorides

In theory, the substrate scope of SRCC reactions should be limited only by the substrate scope of the Pd catalyst employed in the reaction and by the ability to identify SMC conditions under which the rate of boronic acid release is slower than the TOF of the catalyst. A further restriction is that the catalyst must be stable for the duration of the boronic acid release. To probe the generality of the SRCC methodology in the coupling of aryl chlorides with otherwise unstable boronic acids, we evaluated the efficiency of a large number of SRCC reactions in which MIDA boronates **3.2a-3.2g** were engaged in couplings with aryl chlorides that are electron-rich (**3.9b**, **3.9d**, **3.9f**, **3.9g**, **3.9h**), electron-neutral (**3.9c**), electron-poor (**3.9e**, **3.9i**), heteroaryl (**3.9d**, **3.9f**, **3.9g**, **3.9h**, **3.9i**), and sterically encumbered (**3.9b**, **3.9c**, **3.9e**) (Table 3.5). The average yield of these reactions was found to be 92%, indicating that the SRCC protocol is general and highly effective. Each coupling reaction was set up without the use of a glove box or glove bag, was generally complete within 6 hours, and in general was executed following the standard SRCC conditions employing only 1.2 equivalents of the MIDA boronate. Exceptions to this generalization are that couplings with vinyl MIDA boronate **3.2g** and cyclopropyl MIDA boronate **3.2h** required heating at 100 °C, and couplings with **3.2g** were best suited to short reaction times (2 h). Entries 7, 8 and 20 employed 1.5 equivalents of the MIDA boronate. Due to the efficiency of these reactions the formation of byproducts was negligible, and any byproducts that were formed were easily removed via aqueous workup followed by chromatography on SiO_2. In contrast to reports on the SMC of potassium vinyl trifluoroborate,[15d] SRCC reactions with **3.2g** did not lead to the formation of byproducts resulting from Heck coupling of the vinyl borane species.

Table 3.5

MeN, B-O, O air-stable MIDA boronates **3.2** + Cl— **3.9** (1 mmol) → **3.10**

Pd(OAc)$_2$, SPhos, K$_3$PO$_4$
dioxane:H$_2$O 5:1
60 °C, 6 h

entry	3.2	3.9	3.10	% isolated yield
1	3.2a	3.9b	3.10i	99
2	3.2a	3.9c	3.10j	97
3	3.2a	3.9d	3.10k	99
4	3.2a	3.9e	3.10l	91
5	3.2b	3.9b	3.10m	94
6	3.2b	3.9f	3.10n	94
7[b]	3.2b	3.9g	3.10o	85
8[b]	3.2b	3.9h	3.10p	85
9	3.2c	3.9b	3.10q	98
10	3.2c	3.9d	3.10r	99
11	3.2c	3.9i	3.10s	97

[a]General reaction conditions: 1 equiv of aryl halide (1 mmol), 1.2 equiv of MIDA boronate, 5 mol % Pd(OAc)$_2$, 10 mol % SPhos, 7.5 equiv of K$_3$PO$_4$, 0.07 M in dioxane:H$_2$O 5:1, 60 °C, 6 h. [b]1.5 equiv of MIDA boronate. [c]0.5 mmol of aryl halide, 0.6 mmol of MIDA boronate (1.2 equiv). [d] 100 °C. [e]2 h. [f] 24 h.

Table 3.5 (Continued)

	air-stable MIDA boronates **3.2**	Cl—⬡ **3.9** 1 mmol Pd(OAc)$_2$, SPhos, K$_3$PO$_4$ dioxane:H$_2$O 5:1 60 °C, 6 h	→ ⬡—⬡ **3.10**	

entry	3.2	3.9	3.10	% isolated yield
12[c]	3.2e	3.9b	3.10t	81
13[c]	3.2e	3.9d	3.10u	98
14	3.2f	3.9b	3.10v	97
15	3.2f	3.9d	3.10w	93
16[d,e]	3.2g	3.9c	3.10x	91
17[d,e]	3.2g	3.9i	3.10y	87
18[d,e]	3.2g	3.9g	3.10z	76
19[d,e]	3.2g	3.9d	3.10aa	96
20[b,d,f]	3.2h	3.9c	3.10bb	79
21[d]	3.2h	3.9b	3.10cc	97

[a]General reaction conditions: 1 equiv of aryl halide (1 mmol), 1.2 equiv of MIDA boronate, 5 mol % Pd(OAc)$_2$, 10 mol % SPhos, 7.5 equiv of K$_3$PO$_4$, 0.07 M in dioxane:H$_2$O 5:1, 60 °C, 6 h. [b]1.5 equiv of MIDA boronate. [c]0.5 mmol of aryl halide, 0.6 mmol of MIDA boronate (1.2 equiv). [d] 100 °C. [e]2 h. [f] 24 h.

The stoichiometry of K$_3$PO$_4$

During the course of our studies on SRCC we discovered that the stoichiometry of the base that is used in the reaction is critical to the reproducibility of the reaction. Specifically, we discovered that if relative to the halide only 5.0 equivalents of K$_3$PO$_4$ are employed in the reaction, the results of the coupling can become very irreproducible. On the other hand, if relative to the halide 7.5 equivalents of K$_3$PO$_4$ are employed, the results of the SRCC reaction are very reproducible. A possible explanation for this difference is that when reduced base is employed the pH of the aqueous phase changes significantly over the course of the reaction, and as a result the rates of the many process which are balanced under the SRCC condition become varied. In any case, SRCC reactions should always be set up using at least 7.5 equivalents of base relative to the halide.

3-5 SYNTHESIS AND CROSS-COUPLING OF 2-PYRYDYL MIDA BORONATE

Encouraged by the success observed using MIDA boronates as surrogates for otherwise unstable boronic acids in SRCC reactions with aryl chlorides, we questioned if the SRCC approach could be extended to include couplings of the notoriously challenging 2-pyridyl motif. A highly effective and air-stable 2-pyridyl borane building block represented a very important objective, as this subunit is found in many pharmaceuticals,[29] natural products and/or their derivatives,[30] unnatural nucleotides,[31] fluorescent probes,[32] metal-complexing ligands,[33] and materials.[34] However, the corresponding boronic acid is notoriously unstable[5,35] and difficult to cross-couple,[5,9a,15c,36] particularly with aryl chlorides.[9a] Current available surrogates are either not air-stable[9a,9b,10] or cannot be isolated in chemically pure form.[11] Based on the general properties of MIDA boronates, we predicted that if 2-pyridyl MIDA boronate could be synthesized, the resulting compound would be stable and isolable in pure form. At this point the stability and structure of MIDA boronate **4.18** (chapter 4) had been confirmed, providing further evidence that otherwise extremely unstable boranes are rendered stable via transformation into the corresponding MIDA boronate. However, it was unclear how the MIDA boronate group might be introduced to the 2-pyridyl motif, and additionally, it was uncertain if 2-pyridyl MIDA boronate would function as an efficient cross-coupling partner in a SMC reaction.

Synthesis of 2-pyridyl MIDA boronate

Consistent with reports on the instability of 2-pyridylboronic acid,[5,35] accessing this boronic acid proved to be very challenging and precluded a route to 2-pyridyl MIDA boronate (**3.11**) based on standard Dean-Stark condensation of MIDA with the boronic acid.[37] Instead, based on the success of its application in the synthesis of vinyl MIDA boronate **3.2g** (chapter 4), we attempted to form 2-pyridyl MIDA boronate **3.11** through C-Si/C-B exchange[38,39] (Scheme 3.4). In this case no formation of **3.11** was observed, likely due to the incompatibility of the very strong Lewis acid BBr$_3$ with the strongly Lewis basic pyridine. In subsequent studies Brice Uno investigated this route by varying the temperature, varying the equivalents of each reagent, and by shielding the nitrogen lone-pair via complexation with BF$_3$·Et$_2$O; however, this route to **3.11** remained unsuccessful.
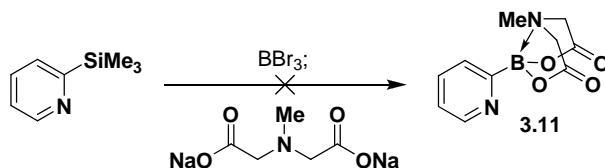
Scheme 3.4. A route to 2-pyridyl MIDA boronate via C-Si/C-B exchange did not prove viable.

Alternatively, 2-pyridyl triisopropyl borate **3.12** can be synthesized from 2-pyridylbromide and can be isolated as a hygroscopic, water-sensitive solid.[9a] Using borate **3.12** as a starting material, we explored conditions for the conversion of **3.12** to **3.11** via complexation with MIDA (Table 3.6). We reasoned that exposure of **3.12** to excess MIDA would neutralize the borate, affording the corresponding diisopropylboronic ester from which two equivalents of *i*-PrOH might be displaced by MIDA to form **3.11**. When **3.12** was contacted with MIDA and the resulting *i*-PrOH formed in the reaction was removed by azeotropic distillation with toluene at up to 110 °C, a small amount (< 2% yield) of **3.11** was isolated (entry 1).[40] When the experiment was repeated and the resulting *i*-PrOH was removed under vacuum from a distilling mixture of DMSO at 45 °C, MIDA boronate **3.11** was isolated in 13% yield (entry 2). Finally, the experiment was repeated employing portion-wise addition of **3.11** as a solid mixture on Celite[41] to a DMSO solution containing **3.12** and MIDA that was distilling at 45 °C under vacuum. Under these conditions a 27% yield of **3.12** was

obtained (entry 3). In agreement with the evidence that the properties of MIDA boronates are general, **3.11** was isolated after SiO$_2$ chromatography as a pure, free-flowing, crystalline solid that demonstrated no change in composition after storage under ambient air at room temperature for 60 days (Figure 3.5). Additionally, **3.11** was found to have good solubility in acetone, MeCN and DMF. To the best of our knowledge, **3.11** represents the first example of an air-stable 2-pyridyl borane that can be isolated in chemically pure form.

Table 3.6
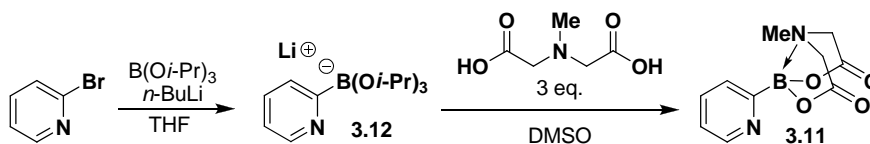
Entry	Distillation temp. (°C)	Pressure (Torr)	Yield of **3.11**
1	110	750	< 2%
2	45	1	18%
3	45	1	27%[a]

[a] **3.12** was added portion-wise to the reaction as a mixture adsorbed on Celite
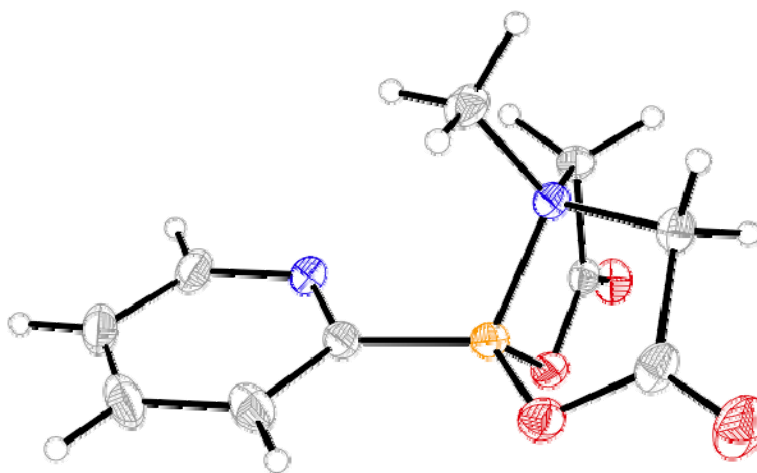
Figure 3.5. The crystal structure of 2-pyridyl MIDA boronate (**3.11**) obtained through X-ray crystallography.

SMC reactions with 2-pyridyl MIDA boronate

With 2-pyridyl MIDA boronate (**3.11**) in hand, our efforts were directed towards identifying conditions under which this reagent could be efficiently utilized in a SMC reaction. When **3.11** was exposed to 4-bromoacetophenone (**3.3**) under conditions similar to the SRCC conditions employed in Table 3.5, no conversion of **3.3** was observed by GC (Table 3.1, entry 1). Copper additives have been reported to be beneficial in SMC reactions employing 2-pyridyl boranes.[9b,11,12c] When the SMC reaction between **3.11** and **3.3** was repeated with the inclusion of 0.2 equivalents of CuI, the formation of **3.13a** was observed by ^{1}H-NMR, in accordance with 11% conversion of **3.3** as observed by GC (entry 2).[42] When DMF:i-PrOH (5:1) was employed in the reaction instead of THF:H_2O (5:1) and K_2CO_3 was used in place of K_3PO_4 the conversion of **3.3** was further improved to 30% (entry 3). By employing pre-catalyst **3.14** in the reaction and adjusting the ratio of DMF:i-PrOH to 1:1 full conversion of **3.3** was realized (entry 4).

Table 3.7
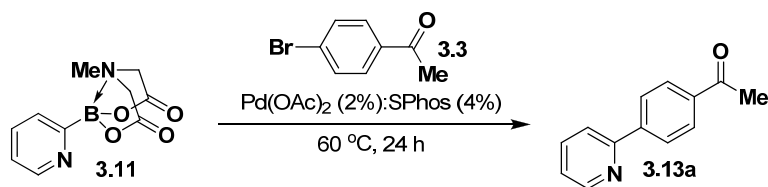
Entry	Solvent	Base (7.5 eq)	Eq. CuI	Conversion of **3.3**
1	THF:H_2O (5:1)	K_3PO_4	0	0%
2	THF:H_2O (5:1)	K_3PO_4	0.2	11%
3	DMF:i-PrOH (5:1)	K_2CO_3	0.2	30%
4	DMF:i-PrOH (1:1)	K_2CO_3	0.2	100%[a]

[a] In place of Pd(OAc)$_2$:SPhos, pre-catalyst **3.14** was employed:

When the optimized condition for the SMC reaction between **3.11** and **3.3** was applied to a SMC reaction between **3.11** and corresponding aryl chloride **3.15a**, only 21% conversion of **3.15a** was observed (Scheme 3.5). In order to improve the conversion of this reaction, we surveyed a number of copper sources [CuI, Cu(SO$_4$)$_2$, CuO, Cu$_2$O,

Cu(NO$_3$)$_2$, CuTC], a number of bases [Ba(OH)$_2$, KOAc, K$_2$CO$_3$, Cs$_2$CO$_3$, CaCO$_3$, TBAF, CsF, K$_3$PO$_4$], and a number of temperatures, solvents and pre-catalysts. From these experiments we determined that Cu(OAc)$_2$ was significantly more effective than CuI; C$_2$CO$_3$ and K$_2$CO$_3$ where equally the most effective bases; and that XPhos:Pd$_2$dba$_3$ was the most useful palladium:ligand combination. Further, the reaction was most successful at 100 °C, with a solvent composition of DMF:*i*-PrOH (4:1). Under these optimized conditions the SMC reaction between **3.11** and **3.15a** afforded the product **3.13a** in 72% yield (Table 3.8, entry 1). Further, we discovered that these conditions were generally effective for a range of aryl chlorides and bromides (Table 3.8). For example, **3.11** underwent efficient coupling with chlorobenzonitrile **3.15b** (entry 2), and chloroheteroarenes **3.15c**–**3.15e** (entries 3–5). SMC reactions between **3.11** and an electron-rich aryl bromide (entry 6) and a heteroaryl bromide (entry 7) were also successful. The coupling between **3.11** and **3.3** furnished **3.14a** in approximately the same yield as the reaction employing the corresponding chloride (entry 8). Finally, bipyridine **3.13h** was accessed through the coupling of **3.11** with 2-bromopyridine (**3.15h**) (entry 9). Collectively, these results and the demonstrated stability of **3.11** to purification and storage indicate that 2-pyridyl MIDA boronate is an effective and useful surrogate for highly unstable 2-pyridylboronic acid in SMC reactions.
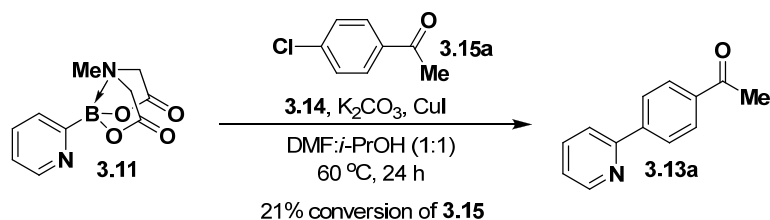
Scheme 3.5. Under conditions optimized for the coupling of 4-bromoacetophenone with **3.11**, coupling of 4-chloroacetophenone with **3.11** remained inefficient.

Table 3.8
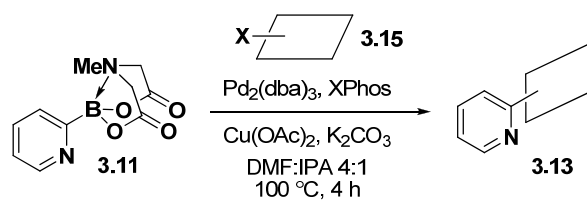
entry	3.15	3.13	% isolated yield
1	3.15a	3.13a	72
2	3.15b	3.13b	60
3	3.15c	3.13c	79
4	3.15d	3.13d	52
5	3.15e	3.13e	74
6	3.15f	3.13f	57
7	3.15g	3.13g	42
8	3.3	3.14a	66
9	3.15h	3.13h	41

[a]Reaction conditions: 1.0 equiv aryl halide **3.15** (1 mmol), 1.5 equiv of MIDA boronate **3.11**, 1.5 mol % Pd$_2$(dba)$_3$, 6 mol % XPhos, 50 mol % Cu(OAc)$_2$, 5 equiv K$_2$CO$_3$, 0.1 M in DMF:IPA 4:1, 100 °C, 4 h.

3-6 AN IMPROVED SYNTHESIS OF 2-PYRIDYL MIDA BORONATE

To improve the efficiency with which 2-pyridyl MIDA boronate (**3.11**) can be accessed, we reinvestigated the synthesis of this reagent. The synthesis of **3.11** as described in Table 3.6 provided small quantities of this boronate that enabled the SMC studies reported above. However, the scalability of this route was limited by the relatively low yield (27%) and technical challenges (solid addition under vacuum) associated with this synthesis. Further, the use of SiO$_2$ chromatography in the purification step made preparation of multi-gram quantities of **3.11** tedious and inefficient. In pursuing the goal of an improved synthesis of **3.11** I had the pleasure of advising a very capable undergraduate student named Graham Dick. The results summarized below are from experiments performed by Graham Dick and are included to place the discoveries of this chapter in the broader context of how SRCC might evolve.

Our first efforts in optimizing the synthesis of **3.11** were directed towards lowering the temperature of the reaction condition used in the conversion of **3.12** to **3.11**, with the goal of suppressing deboronation of **3.12** and/or the corresponding diisopropoxy boronic ester. Further, we intended to eliminate the technically-challenging solid addition of **3.12** associated with our existing procedure by instead adding a THF suspension of **3.12** dropwise to solution of MIDA in DMSO. When this synthesis was performed at temperatures between 25 °C and 55 °C only irreproducible and relatively poor yields of **3.11** were obtained (Figure 3.6). Enabling an alternative approach, it was discovered that 2-pyridyl MIDA boronate does not undergo any detectable change in composition upon heating in DMSO at 130 °C for one hour. This discovery prompted us to investigate *higher* temperatures in the conversion of **3.12** to **3.11**. To our surprise, the yield of the reaction improved substantially as the reaction temperature was increased, where the best yield was obtained when the reaction was run at *130 °C* (Figure 3.6). In practice, a reaction temperature of 115 °C was found to offer the best compromise between a high yield and a technically simple procedure.[43]

Application of the optimized high-temperature MIDA complexation conditions in the synthesis of **3.11** afforded a 59% yield of 2-pyridyl MIDA boronate (Table 3.9, entry 1). These reaction conditions also proved useful in the synthesis of several derivatives of 2-pyridyl MIDA boronate (Table 3.9). Further, a procedure for the isolation of **3.11** was

developed that comprises only trituration and crystallization steps, allowing 2-pyridyl MIDA boronate to be efficiently accessed on a multi-gram scale. Finally, these complexation conditions were found to be effective in the synthesis of 5-thiazole MIDA boronate (**3.19**) (Scheme 3.6) and 2-pyrazinyl MIDA boronate (**3.20**) (Scheme 3.7). To the best of our knowledge, **3.20** represents the first air-stable unsubstituted 2-pyrazinyl borane.
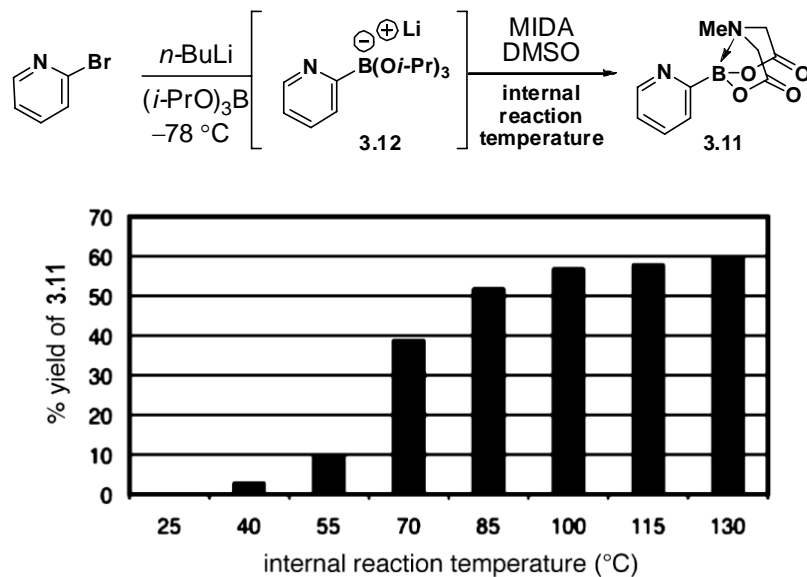
Figure 3.6. Yield of **3.11** (determined via ^{1}H-NMR, average of two runs) as a function of the internal reaction temperature.

Table 3.9

entry	3.17	1	isolated yield (%)
1	3.16i	3.11	59
2	3.17b	3.18b	58
3	3.17c	3.18c	51
4	3.17d	3.18d	42
5	3.17e	3.18e	81
6	3.17f	3.18f	89
7	3.17g	3.18g	56
8	3.17h	3.18h	53
9	3.17i	3.18i	47
10	3.17j	3.18j	69

Reaction conditions: 3.17 → n-BuLi, (i-PrO)$_3$B, THF, -78 °C; MIDA, DMSO, 115 °C → 3.18
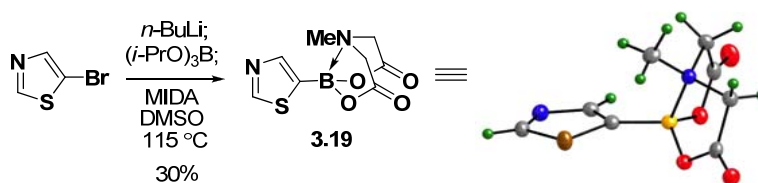
Scheme 3.6. Synthesis of 5-thiazole MIDA boronate (**3.19**).
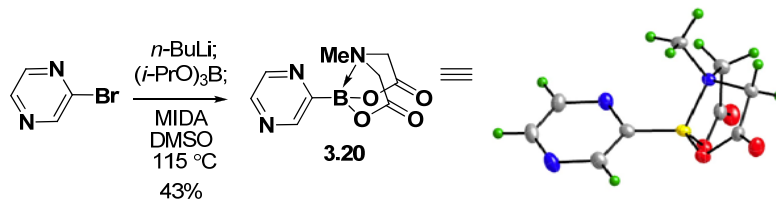
Scheme 3.7. Synthesis of 2-pyrazinyl MIDA boronate (**3.20**).

3-7 SUMMARY

In summary, it was discovered that MIDA boronates, upon treatment with aqueous K_3PO_4, undergo slow hydrolysis to afford the corresponding boronic acid. When MIDA boronates are employed in Suzuki-Miyaura cross-coupling (SMC) reactions with aqueous K_3PO_4 this slow-release phenomenon enables otherwise highly unstable boronic acids to undergo efficient coupling with deactivated aryl chlorides. In combination with the general stability of MIDA boronates to storage under air at room temperature, the slow-release cross-coupling protocol with MIDA boronates represents a general solution to the challenge of utilizing unstable boronic acids in the SMC reaction. As a demonstration of the generality of this approach, a collection of MIDA boronates comprising 2-heterocyclic, vinyl and cyclopropyl motifs was engaged in high yielding SMC reactions with electronically and/or sterically deactivated aryl chlorides. Further, the synthesis of 2-pyridyl MIDA boronate provided the first example of an air-stable 2-pyridyl borane that can be isolated in chemically pure form. Employing modified slow-release cross-coupling conditions, 2-pyridyl MIDA boronate was successfully engaged in SMC reactions with aryl chlorides and aryl bromides. In a subsequent study the synthesis of 2-pyridyl MIDA boronate was substantially improved and a collection of 2-pyridyl

125

MIDA boronate derivatives was accessed. Following the disclosure of the slow-release cross-coupling protocol, others have found this approach useful in different reaction manifolds.[44,45]

3-8 REFERENCES

1 (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457-2483. (b) Miyaura, N. *Top. Cur. Chem.* **2002**, *219*, 11-59.

2 (a) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461-1473. (b) Fu, G. C. *Acc. Chem. Res.* **2008**, *41*, 1555-1564. (c) Marion, N.; Nolan, S. P. *Acc. Chem. Res.* **2008**, *41*, 1440-1449. (d) Littke, A. F.; Fu, G. C. *Angew. Chem. Int. Ed.* **2002**, *41*, 4176-4211.

3 In a recent systematic study, even the powerful biaryldialkylphosphine ligands developed by Buchwald and coworkers failed to promote efficient couplings of 2-substituted furan, thiophene, and pyrrole boronic acids with unactivated aryl chlorides: Billingsley, K.; Buchwald, S.L. *J. Am. Chem. Soc.* **2007**, *129*, 3358-3366.

4 For some examples of coupling 2-heterocyclic boronic acids with activated aryl and acid chlorides, see: (a) Reference 3. (b) Fleckenstein, C.A.; Plenio, H. *J. Org. Chem.* **2008**, *73*, 3236-3244. (c) Burns, M.J.; Fairlamb, I.J.S.; Kapdi, A.R.; Sehnal, P.; Taylor, R.J.K. *Org. Lett.* **2007**, *9*, 5397-5400. (d) Xin, B.; Zhang, Y.; Cheng, K. *J. Org. Chem.* **2006**, *71*, 5725-5731. (e) Pagano, N.; Maksimoska, J.; Bregman, H.; Williams, D.S.; Webster, R.D.; Xue, F.; Meggers, E. *Org. Biomol. Chem.* **2007**, *5*, 1218-1227. (f) There is a single report of coupling excess 2-thiophene and 2-furan boronic acid with the simple unactivated aryl chloride, chlorobenzene: Li, J.-H.; Zhu, Q.-M.; Xie, Y.-X. *Tetrahedron* **2006**, *62*, 10888-10895. For some representative examples of coupling 2-heterocyclic boronic acids with aryl iodides and bromides, see: (g) Takimiya, K.; Kunugi, Y.; Toyoshima, Y.; Otsubo, T. *J. Am. Chem. Soc.* **2005**, *127*, 3605-3612. (h) Thomas, S.W., III; Venkatesan, K.; Mueller, P.; Swager, T.M. *J. Am. Chem. Soc.* **2006**, *128*, 16641-16648. (i) Collis, G.E.; Burrell, A.K.; Blandford, E.J.; Officer, D.L. *Tetrahedron* **2007**, *63*, 11141-11152. (j) Qin, P.; Zhu, H.; Edvinsson, T.; Boschloo, G.; Hagfeldt, A.; Sun, L. *J. Am. Chem. Soc.* **2008**, *130*, 8570-8571. k) Maeda, H.; Haketa, Y.; Nakanishi, T. *J. Am. Chem. Soc.* **2007**, *129*, 13661-13674.

5 Tyrrell, E.; Brookes, P. *Synthesis* **2003**, 469-483.

6 (a) Matteson, D.S. *J. Am. Chem. Soc.* **1960**, *82*, 4228-4233. (b) Peyroux, E. ; Berthiol, F.; Doucet, H.; Santelli, M. *Eur. J. Org. Chem.* **2004**, *5,* 1075-1082. (c) For an

excellent review on the advantages and challenges of vinylation via cross-coupling, see: Denmark, S.E.; Butler, C.R. *Chem. Commun.* **2009**, 20-33.

[7] (a) Cyclopropyl boronic acid decomposes under air primarily via protodeboronation: Todd, R.C.; Josyula, K.V.B.; Gorr, K.; Priebe, K.; Gao, P. *ORGN*780, 233rd ACS National Meeting, Chicago, IL, March 25-29, 2007. For couplings with aryl bromides, see: (b) Wallace, D.J.; Chen, C. *Tetrahedron Lett.* **2002**, *43*, 6987-6990. For couplings with activated aryl and acid chlorides see: (c) Lemhadri, M.; Doucet, H.; Santelli, M. *Synth. Commun.* **2006**, *36*, 121-128. (d) Chen, H.; Deng, M.-Z. *Org. Lett.* **2000**, *2*, 1649-1651.

[8] Silicon reagents can serve as altenative coupling partners for unstable boronic acids: (a) Denmark, S. E.; Smith, R. C.; Chang, W. T.; Muhuhi, J. M. *J. Am. Chem. Soc.*, **2009**, *131*, 3104–3118. (b) Denmark, S. E.; Baird, J. D.; Regens, C. S. *J. Org. Chem.*, **2008**, *73*, 1440–1455. (c) Denmark, S. E.; Baird, J. D. *Org. Lett.* **2006**, *8*, 793-795. (d) Denmark, S. E.; Butler, C. R. *J. Am. Chem. Soc.* **2008**, *130*, 3690-3704.

[9] (a) Lithium triisopropyl 2-pyridylborate salts can be coupled to unactivated aryl chlorides, but the lack of air-stability of these reagents is an important limitation: Billingsley, K.L.; Buchwald, S.L. *Angew. Chem. Int. Ed.* **2008**, *47*, 4695-4698. For additional studies with pre-formed borate salts, see: (b) Yamamoto, Y.; Takizawa, M.; Yu, X.-Q., Miyaura, N. *Angew. Chem. Int. Ed.* **2008**, *47,* 928-931. (c) Cammidge, A.N.; Goddard, V.H.M.; Gopee, H.; Harrison, N.L.; Hughes, D.L.; Schubert, C.J.; Sutton, B.M.; Watts, G.L.; Whitehead, A.J. *Org. Lett.* **2006**, *8*, 4071-4074. (d) O'Neill, B.T.; Yohannes, D.; Bundesmann, M.W.; Arnold, E.P. *Org. Lett.* **2000**, *2*, 4201-4204. (e) Reference 10.

[10] (a) As pointed out by Molander and coworkers, a previously described moderate yielding coupling between an aryl bromide and 2-pyridyl methylboronic ester in fact likely employed the air-sensitive 2- pyridyl trimethylborate salt: Sindkhedkar, M.D.; Mulla, H.R.; Wurth, M.A.; Cammers-Goodwin, A. *Tetrahedron* **2001**, *57*, 2991-2996. (b) The same seems to be the case in: Fernando, S.R.L.; Maharoof, U.S.M.; Deshayes, K.D.; Kinstle, T.H.; Ogawa, M.Y. *J. Am. Chem. Soc.* **1996**, *118*, 5783-5790.

[11] (a) *N*-phenyldiethanolamine 2-pyridylboronate is prepared as a structurally undefined

complex containing variable quantities of isopropyl and *N*-phenyldiethanolamine groups and a stoichiometric quantity of lithium: Hodgson, P.B.; Salingue, F.H. *Tetrahedron Lett.* **2004**, *45*, 685-687. (b) Jones, N.A.; Antoon, J.W.; Bowie, A.L.; Borak, J.B.; Stevens, E.P. *J. Heterocyclic Chem.* **2007**, *44*, 363-367. (c) Solid-supported diethanolamine adducts: M. Gravel, K.A. Thompson, M. Zak, C. Bérubé, D.G. Hall, *J. Org. Chem.* **2002**, *67*, 3-15. (d) A solid-supported diethanolamine-bound 2-pyridyl reagent has also been reported: Gros, P.; Doudouh, A.; Fort, Y. *Tetrahedron Lett.* **2004**, *45* 6239-6241.

[12] (a) Lightfoot, A.P.; Twiddle, S.J.R.; Whiting, A. *SynLett* **2005**, *3*, 529-531. (b) Yang, D.X.; Colletti, S.L.; Wu, K.; Song, M.; Li, G.Y.; Shen, H.C. *Org. Lett.* **2009** *11*, 381-384. (c) 2-pyridyl pinacol boronic esters can be coupled to aryl bromides in the presence of CuCl. However, although there is a single reported example, this approach has not been shown to be generally effective with aryl chlorides: Deng, J.Z.; Paone, D.V.; Ginnetti, A.T.; Kurihara, H.; Dreher, S.D.; Weissman, S.A.; Stauffer, S.R.; Burgey, C.S. *Org. Lett.* **2009**, *11*, 345-347.

[13] (a) Perkins, J.R.; Carter, R.G. *J. Am. Chem. Soc.* **2008**, *130*, 3290-3291. (b) Kerins, F.; O'Shea, D.F. *J. Org. Chem.* **2002**, *67*, 4968-4971. (c) Cioffi, C.L.; Spencer, W.T.; Richards, J.J.; Herr, R.J. *J. Org. Chem.* **2004**, *69*, 2210-2212.

[14] (a) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275-286. (b) Molander, G. A.; Figueroa, R.; *Aldrichimica Acta* **2005**, *38*, 49-56.

[15] For couplings of 2-heterocyclic trifluoroborates see: (a) Molander, G. A.; Beaumard, F. *Org. Lett.* **2010**, *12*, 4022-4025. (b) Molander, G. A.; Canturk, B.; Kennedy, L. E. *J. Org. Chem.* **2009**, *74*, 973-980. (c) Molander, G. A.; Miolatto, B. *J. Org. Chem.* **2003**, *68*, 4302-4314. For couplings of vinyl trifluoroborate see: (d) Molander, G. A.; Brown, A. R. *J. Org. Chem.* **2006**, *71*, 9681-9686. For couplings of cyclopropyl trifluoroborate see: (e) Molander, G. A.; Gormisky, P. E. *J. Org. Chem.* **2008**, *73*, 7481-7485.

[16] (a) Molander, G. A.; Sandrock, D. L. *Curr. Opinion Drug. Disc. Dev.* **2009**, *12*, 811-823. (b) Molander, G. A.; Jean-Gérard, L. *J. Org. Chem.* **2009**, *74*, 1297-1303. (c) Dreher, S. D.; Lim, S-E.; Sandrock, D. L.; Molander, G. A. *J. Org. Chem.* **2009**, *74*, 3626-3631. (d) Molander, G. A.; Jean-Gérard, L. *J. Org. Chem.* **2009**, *74*, 5446-5450.

(e) Dreher, S. P.; Dormer, P. G.; Sandrock, D. L.; Molander, G. A. *J. Am. Chem. Soc.* **2008**, *130*, 9257-9259. (f) Molander, G. A.; Canturk, B. *Org. Lett.* **2008**, *10*, 2135-2138. (g) Molander, G. A.; Gormisky, P. E.; Sandrock, D. L. *J. Org. Chem.* **2008**, *73*, 2052-2057. (h) Molander, G. A.; Petrillo, D. E. *Org. Lett.* **2008**, *10*, 1795-1798. (i) Molander, G. A.; Jean-Gérard, L. *J. Org. Chem.* **2007**, *72*, 8422-8426. (j) Molander, G. A.; Sandrock, D. L. *Org. Lett.* **2007**, *9*, 1597-1600.

[17] Darses, S.; Genet, J.-P. *Chem. Rev.* **2008**, *108*, 288–325.

[18] Molander, G. A.; Cavalcanti, L. N.; Canturk, B.; Pan, P-S.; Kennedy, L. E. *J. Org. Chem.* **2009**, *74*, 7364-7369.

[19] Butters, M.; Harvey, J. N.; Jover, J.; Lennox, A. J. J.; Lloyd-Jones, G.; Murray, P. M. *Angew. Chem. Int. Ed.* **2010**, *49*, 1-6

[20] For the other boronic acids studied the rate of decomposition was either to fast or too slow to determine if the rate of decomposition was accelerating.

[21] For example, isolation of **1g** was complicated by the volatility of this boronic acid. In another case, the boronic acid shown below is stable in solution but decomposes upon concentration (Uenishi, J.; Matsui, K.; Wada, A.; *Tetrahedron Lett.* **2003**, *44*, 3093-3096.):

[22] Smith, B. B.; Sawyer, D. T. *Inorg. Chem.* **1968**, *7*, 1526-1532.

[23] This result was used as a starting point for my colleague Suk Joong Lee to develop and apply "direct release" SMC conditions with a MIDA boronate in the synthesis of ½ of amphotericin B: Lee, S. J.; Gray, K. C.; Paek, J. S.; Burke, M. D. *J. Am. Chem. Soc.* **2008**, *130*, 466-468.

[24] Hall, D. G. *Boronic Acids*; Wiley-VCH: Weinheim, Germany, **2005**, chapter 1.

[25] The absence of a difuranyl byproduct which would indicate homo-coupling of the boronic acid indicates that Pd-catalyzed decomposition of the boronic acid is not a significant factor in the loss of **1a**.

[26] Boudart, M.; Tamaru, K. *Catal. Lett.* **1991**, 15-22.

[27] In this statement and similar usages herein, "a rate slower than the TOF of the catalyst" refers to a rate slower than the TOF of the catalyst if the catalyst were employed in a SMC reaction in which all of the boronic acid was added at the beginning of the reaction.

[28] The use of K_3PO_4 instead of NaOH does not contribute to the difference in yield. The same reaction performed *without* syringe pump addition of **3.1a** leads to a 68% yield. See Table 3.4, entry 1.

[29] (a) DeGoey, D. A.; *et al. J. Med. Chem.* **2009**, *52*, 2571-2586. (b) Heim-Riether, A.; *et al. Bioorg. Med. Chem. Lett.* **2009**, *19*, 5321-5324. (c) Robarge, K. D.; *et al. Bioorg. Med. Chem. Lett.* **2009**, *19*, 5576-5581.

[30] (a) Aida, W.; Ohtsuki, T.; Li, X.; Ishibashi, M. *Tetrahedron* **2008**, *65*, 369-373. (b) Kubota, N. K.; Ohta, E.; Ohta, S.; Koizumi, F.; Suzuki, M.; Ichimura, M.; Ikegami, S. *Bioorg. Med. Chem.* **2003**, *11*, 4569-4575. (c) Nicolaou, K. C.; *et al. Chem. Bio.* **2000**, *7*, 593-599.

[31] (a) Hwang, G. T.; Hari, Y.; Romesberg, F. E. *Nucleic Acids Res.* **2009**, *37*, 4757-4763. (b) Gutierrez, A. J.; Terhost, T. J.; Matteucci, M. D.; Froehler, B. C. *J. Am. Chem. Soc.* **1994**, *116*, 5540-5554.

[32] Tang, B.; Yu, F.; Li, P.; Tong, L.; Duan, X.; Xie, T.; Wang, X. *J. Am. Chem. Soc.* **2009**, *131*, 3016-3023.

[33] (a) Havas, F.; Leygue, N.; Danel, M.; Mestre, B.; Galaup, C.; Picard, C. *Tetrahedron* **2009**, *65*, 7673-7686. (b) Schubert, U. S.; Eschbaumer, C. *Org. Lett.* **1999**, *1*, 1027-1029.

[34] (a) Chi, C. C.; Chiang, C. L.; Liu, S. W.; Yueh, H.; Chen, C. T.; Chen, C. T. *J. Mat. Chem.* **2009**, *19*, 5561-5571. (b) Whittell, G. R.; Manners, I. *Adv. Mat.* **2007**, *19*, 3439-3468. (c) Yamaguchi, Y.; Kobayashi, S.; Miyamura, S.; Okamoto, Y.; Wakamiya, T.; Matsubara, Y.; Yoshida, Z. *Angew. Chem. Int. Ed.* **2004**, *43*, 366-369.

[35] Fischer, F. C.; Havinga, E. *Recl. Trav. Chim. Pays-Bas* **1974**, *93*, 21-24.

[36] Selected examples of coupling 2-pyridyl boranes with aryl bromides and iodides (a) Deshayes, K.; Broene, R. D.; Chao, I.; Knobler, C. B.; Diedrich, F. *J. Org. Chem.* **1991**, *56*, 6787-6795. (b) Mandolesi, S. D.; Vaillard, S. E., Podestá, J. C., Rossi, R. A.

Organometallics **2002**, *21*, 4886-4888. (c) Bouillon, A.; Lancelot, J.-C.; Sopkova de Oliveira Santos, J.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2003**, *59*, 10043-10049. For examples with 2-pyridyl pinacol boronic esters, see references 12b-c and 36c.

[37] However, even the sensitive boronates **3.2a**, **3.2b**, **3.2c**, and **3.2h** can be accessed efficiently through the Dean-Stark protocol.

[38] Li, H.; Sundararaman, A.; Venkatasubbaiah, K; Jäkle, F. *J. Am. Chem. Soc.* **2007**, *129*, 5792-5793.

[39] Uno, B. E.; Gillis, E. P.; Burke, M. D. *Tetrahedron* **2009**, *65*, 3130-3138.

[40] The product was significantly contaminated with hydroxy MIDA boronate. Graham Dick later demonstrated that the formation of hydroxyl MIDA boronate is directly related to the amount of adventitious water present in the MIDA starting material, where hydroxy MIDA boronate likely arises from protodeboronation of 2-pyridylboronic acid and condensation of the boric acid byproduct with MIDA.
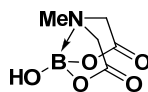
hydroxy MIDA boronate

[41] Addition of **3.12** as a solution in DMSO was not practical because the solution foamed uncontrollably under vacuum.

[42] On the other hand, when AgI, AI, $ZnBr_2$ or ZnI_2 were used in place of CuI the yield of **3.13a** was in all cases found to be < 2 %.

[43] Prolonged reaction temperatures in excess of 120 °C lead to decomposition of DMSO and a strong and displeasing odor in the subsequent workup.

[44] Brak, K.; Ellman, J. A. *J. Org. Chem.* **2010**, *75*, 3147-3150.

[45] Recent evidence indicates that couplings with trifluoroborates are in fact slow-release cross-coupling reactions as well: Butters, M.; Harvey, J. N.; Jover, J.; Lennox, A. J. J.; Lloyd-Jones, G.; Murray, P. M. *Angew. Chem. Int. Ed.* **2010**, *49*, 1-6.

CHAPTER 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 and amines were dried as noted in chapter 2. MIDA boronate **3.2g** was synthesized according to the literature procedure.[1] MIDA boronates **3.2a–3.2f** and **3.2h** and boronic acids **3.1a–3.1h** were prepared by David Knapp.[2] MIDA boronates **3.18b–3.18j**, **3.19** and **3.20** were prepared by Graham Dick.[3]

General Experimental Procedures. The general experimental procedures followed in these studies are the same as those detailed in chapter 2, except where noted. Column chromatography was performed using standard methods[4] or on an Teledyne-Isco CombiFlash Rf purification system using Merck silica gel grade 9385 60Å (230-400 mesh). For loading, compounds were adsorbed onto Celite *in vacuo* from an acetone solution. Specifically, for a 1 g mixture of crude material the sample is dissolved in reagent grade acetone (25 to 50 mL) and to the flask is added Celite 454 Filter Aid (5 to 15 g). The mixture is then concentrated *in vacuo* to afford a powder, which is then loaded on top of a silica gel column. The procedure is typically repeated with a small amount of acetone (5 mL) and Celite (2 g) to ensure quantitative transfer.

Structural analysis. Structural analysis was performed and described as detailed in chapter 2.

Kinetics Studies

Kinetics of boronic acid cross-coupling (Figure 3.1)

Under ambient atmosphere, to a 25 mL Schlenk flask equipped with a stir bar was added 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos) (41 mg, 0.10 mmol), Pd(OAc)$_2$ (11 mg, 0.050 mmol) and freshly-prepared 2-furylboronic acid (**3.1a**) (106 mg, 0.949 mmol). The flask was placed under Ar atmosphere and to the flask was added dioxane (12.5 mL). To the solution was added dodecane (100 μL, internal standard) and 1-*tert*-butoxy-4-chlorobenzene (**3.9a**) (175 μL, 0.980 mmol), and the solution was stirred at 23 °C for 10 minutes. The solution was sampled and analyzed by GC to determine the ratio of halide:dodecane. To the dark amber solution was added aq. K$_3$PO$_4$ (3.0 M, 2.5 mL, degassed by sparging with Ar for 30 min) and the dark mixture was stirred for 5 minutes. The organic phase was sampled as the initial time-point (t=0), and the mixture was then immediately placed in a 60 °C oil bath with stirring. The organic phase was sampled periodically and the consumption of the halide was determined by GC analysis versus the internal standard.

Kinetics of in-situ boronic acid decomposition (Figure 3.2)

A stock solution of 2-furylboronic acid (**3.1a**) and 4-bromoanisole (internal std) in dioxane-d$_8$ was prepared as follows: 2-furylboronic acid (9 mg, 0.08 mmol) and 4-bromoanisole (15 mg, 0.080 mmol) were dissolved in dioxane-d$_8$ (1.0 mL). To each of eight argon-filled 1.5 mL vials equipped with stir bars and sealed with PTFE-lined septum-screwcaps was added the boronic acid stock solution (100 μL), followed by a solution of K$_3$PO$_4$ in D$_2$O (3.0 M, 20 μL) by syringe. The mixtures were heated to 60 °C with stirring for the specified time (10 min, 20 min, 30 min, 1 h, etc.) The mixtures were then immediately quenched by the addition of a solution of pH 7 potassium phosphate buffer in D$_2$O (2M, 120 μL) and were diluted with DMSO-d$_6$ (0.5 mL, containing TMS internal std). The resulting solutions, once cooled to 23 °C, were immediately analyzed by ^{1}H NMR. The percent boronic acid remaining was calculated by comparing the ratio

of the integrated 4-bromoanisole C-H signal (doublet, 7.41 ppm) to that of the boronic acid C-H signal (doublet, 7.74 ppm).

Kinetics of slow-release of boronic acids from MIDA boronates (Figure 3.3)

Stock solutions of the MIDA boronate and 4-bromoanisole (internal std.) in dioxane-d_8 were prepared as follows: 4-tolyl MIDA boronate (16 mg, 0.064 mmol) and 4-bromoanisole (12 mg, 0.065 mmol) were dissolved in dioxane-d_8 (800 μL); 2-furyl MIDA boronate (**3.1a**) (54 mg, 0.24 mmol) and 4-bromoanisole (45 mg, 24 mmol) were dissolved in dioxane-d_8 (3.0 mL); vinyl MIDA boronate (**3.1g**) (11.7 mg, 0.064 mmol) and 4-bromoanisole (12 mg, 0.065 mmol) were dissolved in dioxane-d_8 (800 μL); cyclopropyl MIDA boronate (**3.1h**) (12.8 mg, 0.065 mmol) and 4-bromoanisole (12.0 mg, 0.064 mmol) were dissolved in dioxane-d_8 (800 μL). To each 1.5 mL vial equipped with a small stir bar was added the boronate stock solution (100 μL) followed by a solution of K_3PO_4 in D_2O (3.0 M, 20 μL). The mixtures were stirred at the specified temperature (23 °C, 60 °C, or 100 °C) for the specified time (0.5 h, 1.0 h, 2.0 h, etc.). The mixtures were then immediately cooled to room temperature and were diluted with CD_3CN (0.5 mL containing TMS internal std). The solutions were immediately analyzed by ^{1}H-NMR. The percent MIDA boronate remaining was calculated by comparing the ratio of the integrated 4-bromoanisole OCH_3 singlet (3.76 ppm, internal std) to that of the MIDA boronate NCH_3 singlet (tolyl = 2.47 ppm; furyl = 2.60 ppm; vinyl = 2.77 ppm; cyclopropyl = 2.98 ppm).

"Fast-Release" kinetics

To a 1.5 mL vial equipped with a small stir bar was added the 2-furyl MIDA boronate stock solution (100 μL) followed by a solution of NaOH in D_2O (3.0 M, 20 μL). The mixture was stirred at 60 °C for 10 min. The mixture was diluted with CD_3CN (0.5 mL containing TMS internal std) and was immediately analyzed by ^{1}H-NMR. This analysis revealed complete hydrolysis of the MIDA boronate.

Slow-release cross-coupling with MIDA boronates (Table 3.5)

General Procedure

  Under ambient atmosphere, to a 40 mL I-Chem vial equipped with a stir bar was added the aryl chloride (1.00 mmol), the MIDA boronate (1.20 mmol), dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl (SPhos) (41 mg, 0.10 mmol) and Pd(OAc)$_2$ (11 mg, 0.050 mmol). The vial was sealed with a PTFE-lined septum screw-cap, and then placed under an Ar atmosphere. To the vial was added dioxane (12.5 mL) and the resulting mixture was stirred at 23 °C for 10 min. To the vial was added aq K$_3$PO$_4$ (3.0 M, 2.5 mL, degassed by sparging with Ar for 30 min). The vial was placed in a 60 °C oil bath with stirring for 6 h. The mixture was cooled to room temperature, and was then transferred to a 60 mL separatory funnel and diluted with aq NaOH (1.0 M, 10 mL). The mixture was extracted with Et$_2$O (3 × 10 mL). The combined organic fractions were dried over MgSO$_4$, filtered, and then concentrated *in vacuo*. The resulting residue was subjected to flash-chromatography on silica gel (hexanes:EtOAc).
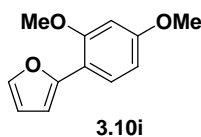
2-(2,4-dimethoxyphenyl)furan[5] (**3.10i**) [Table 3.5, Entry 1]

  The general procedure was followed using 1-chloro-2,4-dimethoxybenzene (**3.9b**) (173 mg, 1.00 mmol), 2-furan MIDA boronate (**3.2a**) (267 mg, 1.20 mmol), SPhos (41 mg, 0.10 mmol) and Pd(OAc)$_2$ (12 mg, 0.052 mmol) to afford **3.10i** as a pale orange liquid (202 mg, 99%).

TLC (hexanes:EtOAc 9:1)
  R$_f$ = 0.36, visualized by UV (λ = 254 nm)

136

^{1}H-NMR (500 MHz, CDCl$_3$ w/ TMS)

δ 7.74 (d, J = 8.5 Hz, 1H), 7.41 (d, J = 1.0 Hz, 1H), 6.79 (d, J = 3.5 Hz, 1H), 6.55 (dd, J = 8.5, 2.5 Hz, 1H), 6.52 (d, J = 2.0 Hz, 1H), 6.46 (q, J = 2.0 Hz, 1H), 3.89 (s, 3H), 3.82 (s, 3H)

^{13}C-NMR (125 MHz, CDCl$_3$)

δ 159.9, 156.5, 150.4, 140.4, 126.8, 113.4, 111.4, 107.8, 104.6, 98.7, 55.4 (2 carbons)

HRMS (EI+)

Calculated for C$_{12}$H$_{12}$O$_3$ (M)$^+$:   204.0787

Found: 204.0790

IR (thin film, cm^{-1})

3002, 2960, 2937, 2836, 1614, 1585, 1514, 1468, 1418, 1307, 1288, 1270, 1208, 1160, 1054, 1029, 1003, 827, 798, 735
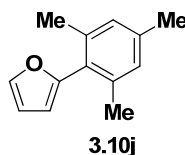
3.10j

2-(2,4,6-trimethylphenyl)furan[6] (**3.10j**) [Table 3.5, Entry 2]

The general procedure was followed using mesityl chloride (**3.9c**) (154 mg, 1.00 mmol), 2-furyl MIDA boronate (**3.2a**) (267 mg, 1.20 mmol), SPhos (42 mg, 0.10 mmol) and Pd(OAc)$_2$ (11 mg, 0.049 mmol) to afford **3.10j** as a colorless crystalline solid (181 mg, 97%).

TLC (hexanes)

R$_f$ = 0.40, visualized by UV (λ = 254 nm)

¹H-NMR (500 MHz, CDCl₃ w/ TMS)

> δ 7.46 (s, 1H), 6.90 (s, 2H), 6.44 (t, *J* = 3.0 Hz, 1H), 6.23 (d, *J* = 3.0 Hz, 1H), 2.28 (s, 3H), 2.15 (s, 6H)

^{13}C-NMR (125 MHz, CDCl₃)

> δ 152.4, 141.4, 138.3, 138.3, 128.2, 128.2, 110.3, 109.0, 21.0, 20.4

HRMS (EI+)

> Calculated for C₁₃H₁₄O (M)$^+$:   186.1045
> Found: 186.1043

IR (thin film, cm^{-1})

> 2975, 2954, 2919, 1612, 1505, 1473, 1440, 1373, 1257, 1212, 1169, 1148, 1028, 1005, 898, 863, 743
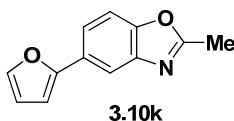
3.10k

5-(2-furanyl)-2-methylbenzoxazole (3.10k) [Table 3.5, Entry 3]

The general procedure was followed using 5-chloro-2-methylbenzoxazole (**3.9d**) (168 mg, 1.00 mmol), 2-furyl MIDA boronate (**3.2a**) (266 mg, 1.19 mmol), SPhos (41 mg, 0.10 mmol) and Pd(OAc)₂ (11 mg, 0.049 mmol) to afford **3.10k** as a pale orange crystalline solid (198 mg, 99%).

TLC (hexanes:EtOAc 3:1)

> R$_f$ = 0.30, visualized by UV (λ = 254 nm)

¹H-NMR (500 MHz, CDCl₃ w/ TMS)

> δ 7.93 (d, *J* = 1.0 Hz, 1H), 7.61 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.47 (d, *J* = 1.0 Hz, 1H), 7.44 (d, *J* = 8.5 Hz, 1H), 6.63 (d, *J* = 3.5 Hz, 1H), 6.47 (dd, *J* = 3.5, 2.0 Hz, 1H), 2.62 (s, 3H)

^{13}C-NMR (125 MHz, CDCl$_3$)

δ 164.5, 153.7, 150.3, 141.9, 141.9, 127.6, 120.8, 114.6, 111.6, 110.3, 104.6, 14.5

HRMS (EI+)

Calculated for C$_{12}$H$_9$NO$_2$ (M)$^+$:   199.0633

Found: 199.0634

IR (KBr, cm^{-1})

2934, 2857, 1576, 1504, 1458, 1383, 1300, 1269, 1228, 1170, 1011, 885, 811
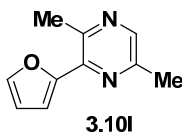
3-(2-furanyl)-2,5-dimethylpyrazine[7] (**3.10l**) [Table 3.5, Entry 4]

The general procedure was followed using 3-chloro-2,5-dimethylpyrazine (**3.9e**) (143 mg, 1.00 mmol), 2-furyl MIDA boronate (**3.2a**) (267 mg, 1.20 mmol), SPhos (41 mg, 0.10 mmol) and Pd(OAc)$_2$ (11 mg, 0.049 mmol) to afford **3.10l** as a golden liquid (159 mg, 91%).

TLC (hexanes:EtOAc 3:1)

R$_f$ = 0.28, visualized by UV (λ = 254 nm)

^{1}H-NMR (500 MHz, CDCl$_3$ w/ TMS)

δ 8.20 (s, 1H), 7.61 (d, J = 1.0 Hz, 1H), 7.00 (d, J = 3.5 Hz, 1H), 6.54 (dd, J = 3.0, 1.5 Hz, 1H), 2.74 (s, 3H), 2.54 (s, 3H)

^{13}C-NMR (125 MHz, CDCl$_3$)

δ 151.7, 150.2, 146.5, 143.9, 142.5, 141.2, 112.3, 111.7, 23.3, 21.2

HRMS (EI+)

Calculated for $C_{10}H_{10}N_2O$ (M)$^+$:   174.0793

Found: 174.0799

IR (thin film, cm^{-1})

3116, 3038, 2966, 2926, 2858, 2359, 2228, 1553, 1537, 1449, 1446, 1389, 1357, 1289, 1255, 1220, 1203, 1174, 1149, 1095, 1061, 1012, 973, 928, 886, 867, 821, 735, 596
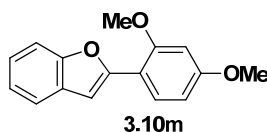
3.10m

2-(2,4-dimethoxyphenyl)benzofuran (**3.10m**) [Table 3.5, Entry 5]

The general procedure was followed using 1-chloro-2,4-dimethoxybenzene (**3.9b**) (172 mg, 1.00 mmol), 2-benzofuranyl MIDA boronate (**3.2b**) (328 mg, 1.20 mmol), SPhos (41 mg, 0.10 mmol) and Pd(OAc)$_2$ (12 mg, 0.051 mmol) to afford **3.10m** as a colorless liquid (239 mg, 94%)

TLC (hexanes:EtOAc 9:1)

R_f = 0.25, visualized by UV (λ = 254 nm)

^{1}H-NMR (500 MHz, CDCl$_3$ w/ TMS)

δ 7.97 (d, *J* = 8.5 Hz, 1H), 7.56 (d, *J* = 7.5 Hz, 1H), 7.48 (d, *J* = 7.5 Hz, 1H), 7.24-7.17 (m, 3H), 6.60 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.55 (d, *J* = 2.0 Hz, 1H), 3.95 (s, 3H), 3.84 (s, 3H)

^{13}C-NMR (125 MHz, CDCl$_3$)

δ 160.8, 157.7, 153.6, 152.4, 130.0, 127.9, 123.5, 122.5, 120.7, 112.7, 110.6, 104.8, 104.2, 98.7, 55.4, 55.4

HRMS (EI+)

Calculated for $C_{16}H_{14}O_3$ $(M)^+$:   254.0943
Found: 254.0941

IR (thin film, cm^{-1})

3002, 2960, 2937, 2834, 1611, 1586, 1503, 1452, 1291, 1255, 1211, 1160, 1050, 1032, 1013
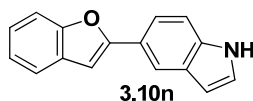
3.10n

5-(2-benzofuranyl)indole[8] (**3.10n**) [Table 3.5, Entry 6]

The general procedure was followed using 5-chloroindole (**3.9f**) (153 mg, 1.01 mmol), 2-benzofuranyl MIDA boronate (**3.2b**) (329 mg, 1.20 mmol), SPhos (41 mg, 0.10 mmol) and Pd(OAc)$_2$ (12 mg, 0.053 mmol). The extraction step was modified to use Et$_2$O (10 mL), then EtOAc (2 x 10 mL). Benzofuran **3.10n** was isolated as a pale yellow solid (220 mg, 94%).

TLC (hexanes:EtOAc 3:1)

R_f = 0.31, visualized by UV (λ = 254 nm)

^{1}H-NMR (500 MHz, acetone-d$_6$)

δ 10.44 (br s, 1H), 8.23 (s, 1H), 7.74 (dd, J = 8.5, 1.5 Hz, 1H), 7.59 (d, J = 7.0 Hz, 1H), 7.56 (app. d, J = 8.5 Hz, 2H), 7.41 (t, J = 3.0 Hz, 1H), 7.26 (td, J = 7.5, 1.0 Hz, 1H), 7.22 (td, J = 7.5, 1.0 Hz, 1H), 7.13 (s, 1H), 6.62 (t, J = 2.0 Hz, 1H)

^{13}C-NMR (125 MHz, acetone-d$_6$)

δ 158.7, 155.4, 137.4, 130.7, 129.2, 126.9, 124.3, 123.6, 122.6, 121.3, 119.7, 118.0, 112.7, 111.5, 103.1, 100.0

HRMS (EI+)

Calculated for $C_{16}H_{11}NO$ (M)$^+$:   233.0841

Found: 233.0843

IR (KBr, cm^{-1})

3439, 1582, 1475, 1458, 1444, 1417, 1332, 1295, 1254, 1020, 1006, 890, 877, 807, 753, 728, 594, 487, 442, 410
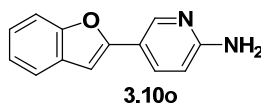
3.10o

5-(2-benzofuranyl)-2-pyridinamine (3.10o) [Table 3.5, Entry 7]

The general procedure was followed using 2-amino-5-chloropyridine (**3.9g**) (128 mg, 1.00 mmol), 2-benzofuranyl MIDA boronate (**3.2b**) (359 mg, 1.50 mmol), SPhos (41 mg, 0.10 mmol) and Pd(OAc)$_2$ (12 mg, 0.052 mmol). The extraction step was modified to use Et$_2$O (10 mL), then EtOAc (2 x 10 mL). Benzofuran **3.10o** was isolated as a pale orange solid (180 mg, 85%).

TLC (EtOAc)

R_f = 0.45, visualized by UV (λ = 254 nm)

^{1}H-NMR (500 MHz, acetone-d$_6$)

δ 8.57 (d, J = 2.0 Hz, 1H), 7.89 (dd, J = 9.0, 2.5 Hz, 1H), 7.57 (d, J = 8.5 Hz, 1H), 7.50 (d, J = 8.5 Hz, 1H), 7.24 (td, J = 7.5, 1.5 Hz, 1H), 7.20 (td, J = 7.5, 1.5 Hz, 1H), 7.03 (d, J = 1.0 Hz, 1H), 6.66 (d, J = 8.5 Hz, 1H), 5.85 (br s, 2H)

^{13}C-NMR (125 MHz, acetone-d$_6$)

δ 160.8, 155.9, 155.3, 146.1, 134.6, 130.4, 124.4, 123.8, 121.3, 116.6, 111.5, 108.8, 99.4

HRMS (EI+)

Calculated for $C_{13}H_{10}N_2O$ $(M)^+$:   210.0793

Found: 210.0793

IR (KBr, cm^{-1})

3436, 3308, 3114, 3106, 2964, 1650, 1614, 1574, 1500, 1451, 1399, 1352, 1321, 1294, 1271, 1254, 1207, 1151, 1142, 1040, 1007, 934, 918, 835, 806, 747, 532, 515, 450, 412
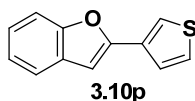
3.10p

2-(3-thienyl)benzofuran[9] (**3.10p**) [Table 3.5, Entry 8]

The general procedure was followed using 3-chlorothiophene (**3.9h**) (119 mg, 1.01 mmol), 2-benzofuranyl MIDA boronate (**3.2b**) (360 mg, 1.50 mmol), SPhos (41 mg, 0.10 mmol) and Pd(OAc)$_2$ (11 mg, 0.050 mmol) to afford **3.10p** as a colorless solid (171 mg, 85%).

TLC (hexanes:EtOAc 9:1)

R$_f$ = 0.53, visualized by UV (λ = 254 nm)

^{1}H-NMR (500 MHz, CDCl$_3$ w/ TMS)

δ 7.67 (d, J = 1.5 Hz, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.40 (d, J = 4.5 Hz, 1H), 7.32 (dd, J = 4.5, 3.0 Hz, 1H), 7.24 (t, J = 7.5 Hz, 1H), 7.19 (t, J = 7.5 Hz, 1H), 6.77 (s, 1H)

^{13}C-NMR (125 MHz, CDCl$_3$)

δ 154.5, 152.6, 132.2, 129.0, 126.5, 125.0, 124.0, 122.9, 121.4, 120.8, 111.0, 101.0

HRMS (EI+)

Calculated for $C_{12}H_8OS$ (M)$^+$:   200.0296

Found: 200.0295

IR (KBr, cm^{-1})

3100, 1607, 1452, 1280, 1255, 1041, 944, 854, 807, 785, 749, 601, 436
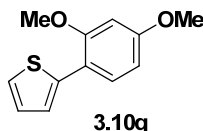
3.10q

2-(2,4-dimethoxyphenyl)thiophene[10] (**3.10q**) [Table 3.5, Entry 9]

The general procedure was followed using 1-chloro-2,4-dimethoxybenzene (**3.9b**) (173 mg, 1.00 mmol), 2-thiophenyl MIDA boronate (**3.2c**) (285 mg, 1.19 mmol), SPhos (41 mg, 0.10 mmol) and Pd(OAc)$_2$ (11 mg, 0.051 mmol) to afford **3.10q** as a pale golden liquid (215 mg, 98%).

TLC (hexanes:EtOAc 9:1)

$R_f = 0.27$, visualized by UV ($\lambda = 254$ nm)

^{1}H-NMR (500 MHz, CDCl$_3$ w/ TMS)

δ 7.53 (d, $J = 9.5$ Hz, 1H), 7.37 (d, $J = 3.5$ Hz, 1H), 7.25 (d, $J = 5.5$ Hz, 1H), 7.05 (t, $J = 4.5$ Hz, 1H), 6.53-6.51 (m, 2H), 3.88 (s, 3H), 3.82 (s, 3H)

^{13}C-NMR (125 MHz, CDCl$_3$)

δ 160.1, 156.7, 139.6, 129.3, 126.7, 124.3, 124.2, 116.5, 105.0, 98.9, 55.5, 55.4

HRMS (EI+)

Calculated for $C_{12}H_{12}O_2S$ (M)$^+$:   220.0558

Found: 220.0563

IR (thin film, cm^{-1})

   3102, 3069, 3000, 3959, 3937, 2835, 1610, 1577, 1528, 1464, 1432, 1417, 1354, 1303, 1273, 1242, 1210, 1160, 1114, 1031, 959, 927, 848, 824, 798, 697, 577
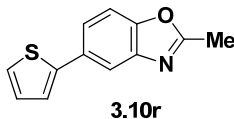
3.10r

2-methyl-5-(2-thienyl)benzoxazole (3.10r) [Table 3.5, Entry 10]

   The general procedure was followed using 5-chloro-2-methylbenzoxazole (**3.9d**) (168 mg, 1.00 mmol), 2-thiophenyl MIDA boronate (**3.2c**) (287 mg, 1.20 mmol), SPhos (41 mg, 0.10 mmol) and Pd(OAc)$_2$ (11 mg, 0.051 mmol) to afford **3.10r** as a crystalline pale yellow solid (213 mg, 99%).

TLC (hexanes:EtOAc 3:1)

   R_f = 0.35, visualized by UV (λ = 254 nm)

^{1}H-NMR (500 MHz, CDCl$_3$ w/ TMS)

   δ 7.85 (d, J = 1.0 Hz, 1H), 7.50 (dd, J = 8.0, 1.5 Hz, 1H), 7.39 (d, J = 8.5 Hz, 1H), 7.26 (d, J = 3.0 Hz, 1H), 7.24 (d, J = 5.0 Hz, 1H), 7.04 (dd, J = 5.0, 3.5 Hz, 1H), 2.59 (s, 3H)

^{13}C-NMR (125 MHz, CDCl$_3$)

   δ 164.4, 150.3, 144.0, 142.1, 130.9, 127.9, 124.6, 123.0, 122.8, 116.6, 110.2, 14.4

HRMS (EI+)

   Calculated for C$_{12}$H$_9$NOS (M)$^+$:   215.0405
   Found: 215.0403

IR (KBr, cm^{-1})

   3098, 3064, 1622, 1577, 1473, 1428, 1380, 1271, 1160, 1050, 923, 867, 798
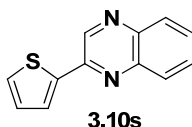
2-(2-thienyl)quinoxaline[11] (**3.10s**) [Table 3.5, Entry 11]

The general procedure was followed using 1-chloroisoquinoline (**3.9i**) (165 mg, 1.00 mmol), 2-thiophenyl MIDA boronate (**3.2c**) (287 mg, 1.20 mmol), SPhos (41 mg, 0.10 mmol) and Pd(OAc)$_2$ (11 mg, 0.050 mmol) to afford **3.10s** as a yellow solid (206 mg, 97%).

TLC (hexanes:EtOAc 3:1)

R_f = 0.42, visualized by UV (λ = 254 nm)

^{1}H-NMR (500 MHz, CDCl$_3$ w/ TMS)

δ 9.20 (s, 1H), 8.04 (app d, J = 8.0 Hz, 2H), 7.82 (s, 1H), 7.71 (t, J = 7.0 Hz, 1H), 7.66 (t, J = 7.0 Hz, 1H), 7.52 (d, J = 4.0 Hz, 1H), 7.17 (s, 1H)

^{13}C-NMR (125 MHz, CDCl$_3$)

δ 147.2, 142.1, 142.0, 141.9, 141.2, 130.3, 129.7, 129.1, 129.0, 129.0, 128.3, 126.8

HRMS (EI+)

Calculated for C$_{12}$H$_8$N$_2$S (M)$^+$:   212.0408

Found: 212.0407

IR (thin film, cm^{-1})

3118, 3093, 1573, 1547, 1491, 1428, 1321, 1238, 1208, 1134, 1054, 998, 941, 926, 852
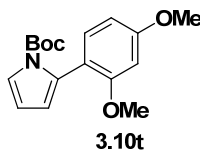
3.10t

N-(*tert*-butoxycarbonyl)-2-(2,3-dimethoxyphenyl)pyrrole (3.10t) [Table 3.5, Entry 12]

The general procedure was followed using 1-chloro-2,4-dimethoxybenzene (**3.9b**) (87 mg, 0.51 mmol), 2-(N-*tert*-butoxycarbonyl)pyrrole MIDA boronate (**3.2e**) (196 mg, 0.61 mmol), SPhos (20 mg, 0.048 mmol), Pd(OAc)$_2$ (6 mg, 0.03 mmol), K$_3$PO$_4$ (3.0 M, 1.25 mL) and dioxane (6.0 mL) to afford **3.10t** as a very pale yellow oil (124 mg, 81%).

TLC (hexanes:EtOAc 3:1)

R$_f$ = 0.59, visualized by UV (λ = 254 nm)

^{1}H-NMR (500 MHz, CDCl$_3$ w/ TMS)

δ 7.32 (s, 1H), 7.17 (d, *J* = 8.0 Hz, 1H), 6.48 (d, *J* = 8.5 Hz, 1H), 6.45 (s, 1H), 6.22 (t, *J* = 3.0 Hz, 1H), 6.10 (s, 1H), 3.82 (s, 3H), 3.72 (s, 3H), 1.36 (s, 9H)

^{13}C-NMR (125 MHz, CDCl$_3$)

δ 160.7, 158.3, 149.4, 131.1, 130.6, 121.6, 117.0, 113.5, 110.2, 103.4, 98.2, 82.6, 55.3, 55.2, 27.6

HRMS (EI+)

Calculated for C$_{17}$H$_{21}$NO$_4$ (M)$^+$:   303.1471

Found: 303.1469

IR (thin film, cm^{-1})

2976, 2938, 2834, 1736, 1617, 1584, 1512, 1464, 1437, 1419, 1394, 1370, 1341, 1316, 1209, 1159, 1127, 1034, 974, 840, 726
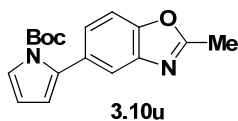
3.10u

5-(N-*tert*-butoxycarbonyl-pyrrole)-2-methylbenzoxazole (3.10u) [Table 3.5, Entry 13]

The general procedure was followed using 5-chloro-2-methylbenzoxazole (**3.9d**) (84 mg, 0.50 mmol), 2-(N-*tert*-butoxycarbonyl)pyrrole MIDA boronate (**3.2e**) (195 mg, 0.61 mmol), SPhos (21 mg, 0.050 mmol), Pd(OAc)$_2$ (6 mg, 0.03 mmol), K$_3$PO$_4$ (3.0 M, 1.25 mL) and dioxane (6.0 mL) to afford **3.10u** as a very pale yellow oil (146 mg, 98%).

TLC (hexanes:EtOAc 3:1)

R$_f$ = 0.42, visualized by UV (λ = 254 nm)

^{1}H-NMR (500 MHz, CDCl$_3$ w/ TMS)

δ 7.63 (s, 1H), 7.43 (d, *J* = 8.5 Hz, 1H), 7.36 (s, 1H), 7.28 (d, *J* = 8.5 Hz, 1H), 6.23 (t, *J* = 3.0 Hz, 1H), 6.20 (s, 1H), 2.64 (s, 3H), 1.34 (s, 9H)

^{13}C-NMR (125 MHz, CDCl$_3$)

δ 164.2, 150.2, 149.1, 140.9, 134.4, 130.6, 126.1, 122.4, 120.0, 114.7, 110.4, 109.0, 83.5, 27.5, 14.5

HRMS (EI+)

Calculated for C$_{17}$H$_{18}$N$_2$O$_3$ (M)$^+$:   298.1318
Found: 298.1317

IR (thin film, cm^{-1})

2982, 1739, 1584, 1584, 1456, 1395, 1365, 1370, 1336, 1313, 1264, 1166, 1140, 985, 906, 836, 809
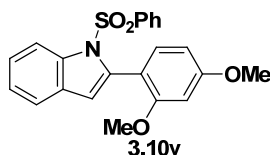
N-phenylsulfonyl-2-(2,3-dimethoxyphenyl)indole (**3.10v**) [Table 3.5, Entry 14]

The general procedure was followed using 1-chloro-2,4-dimethoxybenzene (**3.9b**) (173 mg, 1.00 mmol), 1-(phenylsulfonyl)indole-2-MIDA boronate (**3.2f**) (495 mg, 1.20 mmol), SPhos (42 mg, 0.10 mmol) and Pd(OAc)$_2$ (11 mg, 0.049 mmol) to afford **3.10v** as an off-white solid (382 mg, 97%).

TLC (hexanes:EtOAc 3:1)

Rf = 0.37, visualized by UV (λ = 254 nm)

^{1}H-NMR (500 MHz, acetone-d$_6$)

δ 8.19 (d, J = 8.0 Hz, 1H), 7.57-7.53 (m, 3H), 7.50 (d, J = 7.5 Hz, 1H), 7.43 (t, J = 7.5 Hz, 2H), 7.32 (dt, J = 7.0, 1.0 Hz, 1H), 7.23 (t, J = 7.5 Hz, 1H), 7.17 (d, J = 8.0 Hz, 1H), 6.62 (d, J = 2.0 Hz, 1H), 6.58 (dd, J = 8.0, 2.0 Hz, 1H), 6.56 (s, 1H), 3.87 (s, 3H), 3.72 (s, 3H)

^{13}C-NMR (125 MHz, acetone-d$_6$)

δ 163.0, 160.6, 139.4, 139.3, 138.1, 134.5, 133.2, 131.3, 129.8, 127.4, 125.0, 124.5, 121.5, 116.1, 115.0, 113.0, 104.7, 98.8, 55.7, 55.7

HRMS (EI+)

Calculated for C$_{12}$H$_{19}$NO$_4$S (M)$^+$: 393.1035

Found: 393.1036

IR (KBr, cm^{-1})

3000, 2978, 2938, 2842, 1617, 1501, 1449, 1445, 1360, 1284, 1239, 1187, 1163, 1121, 1093, 1069, 1048, 832, 752, 728, 681, 582, 559
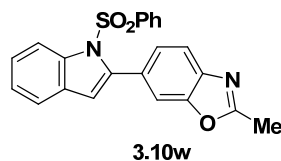
3.10w

5-(N-phenylsulfonyl-indole)-2-methylbenzoxazole (**3.10w**) [Table 3.5, Entry 15]

The general procedure was followed using 5-chloro-2-methylbenzoxazole (**3.9d**) (168 mg, 1.00 mmol), 1-(phenylsulfonyl)indole-2-MIDA boronate (**3.2f**) (495 mg, 1.20 mmol), SPhos (41 mg, 0.10 mmol) and Pd(OAc)$_2$ (12 mg, 0.052 mmol) to afford **3.10w** as an off-white solid (366 mg, 93%).

TLC (hexanes:EtOAc 1:1)

R_f = 0.36, visualized by UV (λ = 254 nm)

^{1}H-NMR (500 MHz, acetone-d$_6$)

δ 8.27 (d, J = 8.5 Hz, 1H), 7.78 (d, J = 1.0 Hz, 1H), 7.61 (d, J = 8.5 Hz, 1H), 7.55 (t, J = 7.5 Hz, 1H), 7.51 (d, J = 8.0 Hz, 2H), 7.45 (app. d, J = 8.0 Hz, 2H), 7.39 (app. t, J = 8.0 Hz, 3H), 7.28 (dt, J = 7.0, 1.0 Hz, 1H), 6.75 (s, 1H), 2.65 (s, 3H)

^{13}C-NMR (125 MHz, acetone-d$_6$)

δ 165.6, 152.3, 142.9, 142.4, 139.3, 138.6, 134.8, 131.7, 129.9, 129.6, 128.2, 127.5, 125.8, 125.4, 122.0, 121.9, 117.3, 114.9, 110.1, 14.4

HRMS (EI+)

Calculated for C$_{22}$H$_{16}$N$_2$O$_3$S (M)$^+$: 388.0882
Found: 388.0880

IR (thin film, cm^{-1})

3063, 3012, 1712, 1623, 1581, 1477, 1449, 1432, 1365, 1262, 1220, 1177, 1157, 1122, 1092, 1065, 1021, 999, 921, 823
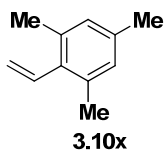
3.10x

2,4,6-trimethylstyrene[12] (**3.10x**) [Table 3.5, Entry 16]

The general procedure was followed using mesityl chloride (**3.9c**) (155 mg, 1.01 mmol), vinyl MIDA boronate (**3.2g**) (220 mg, 1.20 mmol), SPhos (41 mg, 0.10 mmol) and Pd(OAc)$_2$ (12 mg, 0.051 mmol). The reaction time and temperature were modified so that the reaction mixture was heated to 100 °C for 2 h. Styrene **3.10x** was isolated as a colorless liquid (150 mg, 91%; yield corrected for residual **3.9c**).

TLC (hexanes)

R$_f$ = 0.64, visualized by UV (λ = 254 nm)

^{1}H-NMR (500 MHz, CDCl$_3$ w/ TMS)

δ 6.86 (s, 2H), 6.66 (dd, J = 18.0, 11.5 Hz, 1H), 5.50 (dt, J = 11.5, 2.0 Hz, 1H), 5.23 (dt, J = 18.0, 2.0 Hz, 1H), 2.27 (s, 6H), 2.26 (s, 3H)

^{13}C-NMR (125 MHz, CDCl$_3$)

δ 136.1, 135.7, 135.0, 134.8, 128.5, 119.0, 20.9, 20.8

HRMS (EI+)

Calculated for C$_{11}$H$_{14}$ (M)$^+$:   146.1096
Found: 146.1098

IR (thin film, cm^{-1})

3080, 2999, 2952, 2918, 2856, 1631, 1612, 1481, 1442, 1376, 994, 919, 850
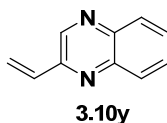
3.10y

2-vinylquinoxaline (3.10y) [Table 3.5, Entry 17]

The general procedure was followed using 2-chloroquinoxaline (**3.9i**) (165 mg, 1.00 mmol), vinyl MIDA boronate (**3.2g**) (219 mg, 1.20 mmol), SPhos (41 mg, 0.10 mmol) and Pd(OAc)$_2$ (11 mg, 0.051 mmol). The reaction time and temperature were modified so that the reaction mixture was heated to 100 °C for 2 h. Following the aqueous workup, the crude residue was subjected to purification on C$_{18}$ silica gel (43g RediSep column) eluting with H$_2$O:THF (95:5 → 55:45, 24 mL/min over 25 min) to afford **3.10y** as an orange oil (133 mg, 87%).

TLC (hexanes:EtOAc 3:1)

R_f = 0.31, visualized by UV (λ = 254 nm)

^{1}H-NMR (500 MHz, CDCl$_3$ w/ TMS)

δ 9.00 (s, 1H), 8.08 (app. t, J = 9.0 Hz, 2H), 7.77-7.70 (m, 2H), 7.04 (dd, J = 17.5, 11.0 Hz, 1H), 6.48 (d, J = 17.5 Hz, 1H), 5.79 (d, J = 11.0 Hz, 1H)

^{13}C-NMR (125 MHz, CDCl$_3$)

δ 150.4, 143.5, 142.1, 141.7, 134.8, 130.2, 129.5, 129.3, 129.1, 122.1

HRMS (ESI+)

Calculated for C$_{10}$H$_9$N$_2$ (M+H)$^+$:   157.0766
Found: 157.0768

IR (thin film, cm^{-1})

3064.0, 3018, 2928, 2847, 1631, 1596, 1546, 1492, 1466, 1414, 1365, 1342, 1331, 1303, 1282, 1258, 1212, 1185, 1121, 1065, 1014, 989, 972, 927, 762
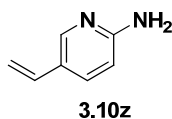
3.10z

2-amino-5-vinylpyridine (**3.10z**) [Table 3.5, Entry 18]

The general procedure was followed using 2-amino-5-chloropyridine (**3.9g**) (129 mg, 1.00 mmol), vinyl MIDA boronate (**3.2g**) (220 mg, 1.20 mmol), SPhos (42 mg, 0.10 mmol) and $Pd(OAc)_2$ (11 mg, 0.050 mmol). The reaction time and temperature were modified so that the reaction mixture was heated to 100 °C for 2 h. The extraction step was modified to use Et_2O (10 mL), then EtOAc (2 x 10 mL). Pyridine **3.10z** was isolated as a pale orange crystalline solid (91 mg, 76%).

TLC (EtOAc)

$R_f = 0.48$, visualized by UV ($\lambda = 254$ nm)

^{1}H-NMR (500 MHz, CDCl$_3$ w/ TMS)

δ 8.05 (s, 1H), 7.56 (dd, J = 8.5, 2.0 Hz, 1H), 6.58 (dd, J = 17.5, 11.0 Hz, 1H), 6.48 (d, J = 9.0 Hz, 1H), 5.56 (d, J = 17.5 Hz, 1H), 5.11 (d, J = 11.0 Hz, 1H), 4.60 (br s, 2H)

^{13}C-NMR (125 MHz, CDCl$_3$)

δ 157.9, 147.0, 134.4, 133.3, 124.0, 111.2, 108.5

HRMS (EI+)

Calculated for $C_7H_8N_2$ (M)$^+$:   120.0688
Found: 120.0688

IR (KBr, cm^{-1})

3448, 3296, 3128, 1631, 1599, 1509, 1388, 1324, 1274, 1144, 1002, 888, 828
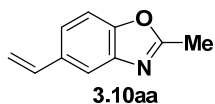
5-vinyl-2-methylbenzoxazole (3.10aa) [Table 3.5, Entry 19]

The general procedure was followed using 5-chloro-2-methylbenzoxazole (**3.9d**) (167 mg, 1.01 mmol), vinyl MIDA boronate (**3.2g**) (218 mg, 1.19 mmol), SPhos (42 mg, 0.10 mmol) and Pd(OAc)$_2$ (11 mg, 0.050 mmol). The reaction time and temperature were modified so that the reaction mixture was heated to 100 °C for 2 h. Benzoxazole **3.10aa** was isolated as a pale golden liquid (152 mg, 96%).

TLC (hexanes:EtOAc 3:1)

R$_f$ = 0.46, visualized by UV (λ = 254 nm)

^{1}H-NMR (500 MHz, CDCl$_3$ w/ TMS)

δ 7.67 (s, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 6.79 (dd, J = 17.5, 11.0 Hz, 1H), 5.74 (d, J = 17.5 Hz, 1H), 5.24 (d, J = 11.0 Hz, 1H), 2.61 (s, 3H)

^{13}C-NMR (125 MHz, CDCl$_3$)

δ 164.3, 150.6, 141.9, 136.5, 134.2, 122.9, 116.8, 113.4, 109.9, 14.5

HRMS (EI+)

Calculated for C$_{10}$H$_9$NO (M)$^+$:   159.0684
Found: 159.0685

IR (thin film, cm^{-1})

3087, 3006, 2984, 2928, 1623, 1622, 1578, 1477, 1433, 1381, 1335, 1262, 1179, 1114, 1040, 989, 918, 881, 840, 815
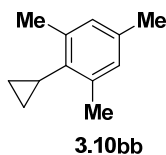
3.10bb

2,4,6-trimethyl-cyclopropylbenzene[13] (**3.10bb**) [Table 3.5, Entry 20]

The general procedure was followed using mesityl chloride (**3.9c**) (155 mg, 1.00 mmol), cyclopropyl MIDA boronate (**3.2h**) (296 mg, 1.50 mmol), SPhos (42 mg, 0.10 mmol) and Pd(OAc)$_2$ (11 mg, 0.047 mmol). The reaction time and temperature were modified so that the reaction mixture was heated to 100 °C for 24 h. The title compound was isolated as a colorless liquid (127 mg, 79%).

TLC (hexanes)

R_f = 0.66, visualized by UV (λ = 254 nm)

^{1}H-NMR (500 MHz, CDCl$_3$ w/ TMS)

δ 6.81 (s, 2H), 2.38 (s, 6H), 2.24 (s, 3H), 1.64 (m, 1H), 0.96 (m, 2H), 0.49 (m, 2H)

^{13}C-NMR (125 MHz, CDCl$_3$)

δ 138.8, 136.0, 135.5, 128.6, 20.8, 20.5, 11.7, 8.0

HRMS (EI+)

Calculated for C$_{12}$H$_{16}$ (M)$^+$:   160.1252

Found: 160.1252

IR (thin film, cm^{-1})

3080, 3003, 2969, 2954, 2918, 2859, 1612, 1485, 1457, 1375, 1223, 1057, 1025, 901, 850, 814
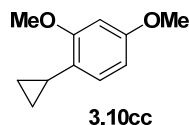
3.10cc

2,4-dimethoxy-cyclopropylbenzene (**3.10cc**) [Table 3.5, Entry 21]

The general procedure was followed using 1-chloro-2,4-dimethoxybenzene (**3.9b**) (173 mg, 1.00 mmol), cyclopropyl MIDA boronate (**3.2h**) (236 mg, 1.20 mmol), SPhos (41 mg, 0.10 mmol) and Pd(OAc)$_2$ (11 mg, 0.048 mmol). The reaction temperature was modified so that the reaction mixture was heated to 100 °C for 6 h. The title compound was isolated as a colorless liquid (175 mg, 97%).

TLC (hexanes:EtOAc 9:1)

R$_f$ = 0.65, visualized by UV (λ = 254 nm)

^{1}H-NMR (500 MHz, CDCl$_3$ w/ TMS)

δ 6.77 (d, J = 8.5 Hz, 1H), 6.44 (d, J = 2.5 Hz, 1H), 6.39 (dd, J = 8.5, 2.5 Hz, 1H), 3.83 (s, 3H), 3.77 (s, 3H), 2.03 (m, 1H), 0.85 (m, 2H), 0.57 (m, 2H)

^{13}C-NMR (125 MHz, CDCl$_3$)

δ 159.2, 158.6, 125.7, 124.2, 103.8, 98.4, 55.5, 55.3, 9.0, 6.9

HRMS (EI+)

Calculated for C$_{11}$H$_{14}$O$_2$ (M)$^+$:   178.0994
Found: 178.0995

IR (thin film, cm^{-1})

3080, 3000, 2955, 2940, 2835, 1615, 1585, 1510, 1464, 1439, 1416, 1370, 1319, 1290, 1261, 1209, 1172, 1158, 1117, 1062, 1037, 938, 884, 834, 823, 799

Synthesis of 2-pyridyl MIDA boronate 3.11
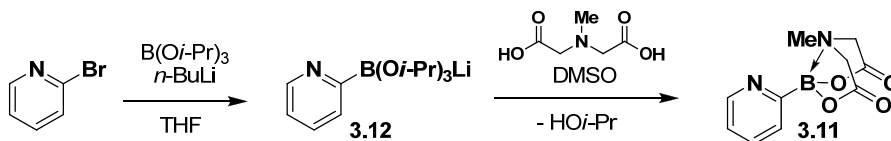
2-pyridyl MIDA boronate (3.11)

To a 250 mL Schlenk flask equipped with a stir bar was added 2-bromopyridine (6.00 mL, 62.9 mmol), triisopropylborate (15.0 mL, 65.2 mmol) and THF (100 mL). The solution was cooled to -78 °C. To the stirred solution was added dropwise *n*-BuLi (25.0 mL, 2.5 M in hexanes) at a rate sufficiently slow as to avoid the accumulation of a red color in the mixture (app. 20 minutes). The resulting beige mixture was stirred for 30 min and then was allowed to warm to room temperature with stirring overnight (12 h). The mixture was concentrated *in vacuo* onto Celite (10 g) to afford a free-flowing powder. Separately, a 500 mL 3-neck round-bottom flask equipped with a stir bar was charged with N-methyliminodiacetic acid (15.77 g, 107.2 mmol) and DMSO (100 mL). To one neck of the flask was fitted a solid addition funnel charged with the Celite-adsorbed lithium triisopropyl 2-pyridylborate. To a second neck was fitted a short-path distillation apparatus connected to vacuum. The third neck of the flask was sealed with a septum. The system was placed under vacuum (1 Torr) and the mixture was heated to 75 °C upon which the DMSO began to distill. The lithium triisopropyl 2-pyridylborate was added to the distilling mixture portion-wise over 1 h. The mixture was further distilled to near dryness (1 h). The resulting residue was suspended in acetone, and then concentrated *in vacuo* onto additional Celite (10 g). The resulting powder was lyophilized for 3 days to remove additional DMSO, and then was subjected to flash chromatography on silica gel (40 g silica gel, Et$_2$O:MeCN, 100:0 → 0:100). The product thus obtained was suspended in acetone (5 mL) and then diluted with Et$_2$O (100 mL) to promote crystallization. The mixture was filtered to isolate **3.11** as an off-white crystalline solid (4.024 g, 27%).

TLC (MeCN)

R$_f$ = 0.26, visualized by UV (λ = 254 nm) and KMnO$_4$ stain

^{1}H-NMR (500 MHz, CD$_3$CN)

δ 8.67 (ddd, *J* = 2.5, 1.5, 1.0 Hz, 1H), 7.70 (td, *J* = 7.5, 1.5 Hz, 1H), 7.62 (dt, *J* = 7.5, 1.0 Hz, 1H), 7.28 (ddd, *J* = 8.5, 1.5 Hz, 1H), 8.67 (ddd, *J* = 4.5, 1.5, 1.0 Hz, 1H), 4,09 (d, *J* = 17 Hz, 2H), 3.98 (d, *J* = 17 Hz, 2H), 2.55 (s, 3H)

^{13}C-NMR (125 MHz, CD$_3$CN)

δ 169.6, 150.8, 135.8, 128.1, 124.3, 62.9, 47.6

^{11}B-NMR (96 MHz, CD$_3$CN)

δ 10.3

HRMS (CI+)

Calculated for C$_{10}$H$_{12}$O$_4$N$_2$B (M+H)$^+$:		235.0890
Found:		235.0895

IR (KBr, cm^{-1})

3004, 2956, 1774, 1749, 1633, 1590, 1466, 1340, 1289, 1279, 1214, 1152, 1095, 1054, 1045, 998, 964, 894, 866, 775, 754, 708, 683

Suzuki-Miyaura cross-coupling of 2-pyridyl MIDA boronate 3.11 (Table 3.8)
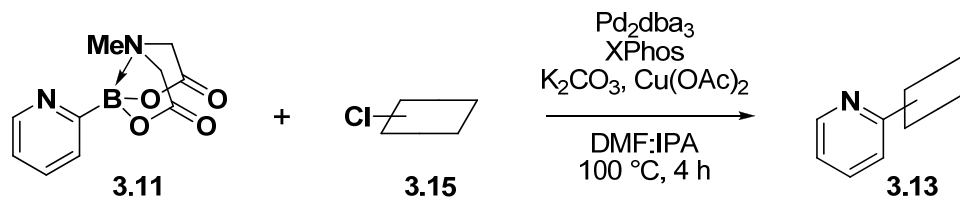
General Procedure

Under ambient atmosphere, to a 15 mL vial equipped with a stir bar was added the halide (1.0 mmol), 2-pyridyl MIDA boronate (**3.11**) (1.5 mmol), K_2CO_3 (5.0 mmol) and $Cu(OAc)_2$ (0.50 mmol). In a glove box, to the vial was added a DMF mixture of 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (X-Phos) (0.06 mmol) and Pd_2dba_3 (0.015 mmol) (8.0 mL DMF, pre-mixed and incubated for 5 min at 100 °C, then transferred at ~40 °C to avoid incomplete solubility at room temperature.) To the vial was added dry and degassed *i*-PrOH (2 mL). The reaction mixture was stirred at 100 °C for 4 h. The mixture was cooled to room temperature and then was transferred to a 60 mL separatory funnel and was diluted with aq NaOH (1.0 M, 10 mL). The mixture was extracted with Et_2O (3 × 10 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was subjected to flash-chromatography on silica gel (hexanes:EtOAc).
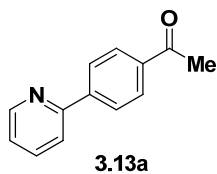
4-(2-pyridinyl)acetophenone[14] (**3.13a**) [Table 3.8, Entry 1]

The general procedure was followed using 4-chloroacetophenone (**3.15a**) (155 mg, 1.00 mmol), 2-pyridyl MIDA boronate (**3.11**) (349 mg, 1.49 mmol), K_2CO_3 (694 mg, 5.02 mmol) and $Cu(OAc)_2$ (90 mg, 0.50 mmol). Flash chromatography on silica gel (hexanes:EtOAc, 100:0 → 80:20) afforded **3.13a** as a colorless solid (142 mg, 72%).

TLC (hexanes:EtOAc 1:1)

    R_f = 0.47, visualized by UV (λ = 254 nm)

^{1}H-NMR (500 MHz, CDCl$_3$)

    δ 8.73 (d, J = 5.0 Hz, 1H), 8.10 (d, J = 8.5 Hz, 2H), 8.06 (d, J = 8.5 Hz, 2H), 7.79 (m, 2H), 7.29 (q, J = 4.5 Hz, 1H), 2.65 (s, 3H)

^{13}C-NMR (125 MHz, CDCl$_3$)

    δ 197.8, 156.0, 149.9, 143.5, 137.1, 136.9, 128.8, 127.0, 122.9, 121.0, 26.7

HRMS (CI+)

    Calculated for C$_{13}$H$_{12}$ON (M+H)$^+$:   198.0919

    Found: 198.0919

IR (KBr, cm^{-1})

    3048, 2999, 1679, 1604, 1584, 1574, 1558, 1466, 1434, 1400, 1356, 1315, 1266, 1156, 1113, 1013, 989, 960, 849, 785, 723, 696, 618, 600, 592
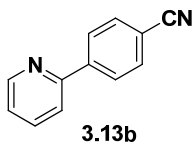
4-(2-pyridinyl)benzonitrile[15] (**3.13b**) [Table 3, Entry 2]

    The general procedure was followed using 4-chlorobenzonitrile (**3.15b**) (137 mg, 1.00 mmol), 2-pyridyl MIDA boronate (**3.11**) (352 mg, 1.50 mmol), K$_2$CO$_3$ (693 mg, 5.01 mmol) and Cu(OAc)$_2$ (91 mg, 0.50 mmol). Flash chromatography on silica gel (hexanes:EtOAc, 9:1) afforded **3.13b** as a pale yellow solid (109 mg, 60%).

TLC (hexanes:EtOAc 1:1)

    R_f = 0.59, visualized by UV (λ = 254 nm)

^{1}H-NMR (500 MHz, CDCl$_3$)

    δ 8.73 (d, *J* = 5.0 Hz, 1H), 8.11 (d, *J* = 9.0 Hz, 2H), 7.81 (td, *J* = 7.5, 1.5 Hz, 1H), 7.75 (m, 3H), 7.31 (ddd, *J* = 7, 4.5, 1 Hz, 1H)

^{13}C-NMR (125 MHz, CDCl$_3$)

    δ 155.2, 150.0, 143.4, 137.1, 132.5, 127.4, 123.3, 121.0, 118.8, 112.5

HRMS (CI+)

    Calculated for C$_{12}$H$_9$N$_2$ (M+H)$^+$:   181.0766

    Found: 181.0765

IR (KBr, cm^{-1})

    2228, 1588, 1466, 1433, 1393, 1303, 1152, 1152, 990, 852, 776, 738, 718, 620, 563, 518
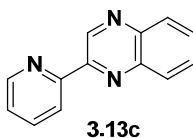
3.13c

2-(2-pyridinyl)quinoxaline[16] (**3.13c**) [Table 3, Entry 3]

    The general procedure was followed using 2-chloroquinoxaline (**3.15c**) (165 mg, 1.00 mmol), 2-pyridyl MIDA boronate (**3.11**) (353 mg, 1.51 mmol), K$_2$CO$_3$ (693 mg, 5.01 mmol) and Cu(OAc)$_2$ (91 mg, 0.50 mmol). Flash chromatography on silica gel (hexanes:EtOAc, 100:0 → 80:20) afforded **3.13c** as a pale orange solid (164 mg, 79%).

TLC (hexanes:EtOAc (1:1)

    R$_f$ = 0.56, visualized by UV (λ = 254 nm)

^{1}H-NMR (500 MHz, CDCl$_3$)

    δ 9.95 (s, 1H), 8.77 (ddd, *J* = 5.0, 1.5, 1.0 Hz, 1H), 8.58 (d, *J* = 8.0 Hz, 1H), 8.15 (m, 2H), 7.88 (td, *J* = 7.5, 1.5 Hz, 1H), 7.77 (m, 2H), 7.39 (ddd, *J* = 7.5, 4.5, 1.0 Hz, 1H)

¹³C-NMR (125 MHz, CDCl$_3$)

δ 154.5, 150.1, 149.4, 144.1, 142.5, 141.7, 137.1, 130.1, 130.0, 129.7, 129.3, 124.6, 122.0

HRMS (CI+)

Calculated for C$_{13}$H$_{10}$N$_3$ (M+H)$^+$:   208.0875
Found: 208.0871

IR (KBr, cm^{-1})

3050, 3004, 1591, 1548, 1492, 1479, 1457, 1437, 1403, 1367, 1143, 1131, 1059, 1043, 996, 961, 806, 785, 772, 742, 716, 670, 556
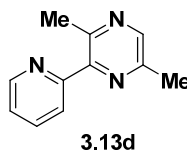
3.13d

2,5-dimethyl-3-(2-pyridinyl)pyrazine (**3.13d**) [Table 3, Entry 4]

The general procedure was followed using 3-chloro-2,5-dimethylpyrazine (**3.15d**) (142 mg, 1.00 mmol), 2-pyridyl MIDA boronate (**3.11**) (352 mg, 1.50 mmol), K$_2$CO$_3$ (694 mg, 5.02 mmol) and Cu(OAc)$_2$ (90 mg, 0.50 mmol). The aqueous phase was extracted an additional time with EtOAc (10 mL). Flash chromatography on silica gel (hexanes:EtOAc, 100:0 → 55:45) afforded **3.13d** as a pale amber liquid (96 mg, 52%).

TLC (hexanes:EtOAc 1:1)

R$_f$ = 0.39, visualized by UV (λ = 254 nm)

¹H-NMR (500 MHz, CDCl$_3$ w/ TMS)

δ 8.72 (d, *J* = 3.5 Hz, 1H), 8.38 (s, 1H), 7.83 (m, 2H), 7.33 (m, 1H), 2.73 (s, 3H), 2.59 (s, 3H)

¹³C-NMR (125 MHz, CDCl$_3$)

δ 157.2, 150.2, 149.9, 149.4, 148.7, 142.6, 136.6, 124.1, 123.0, 120.1, 22.6, 21.0

HRMS (CI+)

Calculated for C$_{11}$H$_{12}$N$_3$ (M+H)$^+$:   186.1031

Found: 186.1034

IR (thin film, cm^{-1})

3055, 2927, 1693, 1589, 1561, 1474, 1452, 1422, 1371, 1292, 1171, 1071, 1048, 995, 804, 752, 744
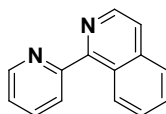
3.13e

1-(2-pyridinyl)isoquinoline (**3.13e**) [Table 3, Entry 5]

The general procedure was followed using 1-chloroisoquinoline (**3.15e**) (164 mg, 1.00 mmol), 2-pyridyl MIDA boronate (**3.11**) (350 mg, 1.49 mmol), K$_2$CO$_3$ (697 mg, 5.05 mmol) and Cu(OAc)$_2$ (89 mg, 0.49 mmol). The aqueous phase was extracted an additional time with EtOAc (10 mL). Flash chromatography on silica gel (hexanes:EtOAc, 70:30 → 30:70) afforded **3.13e** as an off-white solid (152 mg, 74%).

TLC (EtOAc)

R$_f$ = 0.47, visualized by UV (λ = 254 and 366 nm)

¹H-NMR (500 MHz, CDCl$_3$)

δ 8.79 (ddd, J = 5.0, 1.5, 1.0 Hz, 1H), 8.63 (d, J = 5.5 Hz, 1H), 8.60 (d, J = 8.5 Hz, 1H), 7.99 (dt, J = 8.0 Hz, 1.0 Hz, 1H), 7.91 (td, J = 7.5, 2.0 Hz, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 5.5 Hz, 1H), 7.69 (ddd, J = 8.0, 7.0, 1.5, 1H), 7.59 (ddd, J = 8.5, 7.0, 1 Hz, 1H), 7.40 (ddd, J = 7.5, 5.0, 1.0 Hz, 1H)

^{13}C-NMR (125 MHz, CDCl$_3$)

δ 158.2, 157.6, 148.6, 141.8, 137.0, 136.9, 130.0, 127.7, 127.6, 126.8, 126.6, 125.2, 123.2, 121.2

HRMS (CI+)

Calculated for C$_{14}$H$_{11}$N$_2$ (M+H)$^+$:   207.0922

Found: 207.0926

IR (KBr, cm^{-1})

3051, 3012, 1581, 1562, 1551, 1470, 1455, 1434, 1379, 1350, 1322, 1245, 1129, 1095, 992, 979, 966, 826, 811, 780, 753, 742, 713, 674, 644, 618, 573, 465, 441

REFERENCES:

[1] Uno, B.E.; Gillis, E.P.; Burke, M.D. *Tetrahedron* **2009**, *65*, 3130-3138.

[2] Knapp, D. M.; Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2009**, *131*, 6961-6963.

[3] Dick, G. R.; Knapp, D. M.; Gillis, E. P.; Burke, M. D. *Org. Lett.* **2010**, *12*, 2314-2317.

[4] Still, W.C.; Kahn, M.; Mitra, A.; *J. Org. Chem.* **1978**, *43*, 2923-2925.

[5] Kang, S-K.; Ryu, H-C.; Choi, S-C. *Chem. Commun.* **1998**, 1317-1318.

[6] Hashmi, A. S. K.; Salathé, Wolfgang, F. *Chem. Eur. J.* **2006**, *12*, 6991-6996.

[7] Aoyagi, Y; Inoue, A.; Koizumi, I.; Hashimoto, R.; Tokunaga, K.; Gohma, K.; Komatsu, J.; Sekine, K.; Miyafuji, A.; Kunoh, J.; Honma, R.; Akita, Y.; Ohta, A. *Heterocycles* **1992**, *33*, 257-272.

[8] Kitamura, Y.; Sako, S.; Udzu, T.; Tsutsui, A.; Maegawa, T.; Monguchi, Y.; Hironao, S. *Chem. Commun.* **2007**, *47*, 5069-5071.

[9] O'Brien, C. J.; Kantchev, E. A. B.; Valente, C.; Hadei, N.; Chass, G. A.; Lough, A.; Hopkinson, A.; Organ, M. G. *Chem. Eur. J.* **2006**, *12*, 4743-4748.

[10] Littke, A. F.; Schwarz, L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 6343-6348.

[11] Gazit, A.; App, H.; McMahon, G.; Chen, J.; Levitzki, A.; Bohmer, F. D. *J. Med. Chem.* **1996**, *39*, 2170-2177.

[12] Lando, V. R.; Monteiro, A. L. *Org. Lett.*, **2003**, *5*, 2891-2894.

[13] Lemhadri, M.; Doucet, H.; Santelli, M. *Chem. Commun.* **2006**, *36*, 121-128.

[14] Hitchcock, S. A.; Mayhugh, D. R.; Gregory, G. S. *Tetrahedron Lett.* **1995**, *36*, 9085-9088.

[15] Billingsley, K. L.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 4695-4698.

[16] Cui, Y.; Tang, X-B.; Shao, C-X.; Li, J-T.; Sun, W-H. *Chin. J. Chem.* **2005**, *23*, 589-595.

CHAPTER 4

MULTISTEP SYNTHESIS OF COMPLEX BORONIC ACIDS FROM SIMPLE MIDA BORONATES

Eric P. Gillis, Brice E. Uno, and Martin D. Burke

In order to maximize the generality of the ICC approach, efficient access to a large collection of building blocks, including structurally complex boronic acids, is necessary. The significant demand for boronic acids and boronic esters has led to the commercial availability of hundreds of these reagents. However, most of these commercially available compounds are structurally simple, lacking complex functionality and/or stereochemical elements. In theory, multi-step organic synthesis could be used to elaborate simple boronic acids into complex boron-containing building blocks. Due to the incompatibility of boronic acids and esters with many organic reagents and SiO_2 chromatography, only a few reports describe this practice. This chapter details the discovery that MIDA boronates are compatible with a wide range of synthetic reagents and reaction conditions. Enabled by this discovery and the favorable properties of MIDA boronates, including the general compatibility of these reagents with SiO_2 chromatography, it is now possible to readily transform simple boron-containing building blocks into complex boronic acids via multi-step synthesis with MIDA boronates. The potential of this approach was tested in the synthesis of the natural product (+)-crocacin C. Brice E. Uno contributed to the work presented in this chapter by optimizing the synthesis of vinyl MIDA boronate, exploring the utility of this building block in several reactions, and by confirming the structure of Br-B(MIDA) via X-ray crystallography.
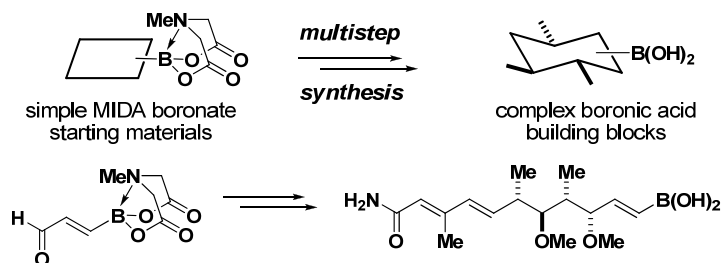
simple MIDA boronate starting materials → multistep synthesis → complex boronic acid building blocks

4-1 BACKGROUND

Efficient access to structurally complex and/or functionally rich boronic acids remains a significant challenge in synthetic chemistry. In theory, multi-step organic synthesis could be used to elaborate simple boronic acids into complex boron-containing building blocks. However, due to the reactive p-orbital of boronic acids and esters, boron functional groups are typically incompatible with many reagents used in organic synthesis. Treatment of boronic acids with oxidants typically leads to oxidation of the C-B bond;[1] exposure to halogens results in exchange of the C-B bond for a C-X bond;[2] mixing with hydride sources leads to formation of the corresponding borohydride species;[3] and treatment with carbon nucleophiles leads to addition at the boron center.[4] Further, boronic acids and esters constitute the key reactive functional group in a number of transformations such as the Suzuki reaction, Chan-Lam coupling, Heck coupling, the Petasis boronic acid Mannich reaction, rhodium-catalyzed 1,4-addition to enones, and allylations of carbonyl compounds. As an alternative approach, complex boronic acids might be accessed by late-stage installation of boron to an already functionally rich substrate. In practice, the scope of substrates which can be accessed by this approach is limited because most methods for installing boron have poor functional group tolerance.[5,6]

Carrying sp^2-hybridized boranes through synthetic steps

The reactivity of a boronic acid can be modulated by its conversion to a boronic ester. Since the goal of this transformation is often to impart added stability to the boron functionality the ligands used in this process are typically sterically bulky diols, the most popular of which is pinacol. Relative to boronic acids, pinacol boronic esters are more easily stored, handled, and characterized; are more readily purified via SiO$_2$ chromatography; and are more stable to common reagents used in organic synthesis. As such, there several reports which detail the carriage of pinacol esters through multiple synthetic steps.[7] In an example reported by Sulikowski and co-workers, a pinacol boronic ester functional group proved stable to the conditions of DMP oxidation, a TiCl$_4$ mediated aldol reaction, silylation, and LiBH$_4$ reduction (Scheme 4.1).[7a] In another example, the pinacol boronic ester functional group was found to be stable to the

conditions of TBAF deprotection, the Horner-Wadsworth-Emmons reaction, DIBAL-H reduction, and Sharpless epoxidation (Scheme 4.2).[7b] Also, Matteson and co-workers reported that a pinacol boronic ester was stable to PDC oxidation (Scheme 4.3).[7c]

Pinanediol derived boronic esters, which have been reported to be more stable than pinacol boronic esters,[8] also demonstrate some compatibility with common reagents. For example, Matteson and co-workers demonstrated that a pinanediol boronic ester was stable to DDQ-mediated debenzylation and Swern oxidation (Scheme 4.4).[9] Likewise, boronic esters derived from a sterically-bulky, tartrate-based ligand have been shown by Pietruszka to be stable to cyclopropanation, oxidation, HF, DIBAL-H, Horner-Wadsworth-Emmons conditions and radical decarboxylation.[10] In fact, these boronic esters are even unreactive under Suzuki-Miyaura cross-coupling (SMC) conditions.[11] Boranes derived from complexation with 1,8-diaminonapthalene (dan) are also inert under the conditions of the SMC reaction and are stable to concentrated aqueous NaOH.[12]
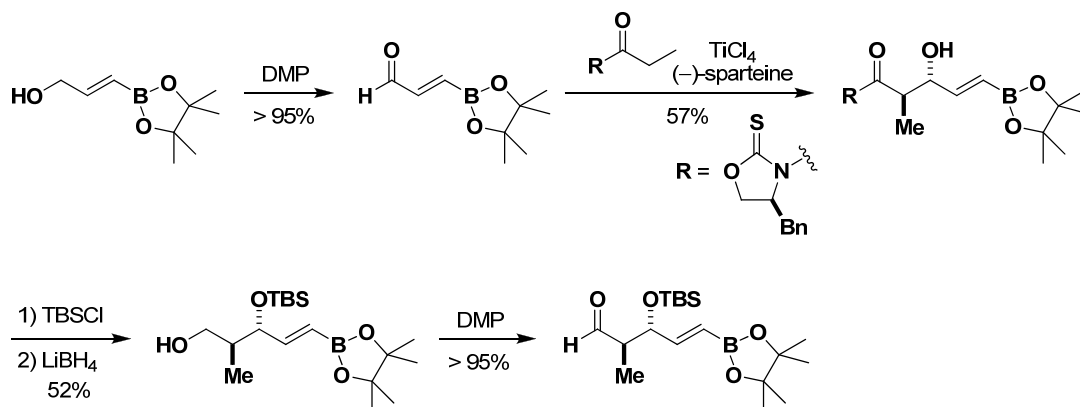
Scheme 4.1. Sulikowski and co-workers executed a synthetic route in which a pinacol boronic ester functional group was carried through multiple synthetic steps.
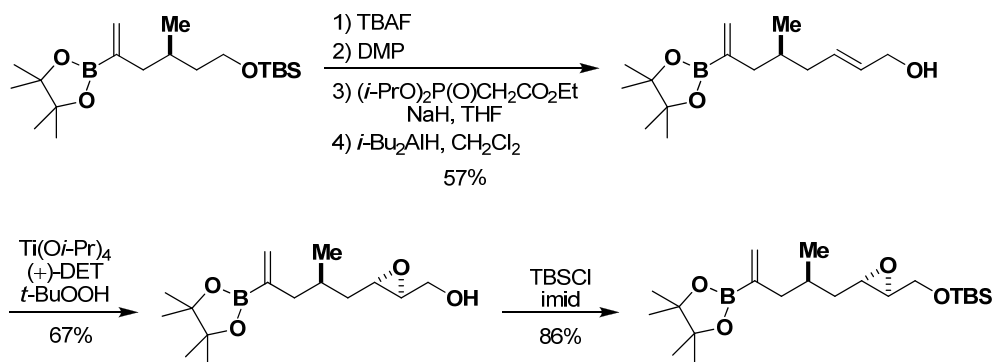
Scheme 4.2. Gopalarathnam and Nelson demonstrated that a pinacol boronic ester group was stable to TBAF, oxidation, Horner-Wadsworth-Emmons, DIBAL-H, Sharpless expoxidation and silylation conditions.
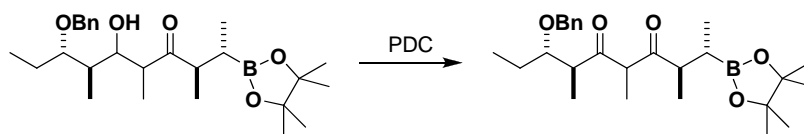
Scheme 4.3. Matteson and co-workers reported that a pinacol boronic ester was stable to PDC oxidation.
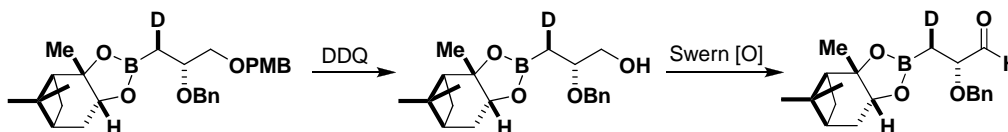
Scheme 4.4. Pinanediol-derived boronic esters are generally highly stable, and in an example by Matteson were shown to be compatible with DDQ-mediate debenzylation and Swern oxidation conditions.

One drawback to utilizing strongly binding ligands to modulate the reactivity of boron is that cleaving these ligands to regenerate the boronic acid generally requires relatively harsh conditions. In some cases removing the ligand is unnecessary since the boronic ester can be utilized directly in the desired reaction. However, some applications demand the use of a boronic acid. Because the equilibrium between a pinacol boronic ester and the corresponding boronic acid lies in favor of the pinacol boronic ester,[8] the hydrolysis of the ester must be biased on Le Chatelier's principle. Specifically, in order to completely hydrolyze a pinacol boronic ester it is often necessary to employ, along with an acid catalyst, an oxidant such as $NaIO_4$ to destroy the free pinacol ligand.[13] Alternatively, pinacol and related diol boronic esters can be hydrolyzed via the intermediacy of an insoluble diethanolamine boronate complex.[8,14] Cleavage of 1,8-diaminonapthalene from boron typically requires treatment with aqueous 5M HCl for 4-8 hours or treatment with aqueous 2M H_2SO_4 for 10-27 hours.[12] Cleavage of Pietruszka's tartrate-based diol from boron typically requires the use of $LiAlH_4$ and proceeds through a borohydride intermediate.[10,11]

For a limited set of reactions it is possible to use the boronic acid directly and thereby avoid the overhead and complications of employing a boronic ester. Specifically, Hall and co-workers demonstrated that boronic acids can be stable to conditions that effect an IBX oxidation of a benzylic or primary alcohol, DIBAL-H reduction of an ester, acetylation, peptide coupling, a Grubbs cross-metathesis reaction, and a cycloaddition.[15] Further, with 4-formylphenylboronic acid it was demonstrated that the boronic acid

moiety was stable to a NaBH$_4$ reduction, BF$_3$·OEt$_2$ promoted allylation, the Horner-Wadsworth-Emmons reaction, and an alkynylation/dipolar cycloaddition sequence.[15] In another example, NBS was employed in the oxidation of *o*-tolylboronic acid (Scheme 4.5).[16] Bromine was also tolerated in this transformation but was not tolerated by *p*-tolylboronic acid. Although boronic acids and esters have been demonstrated to be generally stable to a limited set of reaction conditions, and are tolerant of other reagents in some specific examples, the limited number of published examples on carrying boronic acids and esters through synthetic steps indicates that this approach is not general.
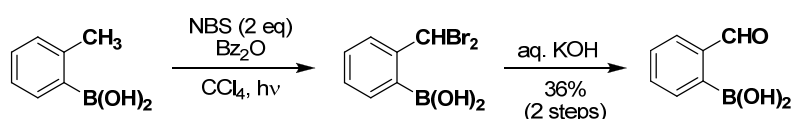
Scheme 4.5. In specific cases the use of NBS in the presence of boronic acids is tolerated. In this example NBS was used to brominate *o*-tolylboronic acid. Bromine was also tolerated. However, bromine was not tolerated in the bromination of *p*-tolylboronic acid.

Carrying sp^3-hybridized boranes through synthetic sequences

Boronic acids and boronic esters are susceptible to reactions with common reagents due to the Lewis acidic p-orbital on boron. On the other hand, sp^3-hybridized boronates lack this p-orbital and are therefore not Lewis acidic. As a result, boronates are stable to a broader range of reagents than their corresponding sp^2-hybridized counterparts. In a straightforward approach to the synthesis of bifunctional boronic acids, Luliński and co-workers employed the lithium borate species that results from trapping of organolithium reagents with B(*i*-OPr)$_3$ or MeOB(Pin) as a protected form of a boronic acid.[17] In a representative example shown in Scheme 4.6, 1,3,5-tribromobenzene was treated with *n*-BuLi followed by trapping with B(*i*-OPr)$_3$. The boron atom of the resulting product is sp^3-hybridized and anionic and is therefore stable to *n*-BuLi. Subsequent treatment with additional *n*-BuLi followed by trapping with CO$_2$ afforded the trifunctional building boronic acid product in 82% overall yield (Scheme 4.6). A limitation of this approach is that trialkoxyborate salts are not generally stable to long term storage and are reactive with many other reagents. In a related approach, the sp^3-hybridized, neutral boronate derived from condensation of 3,4-difluoroboronic acid with N-butyldiethanolamine functioned as a protected boronic acid equivalent in a LDA-

170

mediated lithiation/B(O*i*-Pr)$_3$ trapping sequence (Scheme 4.7).[18] N-butyldiethanolamine boronates are stable to storage and are therefore in some applications more advantageous that trialkoxyborate salts. However, these boronates are prone to hydrolysis and are unstable to SiO$_2$ purification, which limits their utilization in organic synthesis.
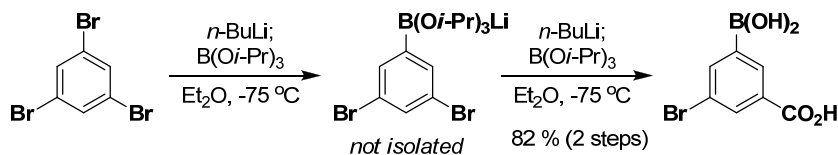
Scheme 4.6. The trialkoxyborate that results from trapping of an aryllithium species with B(O*i*-Pr)$_3$ is not electrophilic and therefore functions as a protected boronic acid in a subsequent lithiation/electrophile trapping sequence.
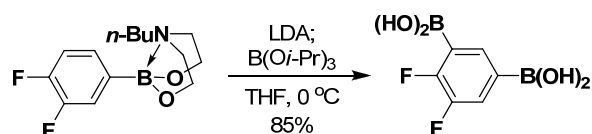
Scheme 4.7. Boronates derived from condensation of boronic acids with N-butyldiethanolamine function as protected boronic acid equivalents in LDA mediated lithiation/electrophile trapping sequences.

The most popular and broadly applicable form of a protected boronic acid equivalent is the trifluoroborate functional group. The facile synthesis of trifluoroborate salts from boronic acids/esters was first described by Vedejs and co-workers,[19] and these reagents have been extensively developed by Molander and Genet.[20,21] Trifluoroborates, unlike trialkoxyborates, are not sensitive to atmospheric moisture and can be easily handled and stored under ambient atmosphere. The improved stability of trifluoroborates is likely due to the very strong boron-fluorine bonds that are inherent to this functional group. Further, although the trifluoroborate functionality is anionic, this borate group is reported to be stable under a broad range of reaction conditions.[22,21,23,24] As such, the development of trifluoroborate salts has contributed to a large number of examples wherein the trifluoroborate group is unaffected by single synthetic operations, a selection of which are summarized in Table 4.1. For example, trifluoroborates were functionalized under oxidative conditions including TPAP/NMR, Swern oxidation, and DMP oxidation (entry 1);[22d] were functionalized via ozonolysis (entry 2);[22g] underwent reductive amination (entry 3);[22i] were utilized as reagents in a Witting olefination (entry 4);[22f] were stable to *n*-BuLi mediated lithiation followed by trapping with electrophiles (entry 5),[22e] and were functionalized via S$_N$2 displacement of a primarily halide followed by simple alkylation (entry 6).[22j]

Table 4.1

Entry	Reaction

1

2

3

4

5

6

Despite the observation that trifluoroborate salts are compatible with a broad range of reagents, the use of trifluoroborate salts in multi-step synthesis is limited.[22,21] In fact, excluding application in SMC reactions, we are aware of few examples in which a trifluoroborate salt is sequentially subjected to more than one reaction condition while maintaining intact the trifluoroborate functionality.[22b,22f,22j,25] One likely explanation for

172

the limited use of trifluoroborates in multi-step synthesis is that trifluoroborate salts are generally not stable to SiO$_2$ purification,[21,26] the most widely utilized technique for isolating intermediate compounds in synthetic organic chemistry. Rather, reaction-specific optimization of aqueous workup and/or crystallization conditions is required for the purification of these reagents.[22] Therefore, at the time of our work there was a significant unmet need for a general strategy for carrying boron reagents through multi-step synthesis to generate complex boronic acids and their derivatives.

4-2 COMPATABILITY OF MIDA BORONATES WITH ORGANIC REAGENTS

Due to the lack of the p-orbital that is typically involved in the reactivity of boronic acids, we hypothesized that sp^3-hybridized MIDA boronates might be stable to mild reagents. At the time of these studies it had already been demonstrated that MIDA boronates were stable to the conditions of the SMC reaction under anhydrous conditions (chapter 2) and were stable to the related Pd-catalyzed reactions: Sonogashira, Stille, Negishi, and Heck coupling, and Miyaura borylation.[27] Our aim was to discover if MIDA boronates might be stable to other reagents commonly used in organic synthesis. Towards this end, we first explored the compatibility of the model substrate p-hydroxymethylphenyl MIDA boronate **4.1a** with a range of oxidants and found that Swern conditions were well tolerated and afforded the desired benzaldehyde **4.2** in 88% yield (Scheme 4.8). PDC, TPAP/NMO, and Dess-Martin periodinane were also tolerated and effective in this transformation. Treatment of benzaldehyde **4.2** with NaBH$_4$ at 0 °C rapidly regenerated **4.1a** in 76% yield, while treatment of **4.2** with DIBAL-H or LiAlH$_4$ at -78 °C led to rapid loss of the MIDA boronate functional group as judged by TLC. Expecting to identify the limits of stability of the MIDA boronate group, **4.1a** was exposed to the aqueous, strongly acidic, and highly oxidizing conditions of the Jones reaction (Scheme 4.9). Surprisingly, these conditions led to a 90% yield of benzoic acid **4.3**.[28] This stability proved to be unique among related boron reagents as the corresponding boronic acid **4.1b**, pinacol boronic ester **4.1c**, 1,8-diaminonaphthalene adduct **4.1d**,[12] trifluoroborate salt **4.1e**,[20] and N-methyldiethanolamine boronate **4.1f** all decomposed rapidly and completely under the same reaction conditions. It is known that **4.1c**, **4.1d**, **4.1e** and **4.1f** are unstable to aqueous acid to varying degrees. However, under

the Jones conditions all of these reagents decomposed at a rate (full decomposition within 5 minutes) that far exceeds the rates of acid-promotoed hydrolysis typically associated with these boron functional groups.[12,13] The surprising difference in stability between MIDA boronate **4.1a** and diethanolamine boronate **4.1f** was probed via X-ray crystallographic studies and variable temperature ^{1}H-NMR studies, the results of which are reported in chapter 2. The high degree of stability observed for the MIDA boronate is attributed the strong conformational rigidity inherent to the MIDA boronate group, while the reactivity of **4.1f** is attributed to the fluxional nature of this complex.
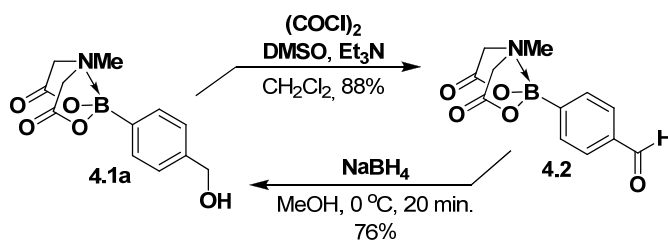
Scheme 4.8. MIDA boronate **4.1a** was discovered to be stable to oxidation under Swern conditions. PDC, DMP and TPAP/NMO were also tolerated in this transformation. The MIDA boronate functionality was stable to treatment with NaBH$_4$ but not to treatment with DIBAL-H or LiAlH$_4$.
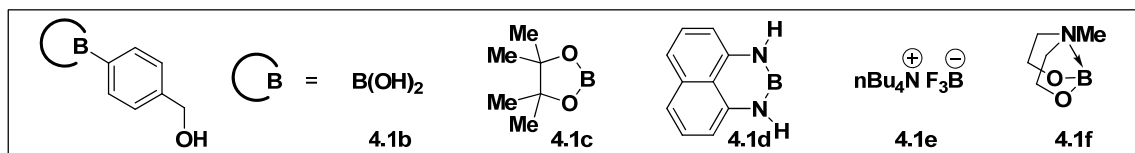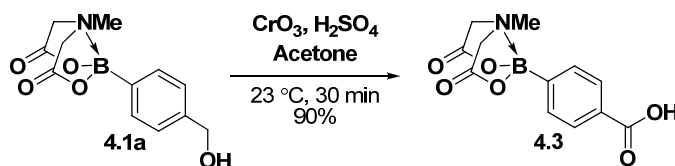
Scheme 4.9. MIDA boronate **4.1a** proved to be stable to the aqueous, highly acidic and highly oxidizing conditions of the Jones reaction. This stability was found to be unique as boron reagents **4.1b–4.1f** rapidly and completely decomposed under the same reaction conditions.

Encouraged by these preliminary studies on the stability of the MIDA boronate functional group to oxidation and reduction, we next tested the compatibility of **4.1a** and its derivatives with a variety of common reagents and conditions (Scheme 4.10). Remarkably, even TfOH (pK_a of -14) was tolerated, enabling the acid-catalyzed *p*-

methoxybenzylation of **4.1a** to yield **4.4**. Treatment of **4.4** with DDQ regenerated **4.1a** in 79% yield. Alcohol **4.1a** was efficiently converted to silyl ether **4.5** under standard conditions. Treatment of **4.5** with 3.9 equivalents of a commercial preparation of 1.0 M TBAF in THF led to a complete loss of the MIDA functional group within 5 minutes as observed by TLC.[29] Because commercial TBAF is never anhydrous and is inevitably contaminated with varying unknown amounts of n-BuN$_4$H$_2$F,[30] it is not clear from this experiment which species is reactive with the MIDA boronate functional group. On the other hand, treatment of **4.5** with an excess of HF·pyr at room temperature followed by quenching with aqueous NaHCO$_3$[31] provided **4.1a** in 83% yield.
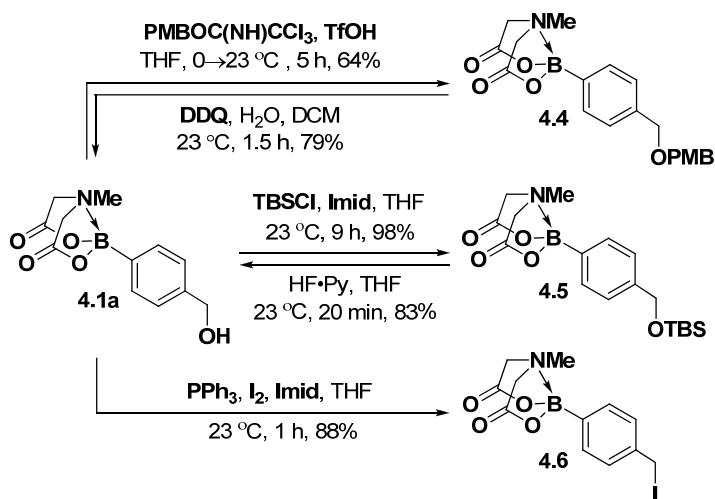
Scheme 4.10. Alcohol **4.1a** and its derivatives were found to be stable to a variety of reagents and conditions.

The compatibility of the MIDA boronate functional group observed with soft nucleophiles encouraged us to explore a series of C-C bond-forming reactions with benzaldehyde **4.2** (Scheme 4.11). The conditions of the Evans aldol reaction[32] proved to be compatible with the MIDA boronate functional group and afforded **4.7** as a single diastereomer as observed by ^{1}H-NMR in 79% yield. The product, which initially contains a dibutylborate complex resulting from the use of dibutylboron triflate in the reaction, could be freed of dibutylborinic acid using aqueous H$_2$O$_2$:MeOH as long as the system was buffered to pH 6.0. Decomposition of **4.7** was observed if the system was unbuffered or was buffered to pH 7.0. The Horner-Wadsworth-Emmons olefination reaction[33] also proved compatible with the MIDA boronate functionality and afforded **4.8** as the pure E-isomer as judged by ^{1}H-NMR in 71% yield. Surprisingly, **4.8** was found have a low

solubility in most organic solvents, [34] and was most conveniently purified by recrystallization. Boronate **4.2** was also engaged in a Takai olefination to provide vinyl iodide **4.9** as a 17:1 *E:Z* mixture as judged by ^{1}H-NMR in 88% yield.
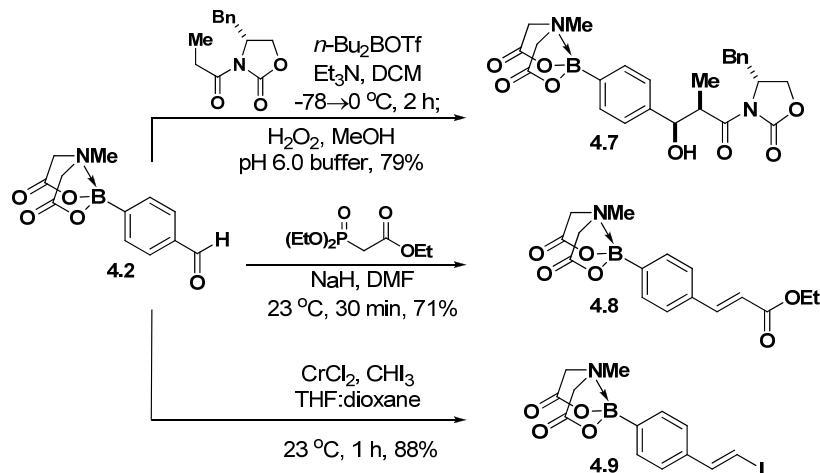
Scheme 4.11. The MIDA boronate functionality was found to be compatible with several C-C bond forming reactions.

MIDA boronates also proved useful in several C-N bond forming reactions (Scheme 4.12). Aldehyde **4.2** underwent one-pot reductive amination with morpholine to afford the tertiary amine **4.10** in 76% yield.[35] Additionally, **4.2** could be transformed into benzimidazole **4.11** via reductive cyclization with 1,2-phenylenediamine. This product was then engaged in a Chan-Lam coupling[36] with *p*-tolylboronic acid to afford a mixture of **4.12**:**4.11** in a 59:41 ratio.
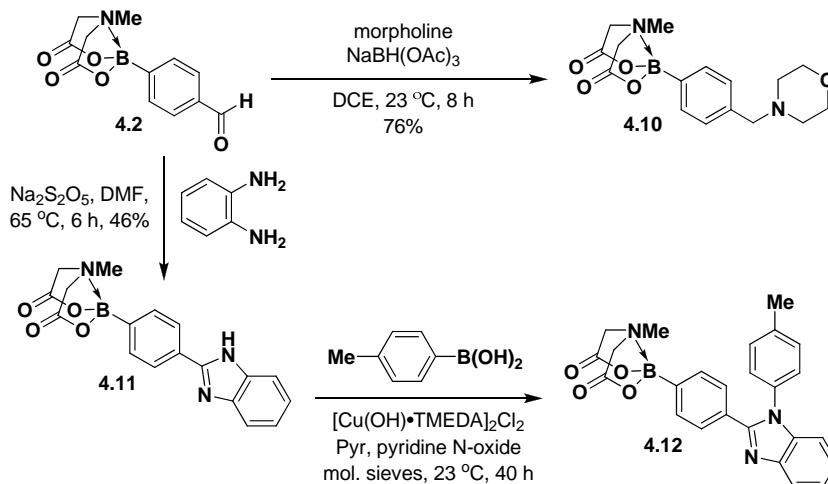
Scheme 4.12. The MIDA boronate functional group was found to be compatible with several C-N bond forming reactions.

4-3 MIDA BORONATES IN CROSS-METATHESIS REACTIONS

As a means to more readily access alkenyl MIDA boronates, we became interested in using the olefin cross-metathesis reaction as a means to install the MIDA boronate group directly to terminal olefins.[37,38] Previous experience with preparing alkenyl boronic acids via hydroboration of alkynes with catecholborane demonstrated to us that a hydroboration approach was less than ideal. Specifically, separating the boronic acid product from the catechol byproduct often proved difficult. On the other hand, if a MIDA boronate functional group could be introduced by the metathesis reaction the product would be amenable to facile SiO_2 chromatography. Further, we hypothesized that the sterically bulky nature of the MIDA boronate group would cause alkenyl MIDA boronates to behave like a type III olefin[39] (analogous to tert-butylethylene) in the cross-metathesis reaction, thereby avoiding any homodimerization and providing high yields and stereoselectivities with many classes of olefins.

In a preliminary study to test the reactivity of a MIDA boronate in a cross-metathesis reaction, a solution of *cis*-propenyl MIDA boronate **4.12** and styrene was treated with Grubbs' second generation ruthenium catalyst (Scheme 4.13). In agreement with the prediction for high *E*-selectivity in this process, the sole product of the reaction as detected by ^{1}H-NMR was the *E*-styrene product **4.13** in 94% yield. A subsequent cross-metathesis reaction was attempted between boronate **4.12** and acrolein but surprisingly this experiment furnished only *trans*-propenyl MIDA boronate (**4.15**) in 93% yield (Scheme 4.14). In fact, boronate **4.12** was used in these studies because *cis*-propenyl boronic acid ($60/g from Aldrich) was approximately 1/3 the price of *trans*-propenyl boronic acid ($200/g from Aldrich). Following optimization, it was found that only 0.5% of Grubbs II catalyst was needed to affect complete isomerization of **4.12**.[40] This finding was paired with the "hot-protocol" procedure developed by Graham Dick[41] to realize a very efficient and scalable synthesis of **4.15** (Scheme 4.15).
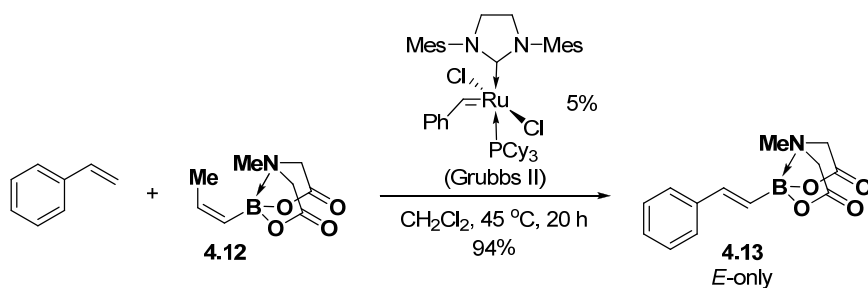
Scheme 4.13. The olefin cross-metathesis reaction between styrene and **4.12** afforded exclusively the *E*-isomer of **4.13** as observed by ^{1}H-NMR.
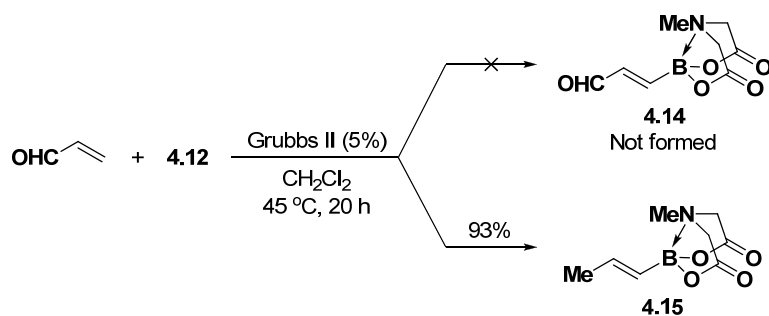
Scheme 4.14. The olefin cross-metathesis reaction between acrolein and **4.12** did not form the expected product but instead completely isomerized **4.12** to the *E*-isomer **4.15**.
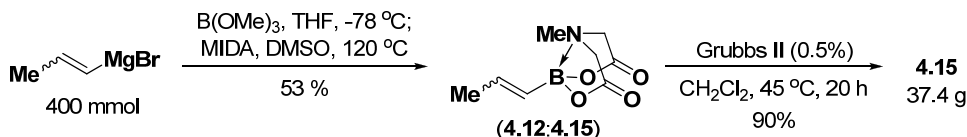
Scheme 4.15. Isomerization of **4.15** via the metathesis reaction enables a practical large-scale synthesis of *trans*-propenyl MIDA boronate. All purifications steps involve a simple recrystallization.

The cross-metathesis of an alkenyl MIDA boronate with acrolein to generate **4.14** was an important goal because the product **4.14** was targeted for use in the synthesis of (+)-crocacin C (see below). Because terminal olefins are generally more reactive than internal olefins in the cross-metathesis reaction,[39] we hypothesized that vinyl MIDA boronate (**4.17**) might be more reactive than **4.12** or **4.15**. However, consistent with reports that vinyl boronic is thermally unstable and is prone to polymerization at elevated temperatures,[42] isolation of vinyl boronic acid followed by exposure to MIDA under Dean-Stark conditions did not afford **4.17**. As a potential alternative route to **4.17**, it is known that arylsilanes under go C-Si/C-B bond exchange when treated with BBr$_3$.[43] Based on this precedent, vinyltrimethylsilane was exposed to BBr$_3$ and the resulting

dibromoborane was treated with the disodium salt of MIDA (**4.16**) to realize a 48% yield of **4.17** (Scheme 4.16). Interestingly, a byproduct was formed in this reaction that produced a ^{1}H-NMR spectrum containing only resonances for the diasteotopic methylene protons and *N*-CH$_3$ protons of MIDA. The same compound was prepared by mixing MIDA with BBr$_3$ in CD$_3$CN (Scheme 4.17), and in a subsequent study the structure of **4.18** was definitively assigned based on X-ray crystallographic data. Remarkably, **4.18** was found to be completely stable to SiO$_2$ chromatography and storage under ambient atmosphere at room temperature!
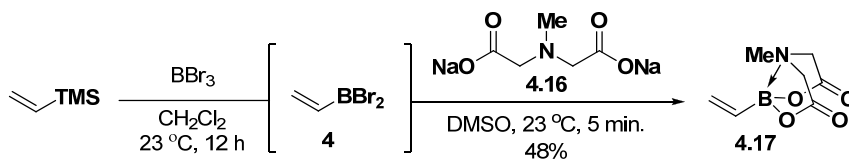
Reproduced with permission from Uno, B. E.; Gillis, E. P.; Burke, M. D. *Tetrahedron* 2009, *65*, 3130-3138. Copyright 2009 Elsevier.

Scheme 4.16. Vinyl MIDA boronate **4.17** was accessed via C-Si/C-B bond exchange with BBr$_3$ followed by trapping with the disodium salt of MIDA (**4.16**).
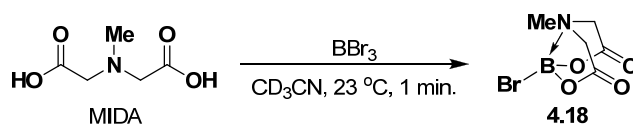
Scheme 4.17. Treatment of MIDA with BBr$_3$ afforded bromo MIDA boronate **4.18**. Remarkably, this compound was found to be stable to SiO$_2$ chromatography and demonstrated no change in composition upon storage under ambient air at room temperature.

Cross-metathesis reactions employing *trans*-propenyl pinacol boronic ester are known to proceed in some cases with moderate *E:Z* selectivity, and can be complicated by the instability of the pinacol boronic ester product to SiO$_2$ chromatography.[37] In contrast, when MIDA boronate **4.17** was employed in cross-metathesis reactions with a range of alkenes, the products were always obtained as the pure *E*-isomers (no *Z*-isomers were detected by ^{1}H-NMR) (Table 4.2). Owing to the general stability of the MIDA boronate functional group to the conditions of the cross-metathesis reaction conditions and to SiO$_2$ chromatography, the yields of these processes were uniformly high. Substrates that previously proved problematic in the cross-metathesis reaction with *trans*-propenyl pinacol boronic ester,[37] such as **4.19a**, **4.19c** and **4.19e**, were found to undergo

an efficient reaction with MIDA boronate **4.17** (entries 1, 3 and 5). Boronates **4.20b** and **4.20c**, both potentially two synthetic steps from **4.14**, were accessed efficiently through the metathesis reaction (entries 2 and 3).[44] As is common with many cross-metathesis reactions,[39] increased substitution at the allylic position was well tolerated (entries 4 and 5). Additionally, the cross-metathesis reaction of styrenes **4.19f-4.19h** was found to provide an efficient route to bromo-MIDA boronates **4.20f-4.20g** (entries 6, 7 and 8).

Expanding the collection of conditions for which MIDA boronates have been demonstrated to be stable, we discovered that boronate **4.17** could be further functionalized under several reaction manifolds (Scheme 4.18). Exposure of **4.17** to $Pd(OAc)_2/CH_2N_2$ resulted in the formation of cyclopropane **4.21**. Further, treatment of **4.17** with m-CPBA followed by SiO_2 chromatography led to the isolation of oxirane **4.22**. Molander and co-workers have demonstrated the epoxidation of substituted alkenyltrifluoroborate salts with DMDO or m-CPBA.[45] However, to the best of our knowledge **4.22** represents the first example of an unsubstituted oxiranylborane. Boronate **4.17** also underwent Heck coupling with p-bromoacetophenone using optimized reaction conditions to afford **4.23**. Consistent with the low reactivity of **4.17** in this reaction, byproducts from Heck coupling are not typically observed in slow-release cross-coupling reactions employing **4.17** (chapter 3). In a different manifold of the Heck reaction, boronate **4.17** participated in an oxidative Heck coupling with phenylboronic acid under the action of the White catalyst to afford **4.24**.[46]

Table 4.2.
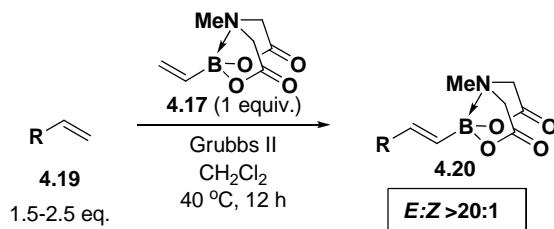
Entry	cross partner	cross product	isolated yield (%)
1	*i*-Pr₃Si, **4.19a**	**4.20a**	85
2	AcO—OAc, **4.19b**	AcO, **4.20b**	84
3	BzO—OBz, **4.19c** (*E:Z* 1:1)	BzO, **4.20c**	98
4	**4.19d**	**4.20d**	96
5	HO, Me Me, **4.19e**	HO, Me Me **4.20e**	94
6	**4.19f** (*ortho*)	**4.20f** (*ortho*)	81
7	**4.19g** (*meta*)	**4.20g** (*meta*)	91
8	**4.19h** (*para*)	**4.20h** (*para*)	89

Scheme 4.18. The MIDA boronate functional group was found to be stable to the conditions of cyclopropanation, epoxidation and Heck coupling.

4-4 THE TOTAL SYNTHESIS OF (+)-CROCACIN C

Based on the observation that MIDA boronates are compatible with a broad range of reagents, we hypothesized that simple MIDA boronates could be efficiently elaborated to functionally dense and synthetically useful building blocks through a series of synthetic steps. Up to this point our studies had focused on single-step manipulations of MIDA boronates, but the products were always obtained as pure compounds in high yield after SiO_2 chromatography, suggesting that the reaction sequence could be extended. To test this hypothesis, and the corollary that complex boronic acid building blocks should enable the efficient synthesis of a natural product, we targeted the total synthesis via ICC of (+)-crocacin C (**4.25**)[47]. The natural product was retrosynthetically fragmented via recursive cross-coupling transforms to afford known building blocks **4.26**[47b] and **4.27**, and the structurally complex halo MIDA boronate **4.28** (Scheme 4.19). Access to **4.28** would depend on the on the ability to elaborate a simply MIDA boronate starting material through multi-step synthesis en route to the complex building block.
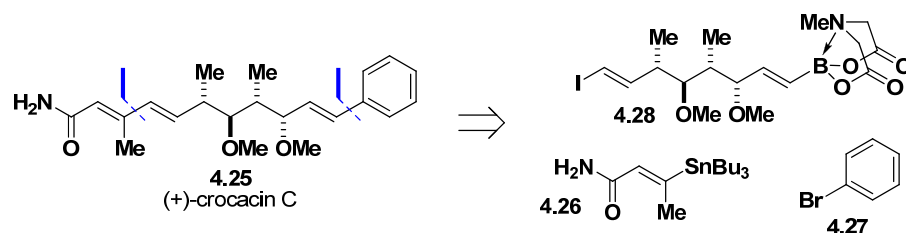
Scheme 4.19. The natural product (+)-crocacin C was retrosynthetically fragmented via recursive cross-coupling transformations to identify known building blocks **4.26** and **4.27**, and the structurally complex halo MIDA boronate **4.28**.

The synthesis of **4.28** commenced with acrolein MIDA boronate **4.14** (Scheme 4.20), which was prepared via condensation of the known boronic acid[48] with MIDA. This building block was engaged in a Sn(OTf)$_2$-mediated Paterson aldol reaction[49] to furnish β-hydroxyketone **4.31** as well as a small amount of the undesired diastereomer which is typical of the Paterson reaction.[49] Enabled by the stability of MIDA boronates to SiO$_2$, simple chromatography was used to separate the diastereomers, and **4.31** was isolated in 70% yield. Although acrolein MIDA boronate **4.29** is not readily soluble in CH$_2$Cl$_2$ at -78 °C, the aldol reaction was nonetheless effective because the product (**4.31**) is readily soluble under these conditions which in accordance with Le Chatelier's principal promotes the continued dissolution of **4.29** throughout the course of the reaction. β-hydroxyketone **4.31**[47d] next underwent diastereoselective reduction with Me$_4$N(AcO)$_3$BH[47d] to afford diol **4.32** in 71% yield. Interestingly, a number of experiments indicated that this reaction needed to be quenched carefully in order to avoid recovering large amounts of **4.31**. Exposure of **4.31** to Meerwein's salt proceeded in 82% yield to furnish **4.33**, which was then treated with aqueous ceric ammonium nitrate (CAN) to effect the cleavage of the PMB ether to afford **4.34**. Although DDQ could be used to convert **4.33** to **4.34**, the removal of excess DDQ and the hydroquinone byproduct following the reaction was much more demanding than the simple aqueous extraction associated with CAN. Subsequent DMP oxidation[50] of **4.34** afforded aldehyde **4.35** which was next engaged in a Takai olefination[47b] to afford *E*-vinyl iodide **4.28** as a single isomer as observed by ^{1}H-NMR in 74% yield. As an important note, although MIDA boronates undergo hydrolysis to the boronic acid when mixed with aqueous NaHCO$_3$ in methanol (chapter two), saturated aqueous solutions of NaHCO$_3$ were used in the workup steps employed in the syntheses of **4.31**, **4.34**, **4.35** and **4.28**, where the

following conditions of the workup were met: the absence of MeOH, favorable partitioning of the MIDA boronate into the organic phase, and an organic phase that is poorly miscible with water. Aqueous washes with NH$_4$Cl (**4.31**), dilute HCl (**4.33**), NaHSO$_3$ (**4.34**) and Na$_2$S$_2$O$_3$ (**4.28**) were also found to be compatible with the MIDA boronate group.
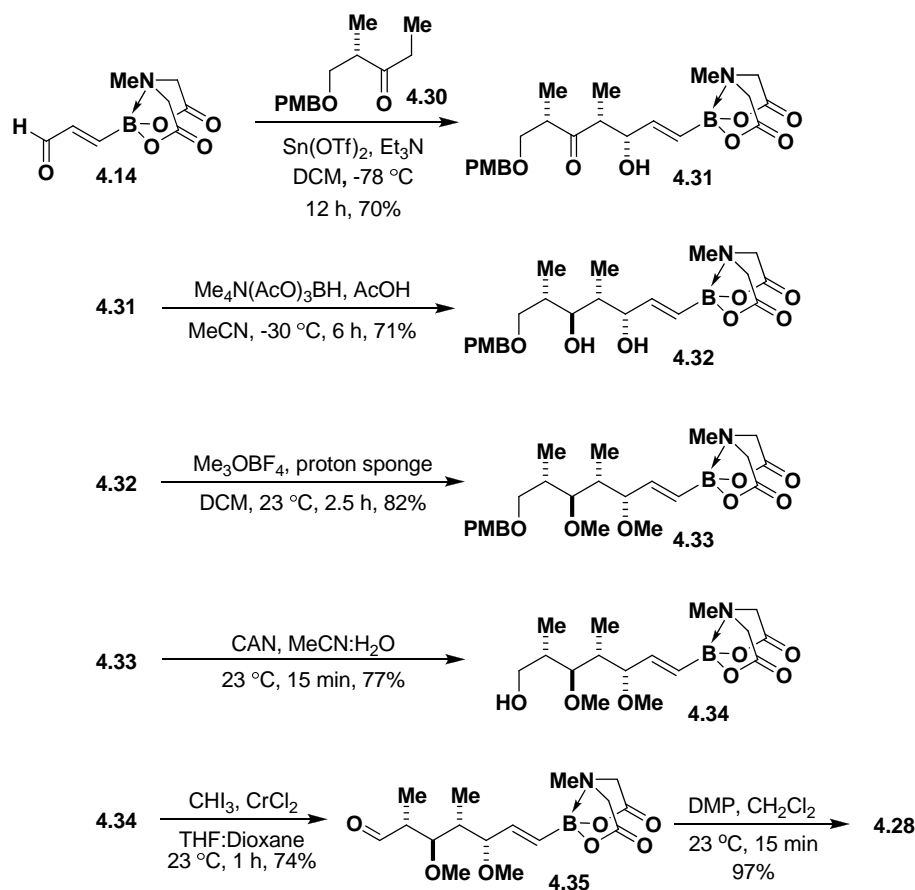
Scheme 4.20. The synthetic route to bifunctional building block **4.28**.
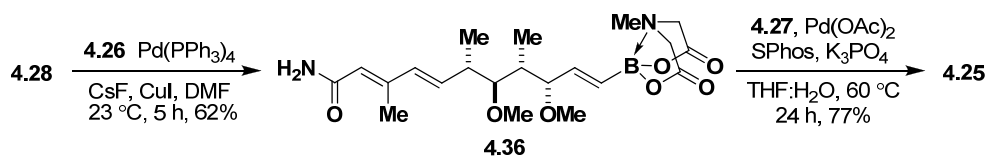
Scheme 4.21. The synthesis of (+)-crocacin C was completed via an ICC sequence involving an initial Stille coupling between **4.28** and **4.26**, and then a SMC reaction between **4.36** and **4.27**.

With bifunctional building block **4.28** in hand, the ICC sequence began with a Stille cross-coupling reaction between **4.26** and **4.28** (Scheme 4.21)[51]. After a brief survey of conditions for the Stille reaction the CsF/CuI conditions reported by Baldwin[52]
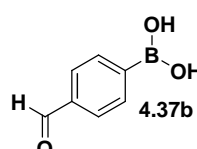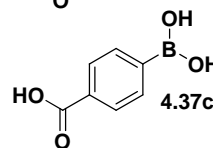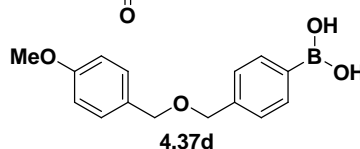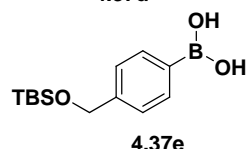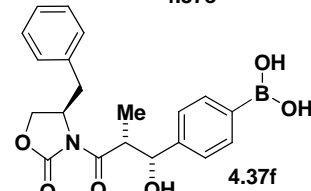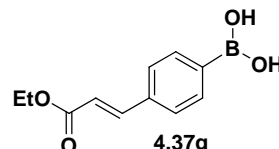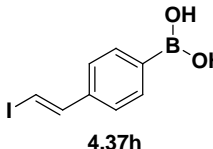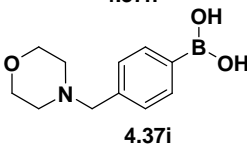
were selected, and under these conditions boronate **4.28** was smoothly transformed into boronate **4.36** in 74% yield. The subsequent SMC between **4.36** and **4.27** presented an early test for the slow-release SMC conditions that were being developed concurrently with David Knapp (chapter 3). In this case, aqueous K_3PO_4 was added to a vial containing **4.36**, **4.27**, and the palladium catalyst in order to effect the slow *in-situ* deprotection of **4.36** to the corresponding boronic acid. This coupling was efficient and afforded (+)-crocacin C (**4.25**) in 77% yield.[47]

4-5 BORONIC ACIDS FROM MIDA BORONATES

The hydrolysis of MIDA boronates upon treatment with aqueous NaOH has been found to be fast and efficient (chapter 2). Therefore, the discovery that MIDA boronate building blocks can be functionalized using many common reagents represents a pathway not only to complex MIDA boronate esters, but also to complex boronic acids. To confirm that the MIDA boronates synthesized in the above studies can indeed be converted to the boronic acids, we exposed boronates **4.1a** and **4.2**-**4.10** to the standard aqueous deprotection conditions (aq. 1 M NaOH:THF, 23 °C, 10 minutes) and isolated the corresponding boronic acids (Table 4.3). MIDA boronate **4.6** was not included in this study because the benzylic iodide functionality is very sensitive to water. In all cases the yields of pure boronic acid were high. The yield of boronic acid **4.37** was increased if the milder aqueous $NaHCO_3$:MeOH conditions (chapter 2) were employed. Similarly, deprotection of **4.7** with aq. NaOH led to apparent epimerization of the product, while aqueous $NaHCO_3$:MeOH-mediated deprotection of **4.7** avoided this problem and afforded the pure boronic acid.

Table 4.3.

aq. 1 M NaOH
THF, 23 °C, 10 min.
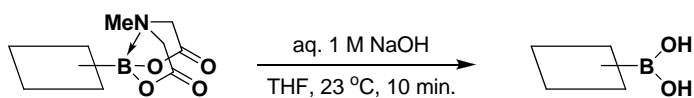
Entry	MIDA Boronate	Boronic Acid	Yield
1	4.1a	4.1b	85%
2	4.2	4.37b	76%
3	4.3	4.37c	89%
4	4.4	4.37d	84%*
5	4.5	4.37e	81%
6	4.7	4.37f	85%*
7	4.8	4.37g	75%
8	4.9	4.37h	89%
9	4.10	4.37i	76%

* Denotes that the MIDA boronate was deprotected using alternative
conditions: sat. aq. $NaHCO_3$: MeOH, 23 °C, 3.5 h

4-6 SUMMARY

In summary, it was discovered that the MIDA boronate functional group is compatible with a broad range of common reagents and reaction conditions. These reagents include oxidants, reductants, soft nucleophiles, carbon nucleophiles, strong acids, Lewis-acids, as well as reagents employed in epoxidation, cyclopropanation, Heck coupling, cross-metathesis and C-N bond forming reactions. Consistent with the observation of a unique susceptibility to hard anionic nucleophiles, it was found that the MIDA boronate functional group was not compatible with NaOH, TBAF, LiAlH$_4$ or DIBAL-H. Because MIDA boronates are generally stable to SiO$_2$ purification, isolation of the products from these reactions was straightforward. Enabled by these collective discoveries, a complex halo MIDA boronate building block was synthesized via multi-step synthesis starting from a simple MIDA boronate. This halo MIDA boronate bifunctional building block was utilized in the ICC synthesis of the natural product (+)-crocacin C. The results described in this chapter demonstrate that it is now possible to reliably access complex MIDA boronate and boronic acid products via multi-step organic synthesis where a boron atom protected as a MIDA boronate is carried through each synthetic step.

4-7 REFERENCES

[1] (a) Kuivila, H. G. *J. Am. Chem. Soc.* **1954**, *76*, 870-874. (b) Kuivila, H. G.; Armour, A. G. *J. Am. Chem. Soc.* **1957**, *79*, 5659-5662. (c) Webb, K. S.; Levy, D. *Tetrahedron Lett.* **1995**, *36*, 5117-5118. (d) Maleczka, R. E.; Shi, F.; Holmes, D.; Smith, M. R. *J. Am. Chem. Soc.* **2003**, *125*, 7792-7793. (e)

[2] (a) Ainley, A. D.; Challenger, F. *J. Chem. Soc.* **1930**, 2171-2180. (b) Thiebes, C.; Prakash, G. K. S.; Petasis, N. A.; Olah, G. A. *Synlett* **1998**, 141-142.

[3] Singaram, B.; Cole, T. E.; Brown, H. C. *Organometallics* **1984**, *3*, 774-777.

[4] Brown, H. C.; Vasumathi, N.; Joshi, N. N. *Organometallics* **1993**, 12, 1058-1067.

[5] Hall, D. G. *Boronic Acids*, Wiley-VCH, Germany, **2005**, chapter 1.

[6] (a) The Miyaura boronation reaction is the most functional group-tolerant, broadly applicable method for introducing boron: Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508-7510. (b) Recent advances have significantly expanded the scope of arenes which can be accessed through metallation and trapping with B(OR)$_3$: Wang, X-j.; Sun, X.; Zhang, L.; Xu, Y.; Krishnamurthy, D.; Senanayake, C. H. *Org. Lett.* **2006**, *8*, 305-307.

[7] (a) Jin, B.; Liu, Q.; Sulikowski, G. A. *Tetrahedron* **2005**, *61*, 401-408. (b) Gopalarathnam, A.; Nelson, S. G. *Org. Lett.* **2006**, *8*, 7-10. (c) Matteson, D. S.; Man, H-W.; Ho, O. C. *J. Am. Chem. Soc.* **1996**, *118*, 4560-4566. (d) Hilt, G.; Bolze, P. *Synthesis* **2005**, *13*, 2091.

[8] Roy, C. D.; Brown, H. C. *Monatshefte für Chemie* **2007**, *138*, 879-887.

[9] Matteson, D. S.; Kandil, A. A.; Soundararajan, R. *J. Am. Chem. Soc.* **1990**, *112*, 3964-3969.

[10] Luithle, J. E. A.; Pietruszka, J. *J. Org. Chem.* **2000**, *65*, 9194-9200.

[11] Luithle, J. E. A.; Pietruszka, J. *J. Org. Chem.* **1999**, *64*, 8287-8297.

[12] (a) Noguchi, H.; Hojo, K.; Suginome, M. *J. Am. Chem. Soc.* **2007**, 129, 758-759. (b) Noguchi, H.; Shioda, T.; Chou, C-M.; Suginome, M. *Org. Lett.* **2008**, *10*, 377-380.

[13] Murphy, J. M.; Tzschuck, C. C.; Hartwig, J. F. *Org. Lett.* **2007**, *9*, 757-760.

[14] (a) Wang, Y-C.; Georghiou, P. E. *Org. Lett.* **2002**, *4*, 2675-2678. (b) Matteson, D. S.; Man, H-W. *J. Org. Chem.* **1996**, *61*, 6047-6051. (c) Brown, H. C.; Prasad, J. V. N. V. *J. Org. Chem.* **1986**, *51*, 4526-4530.

[15] Mothana, S.; Grassot, J-M.; Hall, D. G. *Angew. Chem. Int. Ed.* **2010**, *49*, 2883-2887.

[16] Snyder, H. R.; Reedy, A. J.; Lennarz, W. J. *J. Am. Chem. Soc.* **1958**, *80*, 835-838.

[17] Kurach, P.; Luliński, S.; Serwatowski, J. *Eur. J. Org. Chem.* **2008**, 3171-3178.

[18] Durka, K.; Kurach, P.; Luliński, S.; Serwatowski, J. *Eur. J. Org. Chem.* **2009**, 4325-4332.

[19] Vedejs, E.; Chapman, R. W.; Fields, S. C.; Lin, S.; Schrimpf, M. R. *J. Org. Chem.* **1995**, *60*, 3020-3027.

[20] (a) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275-286. (b) Molander, G. A.; Figueroa, R.; *Aldrichimica Acta* **2005**, *38*, 49-56.

[21] Darses, S.; Genet, J.-P. *Chem. Rev.* **2008**, *108*, 288–325.

[22] (a) Molander, G. A.; Figueroa, R. *Org. Lett.* **2006**, *8*, 75-78. (b) Molander, G. A.; Ham, J. *Org. Lett.* **2006**, *8*, 2767-2700. (c) Molander, G. A.; Figueroa, R. *J. Org. Chem.* **2006**, *71*, 6135-3140. (d) Molander, G. A.; Petrillo, D. E. *J. Am. Chem. Soc.* **2006**, *128*, 9634-9635. (e) Molander, G. A.; Ellis, N. M. *J. Org. Chem.* **2006**, *71*, 7491-7493. (f) Molander, G. A.; Ham, J.; Canturk, B. *Org. Lett.* **2007**, *7*, 821-824. (g) Molander, G. A.; Cooper, D. J. *J. Org. Chem.* **2007**, *72*, 3558-3560. (h) Molander, G. A.; Oliveira, R. A. *Tetrahedron Lett.* **2008**, *49*, 1266-1268. (i) Molander, G. A.; Cooper, D. J. *J. Org. Chem.* **2008**, *73*, 3885-3891. (j) Molander, G. A.; Febo-Ayala, W.; Ortega-Guerra, M. *J. Org. Chem.* **2008**, *73*, 6000-6002. (k) Molander, G. A.; Febo-Ayala, W.; Jean-Gérard, L. *J. Org. Chem.* **2009**, *74*, 5446-5450. (l) Cho, Y. A.; Kim, D-S.; Ahn, H. R.; Canturk, B.; Molander, G. A.; Ham, J. *Org. Lett.* **2009**, *11*, 4330-4333.

[23] Butters, M.; Harvey, J. N.; Jover, J.; Lennox, A. J. J.; Lloyd-Jones, G. C.; Murray, P. M. *Angew. Chem. Int. Ed.* **2010**, *49*, 1-6.

[24] In every reported synthesis in which a trifluoroborate salt is exposed to organic reagents, the synthetic procedure concludes with an aqueous workup involving KHF_2, the same reagent that generates trifluoroborates from the boronic acids/esters. See reference 22.

[25] Groux, L. F.; Weiss, T.; Reddy, D. N.; Chase, P. A.; Piers, W. E.; Ziegler, T.; Masood, P.; Benet-Buchholz, J. *J. Am. Chem. Soc.* **2005**, *127*, 1854-1869.

[26] Molander, G. A.; Cavalcanti, L. N.; Canturk, B.; Pan, P-S.; Kennedy, L. E. *J. Org. Chem.* **2009**, *74*, 7364-7369.

[27] Lee, S. J.; Gray, K. C.; Paek, J. S.; Burke, M. D. *J. Am. Chem. Soc.* **2008**, *130*, 466-468.

[28] Subsequent studies have found that MIDA boronates decompose slowly in aqueous H_2SO_4 at rates that increase with temperature and concentration of H_2SO_4.

[29] This result may indicate an efficient "anhydrous" condition for the deprotection of MIDA boronates, possibly to the trifluoroborate species. However, the product of this reaction was not further characterized.

[30] Sun, H.; DiMagno, S. G. *J. Am. Chem. Soc.* **2005**, *127*, 2050-2051.

[31] The use of an excess of TMSOEt to quench the HF•pyr led to 50% conversion of **4.1a** to the corresponding boronic acid.

[32] Evans, D. A.; Takacs, J. M.; McGee, L. R.; Ennis, M. D.; Mathre, D. J.; Bartroli, J. *Pure. Appl. Chem.* **1981**, *53*, 1109-1127.

[33] Boutagy, J.; Thomas, R. *Chem. Rev.* **1974**, *74*, 87-99.

[34] This is a surprising exception to the generally good solubility observed with MIDA boronates.

[35] An alternative condition for reductive amination that is tolerated by a MIDA boronate is:

BocNH$_2$ (2.95 eq)
Et$_3$SiH (2.95 eq)
TFA (1.95 eq)
MeCN, 23 °C, 19 h
94 %
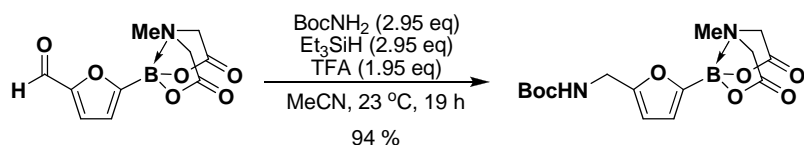
[36] Ley, S. V.; Thomas, A. W. *Angew. Chem. Int. Ed.* **2003**, *42*, 5400-5449.

[37] For a report on using cross-metathesis to synthesis *E*-alkenyl pinacol boronic esters see: Morrill, C.; Grubbs, R. H. *J. Org. Chem.* **2003**, *68*, 6031–6034.

[38] For a report on using ring-closing metathesis to synthesize cyclic alkenyl pinacol boronic esters see: Renaud, J.; Ouellet, S. G.; *J. Am. Chem. Soc.* **1998**, *120*, 7995-7996.

[39] Chatterjee, A. K.; Choi, T.-L.; Snaders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.

[40] Reasons for seeking to minimize the amount of catalyst used in the reaction include reducing the overall cost and simplifying the purification. An additional reason for minimizing the % Grubbs II catalyst is that the styrene moiety present in the pre-catalyst undergoes cross-metathesis with **4.12**:**4.15** to afford small amounts of **4.13** which is difficult to separate from the products.

[41] Dick, G. R.; Knapp, D. M.; Gillis, E. P.; Burke, M. D. *Org. Lett.* **2010**, *12*, 2314-2317.

[42] Matteson, D.S. *J. Am. Chem. Soc.* **1960**, *82*, 4228-4233.

[43] (a) Haubold, W.; Herdtle, J.; Gollinger, W.; Einholz, W. *J. Organomet. Chem.* **1986**, *315*, 1-8. (b) Li, H.; Sundararaman, A.; Venkatasubbaiah, K; Jäkle, F. *J. Am. Chem. Soc.* **2007**, *129*, 5792-5793.

[44] Despite several attempts, conditions were not discovered which would enable an efficient metathesis reaction between acrolein and **4.19**.

[45] Molander, G. A.; Ribagorda, M. *J. Am. Chem. Soc.* **2003**, *125*, 11148–11149.

[46] (a) Delcamp, J. H.; White, M. C. *J. Am. Chem. Soc.* **2006**, *128*, 15076–15077. (b) Delcamp, J. H.; Brucks, A. P.; White, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 11270–11271.

[47] (a) Kunze, B.; Jansen, R.; Hofle, G.; Reichenbach, H. *J. Antibiot.* **1994**, *47*, 881–886. Previous syntheses: (b) Dias, L. C.; de Oliviera, L. G. *Org. Lett.* **2001**, *3*, 3951–3954. (c) Chakraborty, T. K.; Jayaprakash, S. *Tetrahedron Lett.* **2001**, *42*, 497–499. (d) Feutrill, J. T.; Lilly, M. J.; Rizzacasa, M. A. *Org. Lett.* **2000**, *2*, 3365–3367. (e) Sirasani, G.; Paul, T.; Andrade, R. B. *J. Org. Chem.* **2008**, *73*, 6386–6388. (f) Candy, M.; Audran, G.; Bienaymé, H.; Bressy, C.; Pons, J.-M. *J. Org. Chem.* **2010**, *75*, 1354-1359. (g) Sirasani, G.; Paul, T.; Andrade, R. B. *Bioorg. Med. Chem.* **2010**, *18*, 3648-3655.

[48] Touré, B. B.; Hoveyda, H. R.; Tailor, J. ; Ulaczyk-Lesanko, A.; Hall, D. G. *Chem.–Eur. J.* **2003**, *9*, 466-474.

[49] Paterson, I.; Norcross, R. D.; Ward, R. A.; Pedro, R.; Lister, M. A. *J. Am. Chem. Soc.* **1994**, *116*, 11287-11314.

[50] Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

[51] Despite considerable effort, the boronic acid/ester analog of **4.26** could not be prepared due to, appropriately, the difficulty of installing the boron functionality late stage to a primary amide and alternatively, the incompatibility of a pinacol boronic ester to reagents that install the primary amide.

[52] Mee, S. P. H.; Lee, V.; Baldwin, J. E. *Angew. Chem. Int. Ed.* **2004**, *43*, 1132–1136.

CHAPTER 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 and amines were dried as noted in chapter 2. 1,2-Dichloroethane was dried over 4Å molecular sieves for 24 h before use. The following compounds were prepared according to known literature procedures: trifluoroborate **4.1e**[1], stannane **4.26**[2], ketone **4.30**[3]. MIDA boronates **4.17**, **4.20a–4.20h**, **4.21**, **4.22**, **4.23** and **4.24** (via oxidative Heck coupling) were synthesized by Brice Uno.[4]

General Experimental Procedures. The general experimental procedures followed in these studies are the same as those detailed in chapter 2. Column chromatography was performed as described in chapter 3.

Structural analysis. Structural analysis was performed and described as detailed in chapter 2.

MIDA boronate 4.1a

*From boronic acid **4.1b***:
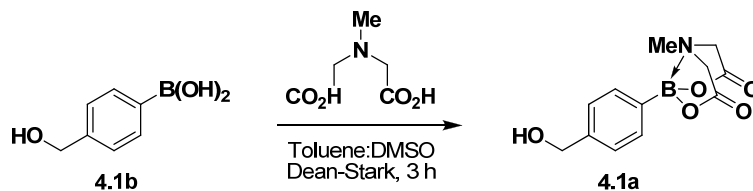
To a 25 mL roundbottom flask was added 4-(hydroxymethyl)phenylboronic acid **4.1b** (759 mg, 5.00 mmol), *N*-methyliminodiacetic acid (808 mg, 5.49 mmol), DMSO (2 mL) and toluene (5 mL). The flask was fitted with a Dean-Stark trap filled with toluene. The Dean-Stark trap was fitted with a water-cooled reflux condenser vented to ambient atmosphere. The stirred mixture was refluxed with azeotropic removal of water for 3 h. The mixture was concentrated *in vacuo* (1 Torr, 100 °C) to afford a yellow oil residue. To the flask was added water (10 mL) which caused the crystallization of a colorless solid. The mixture was filtered. The isolated solid was washed with water (5 mL), and then the residual water was removed via co-evaporation with acetone (2 x 25 mL) to afford MIDA boronate **4.1a** as a colorless crystalline solid (1.241 g, 94%).

*From aldehyde **4.2***:
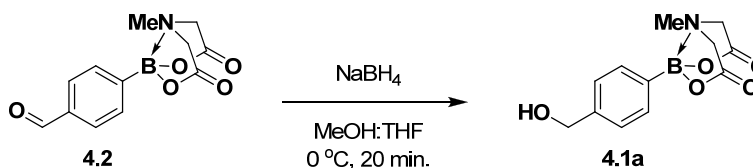
To a 50 mL Schlenk flask charged with aldehyde 4.2 (261 mg, 1.00 mmol) was added MeOH (15 mL) and THF (15 mL). The suspension was cooled to 0 °C. To the stirred mixture was added in one portion NaBH$_4$ (58 mg, 1.5 mmol). The mixture became a homogeneous, colorless solution within 2 min. The solution was stirred for 20 min. and then was carefully quenched via the addition of sat. aq. NH$_4$Cl (10 mL). When the effervescence had ceased the mixture was warmed to room temperature, diluted with H$_2$O

(10 mL) and EtOAc (50 mL) and was transferred to a 100 mL separatory funnel. The mixture was shaken; the phases were separated. The aq. phase was extracted with EtOAc (2 x 50 mL). The combined organics were dried over MgSO$_4$, filtered, then concentrated in vacuo. The resulting white solid residue was adsorbed onto Florisil gel from an acetone suspension and the resulting powder was subjected to flash chromatography on silica gel (Et$_2$O:MeCN 100:0 → 50:50) to afford **4.1a** as a colorless, crystalline solid (201 mg, 76%).

To a 25 mL Schlenk flask charged with aldehyde **4.2** (132 mg, 0.505 mmol) was added dry EtOH (10 mL) and THF (10 mL). The mixture was cooled to 0 °C. NaBH$_4$ (32 mg, 0.85 mmol) was added, and the mixture was stirred for 30 min. Acetaldehyde (1 mL) was then added, and the resulting mixture was stirred for 15 min. Acetic acid (0.1 mL) was then added, and the resulting solution was stirred for 5 min. The solution was then warmed 23 °C, transferred to a 65 mL roundbottom flask, and diluted with EtOAc (25 mL). The solution was then concentrated *in vacuo* and the resulting residue was adsorbed onto Celite *in vacuo* from an acetone solution. The resulting powder was subjected to flash chromatography on silica gel (Et$_2$O:MeCN 100:0 → 50:50) to afford **4.1a** as a colorless, crystalline solid (87 mg, 65%).

*From benzyl ether **4.4***:
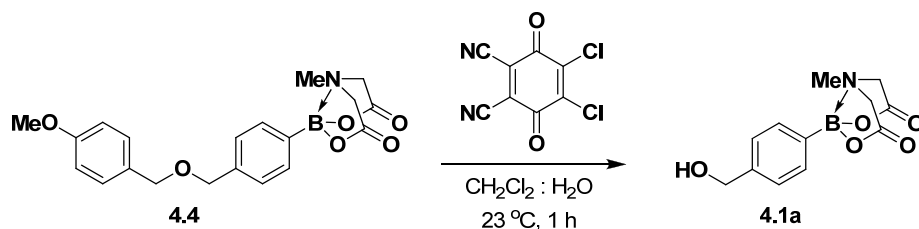
Under ambient atmosphere, to a 15 mL vial charged with boronate **4.4** (96 mg, 0.25 mmol) as a solution in CH$_2$Cl$_2$ (6 mL) was added water (360 μL) and 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (71 mg, 0.31 mmol). The mixture was stirred for 1 h. Na$_2$SO$_4$ (7.5 g) was then added, and the resulting mixture stirred for 15 min. The mixture was then filtered and the isolated purple solids were washed with several portions of

acetone until colorless (75 mL total acetone). The filtrate was concentrated *in vacuo* and the resulting residue was adsorbed onto Celite *in vacuo* from an acetone solution. The resulting powder was subjected to flash chromatography on silica gel (Et$_2$O:MeCN 100:0 ∏ 70:30) to afford **4.1a** as an off-white, crystalline solid (50 mg, 79%).

*From silyl ether **4.5***:
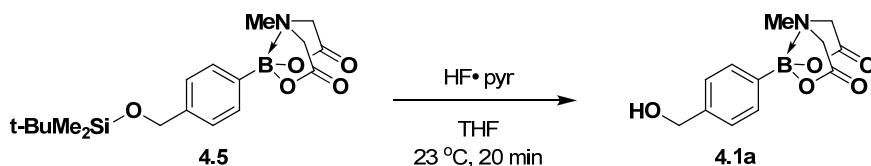
To a 15 mL polypropylene vial charged with silyl ether **4.5** (188 mg, 0.499 mmol) in THF (5 mL) was added HF•pyridine complex (0.5 mL). The resulting solution was stirred for 20 min at 23 °C and then water (0.5 mL) was added. To the resulting mixture was added carefully NaHCO$_3$ (2.00 g – effervescence commenced upon addition) as a solid in several small portions. The mixture was stirred for 30 min, during which time the effervescence ceased. The quench was confirmed via the addition of one drop of aqueous saturated NaHCO$_3$ and the observation of no effervescence. Na$_2$SO$_4$ (3 g) and acetone (20 mL) were then added and the resulting mixture was stirred for 15 min. The mixture was then filtered and the isolated solid was washed with acetone (3 x 10 mL). The combined filtrates were concentrated *in vacuo* and the resulting residue was azeotropically dried using MeCN (20 mL). The residue was then adsorbed onto Celite *in vacuo* from an acetone solution. The resulting powder was subjected to flash chromatography on silica gel (Et$_2$O:MeCN 100:0 → 50:50). The isolated pale-yellow solid was triturated with Et$_2$O (5 mL) to afford **4.1a** as a colorless, crystalline solid (109 mg, 83%).

TLC (Et$_2$O:MeCN 3:1)

　　　R_f = 0.33, stained by KMnO$_4$

^{1}H-NMR (500 MHz, CD$_3$CN)

δ 7.45 (d, J = 8 Hz, 2H), 7.34 (d, J = 8 Hz, 2H), 4.58 (s, 2H), 4.06 (d, J = 17 Hz, 2H), 3.88 (d, J = 17 Hz, 2H), 3.27 (b, 1H), 2.48 (s, 3H).

^{13}C-NMR (125 MHz, CD$_3$CN)

δ 169.7, 144.1, 133.4, 127.2, 64.6, 62.7, 48.4

^{11}B-NMR (96 MHz, CD$_3$CN)

δ 12.1

HRMS (ESI+)

Calculated for C$_{12}$H$_{15}$BNO$_5$:   264.1043
Found: 264.1046

IR (thin film, cm^{-1})

3412, 3010, 2946, 1766, 1611, 1457, 1405, 1340, 1299, 1229, 1038, 994, 891, 867, 790, 710.
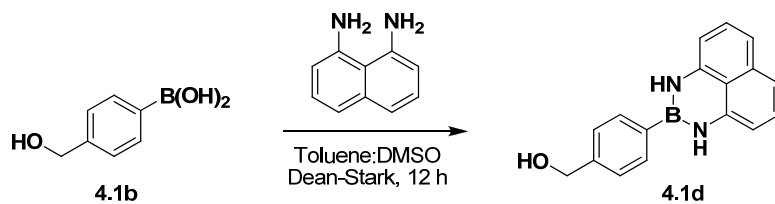
Boronamide 4.1d

In an unoptimized procedure, to a 100 mL roundbottom flask was added 4-(hydroxymethyl)-phenylboronic acid (456 mg, 3.00 mmol), 1,8-diaminonaphthalene (489 mg, 3.09 mmol), toluene (25 mL) and DMSO (2 mL). The flask was fitted with a Dean-Stark trap filled with toluene. The Dean-Stark trap was fitted with a water-cooled reflux condenser vented to ambient atmosphere. The stirred solution was refluxed with azeotropic removal of water for 12 h. The solution was then transferred to a 125 mL

separatory funnel, diluted with EtOAc (25 mL), and washed with brine (25 mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The dark residue was adsorbed onto Celite *in vacuo* from an acetone solution. The resulting powder was subjected to flash chromatography on silica gel (hexanes:EtOAc 85:15 → 50:50) to afford **4.1d** as a pale purple solid (676 mg, 82%).

TLC (Hexanes:EtOAc 1:1)

$R_f = 0.27$, stained by $KMnO_4$

^{1}H-NMR (500 MHz, CD_3CN)

δ 7.74 (d, $J = 8$ Hz, 2H), 7.40 (d, $J = 8$ Hz, 2H), 7.11 (app. t, $J = 7.5$ Hz, 2H), 6.98 (dd, $J = 8.5, 0.5$ Hz, 2H), 6.95 (s, 2H), 6.53 (dd, $J = 7, 1$ Hz, 2H), 4.61 (d, $J = 6$ Hz, 2H), 3.22 (t, $J = 6$ Hz, 1H).

^{13}C-NMR (125 MHz, CD_3CN)

δ 145.2, 142.9, 137.3, 133.1, 128.7, 127.1, 120.7, 117.9, 106.7, 64.6

^{11}B-NMR (96 MHz, CD_3CN)

δ 29.9

IR (thin film, cm^{-1})

3540, 3514, 3411, 3382, 3349, 3044, 2910, 2868, 1623, 1599, 1526, 1494, 1409, 1372, 1330, 1236, 1166, 1086, 1036, 818, 764.
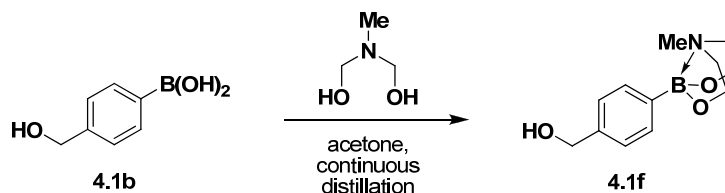
MIDA boronate 4.1f

In an unoptimized procedure, to a 50 mL roundbottom flask was added 4-(hydroxymethyl)phenylboronic acid (1.000 g, 6.581 mmol), *N*-methyldiethanolamine (754 μL, 6.581 mmol) and acetone (30 mL). The flask was fitted with a short-path distillation apparatus. The mixture was distilled with periodic addition of acetone to maintain a volume of 10 to 40 mL. When 60 mL of distillate was collected, the distillation was stopped. The suspension from the distillation pot was transferred to a 500 mL roundbottom flask and then diluted with acetone to a volume of 300 mL. The mixture was filtered through a pad of Celite, and the solution was concentrated *in vacuo* to a minimum volume. The solution was then diluted with Et$_2$O (400 mL), gently agitated, and left to stand at 0 ºC for 2 h. The resulting crystalline solid was collected via vacuum filtration to afford **1f** as a colorless, crystalline solid (1.104 g, 71%).

TLC (EtOAc)

Compound is unstable to SiO$_2$

^{1}H-NMR (500 MHz, CD$_3$CN)

δ 7.50 (d, *J* = 8 Hz, 2H), 7.20 (d, *J* = 8 Hz, 2H), 4.52 (s, 2H), 4.00 (m, 2H), 3.94 (m, 2H), 3.18 (m, 2H), 2.95 (m, 2H), 2.21 (s, 3H).

^{13}C-NMR (125 MHz, CD$_3$CN)

δ 142.3, 134.9, 127.2, 65.6, 63.5, 61.8, 48.7

^{11}B-NMR (96 MHz, CD$_3$CN)

δ 12.7

HRMS (ESI+)

      Calculated for $C_{12}H_{19}BNO_3$:   236.1458

      Found: 236.1455

IR (thin film, cm^{-1})

      3336, 2863, 1607, 1455, 1396, 1217, 1081, 993.

MIDA boronate 4.2

From 4-formylphenylboronic acid:
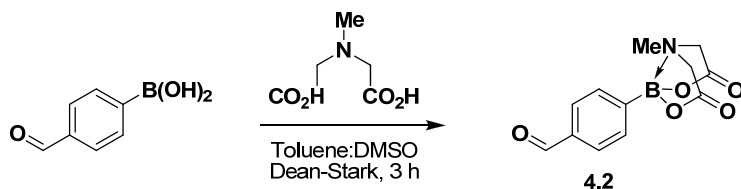
To a 25 mL roundbottom flask was added 4-formylphenylboronic acid (749 mg, 5.00 mmol), *N*-methyliminodiacetic acid (806 mg, 5.48 mmol), DMSO (2 mL) and toluene (4 mL). The flask was fitted with a Dean-Stark trap filled with toluene. The Dean-Stark trap was fitted with a water-cooled reflux condenser vented to ambient atmosphere. The stirred mixture was refluxed with azeotropic removal of water for 3 h. The mixture was concentrated *in vacuo* and then most of the residual DMSO was removed via lypholization (2 days). The resulting colorless solid was adsorbed onto Celite from an acetone solution. The resulting powder was subjected to flash chromatography on silica gel (Et$_2$O:MeCN 100:0 → 65:35) to afford **4.2** as a colorless crystalline solid (1.122 g, 86%).

From alcohol **4.1a**:
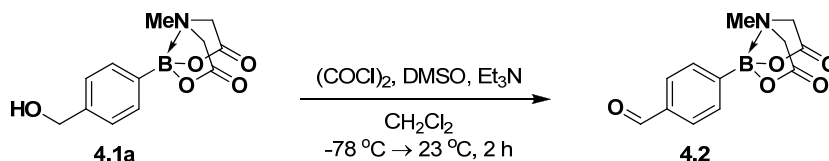
To a 10 mL Schlenk flask was added CH_2Cl_2 (2.0 mL) and oxalyl chloride (0.18 mL, 2.0 mmol). The solution was cooled to $-78\ ^{\circ}C$ and then DMSO (0.35 mL) was added. The solution was stirred for 15 min. To the solution was then added dropwise via cannula MIDA boronate **4.1a** (264 mg, 1.00 mmol) as a solution in CH_2Cl_2:DMSO (1.0 mL : 1.0 mL). The resulting white suspension was stirred for 20 min and then Et_3N (1.0 mL, 7.2 mmol) was added. The mixture was stirred at -78 $^{\circ}C$ for 5 min and then allowed to warm to 23 $^{\circ}C$ with stirring for 2 h. The mixture was then transferred to a 125 mL separatory funnel and diluted with EtOAc (75 mL), saturated aqueous NH_4Cl (5 mL) and water (10 mL). The mixture was shaken and the phases were separated. The aqueous phase was extracted once with EtOAc (75 mL). The combined organics were dried over $MgSO_4$ and then were filtered through a pad of Celite. The filtrate was concentrated *in vacuo* and the residue was adsorbed onto Florisil *in vacuo* from an acetone solution. The resulting powder was subjected to flash chromatography on silica gel (Et_2O:MeCN 3:1 → 1:1) to afford MIDA boronate **4.2** as a colorless crystalline solid (231 mg, 88%).

TLC (EtOAc)

$R_f = 0.23$, stained by $KMnO_4$

^{1}H-NMR (500 MHz, CD_3CN)

δ 10.02 (s, 1H), 7.88 (d, J = 8 Hz, 2H), 7.70 (d, J = 8 Hz, 2H), 4.10 (d, J = 17 Hz, 2H), 3.92 (d, J = 17 Hz, 2H), 2.50 (s, 3H).

^{13}C-NMR (125 MHz, CD_3CN)

δ 193.9, 169.4, 138.2, 134.2, 129.6, 63.0, 48.6

<superscript>11</superscript>B-NMR (96 MHz, CD$_3$CN)

   δ 11.8

HRMS (ESI+)

   Calculated for C$_{12}$H$_{13}$BNO$_5$:   262.0887

   Found: 262.0886

IR (thin film, cm^{-1})

   2951, 2837, 2739, 1746, 1693, 1462, 1439, 1391, 1337, 1288, 1238, 1049, 1025,

   1001, 985, 873, 819.
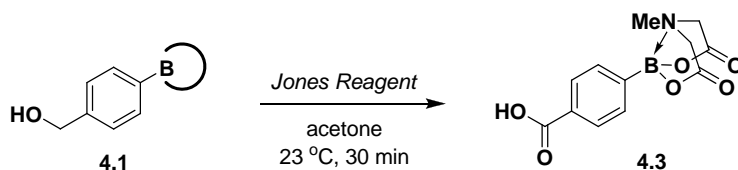
MIDA boronate 4.3

Preparation of Jones reagent stock solution. A stock solution of chromic acid was prepared by the addition of concentrated H$_2$SO$_4$ (app. 18.4 M, 1.82 mL) to a stirred solution of CrO$_3$ (2.1 g, 21 mmol) in water (5.32 mL). The solution was stirred for 5 min. The red solution thus obtained is app. 3 M in chromic acid.

Representative procedure; oxidation of **4.1a**. To a 20 mL vial charged with boronate **4.1a** (132 mg, 0.501 mmol) was added acetone (5 mL). The stirred solution was cooled to 0 °C. To the solution was added the Jones reagent stock solution (0.5 mL, 1.5 mmol). The mixture was stirred for 1 min. and then allowed to warm to 23 °C with stirring for 30 min. To the mixture was added *i*-PrOH (1.0 mL) followed by continued stirring for 5 min. The mixture was then transferred to a 60 mL separatory funnel and diluted with water (10 mL) and EtOAc (25 mL). The mixture was shaken and the phases were separated. The aqueous phase was extracted once with EtOAc (25 mL). The combined organics were dried over MgSO$_4$, filtered, and concentrated *in vacuo*. The residue was adsorbed onto

Celite *in vacuo* from an acetone solution. The resulting powder was subjected to flash chromatography on silica gel (Et$_2$O:MeCN 4:1 with 0.5% AcOH) to afford MIDA boronate **4.3** as a colorless crystalline solid (125 mg, 90%).

TLC (Et$_2$O:MeCN 4:1 with 0.5% AcOH)

　　　R_f = 0.36, stained by KMnO$_4$

^{1}H-NMR (500 MHz, acetone-d6)

　　　δ 8.02 (d, *J* = 8 Hz, 2H), 7.67 (d, *J* = 8 Hz, 2H), 4.39 (d, *J* = 17 Hz, 2H), 4.19 (d, *J* = 17 Hz, 2H), 2.77 (s, 3H).

^{1}H-NMR (500 MHz, CD$_3$CN)

　　　δ 7.98 (d, *J* = 8 Hz, 2H), 7.61 (d, *J* = 8 Hz, 2H), 4.09 (d, *J* = 17.5 Hz, 2H), 3.91 (d, *J* = 17.5 Hz, 2H), 2.49 (s, 3H).

^{13}C-NMR (125 MHz, CD$_3$CN)

　　　δ 169.4, 168.0, 133.7, 131.7, 129.8, 62.9, 48.5

^{11}B-NMR (96 MHz, CD$_3$CN)

　　　δ 11.8

HRMS (ESI+)

　　　Calculated for C$_{12}$H$_{13}$BNO$_6$:　　　278.0836
　　　Found:　　　278.0826

IR (thin film, cm^{-1})

　　　3010, 2956, 1762, 1560, 1507, 1452, 1399, 1340, 1292, 1222, 1186, 1121, 1042, 994, 891, 846, 769, 709.

Oxidation of **4.1b-4.1f**. Following the above procedure exactly, **4.1b**, **4.1c**, **4.1d**, **4.1e** and **4.1f** were each separately exposed to the Jones reagent. Upon workup the crude residues were analyzed by ^{1}H-NMR (acetone-d6). In each case, a complex mixture of oxidized products (four or more compounds) was observed.
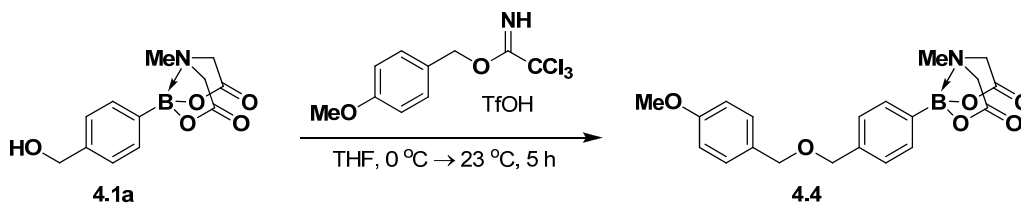
MIDA boronate 4.4

Preparation of 4-methoxybenzyl 2,2,2-trichloroacetimidate. To a 10 mL Schlenk flask charged with NaH (18 mg, 0.76 mmol) was added Et$_2$O (2 mL), and the resulting stirred suspension was cooled to 0 °C. To the suspension was added 4-methoxybenzyl alcohol (375 μL, 3.03 mmol). The resulting solution was warmed to 23 °C with stirring for 30 min and then recooled to 0 °C. Trichloroacetonitrile (135 μL, 2.95 mmol) was then added, and the solution was warmed to 23 °C with stirring for 1.5 h. The reaction mixture was then transferred to a 30 mL separatory funnel containing saturated aqueous NaHCO$_3$ (2 mL). The mixture was diluted with Et$_2$O (2 mL), shaken, and then the phases were separated. The aqueous phase was extracted with Et$_2$O (2 x 2 mL). The combined organic layers were dried over MgSO$_4$, and then filtered through a pad of Celite. The filtrate was concentrated *in vacuo* to afford 4-methoxybenzyl 2,2,2-trichloroacetimidate as a yellow liquid which was used immediately in the next reaction without further purification.

Synthesis of MIDA boronate **4.4**. To a 25 mL Schlenk flask charged with 4-methoxybenzyl 2,2,2-trichloroacetimidate (prepared above, assumed quantitative yield, 2.95 mmol) was added boronate **4.1a** (264 mg, 1.00 mmol) and THF (10 mL). The stirred mixture was cooled to 0 °C and then trifluoromethanesulfonic acid (10 μL, 0.11 mmol) was added. The resulting mixture was allowed to warm to 23 °C and stirred for 5 h. The solution was then transferred to a 60 mL separatory funnel containing water (5 mL) and

brine (5 mL). The mixture was diluted with EtOAc (25 mL) and shaken and the phases were then separated. The aqueous phase was extracted once with EtOAc (25 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting residue was adsorbed onto Celite *in vacuo* from an acetone solution. The resulting powder was subjected to flash chromatography on silica gel (Et_2O:MeCN 100:0 → 70:30) to afford MIDA boronate **4.4** as a colorless solid (248 mg, 64%).

TLC (Et_2O:MeCN 2:1)

R_f = 0.43, stained by $KMnO_4$

^{1}H-NMR (500 MHz, CD_3CN)

δ 7.47 (d, *J*= 7.5 Hz, 2H), 7.35 (d, *J* = 7.5 Hz, 2H), 7.28 (d, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 4.51 (s, 2H), 4.46 (s, 2H), 4.05 (d, *J* = 17 Hz, 2H), 3.87 (d, *J* = 17 Hz, 2H), 3.76 (s, 3H), 2.47 (s, 3H).

^{13}C-NMR (125 MHz, CD_3CN)

δ 169.6, 160.2, 140.9, 133.4, 131.6, 130.4, 128.2, 114.6, 72.6, 72.5, 62.7, 55.8, 48.4.

^{11}B-NMR (96 MHz, CD_3CN)

δ 12.2

HRMS (ESI+)

Calculated for $C_{20}H_{23}BNO_6$:	384.1618
Found:	384.1617

IR (thin film, cm^{-1})

2997, 2951, 2848, 1768, 1612, 1512, 1457, 1336, 1297, 1247, 1171, 1038, 993, 818.
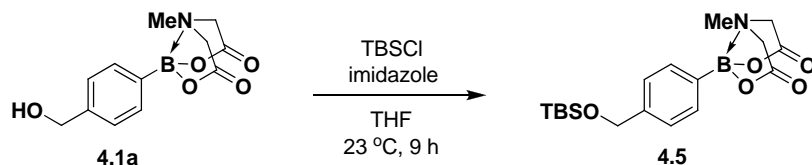
MIDA boronate 4.5

To a 250 mL roundbottom flask was added boronate **4.1a** (2.105 g, 8.002 mmol), *tert*-butyldimethylsilyl chloride (1.448 g, 9.609 mmol), imidazole (763 mg, 11.2 mmol) and THF (100 mL). The mixture was stirred for 9 h and then concentrated *in vacuo*. The resulting colorless solid residue was adsorbed onto Florisil gel *in vacuo* from an acetone solution. The resulting powder was subjected to flash chromatography on silica gel (Et$_2$O:MeCN 100:0 → 1:2) to afford MIDA boronate **4.5** as a colorless solid (2.956 g, 98%).

TLC (EtOAc)

R$_f$ = 0.47, stained by KMnO$_4$

^{1}H-NMR (500 MHz, CD$_3$CN)

δ 7.45 (d, *J* = 8 Hz, 2H), 7.33 (d, *J* = 8 Hz, 2H), 4.74 (s, 2H), 4.05 (d, *J* = 17 Hz, 2H), 3.87 (d, *J* = 17 Hz, 2H), 2.48 (s, 3H), 0.92 (s, 9H), 0.09 (s, 6H).

^{13}C-NMR (125 MHz, CD$_3$CN)

δ 169.6, 143.6, 133.4, 126.7, 65.6, 62.7, 48.4, 26.3, 19.0, -5.1

^{11}B-NMR (96 MHz, CD$_3$CN)

δ 12.1

HRMS (ESI+)

Calculated for C$_{18}$H$_{29}$BNO$_5$Si: 378.1908

Found: 378.1901

IR (thin film, cm^{-1})

3008, 2953, 2925, 2853, 1767, 1464, 1336, 1285, 1253, 1114, 1088, 1035, 837.
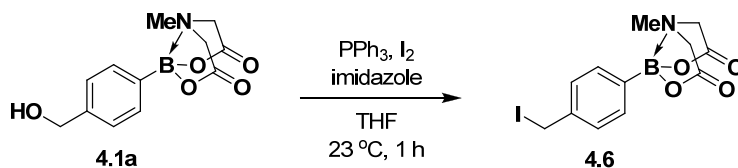
MIDA boronate 4.6

To a 50 mL Schlenk flask was added boronate **4.1a** (264 mg, 1.00 mmol), triphenylphosphine (281 mg, 1.21 mmol), imidazole (104 mg, 1.53 mmol) and CH$_2$Cl$_2$ (20 mL). To the resulting stirred mixture was added solid I$_2$ (303 mg, 1.19 mmol). The suspension was stirred for 1 h and then transferred to a 60 mL separatory funnel and diluted with water (20 mL). The mixture was shaken, the phases were separated, and the aqueous phase was extracted with CH$_2$Cl$_2$ (20 mL). The combined organic layers were dried over MgSO$_4$, filtered, and concentrated *in vacuo*. The resulting residue was adsorbed onto Florisil gel *in vacuo* from an acetone solution. The resulting powder was subjected to flash chromatography on silica gel (Et$_2$O:MeCN 2:1) to afford MIDA boronate **4.6** as a colorless, crystalline solid (329 mg, 88%).

TLC (Et$_2$O:MeCN 2:1)

R$_f$ = 0.64, stained by KMnO$_4$

^{1}H-NMR (500 MHz, CD$_3$CN)

δ 7.42 (m, 4H), 4.55 (s, 2H), 4.05 (d, *J* = 17 Hz, 2H), 3.88 (d, *J* = 17 Hz, 2H), 2.48 (s, 3H).

^{13}C-NMR (125 MHz, CD$_3$CN)

δ 169.5, 141.8, 133.9, 129.1, 62.7, 48.4, 6.7

^{11}B-NMR (96 MHz, CD$_3$CN)

      δ 12.0

HRMS (ESI+)

      Calculated for C$_{12}$H$_{14}$BINO$_4$:   374.0061

      Found: 374.0052

IR (thin film, cm^{-1})

      3015, 2957, 1770, 1696, 1608, 1457, 1400, 1337, 1294, 1252, 1160, 1039, 993, 890, 868, 833, 796.
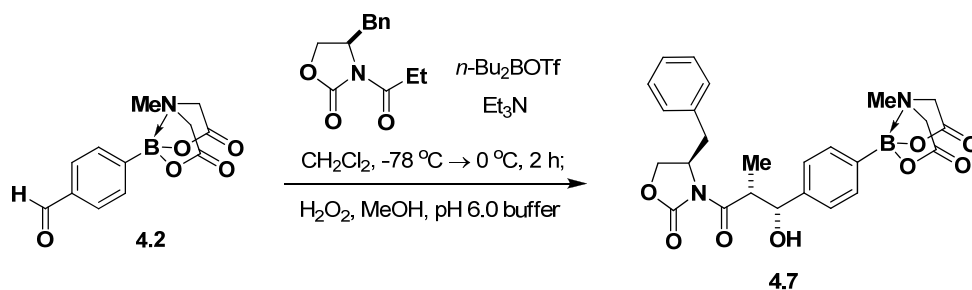
MIDA boronate 4.7

To a 10 mL Schlenk flask charged with (R)-(−)-4-Benzyl-3-propionyl-2-oxazolidinone (118 mg, 0.505 mmol) was added CH$_2$Cl$_2$ (10 mL) and the resulting solution was cooled to 0 °C. To this stirred solution was added di-*n*-butylboron trifluoromethanesulfonate (1.0 M in CH$_2$Cl$_2$, 600 μL, 0.60 mmol) followed by freshly distilled triethylamine (0.65 mmol, 90 μL, dropwise). The solution was cooled to -78 °C. To this solution was then added MIDA boronate **4.2** (144 mg, 1.10 mmol) in one portion as a solid. The mixture was stirred at -78 °C for 20 min. and then allowed to warm to 0 °C with stirring for 2 h. The reaction was then quenched at 0 °C with the addition of aqueous pH 6.0 sodium phosphate buffer (1.0 M, 1.0 mL) followed by MeOH (1.5 mL) and aqueous 30% H$_2$O$_2$. The resulting mixture was stirred at 0 °C for 45 min and then was transferred to a 60 mL separatory funnel. The mixture was diluted with EtOAc (25 mL) and brine (5 mL) and shaken and the layers were separated. The aqueous layer was

extracted with EtOAc (3 x 25 mL). The combined organic layers were dried over MgSO$_4$, filtered, and concentrated *in vacuo*. The residue was adsorbed onto Celite *in vacuo* from an acetone solution. The resulting powder was subjected to flash chromatography on silica gel (hexanes:EtOAc:MeOH 50:50:0 → 45:45:10) to afford MIDA boronate **4.7** as a colorless, crystalline solid (196 mg, 79%).

TLC (hexanes:EtOAc:MeOH 2:2:1)

    R_f = 0.52, UV (λ = 254 nm)

^{1}H-NMR (500 MHz, CD$_3$CN)

    δ 7.44 (d, *J* = 8 Hz, 2H), 7.35 (d, *J* = 8 Hz, 2H), 7.32-7.17 (m, 5H), 4.95 (d, *J* = 5 Hz, 1H), 4.52 (m, 1H), 4.12 (app dd, *J* = 9, 2.5 Hz, 1H), 4.06-3.98 (m, 4H), 3.87 (app dd, *J* = 17, 4 Hz, 2H), 3.01 (dd, *J* = 14, 4 Hz, 1H), 2.95 (dd, *J* = 14, 7.5 Hz, 1H), 2.46 (s, 3H), 1.14 (d, *J* = 6.5 Hz, 3H).

^{13}C-NMR (125 MHz, CD$_3$CN)

    δ 176.3, 169.6, 169.6, 154.2, 144.8, 136.6, 133.2, 130.7, 129.6, 128.0, 126.6, 74.5, 67.2, 62.7, 62.7, 55.8, 48.4, 45.9, 37.8, 11.8

^{11}B-NMR (96 MHz, CD$_3$CN)

    δ 12.1

HRMS (ESI+)

    Calculated for C$_{25}$H$_{27}$BN$_2$O$_8$Na: 517.1758

    Found: 517.1746

IR (thin film, cm^{-1})

    3502, 3004, 2951, 1770, 1695, 1456, 1390, 1340, 1287, 1226, 1114, 1038, 993, 887, 815, 763, 707.

$[\alpha]_D^{24}$ +86.5 (*c* 1.0, MeOH)
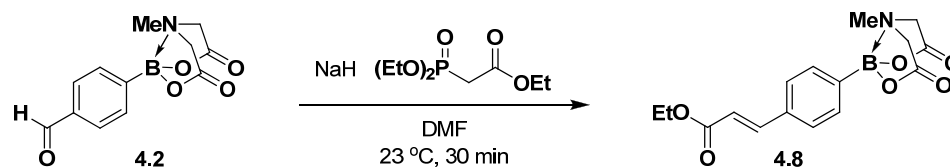
MIDA boronate 4.8

To a 10 mL Schlenk flask charged with NaH (27 mg, 1.1 mmol) and DMF (5 mL) was added triethyl phosphonoacetate (250 µL, 1.25 mmol). The resulting mixture was stirred at 23 °C for 30 min and then boronate **4.2** (262 mg, 1.00 mmol) was added as a solid in one portion. The resulting solution was stirred for 30 min and then poured into a 60 mL separatory funnel containing saturated aqueous NH$_4$Cl (10 mL). The mixture was diluted with EtOAc (25 mL) and shaken and the layers were separated allowing the colorless precipitate to be collected along with the organic phase. The aqueous phase was extracted with EtOAc (2 x 25 mL). The combined organic phases were diluted with acetone (app. 20 mL) to afford a homogeneous solution. The solution was dried over MgSO$_4$, filtered, and concentrated *in vacuo* to a volume of app. 75 mL. To the solution was added Et$_2$O (75 mL) which caused a colorless solid to crystallize. The mixture was left to stand at room temperature with periodic agitation for 1 h. The mixture was then filtered and the isolated solid was washed with Et$_2$O (20 mL). Residual solvent was removed *in vacuo* to afford MIDA boronate **4.8** as a colorless solid (235 mg, 71%). Alternatively, the product can be purified via column chromatography on silica gel (Hexanes:EtOAc:MeOH).

TLC (Hexanes:EtOAc:MeOH 2:2:1)

R_f = 0.60, stained by KMnO$_4$

^{1}H-NMR (500 MHz, DMSO-d6)

δ 7.69 (d, *J* = 8 Hz, 2H), 7.64 (d, *J* = 16 Hz, 1H), 7.47 (d, *J* = 8 Hz, 2H), 6.65 (d, *J* = 16 Hz, 1H), 4.34 (d, *J* = 17 Hz, 2H), 4.18 (q, *J* = 7 Hz, 2H), 4.12 (d, *J* = 17 Hz, 2H), 2.51 (s, 3H), 1.25 (t, *J* = 7 Hz, 3H).

¹³C-NMR (125 MHz, DMSO-d6)

δ 169.3, 166.2, 144.4, 134.4, 133.0, 127.5, 118.2, 61.8, 60.0, 47.6, 14.2

¹¹B-NMR (96 MHz, DMSO-d6)

δ 11.4

HRMS (ESI+)

Calculated for $C_{16}H_{19}BNO_6$:		332.1305
Found:		332.1297

IR (thin film, cm^{-1})

2996, 2971, 1746, 1697, 1636, 1465, 1450, 1365, 1340, 1325, 1308, 1225, 1188, 1046, 1021, 980, 960, 827.
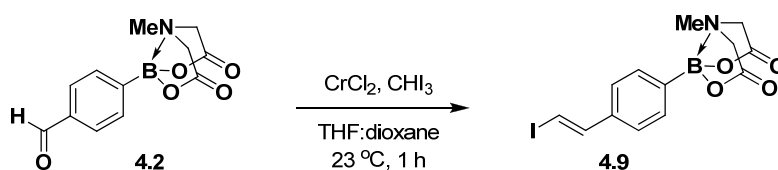
MIDA boronate 4.9

With the exclusion of light, to a 50 mL Schlenk flask charged with a suspension of anhydrous $CrCl_2$ (1.007 g, 8.332 mmol) in THF (20 mL) was added dropwise via cannula a solution of CHI_3 (1.085 g, 2.755 mmol) in dioxane (5 mL + 5 mL washing). To the resulting deep red mixture was added MIDA boronate **4.2** (132 mg, 0.504 mmol) as a solid in one portion. The mixture was stirred at 23 °C for 1 h and then was transferred to a 250 mL roundbottom flask equipped with a large stir bar. The mixture was then diluted with EtOAc (100 mL), and to the resulting solution was added saturated aqueous $NaHCO_3$ (50 mL). This mixture was stirred at 23 °C for 5 min and then filtered through a pad of Celite. The filtrate was transferred to a 250 mL separatory funnel and the layers were separated. The organic layer was washed with 0.5 M aqueous $Na_2S_2O_3$ (50 mL) and then brine (25 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated

in vacuo. The residue was adsorbed onto Celite *in vacuo* from an acetone solution, and the resulting powder was subjected to flash chromatography on silica gel (Et$_2$O:MeCN 100:0 → 70:30) to afford MIDA boronate **4.9** as a pale orange solid (170 mg, 88%, E:Z 17:1).

TLC (Et$_2$O:MeCN 3:1)

  R_f = 0.55, UV (λ = 254 nm)

^{1}H-NMR (500 MHz, CD$_3$CN, E-isomer)

  δ 7.51 (d, J = 15 Hz, 1H), 7.46 (d, J = 8 Hz, 2H), 7.37 (d, J = 8 Hz, 2H), 7.07 (d, J = 15 Hz, 1H), 4.05 (d, J = 17 Hz, 2H), 3.87 (d, J = 17 Hz, 2H), 2.48 (s, 3H).

^{13}C-NMR (125 MHz, CD$_3$CN, E-isomer)

  δ 169.5, 145.7, 139.3, 133.9, 126.4, 78.8, 62.7, 48.4

^{11}B-NMR (96 MHz, CD$_3$CN)

  δ 12.1

HRMS (ESI+)

  Calculated for C$_{13}$H$_{14}$BINO$_4$: 386.0061
  Found: 386.0067

IR (thin film, cm^{-1})

  3049, 3008, 2951, 1768, 1457, 1337, 1290, 1231, 1038, 993, 834, 772.
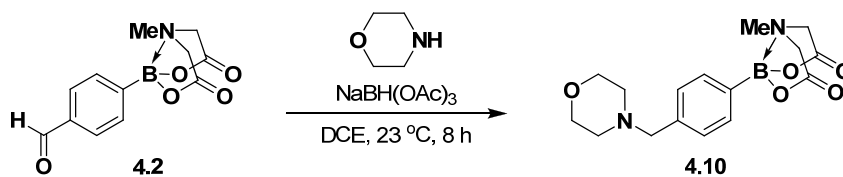
MIDA boronate 4.10

To a 10 mL Schlenk flask charged with boronate **4.2** (262 mg, 1.00 mmol) in 1,2-dichloroethane (5 mL) was added morpholine (96 µL, 1.1 mmol) followed by sodium triacetoxyborohydride (299 mg, 1.41 mmol) and the resulting mixture was stirred at 23 °C for 8 h. Aqueous dibasic sodium tartrate solution (0.5 M, 5 mL) was then added, and the mixture was stirred for 5 min and then transferred to a 60 mL separatory funnel. The mixture was diluted with EtOAc (25 mL), shaken, and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 25 mL). The combined organics were dried over $MgSO_4$, filtered, and then concentrated *in vacuo*. The residue was adsorbed onto Celite *in vacuo* from an acetone solution, and the resulting powder was subjected to flash chromatography on silica gel (Et_2O:MeCN 100:0 → 50:50) to afford MIDA boronate **4.10** as a colorless solid (255 mg, 76%).

TLC (Et_2O:MeCN)

R_f = 0.16, stained by $KMnO_4$

^{1}H-NMR (500 MHz, CD_3CN)

δ 7.44 (d, *J* = 8 Hz, 2H), 7.32 (d, *J* = 8 Hz, 2H), 4.05 (d, *J* = 17 Hz, 2H), 3.87 (d, *J* = 17 Hz, 2H), 3.59 (app t, *J* = 4.5 Hz, 4H), 3.47 (s, 2H), 2.47 (s, 3H), 2.37 (m, 4H).

^{13}C-NMR (125 MHz, CD_3CN)

δ 169.6, 140.3, 133.3, 129.6, 67.5, 63.7, 62.7, 54.4, 48.4

^{11}B-NMR (96 MHz, CD_3CN)

δ 12.2

HRMS (ESI+)

Calculated for $C_{16}H_{22}BN_2O_5$:	333.1622
Found:	333.1607

IR (thin film, cm^{-1})

3003, 2954, 2806, 1768, 1457, 1336, 1292, 1233, 1114, 1039, 994, 890, 864, 792.
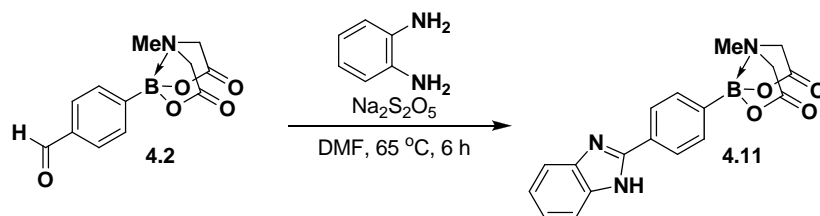
MIDA boronate 4.11

To a 10 mL round-bottom flask was added aldehyde **4.2** (261 mg, 1.00 mmol), 1,2-phenylenediamine (108 mg, 1 mmol), $Na_2S_2O_5$ (192 mg, 1.01 mmol) and DMF (2 mL). The flask was sealed with a rubber septum, then was placed in a 65 °C oil bath with stirring for 6 h. The solution was allowed to cool to room temperature, and then was concentrated *in vacuo*. The residue was adsorbed onto Florisil gel from an acetone suspension and the resulting powder was subjected to flash chromatography on silica gel (Et$_2$O:MeCN 100:0 → 25:75) to afford MIDA boronate **4.11** as an off-white, free-flowing solid (161 mg, 46%).

TLC (Et$_2$O:MeCN, 2:1)

R_f = 0.32, yellow, visualized by UV

TLC C$_{18}$ (H$_2$O:MeCN, 1:1)

R_f = 0.63, yellow, visualized by UV

^{1}H-NMR (500 MHz, acetone-d$_6$)

δ 8.22 (d, J = 8.0 Hz, 2H), 7.69 (d, J = 8.0 Hz, 2H), 7.68 (dd, J = 0.5, 0.4 Hz, 1H), 7.51 (dd, J = 0.5, 0.4 Hz, 1H), 7.21 (m, 2H), 5.62 (s, 1H), 4.39 (d, J = 17.0 Hz, 2H), 4.20 (d, J = 17.0 Hz, 2H)

^{13}C-NMR (125 MHz, CD$_3$CN)

δ 169.2, 133.9, 126.6, 123.5, 122.6, 120.1, 111.9, 62.8, 48.3

^{11}B-NMR (96 MHz, CD$_3$CN)

δ 12.0
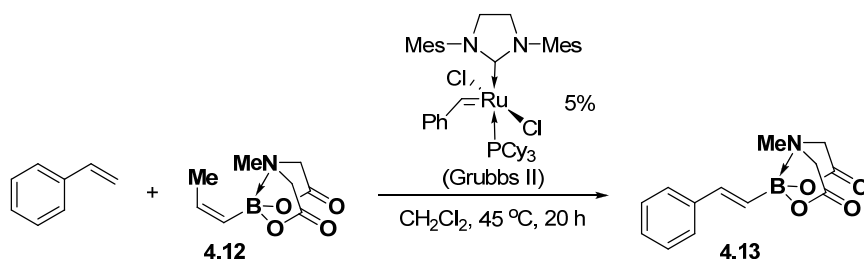
MIDA boronate 4.13

In a glove box, to a 10 mL Schlenk flask was added Grubbs II catalyst (21 mg, 0.025 mmol). On the Schlenk line, to the flask was added MIDA boronate **4.12** and CH$_2$Cl$_2$ (2.5 mL), and then styrene (63 µL, 0.55 mmol). The flask was fitted with a water-cooled reflux condenser vented to inert atmosphere. The flask was placed in a 45 °C oil bath with stirring for 20 h. The solution was allowed to cool to room temperature. To the solution was added Florisil gel. The solution was concentrated *in vacuo* and the resulting powder was subjected to flash chromatography on silica gel (Et$_2$O:MeCN 100:0 → 75:25) to a afford colorless solid (124 mg, 94%) determined by ^{1}H-NMR to be a mixture of **4.13**:**4.12** (92:8). An optimized synthesis of **4.13** was later developed by Brice Uno.[4]

TLC (Et$_2$O:MeCN, 2:1)

R$_f$ = 0.28, stained with KMnO$_4$

[1H-NMR (500 MHz, CD3CN)]

¹H-NMR (500 MHz, CD₃CN)

δ 7.51 (d, *J* = 9.0 Hz, 2H), 7.33 (m, 3H), 6.94 (d, *J* = 18.0 Hz, 1H), 6.35 (d, *J* = 18.5, 1H), 4.25 (d, *J* = 17.0 Hz, 2H), 4.07 (d, *J* = 17.0 Hz, 2H), 3.05 (s, 3H)

¹³C-NMR (125 MHz, CD₃CN)

δ 169.6, 143.3, 139.0, 129.5, 129.0, 127.6, 62.3, 47.6

HRMS (ESI+)

Calculated for C₁₃H₁₄BNO₄ (M)⁺:   259.1016

Found: 259.1017

MIDA boronate 4.15
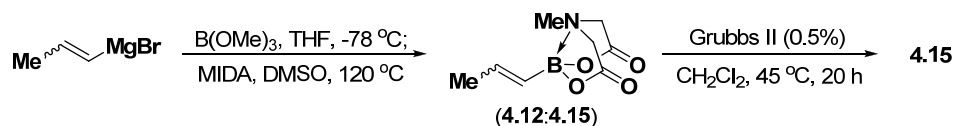
Synthesis of **4.12**:**4.15** *via the "Hot Protocol"*[5]

To a 2 L 3-neck round-bottom equipped with a large stir bar and charged with a stirred solution of B(OMe)₃ (47 mL, 0.42 mol) in THF (400 mL) cooled to -60 °C internal temperature was added was added via cannula over 60 min. propenylmagnesiumbromide (800 mL, 0.5 M in THF). During the transfer the internal temperature of the reaction solution was maintained below -50 °C. Upon completion of the addition the reaction solution was stirred for 2.5 h maintaining the internal temperature of the mixture below -60 °C. The mixture was then allowed to warm to room temperature with stirring for 2 h.

Separately, a 2 L 3-neck round-bottom flask was charged with N-methyliminodiacetic acid (144.3g, 0.9810 mol), DMSO (400 mL) and hexanes (600 mL). The round-bottom necks were fitted as follows: 1) a thermometer, 2) a rubber septum, and 3) a distillation apparatus collecting into a 2 L round-bottom flask. [Note: for safety,

the distillation should be conducted under inert atmosphere at around 1 atm.] The mixture was heated to distill the hexanes which removed residual water via azeotrope. Through the septum was placed a large-gauge cannula connecting the distillation pot to the borate solution from the first step, such that once the internal temperature had reached 120 °C transfer of the borate solution was immediately started. The rate of addition was controlled to maintain the temperature of the reaction mixture between 95-120 °C. During this time the THF is rapidly distilled and was collected in the receiving flask. When the addition was complete and the temperature of the mixture rose to 125 °C, the heat source was removed and the mixture was allowed to cool to room temperature. The mixture was transferred to a 6 L separatory funnel using water (1.0 L), brine (1.0 L), acetone (1.0 L) and EtOAc (2.0 L). The mixture was shaken; the phases were separated. The aqueous phase was twice extracted with EtOAc:acetone (400 mL:200 mL). The combined organics were washed twice with water (125 mL); the water washes were combined and extracted with EtOAc:acetone (200 mL:100 mL). The combined organics were dried over $MgSO_4$, filtered, and then concentrated *in vacuo* to afford the crude product as off-white solid which was purified via recrystallization from a minimum of hot acetone slowly diluted with Et_2O to a total volume of 2 L. Isolation of the crystals via filtrated afforded a colorless crystalline solid, an otherwise pure mixture of **4.12**:**4.15** (2:1) (41.4 g, 53%).

Isomerization of **4:12**:**4.15**

To a 2 L round-bottom flask was added the mixture of **4.12**:**4.15** obtained from above (41.4 g, 210 mmol) and Grubbs II metathesis catalyst (892 mg, 1.05 mmol). To the flask was added CH_2Cl_2. The flask was fitted with a water-cooled condenser connected to a slightly >1 atm. supply of N_2. The flask was warmed with a 45 °C oil bath with stirring for 20 h. The mixture was filtered through a thin pad of SiO_2, eluting with acetone. The filtrate was stirred with 3-aminopropyl-functionalized silica gel (5.0 g) for 60 min. to remove ruthenium. The mixture was then filtered concentrated *in vacuo*. The resulting solid residue was purified via recrystallization from a minimum of hot acetone slowly diluted with Et_2O to a total volume of 2 L. Isolation of the crystals via filtrated afforded **4.15** as an off-white crystalline solid (37.4 g, 90%).

Total Synthesis of (+)-Crocacin C
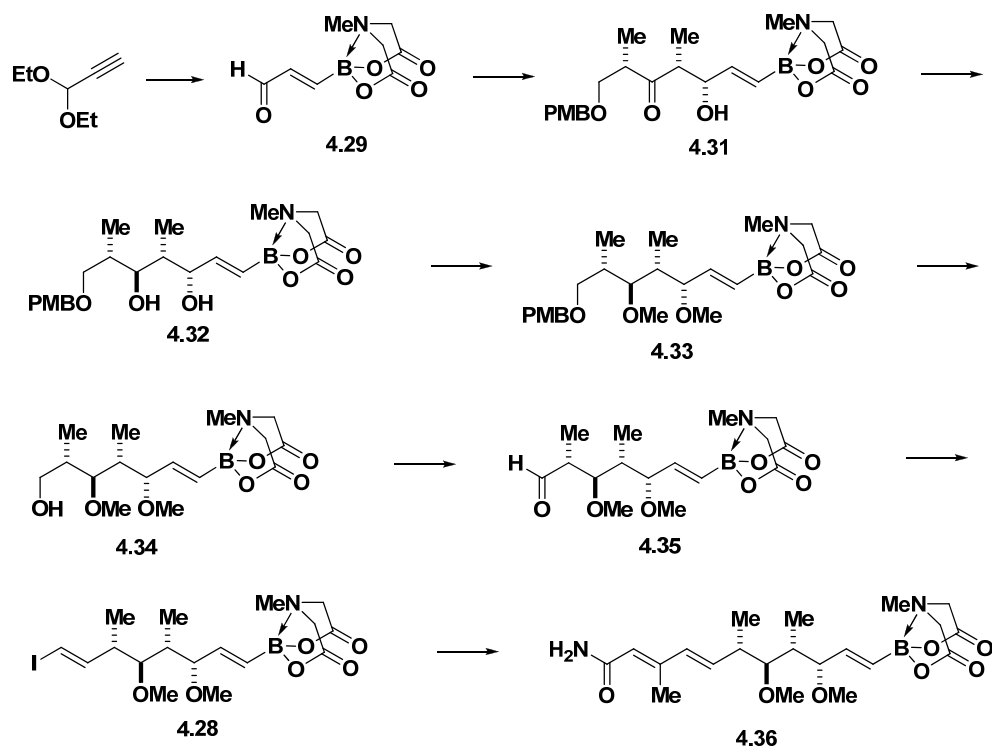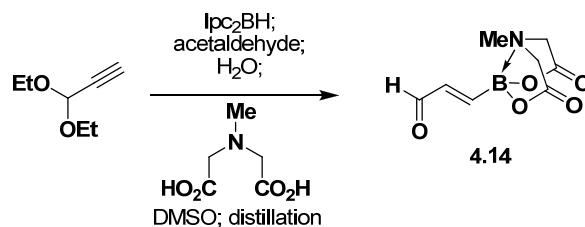
MIDA boronate 4.14

Following the literature procedure for the synthesis of 3-acroleinboronic acid,[6] to a 20 mL Schlenk flask was added $BH_3 \cdot SMe_2$ (695 µL, 7.33 mmol) and THF (2.5 mL) and the resulting stirred solution was cooled to 0 °C. (R)-(+)-α-pinene (2.38 mL, 15.0 mmol) was added, and the solution was stirred for 10 min at 0 °C and then was allowed to warm to 23 °C with stirring for 2 h, during which time a colorless precipitate was formed. The mixture was recooled to 0 °C and propionaldehyde diethyl acetal (1.00 mL, 6.98 mmol) was added. Effervescence was observed and the mixture became a homogeneous, pale yellow solution. The solution was stirred at 0 °C for 30 min and then allowed to warm to 23 °C and stirred for 2.5 h. The solution was then cooled to 0 °C, acetaldehyde (5.0 mL, 89 mmol) was added, and the flask was fitted with a water-cooled reflux condenser sealed with a rubber septum. The solution was then warmed to 45 °C in a closed-system with stirring for 12 h. The solution was then cooled to 0 °C, water (2.5 mL) was added, and the resulting mixture was stirred at 0 °C for 1 h and then warmed to 23 °C with stirring for 2 h. The mixture was then transferred to a 125 mL separatory funnel and was diluted with Et_2O (20 mL) and EtOAc (20 mL). Solid NaCl (app. 0.5 g) was added and the mixture was shaken. The layers were separated, and the aqueous layer was extracted with Et_2O:EtOAc (20 mL:20 mL). The combined organic layers were concentrated *in vacuo* upon which a colorless solid precipitated. The resulting mixture was diluted with hexanes (20 mL), agitated, and then allowed to stand at 23 °C for 1 h. The solution was decanted to leave the crude boronic acid as a white solid. To a 100 mL roundbottom flask containing this boronic acid was added *N*-methyliminodiacetic acid (984 mg, 6.70 mmol) and DMSO (25 mL). The flask was fitted with a short-path distillation apparatus. The DMSO mixture was distilled to dryness under vacuum (40 °C, 1 Torr, bath temp = 75 °C). The resulting residue was lyophilized overnight to further remove residual DMSO and then adsorbed onto Florisil gel *in vacuo* from an acetone

solution. The resulting powder was subjected to flash chromatography on silica gel (Et$_2$O:MeCN 100:0 → 50:50) to afford MIDA boronate **4.14** as a colorless, crystalline solid (806 mg, 55%).

TLC (Et$_2$O:MeCN 1:1)

      R$_f$ = 0.69, stained by KMnO$_4$

^{1}H-NMR (500 MHz, CD$_3$CN)

      δ 9.57 (d, J = 8 Hz, 1H), 6.94 (d, J = 17.5 Hz, 1H), 6.46 (dd, J = 17.5, 7.5 Hz, 1H), 4.03 (d, J = 17, 2H), 3.87 (d, J = 17, 2H), 2.82 (s, 3H).

^{13}C-NMR (125 MHz, CD$_3$CN)

      δ 196.1, 169.0, 143.7, 62.9, 48.0

^{11}B-NMR (96 MHz, CD$_3$CN)

      δ 10.7

HRMS (ESI+)

      Calculated for C$_8$H$_{11}$BNO$_5$:   212.0730

      Found: 212.0733

IR (thin film, cm^{-1})

      2997, 2970, 2819, 2724, 1761, 1685, 1617, 1465, 1445, 1344, 1294, 1227, 1120, 1026, 1003, 954, 882, 803, 715.
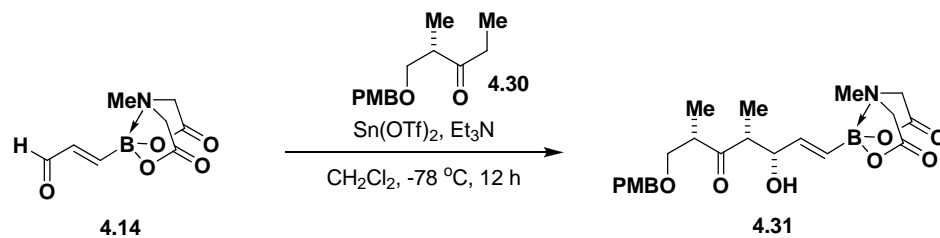
MIDA boronate 4.31

To a 100 mL Schlenk flask charged with Sn(OTf)$_2$ (5.141 g, 12.33 mmol) was added CH$_2$Cl$_2$ (90 mL) and triethylamine (1.85 mL, 13.3 mmol). The resulting orange-brown suspension was cooled to -78 °C and then (S)-1-(p-methoxybenzyloxy)-2-methylpentan-3-one[7] (1.98 g, 2.00 mL, 8.38 mmol) was added. The mixture was stirred for 2 h at -78 °C and then boronate **4.14** (1.732 g, 8.208 mmol) was added as a powder in one portion. The mixture was stirred for 12 h at -78 °C, and then poured into a 1000 mL separatory funnel containing saturated aqueous NH$_4$Cl (150 mL). The mixture was diluted with CH$_2$Cl$_2$ (500 mL) and shaken, and the layers were separated. The aqueous phase was extracted with CH$_2$Cl$_2$ (2 x 500 mL). (The majority of a beige precipitate remained in the aqueous phase). The combined organic layers were dried over MgSO$_4$, filtered through Celite, and then concentrated *in vacuo* to afford a yellow oil. This residue was adsorbed onto Celite *in vacuo* from an acetone solution and the resulting powder was subjected to flash chromatography on silica gel (hexanes:EtOAc:MeOH 9:9:2) to afford MIDA boronate **4.31** as a colorless, solid foam (2.558 g, 70%).

TLC (CH$_2$Cl$_2$:hexanes:MeOH 2:2:1)

    R$_f$ = 0.51, stained by KMnO$_4$

^{1}H-NMR (500 MHz, CD$_3$CN)

    δ 7.22 (dt, *J* = 8.5, 2 Hz, 2H), 6.88 (dt, *J* = 8.5, 2 Hz, 2H), 6.00 (dd, *J* = 18, 4.5 Hz, 1H), 5.61 (dd, *J* = 18, 1.5 Hz, 1H), 4.43 (m, 1H), 4.37 (s, 2H), 3.93 (app dd, *J* = 17, 2 Hz, 2H), 3.76 (s, 3H), 3.74 (app dd, *J* = 17, 2 Hz, 2H), 3.57 (dd, *J* = 9, 8 Hz, 1H), 3.40 (dd, *J* = 9, 5.5 Hz, 1H), 3.10 (m, 1H), 2.88 (m, 1H), 2.73 (s, 3H), 0.98 (d, *J* = 7 Hz, 3H), 0.96 (d, *J* = 7 Hz, 3H).

<superscript>13</superscript>C-NMR (125 MHz, CD$_3$CN)

δ 216.7, 169.3 (2 carbons), 160.2, 146.3, 131.3, 130.4, 114.6, 73.6, 73.3, 72.9, 62.3, 62.3, 55.8, 51.2, 47.6, 45.9, 14.0, 11.0

<superscript>11</superscript>B-NMR (96 MHz, CD$_3$CN)

δ 11.2

HRMS (ESI+)

| Calculated for C$_{22}$H$_{31}$BNO$_8$: | 448.2143 |
| Found: | 448.2151 |

IR (thin film, cm^{-1})

3503, 2937, 1762, 1707, 1612, 1512, 1457, 1337, 1289, 1248, 1156, 1117, 1090, 1030, 1006, 962, 852, 820.

$[\alpha]_D^{23}$ -9.7 (c 1.2, CH$_2$Cl$_2$)
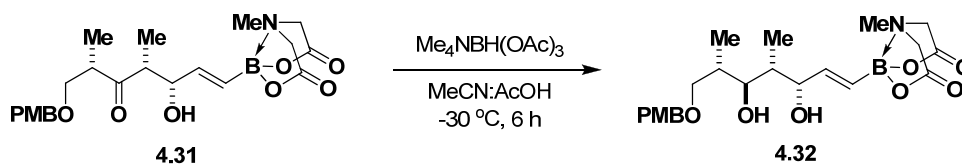
MIDA boronate 4.32

To a 25 mL Schlenk flask charged with tetramethylammonium triacetoxy-borohydride (1.320 g, 5.017 mmol) was added dry acetic acid (8.5 mL) and MeCN (12 mL). The resulting solution was stirred for 30 min at 23 °C and then cooled to -30 °C. To this cooled solution was added dropwise over 5 min MIDA boronate **4.31** (448 mg, 1.00 mmol) as a solution in MeCN (2.5 mL + 2.5 mL washings). The resulting solution was stirred at -30 °C for 6 h. The solution was then transferred to a 300 mL roundbottom flask at 23 °C and diluted with EtOAc (140 mL). The solution was stirred for 20 min upon which the solution became cloudy. Aqueous dibasic sodium tartrate solution (0.5 M, 140

mL) was added, and the resulting mixture was stirred for 15 min. The mixture was then transferred to a 500 mL separatory funnel and the layers were separated. The organic layer was washed with saturated aqueous NaHCO$_3$ (50 mL) and then brine (50 mL), dried over MgSO$_4$, filtered, and concentrated *in vacuo*. The residue was adsorbed onto Celite *in vacuo* from an acetone solution. The resulting powder was subjected to flash chromatography on silica gel (Et$_2$O:MeCN 100:0 → 60:40) to afford MIDA boronate **4.32** as a colorless, crystalline solid (317 mg, 71%).

TLC (Et$_2$O:MeCN 2:1)

　　R$_f$ = 0.24, stained by KMnO$_4$

^{1}H-NMR (500 MHz, CD$_3$CN)

　　δ 7.25 (d, *J* = 8.5 Hz, 2H), 6.98 (d, *J* = 8.5 Hz, 2H), 6.07 (dd, *J* = 17.5, 4 Hz, 1H), 5.63 (dd, *J* = 17.5, 2 Hz, 1H), 4.47 (m, 1H), 4.41 (s, 2H), 3.93 (app dd, *J* = 17, 0.5 Hz, 2H), 3.77 (app dd, *J* = 17, 6 Hz, 2H), 3.77 (s, 3H), 3.53-3.57 (m, 2H), 3.48 (dd, *J* = 9, 5.5 Hz, 1H), 2.76 (s, 3H), 1.96 (m, 1H), 1.82 (m, 1H), 0.93 (d, *J* = 7 Hz, 3H), 0.83 (d, *J* = 7 Hz, 3H).

^{13}C-NMR (125 MHz, CD$_3$CN)

　　δ 169.4, 169.4, 160.2, 148.0, 131.6, 130.3, 114.6, 79.3, 73.8, 73.8, 73.4, 62.3, 62.3, 55.8, 47.7, 40.1, 36.8, 15.2, 11.8.

^{11}B-NMR (96 MHz, CD$_3$CN)

　　δ 11.5

HRMS (ESI+)

　　Calculated for C$_{22}$H$_{32}$BNO$_8$Na:　　472.2119
　　Found:　　　　　　　　　　　　472.2127

IR (thin film, cm^{-1})

    3434, 2962, 1764, 1646, 1612, 1513, 1459, 1338, 1300, 1248, 1116, 1089, 1028, 1002, 819.

$[\alpha]_D^{23}$ -5.1 (*c* 1.1, CH$_2$Cl$_2$)
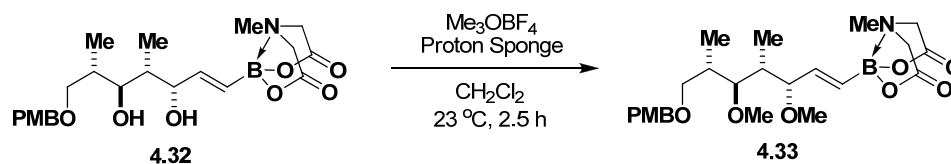
MIDA boronate 4.33

    To a 10 mL Schlenk flask charged with MIDA boronate **4.32** (751 mg, 1.67 mmol) was added CH$_2$Cl$_2$ (60 mL). To the stirred solution was added proton sponge (2.511 g, 11.72 mmol) as a solid in one portion followed by trimethyloxonium tetrafluoroborate (1.357 g, 9.172 mmol) as a solid in one portion. The resulting mixture was stirred at 23 °C for 2.5 h. The orange mixture was then transferred to a 500 mL separatory funnel. EtOAc (150 mL), aqueous 0.5 M HCl (75 mL), and brine (30 mL) were added and the mixture was shaken resulting in the formation of a precipitate. The mixture was filtered and then returned to the separatory funnel, and the phases were separated. The organic layer was washed twice with a solution of aqueous 0.5 M HCl:brine (75 mL:30 mL). The organic layer was then dried over MgSO$_4$, filtered, and concentrated *in vacuo* to afford a pale yellow residue. This residue was adsorbed onto Celite *in vacuo* from an acetone solution. The resulting powder was subjected to flash chromatography on silica gel (Et$_2$O:MeCN 100:0 → 50:50) to afford MIDA boronate **4.33** as a colorless solid (611 mg, 82%).

TLC (Et$_2$O:MeCN 2:1)

    R$_f$ = 0.71, stained by KMnO$_4$

¹H-NMR (500 MHz, CD₃CN)

> δ 7.21 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 5.97 (dd, *J* = 18, 6 Hz, 1H), 5.59 (dd, *J* = 18, 1 Hz, 1H), 4.34 (m, 2H), 3.94 (app dd, *J* = 17, 2.5 Hz, 2H), 3.88 (m, 1H), 3.77 (app dd, *J* = 17, 4.5 Hz, 2H), 3.76 (s, 3H), 3.51 (dd, *J* = 9, 5 Hz, 1H), 3.38 (s, 3H), 3.22 (s, 3H), 3.21 (m, 1H), 3.06 (dd, *J* = 9, 3 Hz, 1H), 2.74 (s, 3H), 2.01 (m, 1H), 1.72 (m, 1H), 1.02 (d, *J* = 7 Hz, 3H), 0.77 (d, *J* = 7 Hz, 3H).

¹³C-NMR (125 MHz, CD₃CN)

> δ 169.3, 160.1, 146.1, 132.1, 130.1, 114.5, 86.5, 83.3, 73.1, 72.2, 62.4, 62.4, 61.5, 57.0, 56.9, 55.9, 55.8, 47.8, 47.8, 16.8, 10.8.

¹¹B-NMR (96 MHz, CD₃CN)

> δ 11.1

HRMS (ESI+)

> Calculated for $C_{24}H_{37}BNO_8$: 478.2612
>
> Found: 478.2617

IR (thin film, cm⁻¹)

> 2934, 1762, 1612, 1512, 1457, 1289, 1247, 1089, 1028.

$[\alpha]_D^{23}$ +4.3 (*c* 1.0, CH₂Cl₂)

MIDA boronate 4.32

To a 50 mL roundbottom flask charged with boronate **4.33** (331 mg, 0.740 mmol) was added MeCN (6 mL) and H₂O (600 μL). Ceric ammonium nitrate (1.011 g, 1.844 mmol) was added, and the resulting solution was stirred for 15 min at 23 °C. Saturated

aqueous NaHCO$_3$ (7.5 mL) and NaHSO$_3$ (0.5 g) were then added, and the resulting mixture was vigorously stirred for 5 min and then transferred to a 60 mL separatory funnel. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over MgSO$_4$, filtered, and concentrated *in vacuo*. The resulting residue was adsorbed onto Celite *in vacuo* from an acetone solution. The resulting powder was subjected to flash chromatography on silica gel (Et$_2$O:MeCN 85:15 $\prod$ 65:35) to afford MIDA boronate **4.32** as a colorless solid (202 mg, 77%).

TLC (Et$_2$O:MeCN 2:1)

      R$_f$ = 0.21, stained by KMnO$_4$

^{1}H-NMR (500 MHz, CD$_3$CN)

      δ 5.98 (dd, J = 18, 6 Hz, 1H), 5.61 (dd, J = 18, 1 Hz, 1H), 3.94 (d, J = 17 Hz, 2H), 3.90 (ddd, J = 6, 2.5, 1.5 Hz, 1H), 3.79 (d, J = 17 Hz, 2H), 3.51 (m, 1H), 3.43 (m, 1H), 3.42 (s, 3H), 3.23 (s, 3H), 3.11 (dd, J = 9.5, 3 Hz, 1H), 2.78 (s, 3H), 1.83 (m, 1H), 1.73 (m, 1H), 1.05 (d, J = 7 Hz, 3H), 0.78 (d, J = 7 Hz, 3H).

^{13}C-NMR (125 MHz, CD$_3$CN)

      δ 169.4, 169.4, 145.9, 87.5, 83.2, 64.0, 62.4, 62.4, 61.6, 56.9, 47.8, 42.0, 38.0, 16.3, 10.7.

^{11}B-NMR (96 MHz, CD$_3$CN)

      δ 11.3

HRMS (ESI+)

      Calculated for C$_{16}$H$_{29}$BNO$_7$:   358.2037
      Found: 358.2047

IR (thin film, cm^{-1})

      3467, 2966, 2937, 2827, 1762, 1642, 1457, 1340, 1291, 1243, 1089, 1026, 957, 862.

$[\alpha]_D^{22}$ +8.2 (c 1.1, CH$_2$Cl$_2$)
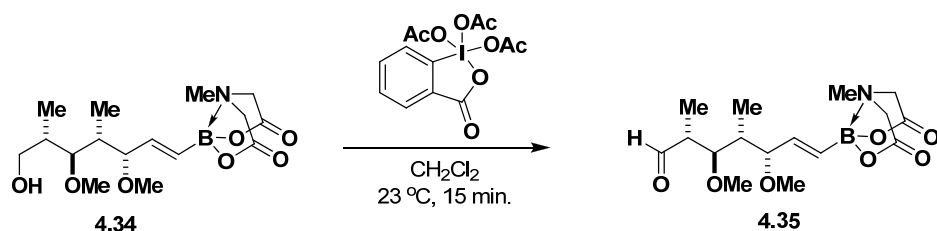
MIDA boronate 4.35

      To a 100 mL roundbottom flask charged with MIDA boronate **4.34** (155 mg, 0.433 mmol) was added CH$_2$Cl$_2$ (10 mL). To this stirred solution was added Dess-Martin periodane (278 mg, 0.655 mmol) and the resulting mixture was stirred for 15 min under ambient atmosphere at 23 °C. Saturated aqueous NaHCO$_3$ (5 mL) and 1.5 M aqueous Na$_2$S$_2$O$_3$ (5 mL) were then added and the mixture was stirred for 15 min and then transferred to a 60 mL separatory funnel. The layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (2 x 10 mL). The combined organic layers were dried over MgSO$_4$, filtered, and concentrated *in vacuo* to afford MIDA boronate **4.35** as a colorless, crystalline solid (149 mg, 97%). The product thus obtained was of a high purity and was used directly in further steps. Further purification through a short plug of SiO$_2$ is possible with <5% observed epimerization.

TLC (Et$_2$O:MeCN 2:1)

      R$_f$ = 0.61, stained by KMnO$_4$

^{1}H-NMR (500 MHz, CD$_3$CN)

δ 9.69 (d, J = 1 Hz, 1H), 5.97 (dd, J = 18, 6 Hz, 1H), 5.63 (dd, J = 18, 1 Hz, 1H), 3.95 (d, J = 17 Hz, 2H), 3.95 (m, 1H), 3.79 (app dd, J = 17, 1.5 Hz, 2H), 3.48 (dd, J = 9.5, 3 Hz, 1H), 3.39 (s, 3H), 3.25 (s, 3H), 2.77 (s, 3H), 2.71 (m, 1H), 1.81 (m, 1H), 1.09 (d, J = 7 Hz, 3H), 0.71 (d, J = 7 Hz, 3H).

^{13}C-NMR (125 MHz, CD$_3$CN)

δ 205.3, 169.3 (2 carbons), 145.4, 84.7, 82.9, 62.4, 62.4, 59.9, 57.3, 48.9, 47.8, 41.7, 10.8, 10.4.

^{11}B-NMR (96 MHz, CD$_3$CN)

δ 11.1

HRMS (ESI+)

Calculated for C$_{16}$H$_{27}$BNO$_7$:	356.1881
Found:	356.1870

IR (thin film, cm^{-1})

2975, 2935, 2828, 1761, 1717, 1645, 1456, 1338, 1286, 1238, 1154, 1115, 1088, 1027, 1003, 955, 866.

$[\alpha]_D^{23}$ -8.3 (c 1.0, CH$_2$Cl$_2$)
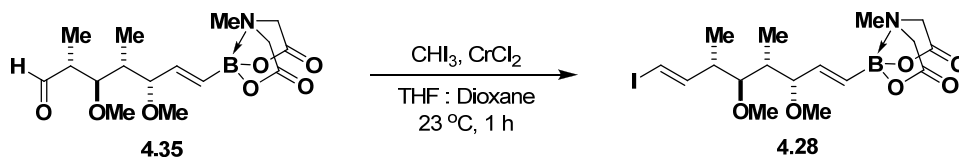
MIDA boronate 4.28

To a 50 mL Schlenk flask charged with anhydrous $CrCl_2$ (740 mg, 6.12 mmol) was added THF (10 mL) and dioxane (5 mL). With the exclusion of light, to the stirred suspension was added dropwise via cannula a solution of MIDA boronate **4.35** (132 mg, 0.370 mmol) and CHI_3 (801 mg, 2.03 mmol) in THF:dioxane 10 mL:5 mL. The resulting red mixture was stirred at 23 °C for 1 h and then transferred to a 500 mL roundbottom flask equipped with a large stir bar and diluted with EtOAc (200 mL). To this stirred mixture was added saturated aqueous $NaHCO_3$ (75 mL) followed by continued stirring for 10 min. The mixture was then filtered through a pad of Celite. The filtrate was transferred to a 500 mL separatory funnel and the layers were separated. The organic layer was washed with 0.5 M aqueous $Na_2S_2O_3$ (75 mL) and then brine (50 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting residue was adsorbed onto Celite *in vacuo* from an acetone solution. The resulting powder was subjected to flash chromatography on silica gel (Et_2O:MeCN 100:0 → 50:50) to afford MIDA boronate **4.28** as a colorless solid (132 mg, 74%).

TLC (Et_2O:MeCN 5:1)

Rf = 0.28, stained by $KMnO_4$

^{1}H-NMR (500 MHz, CD_3CN)

δ 6.51 (dd, J = 15, 9 Hz, 1H), 6.09 (d, J = 15 Hz, 1H), 5.97 (dd, J = 18, 6 Hz, 1H), 5.61 (dd, J = 18, 1 Hz, 1H), 3.95 (d, J = 17 Hz, 2H), 3.91 (m, 1H), 3.79 (app dd, 17, 1 Hz, 2H), 3.43 (s, 3H), 3.23 (s, 3H), 3.01 (dd, J = 9.5, 2 Hz, 1H), 2.78 (s, 3H), 2.50 (m, 1H), 1.45 (m, 1H), 1.10 (d, J = 7 Hz, 3H), 0.71 (d, J = 7 Hz, 3H).

¹³C-NMR (125 MHz, CD₃CN)

^{13}C-NMR (125 MHz, CD$_3$CN)

δ 169.3 (2 carbons), 149.1, 145.7, 86.7, 82.8, 75.8, 62.4, 62.4, 61.7, 56.9, 47.8, 43.8, 42.6, 18.3, 10.0

^{11}B-NMR (96 MHz, CD$_3$CN)

δ 11.2

HRMS (ESI+)

Calculated for C$_{17}$H$_{28}$BNO$_6$I: 480.1054

Found: 480.1057

IR (thin film, cm^{-1})

2970, 2925, 2827, 1761, 1456, 1339, 1287, 1238, 1090, 1025, 956.

$[\alpha]_D^{23}$ +4.6 (c 1.0, CH$_2$Cl$_2$)
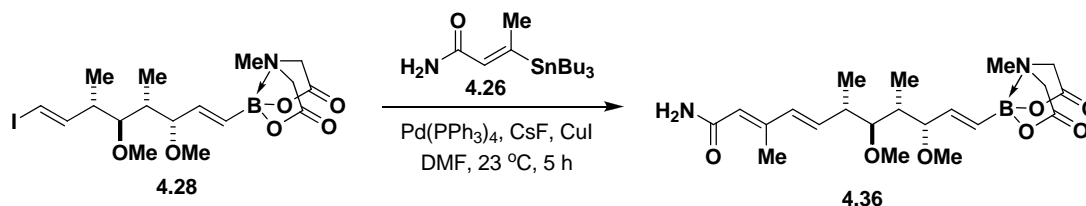
MIDA boronate 4.36

In a glove box, to a dry 15 mL vial charged with stannane **4.26** (481 mg, 1.29 mmol) was added MIDA boronate **4.28** (307 mg, 0.640 mmol) as a solution in DMF (8.8 mL). To the vial was added Pd(PPh$_3$)$_4$ (36 mg, 0.031 mmol), then CsF (199 mg, 1.31 mmol), then CuI (15 mg, 0.078 mmol). The mixture quickly darkened. The mixture was stirred at 23 °C for 5 h. The vial was removed from the glove box and the black reaction mixture was transferred to a 125 mL separatory funnel. The mixture was diluted with EtOAc (80 mL) and brine (40 mL). The mixture was shaken and the phases were separated. The aqueous phase was extracted with EtOAc (80 mL). The combined organic phases were dried over MgSO$_4$, then were filtered. The filtrate was concentrated *in vacuo*

and the resulting residue oil was adsorbed onto Celite *in vacuo* from an acetone solution. The resulting powder was subjected to flash chromatography on silica gel (Et$_2$O:MeCN 80:20 $\prod$ 25:75 → 0:100) to afford MIDA boronate **4.36** as an off-white solid (173 mg, 62%). A portion of **4.36** thus obtained was re-subjected to flash chromatography on a Teledyne Isco RediSep amine-functionalized SiO$_2$ column (Et$_2$O:MeCN 100:0 → 60:40) to provide an analytical sample.

TLC (Et$_2$O:MeCN 1:2)

R$_f$ = 0.51, UV (λ = 254 nm)

^{1}H-NMR (500 MHz, CD$_3$CN)

δ 6.18 (s, 1H), 6.09 (d, *J* = 16 Hz, 1H), 6.03 (dd, *J* = 16, 8 Hz, 1H), 5.95 (dd, *J* = 18, 6 Hz, 1H), 5.78 (s, 1H), 5.71 (s, 1H), 5.59 (dd, *J* = 18, 1.5 Hz, 1H), 3.94 (d, *J* = 17 Hz, 2H), 3.93 (m, 1H), 3.78 (d, *J* = 17 Hz, 2H), 3.44 (s, 3H), 3.23 (s, 3H), 3.09 (dd, *J* = 10, 2 Hz, 1H), 2.76 (s, 3H), 2.54 (m, 1H), 2.16 (d, *J* = 1 Hz, 3H), 1.46 (m, 1H), 1.13 (d, *J* = 7 Hz, 3H), 0.72 (d, *J* = 7 Hz, 3H).

^{13}C-NMR (125 MHz, CD$_3$CN)

δ 169.7, 169.4 (2 carbons), 149.0, 145.7, 137.8, 134.7, 121.4, 87.2, 82.9, 62.4, 62.4, 61.6, 57.0, 47.8, 42.6, 40.6, 19.0, 13.6, 10.1.

^{11}B-NMR (96 MHz, CD$_3$CN)

δ 11.5

HRMS (ESI+)

Calculated for C$_{21}$H$_{34}$BN$_2$O$_7$:   437.2459
Found: 437.2450

IR (thin film, cm^{-1})

3441, 3348, 3194, 2962, 2930, 2825, 1765, 1709, 1662, 1602, 1452, 1363, 1337, 1293, 1247, 1191, 1153, 1117, 1089, 1026, 1001, 961, 864.

$[\alpha]_D^{23}$ +11.3 (*c* 1.0, CH$_2$Cl$_2$)
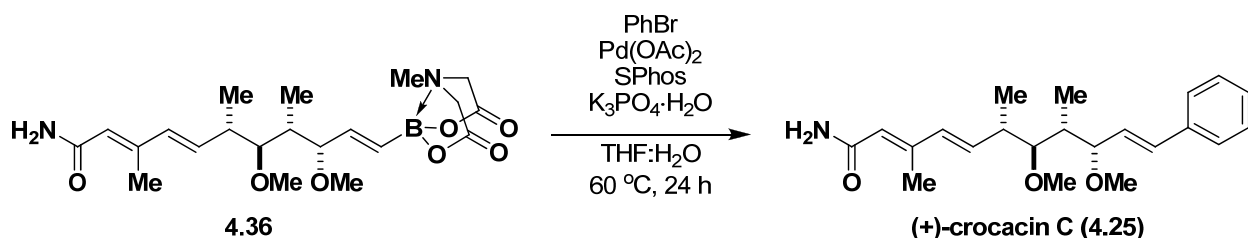
(+)-Crocacin C (4.25)

Preparation of catalyst stock solution. In a glove box, to a dry 7 mL vial charged with 2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl (S-PHOS, 4.5 mg, 0.11 mmol) was added a freshly prepared 0.01 M solution of Pd(OAc)$_2$ in THF (0.55 mL, 5.5 µmol). The solution was stirred at 60 °C for 30 min to afford a golden solution, 0.01 M in catalyst.

Synthesis of (+)-crocacin c. In a glove box, to a 7.0 mL vial charged with MIDA boronate **4.36** (31 mg, 0.071 mmol) and K$_3$PO$_4$·H$_2$O (82 mg, 0.36 mmol) was added the catalyst stock solution (95 µL, 9.5 µmol). The vial was sealed with a septum cap and removed from the glove box. To the vial was added by needle a freshly prepared 0.10 M solution of bromobenzene in THF (475 µL, 0.0475 mmol). To the vial was then added by needle degassed H$_2$O (100 µL). The vial was placed in a 60 °C heating block with stirring for 24 h. The reaction mixture (yellow organic phase, colorless aqueous phase) was transferred to a 30 mL separatory funnel and was diluted with EtOAc (10 mL) and H$_2$O (2 mL). The mixture was shaken, the layers were separated, and the aqueous layer was extracted once with EtOAc (10 mL). The combined organic layers were dried over MgSO$_4$, filtered, and concentrated *in vacuo*. The pale yellow solid residue was adsorbed onto Celite *in vacuo* from an acetone solution. The resulting powder was subjected to flash chromatography on C$_{18}$ silica gel (H$_2$O:MeCN 100:0 → 50:50) to afford **4.25** as a colorless solid (13.1 mg, 77%).

TLC (hexanes:EtOAc 1:2)

R_f = 0.43, stained by $KMnO_4$

^{1}H-NMR (500 MHz, acetone-d6)

δ 7.46 (d, J = 7.5 Hz, 2H), 7.31 (t, J = 7.5 Hz, 2H), 7.22 (t, J = 7.5 Hz, 1H), 6.71 (s, 1H), 6.58 (d, J = 16 Hz, 1H), 6.24 (dd, J = 16, 7.5 Hz, 1H), 6.15 (m, 1H), 6.10 (d, J = 15.5 Hz, 1H), 6.05 (dd, J = 15.5, 7.5 Hz, 1H), 5.79 (s, 1H), 4.07 (ddd, J = 7.5, 2.5, 1 Hz, 1H), 3.51 (s, 3H), 3.28 (s, 3H), 3.16 (dd, J = 10, 2.5 Hz, 1H), 2.57 (m, 1H), 2.21 (d, J = 1.5 Hz, 3H), 1.54 (m, 1H), 1.16 (d, J = 7 Hz, 3H), 0.84 (d, J = 7 Hz, 3H).

^{13}C-NMR (125 MHz, acetone-d6)

δ 169.0, 148.1, 137.8, 137.0, 135.0, 132.5, 130.4, 129.4, 128.2, 127.2, 122.0, 87.1, 81.7, 61.5, 56.4, 43.4, 40.7, 19.3, 13.4, 10.1

HRMS (ESI+)

Calculated for $C_{22}H_{31}NO_3Na$:   380.2202

Found: 380.2191

IR (thin film, cm^{-1})

3336, 3185, 3024, 2972, 2929, 2820, 1661, 1602, 1491, 1448, 1404, 1367, 1367, 1321, 1186, 1155, 1120, 1088, 1030, 972, 909.

$[\alpha]_D^{23}$ +46.3 (c 0.3, MeOH)

^{1}H NMR data for natural[8] and synthetic (+)-crocacin C (**4.25**): δ_H/ppm (integration)

Natural **4.25** (400 MHz, acetone-d_6)	Synthetic **4.25** (500 MHz, acetone-d_6)
7.46 (2H)	7.46 (2H)
7.31 (2H)	7.31 (2H)
7.22 (1H)	7.22 (1H)
6.65 (1H)	6.71 (1H, NH)
6.65 (1H)	6.15 (1H, NH)
6.59 (1H)	6.58 (1H)
6.25 (1H)	6.24 (1H)
6.09 (1H)	6.10 (1H)
6.07 (1H)	6.05 (1H)
5.80 (1H)	5.79 (1H)
4.08 (1H)	4.07 (1H)
3.52 (3H)	3.51 (3H)
3.30 (3H)	3.28 (3H)
3.19 (1H)	3.16 (1H)
2.62 (1H)	2.57 (1H)
2.21 (3H)	2.21 (3H)
1.58 (1H)	1.54 (1H)
1.20 (3H)	1.16 (3H)
0.88 (3H)	0.84 (3H)

^{13}C NMR data for natural[8] and synthetic (+)-crocacin C (**4.25**): δ_C/ppm

Natural **4.25** (100 MHz, acetone-d_6)	Synthetic **4.25** (125 MHz, acetone-d_6)
169.0	169.0
148.1	148.1
137.8	137.8
137.1	137.0
135.0	135.0
132.5	132.5
130.4	130.4
129.4	129.4
128.2	128.2
127.2	127.2
122.0	122.0
87.1	87.1
81.8	81.7
61.4	61.5
56.5	56.4
43.4	43.4
40.8	40.7
19.2	19.3
13.5	13.4
10.2	10.1

Boronic acids from MIDA boronates
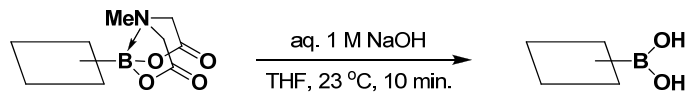
General procedure for the NaOH-mediated hydrolysis of boronate esters

To a 7 mL vial equipped with a stir bar and charged with the boronate ester (0.1 mmol) was added THF (1 mL) and 1M aq. NaOH (0.3 mL). The mixture was vigorously stirred at 23 °C for 10 minutes. The reaction mixture was then diluted with aq. sodium phosphate buffer (0.5 M, pH 7.0, 1 mL) and Et$_2$O (1 mL). The mixture was shaken and the layers were separated. The aq. phase was extracted with THF:Et$_2$O 1:1 (2 x 2 mL). (On some occasions phosphate salts precipitated during the extraction process and were redissolved by the addition of water.) The combined organics were dried over MgSO$_4$, filtered, and then concentrated *in vacuo* at 30-40 °C. Residual solvent was co-evaporated with MeCN.
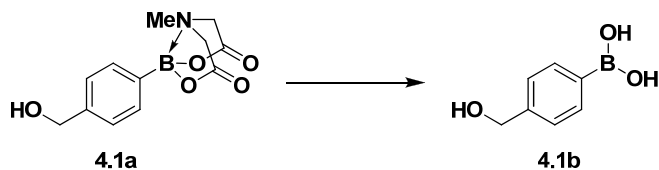
Boronic acid 4.1b

The general procedure was followed using **4.1a** (28 mg, 0.11 mmol). The product was extracted with THF:Et$_2$O 1:1 (3 x 2 ml). The title compound was isolated as a colorless solid (14 mg, 85%).

^{1}H-NMR (500 MHz, DMSO-d6:D$_2$O 95:5)

δ 7.75 (d, *J* = 7.5 Hz, 2H), 7.29 (d, *J* = 7.5 Hz, 2H), 4.50 (s, 2H).

^{13}C-NMR (125 MHz, DMSO-d6:D$_2$O 95:5)

δ 144.2, 133.9, 125.4, 62.7
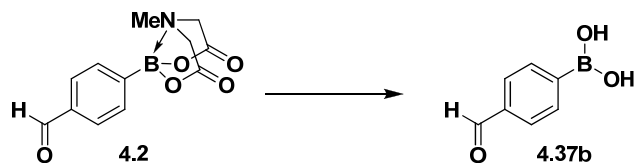
Boronic acid 4.37b

The general procedure was followed using **4.2** (27 mg, 0.10 mmol). The title compound was isolated as a colorless solid (12 mg, 76%).

^{1}H-NMR (500 MHz, DMSO-d6:D$_2$O 95:5)

δ 10.04 (s, 1H), 7.99 (d, J = 7 Hz, 2H), 7.89 (d, J = 7 Hz, 2H).

^{13}C-NMR (125 MHz, DMSO-d6:D$_2$O 95:5)

δ 193.6, 137.1, 134.5, 128.3
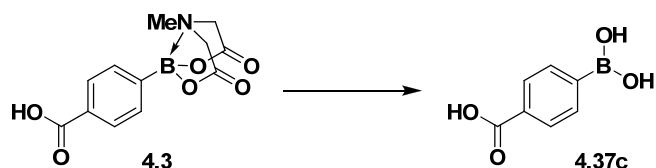
Boronic acid 4.37c

To a 7 mL vial equipped with a stir bar and charged with **4.3** (28 mg, 0.10 mmol) was added THF (1 mL) and 1M aq. NaOH (0.4 mL). The mixture was vigorously stirred at 23 °C for 10 minutes. The reaction mixture was diluted with aq. 2M HCl (1 mL) and Et$_2$O (1 mL). The mixture was shaken and the layers were separated. The aq. phase was extracted with THF:Et$_2$O 1:1 (3 x 2 mL). The combined organics were dried over MgSO$_4$, filtered, and then concentrated *in vacuo* at 30-40 °C. Residual solvent was co-evaporated with MeCN. The title compound was isolated as a colorless solid (15 mg, 89%).

^{1}H-NMR (500 MHz, DMSO-d6:D$_2$O 95:5)

δ 7.92 (d, J = 8 Hz, 2H), 7.90 (d, J = 8 Hz, 2H).

^{13}C-NMR (125 MHz, DMSO-d6:D$_2$O 95:5)

δ 167.4, 134.0, 131.7, 128.1
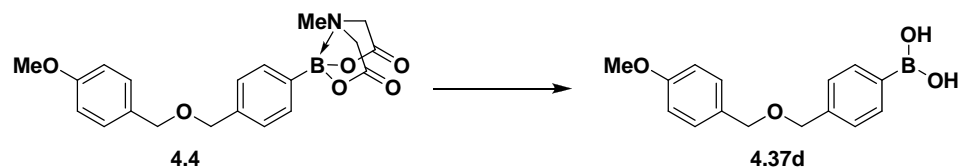
Boronic acid 4.37d

To a 7 mL vial equipped with a stir bar and charged with **4.37d** (38 mg, 0.10 mmol) was added MeOH (1 mL) and sat. aq. NaHCO$_3$ (0.5 mL). The mixture was vigorously stirred at 23 °C for 3.5 h. The reaction mixture was then diluted with sat. aq. NH$_4$Cl (1 mL) and Et$_2$O (2 mL). The mixture was shaken and the layers were separated. The aq. phase was extracted with Et$_2$O (3 x 2 mL). The combined organics were dried over MgSO$_4$, filtered, and then concentrated *in vacuo* at 30-40 °C. Residual solvent was co-evaporated with MeCN. The title compound was isolated as a colorless residue (22.6 mg, 84%).

^{1}H-NMR (500 MHz, DMSO-d6:D$_2$O 95:5)

δ 7.79 (d, *J* = 8 Hz, 2H), 7.31 (d, *J* = 8 Hz, 2H), 7.29 (d, *J* = 9 Hz, 2H), 6.93 (d, *J* = 9 Hz, 2H), 4.50 (s, 2H), 4.45 (s, 2H), 3.75 (s, 3H)

^{13}C-NMR (125 MHz, DMSO-d6:D$_2$O 95:5)

δ 158.6, 140.3, 134.0, 130.1, 129.2, 126.4, 113.6, 71.1, 71.0, 55.0

4.5 → 4.37e
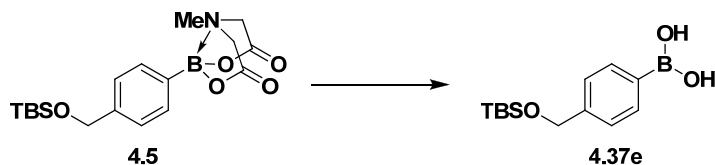
Boronic acid 4.37e

The general procedure was followed using **4.5** (38 mg, 0.10 mmol). The title compound was isolated as a colorless solid (22 mg, 81%).

^{1}H-NMR (500 MHz, DMSO-d6:D$_2$O 95:5)

δ 7.76 (d, J = 8 Hz, 2H), 7.28 (d, J = 8 Hz, 2H), 4.71 (s, 2H), 0.90 (s, 9H), 0.08 (s, 6 H).

^{13}C-NMR (125 MHz, DMSO-d6:D$_2$O 95:5)

δ 143.0, 133.9, 124.9, 64.2, 25.7, 17.9, -5.4

4.7 → 4.37f
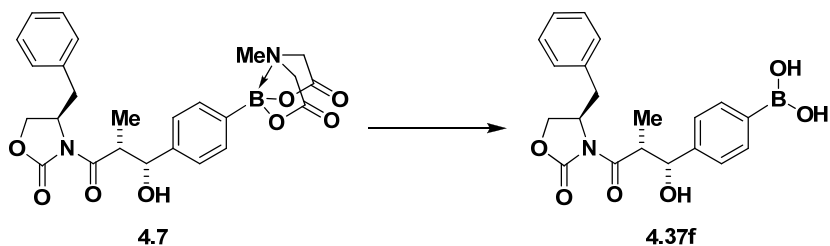
Boronic acid 4.37f

To a 7 mL vial equipped with a stir bar and charged with **4.7** (47 mg, 0.10 mmol) was added MeOH (1 mL) and sat. aq. NaHCO$_3$ (0.5 mL). The mixture was vigorously stirred at 23 °C for 3.5 h. The reaction mixture was then diluted with sat. aq. NH$_4$Cl (1 mL) and Et$_2$O (2 mL). The mixture was shaken and the layers were separated. The aq. phase was extracted with Et$_2$O (3 x 2 mL). The combined organics were dried over MgSO$_4$, filtered, and then concentrated *in vacuo* at 30-40 °C. Residual solvent was co-evaporated with MeCN. The title compound was isolated as a colorless solid (31 mg, 85%).

^{1}H-NMR (500 MHz, DMSO-d6:D$_2$O 95:5)

δ 7.73 (d, J = 8 Hz, 2H), 7.33-7.24 (m, 5H), 7.17 (d, J = 8 Hz, 2H), 4.78 (d, J = 6 Hz, 1H), 4.42 (m, 1H), 4.14 (d, J = 9 Hz, 1H), 3.98 (m, 2H), 2.95 (d, J = 5 Hz, 2H), 1.12 (d, J = 6.5 Hz, 3H).

^{13}C-NMR (125 MHz, DMSO-d6:D$_2$O 95:5)

δ 173.0, 151.8, 144.2, 134.3, 132.6, 128.4, 127.4, 125.9, 124.0, 72.1, 64.9, 53.6, 43.8, 35.4, 10.8
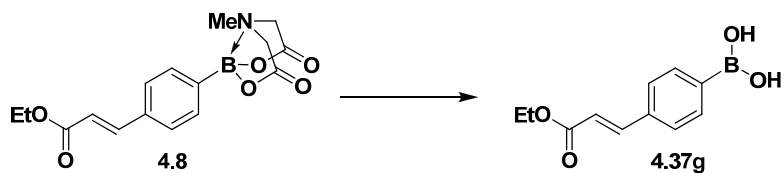
Boronic acid 4.37g

The general procedure was followed using **4.8** (32 mg, 0.10 mmol). The title compound was isolated as a colorless solid (16 mg, 75%).

^{1}H-NMR (500 MHz, DMSO-d6:D$_2$O 95:5)

δ 7.84 (d, J = 8 Hz, 2H), 7.68 (d, J = 8 Hz, 2H), 7.66 (d, J = 16 Hz, 1H), 6.66 (d, J = 16 Hz, 1H), 4.20 (q, J = 7.5 Hz, 2H), 1.27 (t, J = 7.5 Hz, 3H).

^{13}C-NMR (125 MHz, DMSO-d6:D$_2$O 95:5)

δ 166.2, 144.3, 135.3, 134.5, 127.2, 118.4, 60.1, 14.1
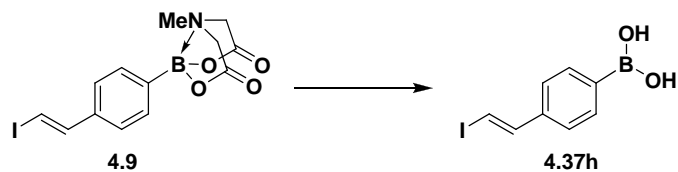
Boronic acid 4.37h

The general procedure was followed using **4.9** (37 mg, 0.10 mmol). The title compound was isolated as a colorless solid (24 mg, 89%).

^{1}H-NMR (500 MHz, DMSO-d6:D$_2$O 95:5)

δ 7.76 (d, *J* = 8 Hz, 2H), 7.50 (d, *J* = 15 Hz, 1H), 7.42 (d, *J* = 8 Hz, 2H), 7.30 (d, *J* = 15 Hz, 1H).

^{13}C-NMR (125 MHz, DMSO-d6:D$_2$O 95:5)

δ 144.3, 138.8, 134.3, 125.0, 80.6
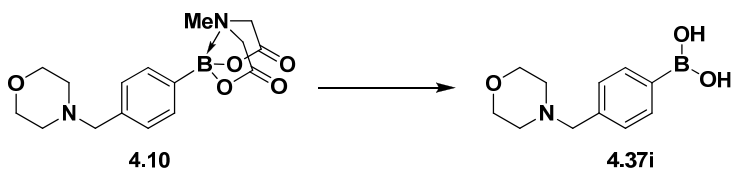
Boronic acid 10b

The general procedure was followed using **4.10** (32 mg, 0.10 mmol). The title compound was isolated as a colorless solid (16 mg, 76%).

^{1}H-NMR (500 MHz, DMSO-d6:D$_2$O 95:5)

δ 7.74 (d, *J* = 8 Hz, 2H), 7.28 (d, *J* = 8 Hz, 2H), 3.57 (t, *J* = 4.5 Hz, 4H), 3.46 (s, 2H), 2.34 (s, 4H).

^{13}C-NMR (125 MHz, DMSO-d6:D$_2$O 95:5)

δ 139.5, 133.9, 128.0, 66.0, 62.4, 53.0

REFERENCES:

[1] Molander, G. A.; Petrillo, D. E. *J. Am. Chem. Soc.* **2006**, *128*, 9634-9635.

[2] Dias, L. C.; de Oliveria, L. G. *Org. Lett.* **2001**, *3*, 3951-3954.

[3] Paterson, I.; Temal-Laib, T. *Org. Lett.* **2002**, *4*, 2473-2476.

[4] Uno, B. E.; Gillis, E. P.; Burke, M. D. *Tetrahedron* **2009**, *65*, 3130-3138.

[5] Dick, G. R.; Knapp, D. M.; Gillis, E. P.; Burke, M. D. *Org. Lett.* **2010**, *12*, 2314-2317.

[6] Touré, B. B.; Hoveyda, H. R.; Tailor, J.; Ulaczyk-Lesanko, A.; Hall, D. G. *Chem. Eur. J.* **2003**, *9*, 466-474.

[7] Paterson, I.; Temal-Laib, T. *Org. Lett.* **2002**, *4*, 2473-2476.

[8] (a) Jansen, R.; Washausen, P.; Kunze, B.; Reichenbach, H.; Höfle, G. *Eur. J. Org. Chem.* **1999**, 1085-1089. (b) Dias, L.C.; Oliveira, L.G. *Org. Lett.* **2001**, *3*, 3951-3954.

CHAPTER 5

AN AUTOMATED SMALL MOLECULE SYNTHESIZER

Eric P. Gillis, Steven G. Ballmer, Seiko Fujii and Martin D. Burke

This chapter describes the development of a machine with the capacity to execute fully automated iterative cross-coupling (ICC) sequences utilizing bifunctional MIDA boronate building blocks. Critical to the development of this machine was the discovery that the unique chromatographic properties of MIDA boronates can be harnessed to enable a simple and highly general "catch-and-release" purification strategy. Additionally, it was that discovered MIDA boronates undergo hydrolysis in the absence of bulk water upon treatment with solid-supported hydroxide base (Amberlyst A26). Applying these discoveries in the context of an automated ICC protocol required the development and programming of a number of hardware components which are herein described. Additionally, a custom software program was authored in order to provide a simple interface to the machine and to allow eight syntheses to be executed in parallel. The viability of the automated ICC machine was tested in the syntheses of several natural products. Steven G. Ballmer performed many of the experiments on solid-phase iterative cross-coupling (ICC) with MIDA boronates that helped influence the alternative development of a solution-phase automated ICC approach. Additionally, Steven Ballmer helped assemble some components of the machine, ran a number of automated ICC experiments that contributed to the development of the machine, and performed the syntheses described in Scheme 5.13 and Scheme 5.14. Seiko Fujii contributed building block **5.31**.
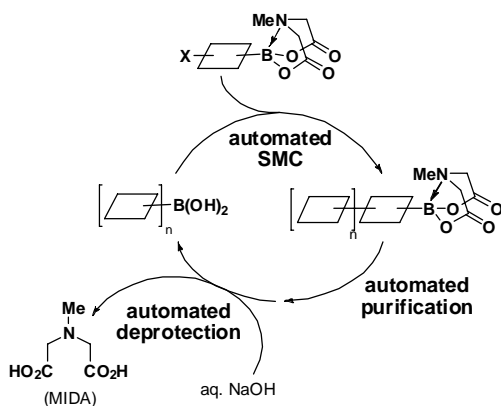
5-1 TOWARDS AN AUTOMATED ITERATIVE CROSS-COUPLING APPROACH TO SMALL MOLECULE SYNTHESIS

Small molecule synthesis can broadly and powerfully enable the advancement of science. The development of a fully automated iterative-cross coupling (ICC) platform for making small molecules could help shift the focus in small molecule science from synthesis to function. At the same time, developments in synthetic chemistry could be expected to expand the collection of building blocks that are available and applicable to the ICC strategy, thereby broadening the collection of products that might be accessed by this approach. It is our ultimate hope that the realization of an automated platform for ICC will help enable scientists from a diverse array of disciplines, regardless of expertise in chemical synthesis, to be able to access and apply novel small molecules in their research.

The discovery that MIDA boronates enable an ICC strategy was detailed in chapter 2. The scope of coupling partners which can be coupled in a final SMC step was expanded through the development of the slow-release cross-coupling (SRCC) protocol for the SMC reaction (chapter 3). As detailed in chapter 3, it was also discovered that slow addition of boronic acids to the SMC reaction via a syringe pump can overcome issues of instability associated with even highly sensitive boronic acids. Chapter 4 described approaches that can be used to access a broad range of complex MIDA boronate building blocks. Together, this work has led to the commercialization of many MIDA boronates.[1] Collectively, these advances well positioned us to address the challenge of developing a machine to automate the ICC process.

This chapter describes the design and operation of a proof-of-concept, first generation machine that is capable of performing automated ICC.[2] This chapter is structured as follows: First, the general design concepts of the machine are discussed. Next, the individual components of the machine are presented accompanied by a brief account of the evolution of the various methods described. Following this, the components of the machine are discussed in the context of the entire machine, with attention focused on the connectivity and software design that allows the machine to function as a cohesive unit. Finally, a collection of proof-of-concept experiments is presented which demonstrate the viability of the automated ICC approach.

5-2 OVERVIEW OF THE DESIGN OF A MACHINE FOR AUTOMATED ICC

In considering the design of a machine to automate the ICC process, we aimed to maximize its simplicity and thereby simplify its development to in turn minimize its cost, the level of expertise required to operate it, and minimize susceptibility to mechanical failure. We felt that controlling these factors would be important if the machine were to become broadly applicable outside of our own laboratories. We also aimed to maximize the generality of our automated process. This restriction posed a significant challenge because in general, realizing full conversions and high yields in SMC reactions requires substrate-specific optimization of the catalyst identity, base identity, solvent composition, reaction time and reaction temperature. Also, properties of boronic acids, a key reagent in the SMC reaction, are not general. As described in chapter 3, the reactivity and stability of boronic acids varies significantly depending on the identity of the organic group appended to boron. Further, many of the purification strategies used in organic synthesis require exploiting differences in the properties between the desired product and the undesired impurities: for example, differences in solubility, boiling point, and chromatographic properties of the components. Finally, isolating the correct chemical species from a mixture requires properly identifying the compound, typically based on its mass or spectroscopic properties. In spite of these challenges, we sought to design a machine that always executed successful ICC sequences simply by sending the same set of scripted commands to the machine equipment, never requiring feedback on the outcome of these operations. This level of sophistication is similar to that encountered in the first peptide synthesizer.[3]

In our pursuit of maximizing generality, we found it instructive to consider all of the steps of the ICC cycle. The generality of the ICC approach could be limited by substrate-specific complications in two broadly defined areas: the *reactivity* of each chemical component in the ICC approach, and the *isolation* of intermediates and final products. Regarding the reactivity of the chemical components, we felt that based on the results described in chapters 2, 3, and 4 we could consider the reactivity of the MIDA boronates to be general. Specifically, irrespective of the identity of the corresponding boronic acid, a MIDA boronate will be inert under anhydrous SMC conditions (chapter 2),

will be hydrolyzed under the same conditions and at the same rate as any other MIDA boronate (chapters 2 and 3), and can be expected to be stable/unstable to the same reagents described for other MIDA boronates (chapter 4). Therefore, the ICC steps that involve direct manipulation of a MIDA boronate group would likely be general.

There are no reports of a single generally effective anhydrous SMC reaction condition, although there are catalysts that have been found to be widely applicable in this context.[4] On the other hand, our work on SRCC (chapter 3) indicated that for aqueous couplings we had discovered a highly general SMC condition. Therefore, we sought to translate the principals of SRCC to an anhydrous SMC condition which would be applicable in ICC. Specifically, we predicted that a high catalyst loading accompanied by slow syringe-pump addition of the boronic acid would provide a generally effective protocol for anhydrous SMC reactions. To ensure full conversion in the SMC reaction, we proposed employing a three to four-fold excess of the boronic acid coupling partner to ensure that the boronic acid would not become the limiting reagent in the SMC step. Additionally, this excess would provide some tolerance for variability in the yields of the prior reactions that generate the boronic acid. However, the addition of excess reagents would only be possible if these reagents and the resulting byproducts could be effectively removed in a subsequent purification step. Specifically, we anticipated that the crude SMC product would be contaminated with several equivalents of boronic acid and/or deboronated material, as well as lesser amounts of Pd catalyst, phosphine oxide, and possibly reagents from previous steps. Thus, of the number of potential challenges faced in developing an automated ICC platform, we felt that identifying a general, effective and robust purification strategy was the most important component.

An early and important decision in the development of the machine was whether to develop the automated iterative cross-coupling (ICC) platform as a solution-phase or solid-phase method. A solution-phase method would offer the advantage that the reaction conditions developed in chapter 2 for ICC would be applicable to automated ICC. However, it was not clear how the general purification and isolation of the MIDA boronate products and/or boronic acid intermediates would be accomplished. Alternatively, a solid-phase approach in which the SMC reaction product would be bound to a resin might allow a general purification method based on simple washing and

filtration. However, it was not clear if the reaction conditions developed for solution-phase ICC would be applicable to solid-phase ICC.

Although we initially examined a solid-phase approach to automated ICC, this approach proved to be quite challenging. In particular, it was not possible to achieve proper mixing of the solid-phase resin with the insoluble bases that are typically employed in anhydrous SMC reactions. On the other hand, several discoveries with MIDA boronates made a solution-phase approach much more attractive. Specifically, the discovery that MIDA boronates are amenable to "catch-and-release" chromatography[5,6,7,8,9,10,11,12,13] (see below) provided the general purification method that was required to automate a solution-phase ICC process. Additionally, our studies in slow-release cross-coupling (chapter 3) informed us that the generality of the SMC reaction is greatly increased if the boronic acid is added slowly to the reaction via a syringe-pump. Further, it was discovered that solid-supported hydroxide (Amberlyst A26) is capable of effecting the general hydrolysis of MIDA boronates under minimally wet conditions.

Harnessing these discoveries, we proposed the design of an automated ICC machine to be comprised of three modules representing the three discrete steps of the automated ICC cycle: a reaction module, a purification module, and a deprotection module (Figure 5.1). As a central component in this design, a syringe pump would perform all solution handling operations and would allow for slow addition of a boronic acid solution to a SMC reaction (Figure 5.1B).
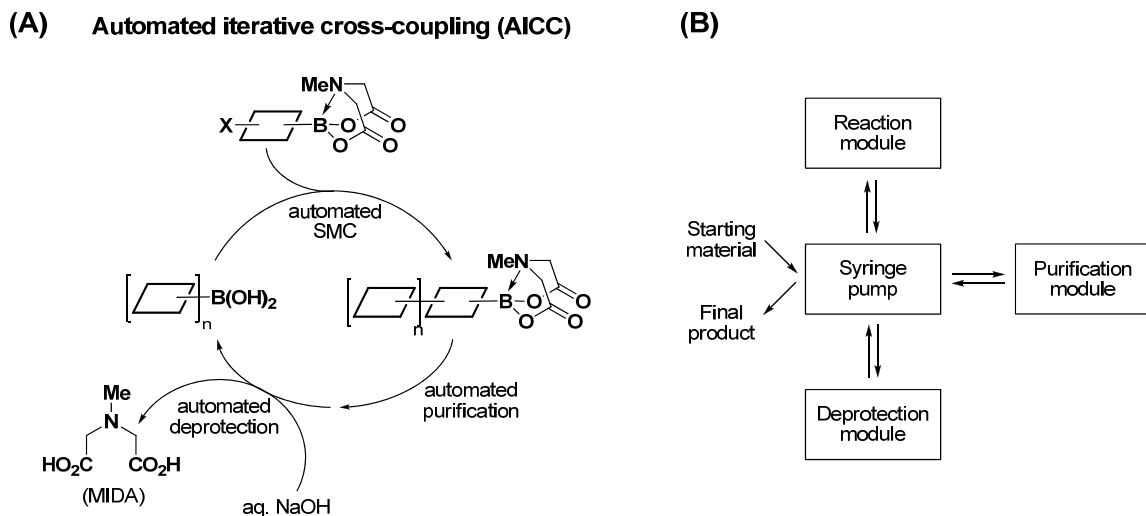
Figure 5.1. (A) The automated iterative cross-coupling cycle. (B) The automated ICC machine is organized around a syringe pump unit which operates three modules: the deprotection module, the reaction module, and the purification module.

5-3 THE PURIFICATION MODULE

The purification module comprises all of the equipment necessary to input a THF solution containing the crude MIDA boronate product from a SMC reaction and to output a THF solution containing the purified product. The purification approach employed by this module exploits the specific elution properties of MIDA boronates (see below) and is therefore best applicable to the purification of compounds that contain this functional group or possibly its derivatives. Products obtained in the final coupling of the automated ICC cycle that do not contain a MIDA boronate functional group must be purified by an alternative technique such as standard SiO_2 chromatography or HPLC chromatography, as is typically done with automated peptide synthesis. Provided below is a detailed description of the principals on which the purification module is based. A description of the design and design rationale for the purification module is then presented, followed by experimental data which validates the effectiveness of this module.

"Catch-and-release" chromatography with MIDA boronates

Studies during the course of the development of the ICC platform indicated that MIDA boronates possess a very special and remarkably general affinity for silica gel in the presence of certain eluents. Specifically, it was discovered that MIDA boronates

247

always have an R_f of value of zero when diethyl ether is used as the eluent. This observation has proven to be general, and applies to *every MIDA boronate* that has been synthesized in the Burke group to this date. This rule holds true regardless of the formula weight of the molecule, the polarity of the compound, or the solubility of the MIDA boronate in diethyl ether. Most other organic molecules have an R_f greater than zero when eluted through SiO_2 with Et_2O, allowing MIDA boronates to be easily separated from these compounds on SiO_2 by eluting an adsorbed mixture with copious volumes of Et_2O. On the other hand, MIDA boronates generally have a very high R_f when eluted with acetonitrile. Thus, following flushing of the SiO_2-adsorbed product with Et_2O, the MIDA boronate can be efficiently eluted with MeCN. These features enable a powerful and remarkably general "catch-and-release"[5-13]-type purification of compounds that contain the MIDA boronate functional group. The immobilization of the MIDA boronate on SiO_2 while flushing with Et_2O is the "catch", and the elution of the MIDA boronate with MeCN is the "release". The highly unique and enabling feature of "catch-and-release" chromatography is that all MIDA boronates can be efficiently purified through this general approach regardless of the identity of the organic group appended to boron. Thus, implementing this approach under automation might simply involve depositing the product mixture onto SiO_2, performing an initial flush with a fixed volume of Et_2O, and subsequently eluting the purified product with a fixed volume of MeCN.

In practice, it would be desirable if solvents other than Et_2O and MeCN could be employed in the "catch-and-release" chromatography protocol. For one, it has been observed that some boronic acids tend to elute inefficiently in Et_2O, possibly due to hydrogen-bonding interactions of the boron group with the SiO_2. To address this, it would be ideal to include in the eluent a protic solvent to disrupt the hydrogen-bonding interaction of boron with SiO_2. Secondly, if the product could be eluted directly in the solvent required for a subsequent SMC reaction at a reasonable molarity this would avoid an additional solvent exchange and/or concentration step. Fortuitously, it was discovered that a number of solvents fit the criteria of functioning as a "catch" solvent. Specifically, both Et_2O:MeOH (98.5:1.5) and hexanes:THF (3:1) function as "catch" solvents, meaning that all MIDA boronates surveyed have an R_f of zero when eluted on SiO_2 with these eluents. For the hexane:THF system it was found that solutions containing greater

than 25% THF (v/v) began to demonstrate non-zero R_f values for highly non-polar MIDA boronates such as **5.1** (Table 5.1). Regarding alternative "release" solvents, it was discovered that acetone and THF also efficiently elute most MIDA boronates through SiO$_2$. The latter is preferred since it is a standard solvent in SMC reactions. Thus a "catch-and-release" protocol well suited to an automated ICC approach would involve flushing a SiO$_2$-adsorbed product mixture with Et$_2$O:MeOH (98.5:1.5) followed by "release" with THF. Interestingly, the requirements for a "catch" solvent or a "release" solvent do not appear to necessarily follow a trend in polarity as would be expected for standard SiO$_2$ chromatography. For example, although chloroform has a higher polarity than THF,[14] chloroform functions as a "catch" solvent while THF functions as a "release" solvent (Figure 5.2).

Table 5.1. Elution properties of a non-polar MIDA boronate on SiO$_2$.

Entry	hexanes:THF	R_f on SiO$_2$
1	3:1	0.00
2	2:1	0.06
3	1:1	0.56

Et$_2$O
R_f = 0.00
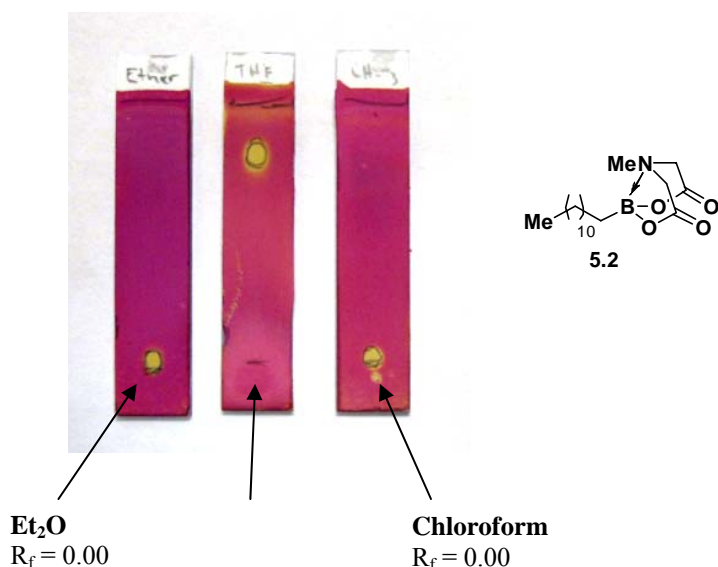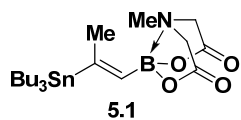
Chloroform
R_f = 0.00

Figure 5.2. The requirements for a "catch" or a "release" solvent do not appear to necessarily follow a trend in polarity. For example, although chloroform has a higher polarity than THF, chloroform functions as a "catch" solvent while THF functions as a "release" solvent as demonstrated for the highly non-polar MIDA boronate **5.2**.

Precipitation-based purification with MIDA boronates

Implementing "catch-and-release" chromatography in an automated fashion required a straightforward approach to adsorbing the crude reaction solution onto SiO_2. Because hexanes:THF (3:1) functions as a "catch" solvent, immobilizing the MIDA boronate onto SiO_2 was found to simply involve diluting the THF reaction solution with three parts hexane and then passing the resulting solution through the SiO_2 column. Regardless of the volume of solvent used in this step, the final result is that the MIDA boronate is always immobilized at the first point of contact with the SiO_2. Pads of SiO_2 that were only 0.5 cm in height were found to be effective when this approach was used to purify 0.50 mmol of MIDA boronate.

In practice, most MIDA boronates precipitate from hexanes:THF (3:1). This phenomenon offers a second mode of purification that is complementary to the "catch-and-release" chromatography approach.[15,16,17] TLC experiments indicated that most often the impurities from of a SMC reaction remained in the hexanes:THF (3:1) solution while the MIDA boronate components were quantitatively precipitated. This phenomenon might be harnessed to enable purification of MIDA boronates simply through selective precipitation of the boronate followed by filtration; however, because not *all* MIDA boronates are insoluble in hexanes:THF (3:1), this purification method is less general than "catch-and-release" chromatography. On the other hand, these two purification approaches can be implemented as complimentary methods. For cases in which the MIDA boronate substrate is at least partially soluble in hexanes:THF (3:1), filtration of the mother liquor through a SiO_2 pad serves as an entry point for "catch-and-release" chromatography. In cases where the MIDA boronate is completely insoluble in hexanes:THF (3:1) and all subsequent wash solvents, the purification step is accomplished without the product contacting the SiO_2.

Design of the purification module

The design of the purification module is presented in Figure 5.3, and is composed of two sub-units: the precipitation chamber and the SiO_2 column for catch-and-release chromatography. Unless stated otherwise, the tubing that connects all of the components and the vessels themselves is air- and liquid-tight. The precipitation chamber is a

polypropylene tube (25 mL volume capacity) with an opening at the top and the bottom of the tube. The bottom opening is guarded by a polypropylene frit that spans the diameter of the tube. The bottom of the tube is connected via tubing to a 3-way union. The top of the tube is fitted with a needle that allows solvents to be inputted from the "main pump". The "main pump" refers to the syringe pump that is responsible for most of the solution handling in the automated ICC machine. The top connection is loosely fitted such that air can vent out of the tube. The solvent that is inputted through the top of the tube is delivered to the bottom of the tube without contacting the sidewalls of the vessel. Positioned above the frit, the tube is also equipped with a weakly magnetic stir bar and is charged with a mixture of 3-propylamine-functionalized SiO_2 and Celite (approximately 0.4 g total). The precipitation chamber is positioned over a magnetic stir plate that is stirred at approximately 600 revolutions-per-minute (rpm).

The SiO_2 column is a small Teflon tube (12 mm ID x 22 mm height) with openings as the top and the bottom of the tube. Both of the openings to the tube are guarded by polypropylene frits that span the diameter of the tube; in between the frits is placed tightly-packed SiO_2. The bottom of the column is connected via tubing to the "auxiliary pump". The "auxiliary pump" refers to a syringe pump that is dedicated solely to the purification module and can be operated independently and simultaneously with the "main pump". The top of the SiO_2 column is connected via tubing to the 3-way union. The 3-way union is also connected via tubing to the main syringe pump. Although solutions inputted through the 3-way union could potentially output through two ports simultaneously, in practice one of the two output ports is always terminated during a solvent transfer operation, such that the 3-way union functions similar to 2-way valve.
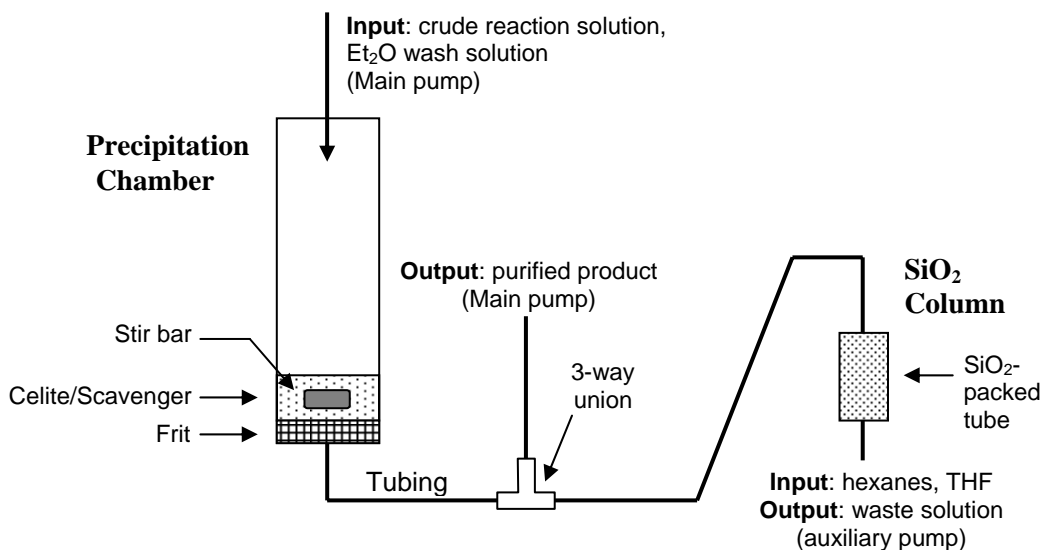
Figure 5.3. The schematic design of the purification module from a side view.

The operation of the purification module occurs as follows: First, the auxiliary pump injects hexanes through the SiO_2 column, through the 3-way union, and into the bottom of the precipitation chamber. When the precipitation chamber is free of solvent, the stir bar is embedded in the Celite/SiO_2 mixture and does not stir. However, when solvent is injected into the precipitation chamber the stir bar is dislodged and the mixture becomes vigorously stirred. This phenomenon ensures that the stir bar operates only when stirring is required–i.e., when solution is present in the precipitation chamber.[18] Once the precipitation chamber becomes partially filled with stirred hexanes, the main pump delivers the crude reaction solution (THF) through the top of the precipitation chamber to establish a hexanes:THF ratio of 3:1. As described above, most MIDA boronates precipitate immediately upon dilution with hexanes. Therefore, the hexanes must initially contact the THF solution only at a location where the accumulation of solid MIDA boronate is acceptable. In the development of the machine it was noted that clogging resulted if this contact point occurred within the tubing, within the syringe of the syringe pump, or within a more constricted vessel. Additionally, if the contact point could not be washed later with THF–for example, if the boronate precipitated on the sidewalls near to top of the precipitation chamber–the boronate that precipitated could not be recovered. We also discovered that during the precipitation event unidentified impurities from the SMC reaction often precipitate, and that these impurities can form a

252

sticky layer that clogs the frit. The inclusion of Celite in the precipitation chamber prevents this clogging since the precipitated impurities contact and bind to the Celite before they contact the frit. The inclusion of 3-propylamine-functionalized SiO_2 (solid-supported scavenger for Pd) in the precipitation chamber serves to decolorize the crude reaction solution, presumably by binding palladium compounds. It was discovered in the context of automated ICC of polyene compounds that solutions decolorized with 3-propylamine-functionalized SiO_2 led to higher conversion in subsequent SMC reaction steps. By placing the functionalized silica gel in the precipitation chamber rather than using this reagent in a chromatography step, the crude THF reaction solution is exposed to a larger surface area of this functionalized silica gel for a longer residence time.

The chromatography step in the purification procedure is performed by withdrawing solutions through the SiO_2 chamber under vacuum rather than applying positive pressure as is typical in flash chromatography. Specifically, once the reaction solution has been diluted to a hexanes:THF ratio of 3:1, the auxiliary pump withdraws the solution through the frit of the precipitation chamber, through the 3-way union, and through the SiO_2 column. The solution is then discarded to the waste can. To the precipitation chamber is added Et_2O:MeOH (98.5:1.5) via the main pump; the solid mixture in the precipitation chamber is allowed to stir, and then the solution is withdrawn through the SiO_2 column and discarded to waste. A final cycle of chromatography is executed using Et_2O which is added to the precipitation chamber by the main pump in order to remove residual MeOH which, if carried through to the next ICC cycle, would lead to solvolysis of the MIDA boronate group in a subsequent SMC reaction. At this point the purified MIDA boronate product is distributed in the SiO_2 column and/or the precipitation chamber, and is available to be dissolved in THF and outputted from the purification module.

An important criterion for the purification module is that the MIDA boronate must be outputted from this module as a THF solution at the highest molarity possible. In theory, the molarity of the product solution is limited by the solubility of the MIDA boronate product in THF. In practice, this molarity is not possible to achieve without a step that concentrates the THF solution. Although we explored possible approaches towards concentrating an organic solution in an automated fashion, a simple and efficient

protocol for such a manipulation was not discovered. Therefore, the molarity of the outputted solution is directly related to the amount of solvent required to saturate the surfaces on which the product is distributed, the amount of solvent required to dissolve the product, and the amount of solvent required to elute the product from the SiO_2 column.

The volume of THF required to elute the product from the SiO_2 column is dependent on the R_f of the product multiplied by the volume of SiO_2 the product must pass through in order to exit the column (the effective column volume). Based on the elution properties observed experimentally with MIDA boronates, Figure 5.4A represents schematically the most likely situation to result following deposition of the MIDA boronate onto the SiO_2 column through the "catch" chromatography steps described above. Because an R_f of zero is predicted for all MIDA boronates eluted on SiO_2 with hexane:THF (3:1), Et_2O:MeOH (98.5:1.5) and Et_2O, the MIDA boronate is predicted to be immobilized at the top of the SiO_2 column. If the top portion of SiO_2 were deactivated by impurities in the reaction solution, the MIDA boronate might be deposited slightly below the surface of the SiO_2 pad. If the column were to be eluted from top to bottom, the effective column volume would be maximized (Figure 5.4B). Alternatively, if the column were eluted from the bottom to the top, the effective column volume would be theoretically as small as possible (Figure 5.4C). Further, the amount of solvent required to elute the product in Figure 5.4B cannot be predicted for every MIDA boronate. On the other hand, in the case of Figure 5.4C it reasons that the MIDA boronate product should always be completely eluted from the SiO_2 column if the volume of solvent used in the elution step is equal or greater than the volume of solvent used in the deposition step because 1) the effective column volume is smaller in the elution step than it is the deposition step and 2) the product has a higher R_f value for the solvent used in the elution step than in the deposition step. In practice, we have found that adopting the method of Figure 5.4C has enabled a very efficient elution process. Further, the purity of the product obtained through the approach of Figure 5.4C is the same as that obtained through the approach of Figure 5.4B.
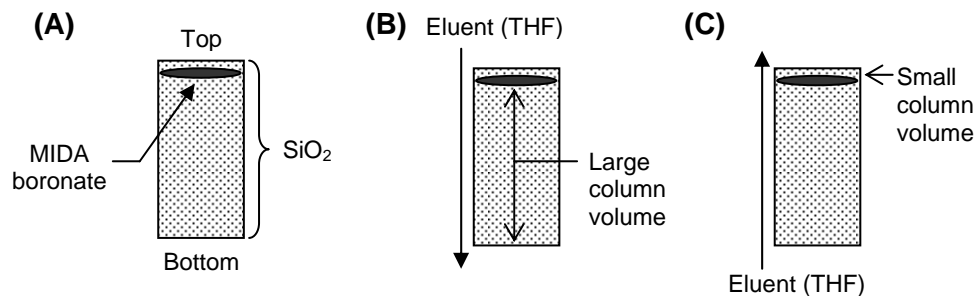
Figure 5.4. (A) A theoretical, schematic representation of the SiO₂ column following deposition of a MIDA boronate through "catch" chromatography (side view of column). (B) Elution from top to bottom would result in the largest effective column volume. (C) Elution from the bottom to the top would result in the smallest effective column volume.

The transfer of the product as a THF solution from the purification module occurs as follows: First, the auxiliary pump injects THF (11 mL) through the bottom of the SiO₂ column, out through the top of the SiO₂ column, through the 3-way union, and through the bottom of the precipitation chamber (Figure 5.3). In this process the all of the surfaces used in the purification process are contacted with THF and any MIDA boronate that remained in the precipitation chamber is exposed to THF for a long residence time to promote dissolution. After the mixture in the precipitation chamber is stirred for 30 minutes, the solution is filtered through the bottom of the precipitation chamber and is withdrawn through the 3-way union and out to the main pump. The process is repeated with an additional small portion of THF to transfer any residual product. At this point the purification step is complete and the purified product is available for the next step in automated ICC, typically the deprotection step.

Experimental results in the development of the purification module

To test the efficiency of the purification module, a THF solution of MIDA boronate **5.3** and 4-formylphenylboronic acid was introduced into the purification module (Scheme 5.1). The amounts of these reagents represent the quantity of these materials that is typically encountered in the first coupling step of an automated ICC synthesis. Further, 4-formylphenylboronic acid was selected as a test substrate because this boronic is relatively difficult to elute from SiO₂ and should provide a rigorous test of the purification method. The purification module was operated according to the procedures described above to afford a THF solution of purified **5.3**. Concentration of the THF

solution followed by ^{1}H-NMR analysis indicated that the material was quantitatively recovered in > 95% purity. An additional purification was performed with MIDA boronate **5.4** (Scheme 5.2). In this experiment **5.4** was combined with Pd(OAc)$_2$ and S-Phos in THF to produce an orange solution. This solution was inputted to the purification module which was operated as described above to afford a very pale yellow THF solution. Concentration of the THF solution followed by ^{1}H-NMR analysis indicated that the MIDA boronate was quantitatively recovered in > 95% purity. Collectively, these experiments demonstrate that the purification module can effectively separate MIDA boronates from palladium, phosphine/phosphine oxide and boronic acid impurities. Results obtained from subsequent automated ICC experiments are consistent with the efficiency indicated in these early trials.
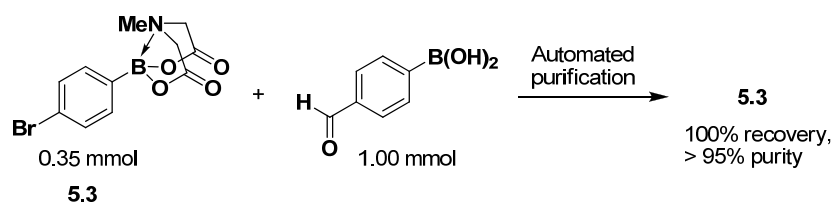
Scheme 5.1. The effectiveness of the purification module was evaluated in the purification of MIDA boronate **5.3**.
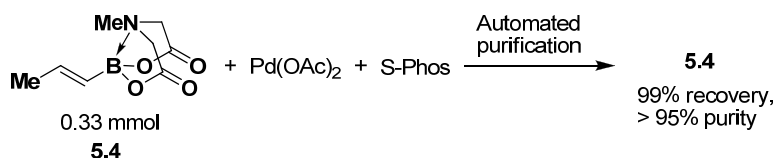
Scheme 5.2. The effectiveness of the purification module was evaluated in the purification of MIDA boronate **5.4**.

5-4 THE DEPROTECTION MODULE

The deprotection module comprises all of the equipment necessary to input a THF solution containing a pure MIDA boronate and to output a dry and deoxygenated THF solution containing the corresponding boronic acid. Provided below is a detailed description of early studies on the automated deprotection of MIDA boronates, followed by a description of the use of solid-supported hydroxide (Amberlyst) in the automated deprotection of MIDA boronates. The design and operation of the deprotection module is also detailed.

Early approaches to automated MIDA boronate hydrolysis

Previous studies indicated that MIDA boronates are generally and efficiently hydrolyzed to the corresponding boronic acid upon treatment with aqueous NaOH at room temperature (chapters 2,3,4). However, translating this procedure to an automated platform represented a considerable challenge. For one, the partition coefficient of boronic acids between organic solvents and water is not general. This presented a problem in designing a generally effective workup condition by which the aqueous NaOH used in the deprotection step could be neutralized and the boronic acid product could be carried forward in high yields as a dry organic solution. Further complicating this approach was the lack of a simple and efficient automated method for concentrating an organic solution. One deprotection approach that was evaluated involved adding aqueous NaOH to a THF solution of the MIDA boronate, allowing the hydrolysis reaction to proceed, and then quenching the reaction with HCl dissolved in water saturated with NaCl. The organic phase was separated from the aqueous phase and was then dried over a solid desiccant. The efficiency of the drying step was evaluated by executing a mock deprotection sequence[19] in which the water content of the resulting THF solution as it stirred over the desiccant was monitored by Karl Fisher analysis. The desiccants that were tested were $MgSO_4$, Na_2SO_4, $CaSO_4$, SiO_2, K_2CO_3, and activated molecular sieves,[20] where the only effective desiccant was found to be activated mol. sieves. However, 8.5 g of mol. sieves were required in order to reduce the water content of the THF to below 60 μg/mL. When this amount of mol. sieves was employed in a deprotection sequence with *p*-tolyl MIDA boronate, most of the resulting *p*-tolyl boronic

acid became adsorbed onto the mol. sieves as indicated by TLC. Further, the water introduced in the deprotection step was difficult to completely remove from the syringe pump and other machine equipment.

An alternative approach for the deprotection step that was evaluated involved using a minimal amount of water in the hydrolysis step followed by quenching with anhydrous acid. Specifically, when a THF:H$_2$O (99:1) solution containing p-tolyl MIDA boronate (**5.5**) was treated with solid NaOH or KOH pellets, complete hydrolysis of the MIDA boronate was observed by TLC within 60 minutes (Scheme 5.3). Reactions performed with THF solutions containing less than 1% of water (v/v) resulted in only partial conversion. The formation of a large amount of solid ppt. and the disappearance of any organic compounds from the organic phase as analyzed by TLC is consistent with the formation of borate **5.6** as the insoluble product (Scheme 5.3).[21] The dibasic potassium salt of MIDA is predicted to be a byproduct of this reaction and although not specifically analyzed for, was likely also part of the solid ppt. Upon treatment of the mixture with HCl in dioxane the majority of the solid ppt. disappeared and TLC analysis of the organic phase indicated the presence of a large amount of boronic acid. A sticky solid residue was also present in the tube which was likely MIDA, KCl and water. The boronic acid solution obtained through this step was further processed in a step that involved neutralization over solid K$_2$CO$_3$, drying with mol. sieves and sparging with Ar. The resulting boronic acid solution was then utilized in a successful automated SMC reaction (Scheme 5.11, see below). Thus, this deprotection protocol was found to be a viable approach for at least a certain set of MIDA boronates/boronic acids. However, when MIDA boronate **5.8** was engaged in the same procedure the hydrolysis stalled at approximately 50% conversion of the MIDA boronate as judged by TLC. In this reaction formation of a precipitate (attributed to borate **5.2b** and the dibasic MIDA salt) led to separation of a large organic phase and a very small aqueous phase. Consequently, the unreacted KOH became sequestered within a sticky solid substance at the interface of the phases, a fact that likely accounts for the limited conversion observed in the reaction. The hydrolysis of E-propenyl MIDA boronate (**5.4**) under this protocol was similarly problematic.
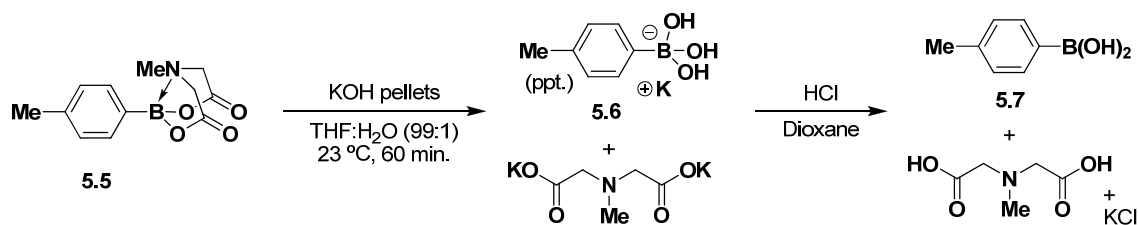
Scheme 5.3. Boronate **5.5** was underwent hydrolysis when minimally wet conditions were employed.
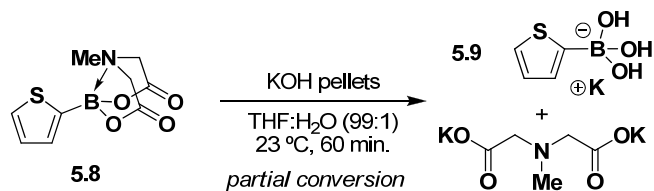
Scheme 5.4. The conversion of boronate **5.8** stalled at approximately 50% conversion when minimally wet conditions were employed.

To avoid the problem of phase separation observed in the approach described above, a new approach was tested employing anhydrous THF and NaOMe. Specifically, a THF solution of **5.10** was treated with NaOMe with stirring at room temperature for 60 minutes to afford a gel that was difficult to stir, presumably a mixture of THF and borate **5.11** (Scheme 5.5).[22] Treatment of the gel with concentrated aqueous HCl afforded a low-viscosity THF solution that upon analysis by TLC indicated the presence of boronic acid **5.12**. The acidification step was accompanied by the formation of a fine, colorless ppt. that was likely a form of the MIDA ligand or its methyl ester. The resulting THF solution was neutralized over K_2CO_3, treated with 5 Å mol. sieves to remove MeOH and H_2O, sparged with Ar, and then introduced to an automated SMC reaction with 4-bromophenyl MIDA boronate. However, the SMC reaction proceeded to only partial conversion (68%) and the mass recovery of MIDA boronate starting material and product was low (56%). Further, treatment of boronate **5.5** with NaOMe under the same protocol led to a *very* thick gel that could not be stirred and which resulted in stalling of the deprotection reaction. However, the greatest problem in this approach was that at unpredictable points in downstream manipulations a fine solid would precipitate, resulting in clogs to the plumbing of the machine. Several approaches were investigated in which the boronic acid solution was scrubbed with solid reagents in order to remove the fine precipitate, but ultimately the problem could not be solved.
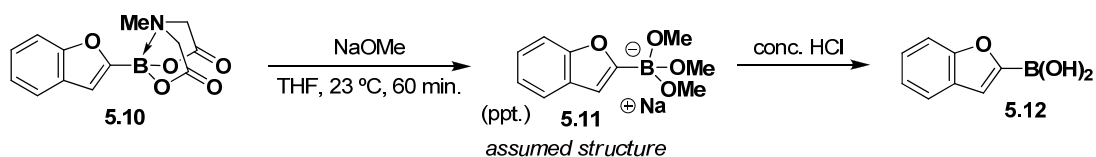
Scheme 5.5. Treatment of boronate **5.10** with NaOMe led to a thick gel, presumably borate **5.11** and a MIDA species. Treatment of the gel with concentrated aqueous HCl afforded a low-viscosity solution which by TLC indicated the presence of a boronic acid **5.12**.
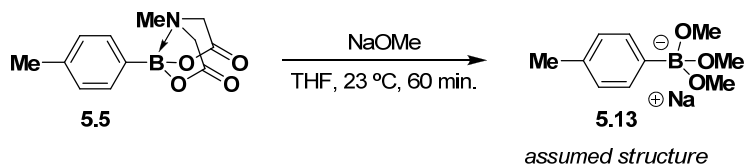
Scheme 5.6. Treatment of boronate **5.5** with NaOMe resulted in the formation of a very thick gel which stalled the reaction.

Deprotection of MIDA boronates with Amberlyst A26(OH)

A key advance in the development of the deprotection module was the discovery that MIDA boronates undergo hydrolysis upon treatment with Amberlyst A26(OH).[23] Amberlyst A26(OH) is a macroporous resin that is functionalized with ammonium residues with a hydroxide counter ion.[24] One advantage of employing Amberlyst in the deprotection of MIDA boronates is that the hydrolysis reaction proceeds with simple mixing via air bubbling through the resin/THF mixture—all other deprotection approaches required vigorous stirring. A second advantage to this approach is that the MIDA ligand that is produced as a byproduct in the hydrolysis reaction becomes completely sequestered within the Amberlyst resin. This allows the resin/THF mixture to be filtered without concern that residual MIDA will clog the equipment. However, the most important aspect of this approach is that it is highly general. This approach has been evaluated with a broad range of MIDA boronates and it has been found that hydrolysis of the boronate always proceeds to full conversion within 60 minutes upon treatment with Amberlyst A26(OH).

During the development of the deprotection module it was discovered that the preparation of the Amberlyst resin has a significant impact on the yield of boronic acid obtained from the hydrolysis step. Amberlyst resin as received from commercial sources is greater than 60% water by mass and if this resin is used directly in the machine the

large amount of water introduced cannot be effectively removed with mol. sieves. Therefore, prior to use in the deprotection module the resin must be washed with an organic solvent to remove a large amount of this water. However, when rigorously dried Amberlyst resin was employed in a deprotection reaction with MIDA boronate **5.14**, a 41% yield of the proto-deboronated product **5.15** was observed by GC (Scheme 5.7). This result prompted us to evaluate the impact of washing the Amberlyst resin with various solvents [EtOAc, CH_2Cl_2, acetone, MeCN, sat. aq. NaCl, THF]. Specifically, the different wash cycles were evaluated in regard to the amount of water removed from the resin, the efficacy of the washed resin to effect the hydrolysis of a MIDA boronate, and the amount of deboronated material obtained when the washed resin was used in a MIDA boronate deprotection reaction. From these studies THF was determined to be at least as effective as the other solvents, and therefore was selected as the solvent of choice for the wash step.[25] It reasons that since THF is also the solvent used in the deprotection step, residual THF from the resin wash cycle should be minimally impacting in the subsequent MIDA boronate hydrolysis reaction. In a subsequent study, Amberlyst resin was equilibrated in various ratios of $THF:H_2O$ by performing five washes of the resin with this solvent combination. The resin was then employed in a standard deprotection step with MIDA boronate **5.14** and the yield of deboronated benzofuran **5.15** was determined by GC analysis of the THF reaction solution (Table 5.2). Under the conditions of the experiment the desired boronic acid was retained inside the resin and was not observed in the analysis (see below). In this study it was discovered that equilibration of the resin with a solution of $THF:H_2O$ (50:1) led to the best balance of low water content in the resin and a low associated rate of deboronate in the deprotection step. Therefore, all Amberlyst employed in the deprotection module is now equilibrated with $THF:H_2O$ (50:1) immediately prior to use in a MIDA boronate hydrolysis reaction.
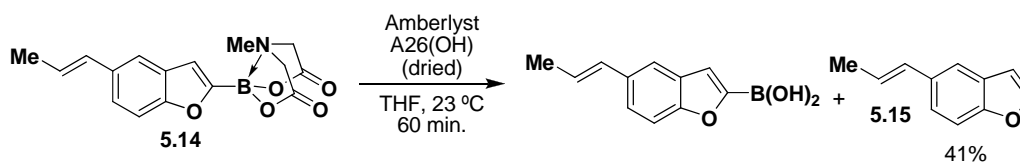
Scheme 5.7. Treatment of boronate **5.14** with rigorously dried Amberlyst A26(OH) resin resulted in significant formation of the deboronated side-product **5.15**.

Table 5.2
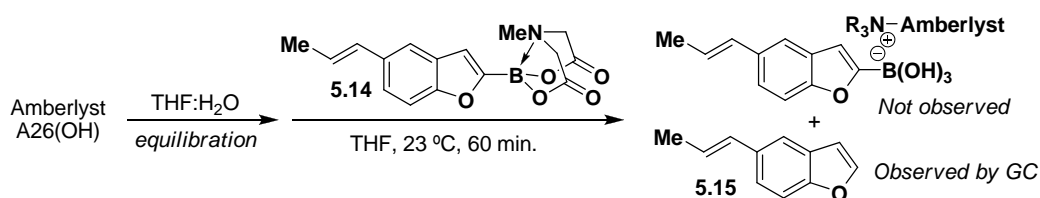
Entry	THF:H$_2$O (equilibration)	% yield **5.15** [*]
1	1:0	18%
2	200:1	15%
3	100:1	8%
4	50:1	4%
5	20:1	3%

[*] Determined by GC against internal standards biphenyl and dodedane, response corrected, avg. of two runs

In order to release the boronic acid from the Amberlyst resin following deprotection of a MIDA boronate, the resin must be treated with acid. As is described in Scheme 5.8, upon exposure to Amberlyst A26(OH) in THF most boronic acids become trapped within the resin, presumably as the corresponding borate salt. As a specific example, exposure of *p*-tolyl MIDA boronate to Amberlyst A26(OH) resin for 60 minutes followed by TLC analysis of the solution indicated the complete absence of both *p*-tolyl MIDA boronate *and* *p*-tolyl boronic acid in the THF solution. Subsequent treatment of the mixture with HCl led to release of the boronic acid into the THF solution, as indicated by TLC analysis. It is possible to envision a purification strategy based on this phenomenon in which the THF reaction solution could be exchanged for pure solvent while the borate remained trapped within the resin. Such a strategy would be similar to the method recently described by Hall,[26] but would occur on the solid phase. However, such a purification approach was not implemented in the development of the machine because highly non-polar boronic acids appear to be an exception to the general trend of boronic acid sequestration. For example, when dodecyl MIDA boronate is exposed to Amberlyst A26(OH) resin, the resulting boronic acid does *not* become entrapped in the resin but instead is present in the THF solution.

In regards to the acid that is used in the acidification step, both HCl in dioxane and AcOH in THF were found to be effective. Further, neither acid adversely affected downstream processes despite the potential of this complication. Specifically, the use of HCl in the treatment of a *E,E*-dienyl boronic acid did not lead to observation of Z-isomers of the trienyl MIDA boronate product obtained in a subsequent step (Scheme 5.9). Additionally, a MOM protecting group was found to be stable to treatment with HCl in THF:dioxane despite the presence of a small amount of water in the solution (Scheme 5.10). Alternatively, the use of AcOH could potentially result in AcOH and/or AcONa/AcOK being carried through subsequent steps and into a SMC reaction. However, downstream SMC reactions were equally successful when ether AcOH or HCl was used to treat the Amberlyst resin in the deprotection step. Further, neither acid produced salts that accumulated or clogged the equipment.
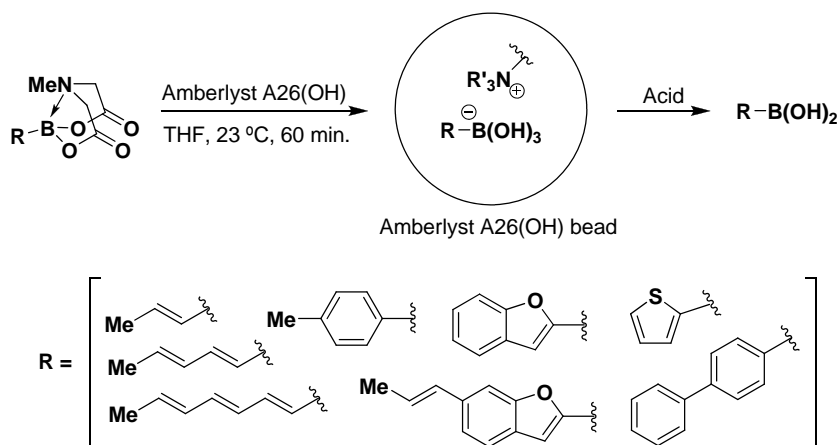
Scheme 5.8. Most boronic acids upon exposure to Amberlyst A26(OH) become sequestered within the resin beads leaving the reaction solution free of boronic acid and MIDA boronate. Presumably the boronic acid is trapped as the corresponding boronate species. Treatment of the resin with an acid results in the release of the boronic acid.
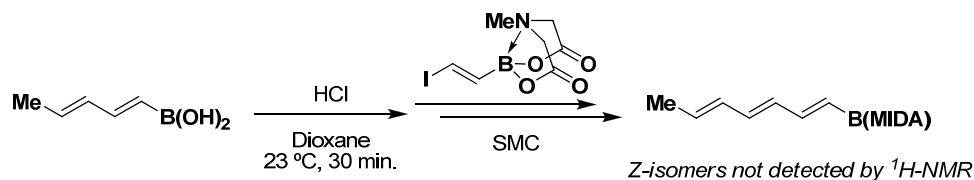
Scheme 5.9. Treatment of a dienyl boronic acid with HCl did not lead to the observation of Z-alkene products in a subsequent SMC reaction.

*phenol products not
detected by ¹H-NMR*
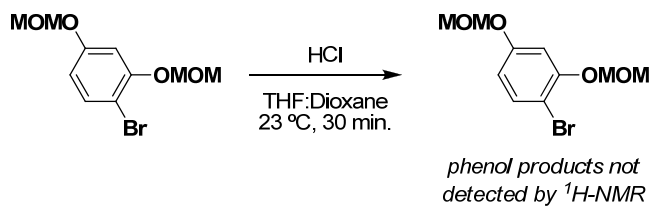
Scheme 5.10. The MOM protecting group is stable to the acidic conditions employed in the deprotection module.

Design of the deprotection module

The design of the deprotection module is presented in Figure 5.5, and is composed of four sub-units: the deprotection tube, the pre-drying tube, the drying tube, and the degassing tube. All of the vessels are polypropylene tubes (25 mL volume capacity) with an opening at the top and the bottom of the tube. The bottom opening is guarded by a polypropylene frit that spans diameter of the tube. The deprotection module does not require stirring in any step and therefore does not incorporate a stir plate. All of the solution handling operations in the deprotection module are performed by the "main" syringe pump which, as defined above, refers to the syringe pump that is responsible for most of the solution handling in the automated ICC machine. The tubes in the deprotection module are charged with reagents as follows: The deprotection tube is charged with water-washed Amberlyst A26(OH); the pre-drying tube is charged with a 2:1 mixture by mass of $MgSO_4$:Celite; the drying tube is charged with activated 4 Å molecular sieves, $BaCO_3$ and a small amount of Celite; and the degassing tube remains empty. The tops of the deprotection tube and pre-drying tubes are vented to ambient atmosphere while the tops of the drying tube and degassing tube are vented to a N_2 gas manifold. The bottoms of each vessel are connected via tubing to the main syringe pump, and it is through this connection that all reagents and gasses are inputted and withdrawn from the vessels.
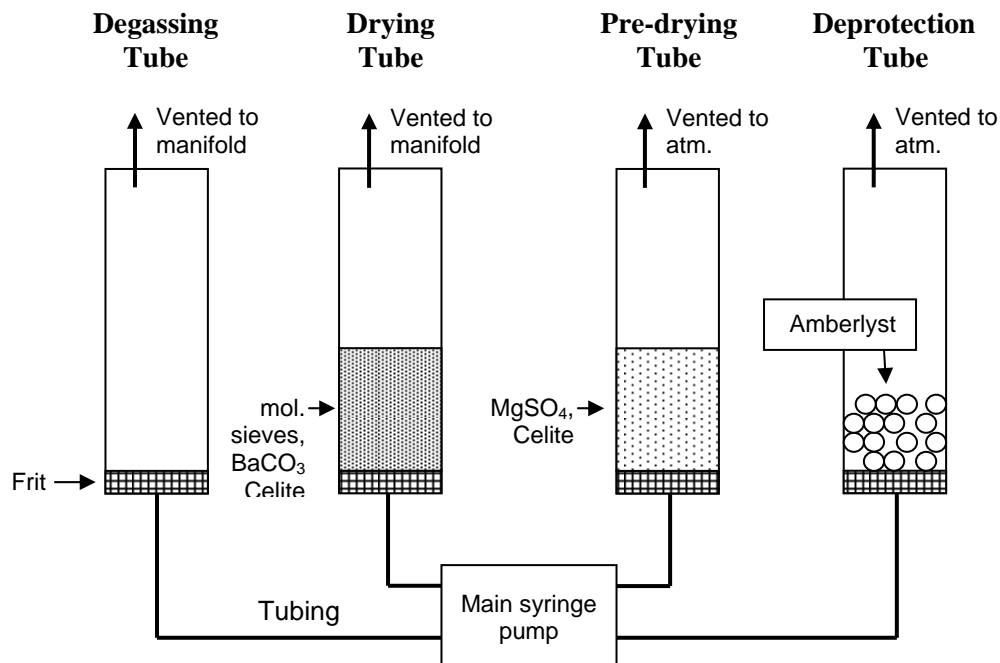
Figure 5.5. The schematic layout of the deprotection module from a side view.

The operation of the deprotection module occurs as follows: First, the resin in the deprotection tube is washed five times with THF:H_2O (50:1), where each wash solution is discarded to waste. A THF solution containing the MIDA boronate is then introduced to the deprotection tube and the mixture is agitated for 60 minutes via periodic injections of N_2 gas through the bottom of the tube. The solution is then transferred to the pre-drying tube and the mixture is mixed via repeated injection/withdrawal sequences executed by the main syringe pump. As described above, during this step most boronic acids will remain completely sequestered within the Amberlyst resin. Further, it reasons that if the boronic acid is sufficiently non-polar such that it does not become trapped in the resin, it will likewise not become strongly adsorbed onto the $MgSO_4$ in the pre-drying tube. Therefore, this step allows bulk water to be removed without the loss of boronic acid to adsorption on a solid desiccant. The THF solution is then returned to the deprotection tube and to the deprotection tube is added HCl in dioxane. The mixture is agitated for ten minutes via periodic injections of N_2 gas through the bottom of the frit, and the resulting boronic solution is then transferred to the drying tube.

At this point the THF solution is acidic and must be neutralized with a weak, insoluble base. The base must be weak in order to avoid formation and subsequent

precipitation of a boron "ate" species, and the base must be insoluble so that it is not outputted from the deprotection module. The base that was chosen for this purpose is $BaCO_3$ because this base is insoluble in water and therefore cannot be dissolved in the initially wet THF solution. On the other hand, when K_2CO_3 was employed in this application it was observed that this base became partially dissolved and then was re-precipitated as a fine powder which subsequently clogged the machine equipment. Also included in the drying tube are activated 4 Å mol. sieves which over 30 minutes effectively dry the THF solution. Upon drying of the THF solution it has been observed that fine salts may precipitated and clog the frit, but this problem can be avoided if Celite is included in the drying tube to act as a filtering aid. Thus the operation of the machine in the drying step is as follows: After the THF solution is introduced into the drying tube, the mixture is mixed over the course of 30 minutes by period withdrawal/re-injection of the solution as executed by the main syringe pump. Following this step, the THF solution is transferred to the degassing tube where it is sparged for 15 minutes under a constant stream of argon that originates from the main syringe pump. At this point the boronic acid is outputted from the deprotection module as a dry, deoxygenated THF solution.

5-5 THE REACTION MODULE

The reaction module comprises all of the equipment necessary to input a dry and deoxygenated THF solution containing a boronic acid and to output a homogeneous THF solution containing the crude product of a SMC reaction. The reaction module, although critical to the automated ICC process, is the least complex of the three main modules. Provided below is a detailed description of the design of this module and its operation.

Design of the reaction module

The vessel used in the reaction module is a polypropylene tube (25 mL volume capacity) with an opening at the top and the bottom of the tube (Figure 5.6). The reaction vessel is charged with base (K_3PO_4 for aryl couplings, Cs_2CO_3 for polyene couplings), $Pd(OAc)_2$, S-Phos and the halide. For all steps except the final coupling step, the halide is a halo MIDA boronate. The bottom opening of the vessel is connected to the main

syringe pump with tubing and is guarded by a polypropylene frit that spans the diameter of the vessel. On top of this frit sits a smaller diameter frit which is held in position by a piece of wire (wire not shown). A large and powerful stir bar rests on top of the second frit. The reason for this design is that many experiments in the development the reaction module indicated that high reproducibility in the automated SMC reaction requires that the reaction is stirred at > 500 rpm. At slower stir speeds the solid base that is used in the reaction may not be properly mixed. However, at stir speeds > 150 rpm the surface of the frit becomes damaged by the stir bar continuously grinding solid base into the surface pores of the frit. In earlier designs in which only one frit was employed in the reaction tube but a stir rate of > 500 rpm was applied, the frit in the reaction tube often became impenetrable to liquid and thus the solution could not be withdrawn following the SMC reaction. On the other hand, in a two frit design the top frit provides a surface that can be damaged while at the same time preventing the stir bar from contacting and damaging the lower frit. In this setup the lower frit is the only surface which must provide filtration for the reaction tube.
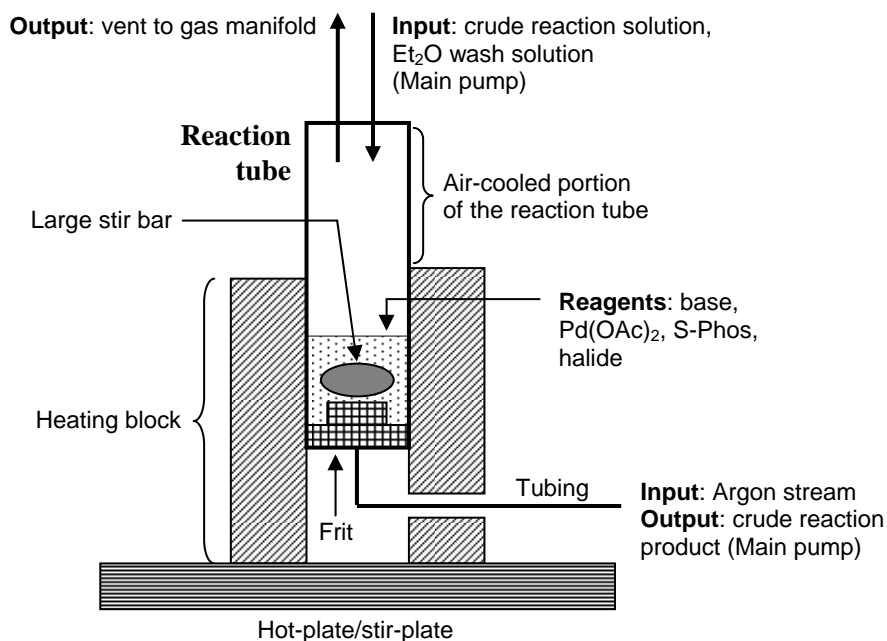
Figure 5.6. A schematic depiction of the reaction module from a side view.

The top of the reaction vessel is air-tight except for an input needle and an output vent. The output vent is connected to a N_2 gas manifold in order to allow the tube to be purged with argon while maintaining an inert atmosphere. Specifically, argon is inputted through the bottom of the reaction tube and exits through the vent in the top of the tube and out through the N_2 gas manifold. The input needle is positioned directly over the center of the tube and is used to deliver the boronic acid solution slowly to the reaction mixture. A principal design feature of the automated ICC machine is that, based on the discoveries described in chapter 3, the boronic acid is introduced slowly to the SMC reaction in order to allow efficient coupling of even unstable boronic acids. The reason that the boronic acid is added dropwise from the *top* of the reaction tube is to ensure that the boronic acid solution remains at room temperature until it contacts the reaction mixture. In this case the boronic acid is not exposed to heating that might degrade the boron reagent prior to the SMC reaction. Alternatively, if the boronic acid solution was added through the bottom of the reaction tube the boronic acid would be heated in the dead-volume of frit before the boronic acid could be utilized in the SMC reaction.

The reaction tube is placed inside an aluminum heating block that jackets the lower half of the tube. The heating block is placed over a temperature-controlled hot-plate, where the role of the heating block is to conduct the heat from the hot-plate to the reaction tube. Measurements have confirmed that the temperature of the THF solution inside of the reaction vessel is the same as the temperature specified on the hot-plate. The heating block also has an opening in the side of the block to accommodate the tubing connection between the bottom of the reaction vessel and the main syringe pump. Importantly, the polypropylene reaction vessel is a poor conductor of heat and as such only the surface of the vessel in contact with the heating block is heated. The portion of the reaction tube that is not in contact with the heating block functions as an air-cooled condenser and prevents heated solvent vapors from exiting the reaction tube. In practice, THF reaction solutions are typically heated to 60 ºC for at least six hours without an observable change in solvent volume.

Operation of the reaction module:

The operation of the reaction module occurs as follows: First, the reaction tube is purged with a constant stream of argon for fifteen minutes. Then to the reaction tube is added THF to allow the palladium, phosphine ligand and halide to pre-equilibrate prior to the introduction of the boronic acid. Once the reaction mixture has been stirred for ten minutes, the boronic acid is then added dropwise to the mixture over two hours. Following the complete addition of the boronic acid, the reaction mixture is stirred for four hours for arene couplings run at 60 ºC and for twenty-two hours for polyene couplings run at 23 ºC. Finally, the reaction solution is drawn through the frit in the bottom of the reaction tube and is outputted to the machine.

5-6 CONNECTIVITY IN THE MACHINE AND SOFTWARE CONTROL

The automated ICC machine is designed to with the capacity to execute the fully automated synthesis of eight small molecules simultaneously. Each synthesis consists of between one and three iterative coupling sequences, where each sequence can include a deprotection step, cross-coupling step and a purification step. The organization of the machine is centered on eight "main" syringe pumps, where each main syringe pump is dedicated to only one synthesis. The previous sections described the modules that are used in a single step by a single synthesis. However, in the actual automated ICC machine there are many instances of the deprotection module, reaction module and purification module. Further, the eight main syringe pumps operate independently to execute iterative coupling sequences in parallel. This section describes how the various pieces of equipment in the machine are compartmentalized and connected in order to enable multiple processes to be executed simultaneously. This section also describes what resources are shared between the main syringe pumps, and how the resources are distributed and managed. Finally, this section describes how a piece of custom software is used to operate the machine and to coordinate the multiple processes that run simultaneously.

Connectivity of machine equipment

The automated ICC machine is composed of ten syringe pumps, twenty-six eight-port valves, and approximately 400 feet of Teflon tubing that links these parts together and connects this equipment to the three modules previously described: the deprotection module, the reaction module and the purification module. Shown in Figure 5.7 is a schematic front view of the machine, which serves and an aid in identifying the equipment presented in the photograph of the machine (Figure 5.8).

Each valve and each syringe pump is assigned within the software a virtual name that allows the equipment to be specifically addressed and controlled programmatically. The virtual names that are assigned to each piece of equipment are detailed in **Figure 5.9**. Although there is physically only one machine, in the software environment that controls the machine equipment there are eight virtual machines, where one virtual machine corresponds to each main pump. Each virtual machine is assigned one actual main syringe pump, one auxiliary pump, and valves numbered one through twelve. The same actual auxiliary pump and "valve #3" through "valve #12" are assigned to all eight virtual machines (they will share these resources), while each main pump and each "valve #1" and "valve #2" are assigned to solely their corresponding virtual machine (**Figure 5.9**). For example, "virtual machine #1" comprises "main syringe pump #1", "pump 1's valve #1", "pump 1's valve #2", "shared valve #3" through "shared valve #12", and the "auxiliary pump". The aqueous solutions pump depicted in Figure 5.7 and Figure 5.8 is not used in the current generation of the machine but cannot be removed from the machine because communications to the hardware are directed through this equipment.

The use of virtual machines within the software environment serves to compartmentalize the equipment from a programming standpoint. As discussed below, this approach greatly simplifies the programming of the machine and makes the scripts that operate the equipment universal across the eight pumps. However, the compartmentalization of the equipment also influences how physical connections between the valves are mapped. The connectivity of the equipment is detailed in Figure 5.10. The connectivity described in Figure 5.10 is specific to virtual machine #1, but this diagram also illustrates how the connectivity would be established for virtual machines #2 through #8. Features of this arrangement are that all of the connections to the

deprotection modules, reaction modules and purification module are made on valve #1 and valve #2, the valves that are unique to each virtual machine. This means that any operations involving this equipment can occur without regard to the state of the other virtual machines. In contrast, the connections to solvents, such as THF, are made through valve #3 and valve #4 which are shared equipment, meaning that "valve #3" of each virtual machine maps to the same actual valve. A virtual machine may only manipulate a piece of shared equipment if the equipment is not in use by any other virtual machines, a condition that is enforced by the software (see below). In terms of mapping the equipment, care was taken to ensure that most pieces of equipment that are used regularly in the automated ICC process are not shared. If the equipment must be shared, operations on the equipment should be kept relatively brief, such that a synthesis does not become greatly slowed by many virtual machines queuing to use the same shared hardware.

Figure 5.7. Layout of the components of the machine
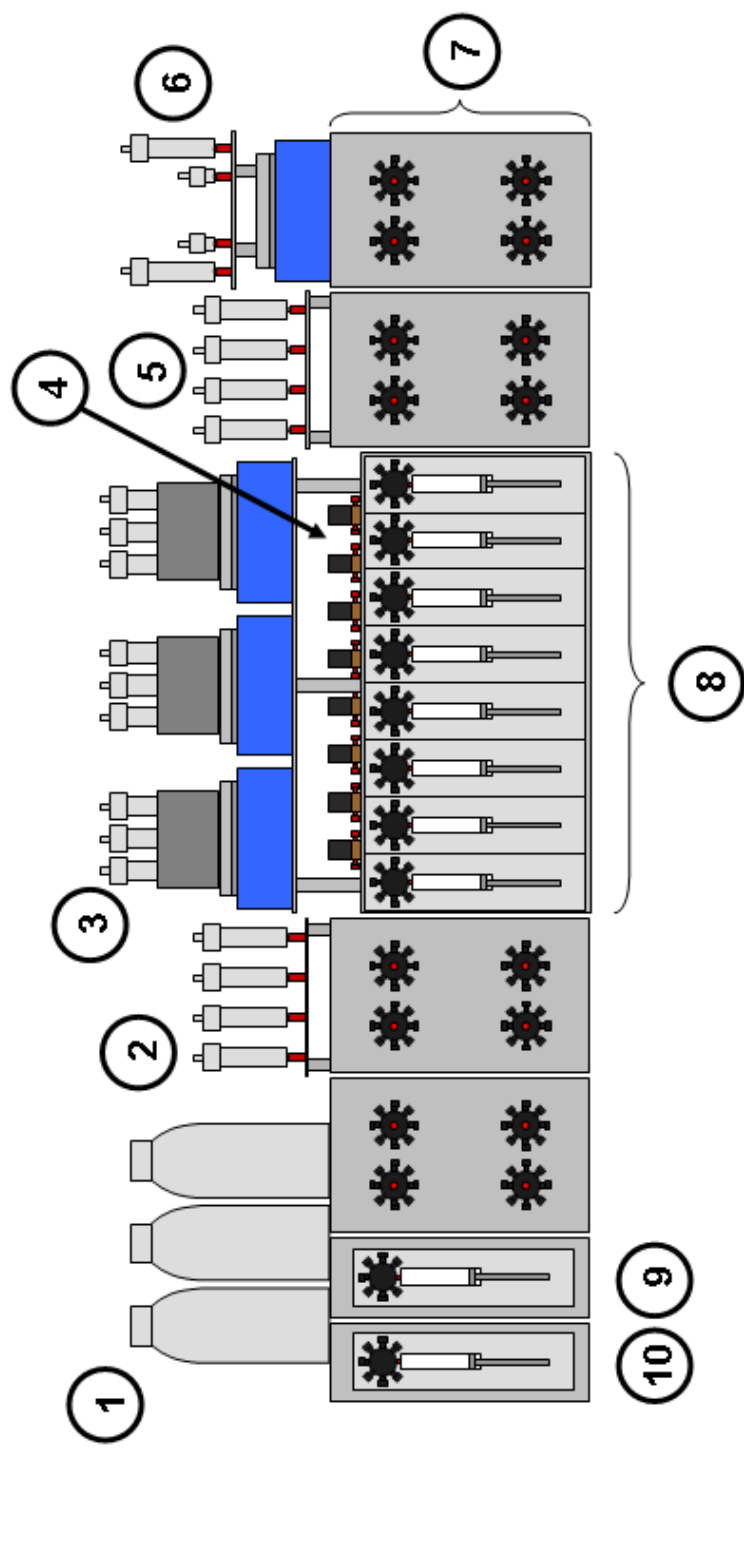
1. Solvent reservoirs
2. Drying and degassing
3. Reaction module
4. Solenoid valves and gas manifolds
5. Deprotection tubes
6. Purification module
7. Valve equipment
8. Main syringe pump
9. Syringe pump for purifications
10. Syringe pump for aq. reactions
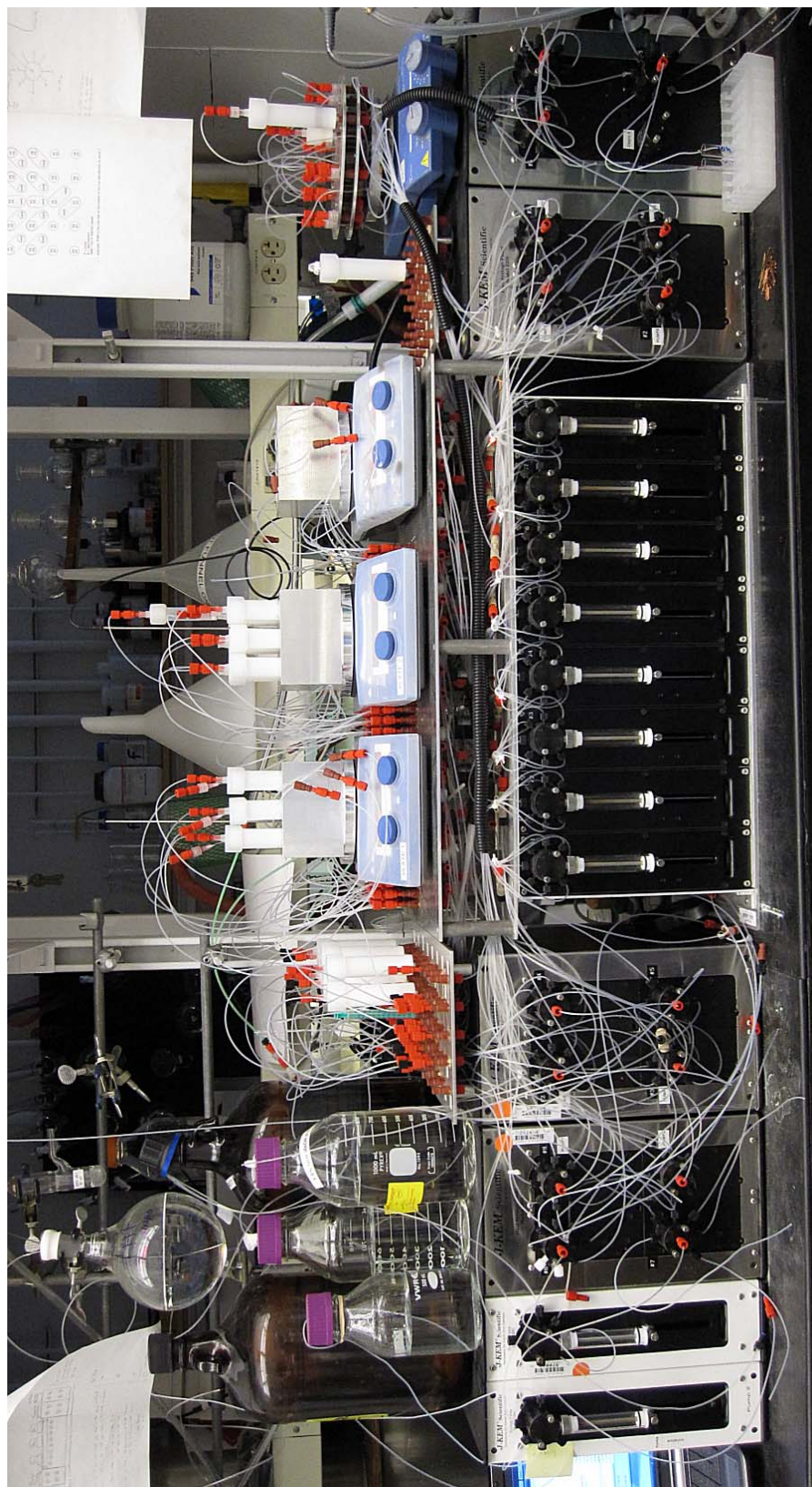
Figure 5.8. A picture of the automated ICC machine. This photo was taken on 7/22/10.
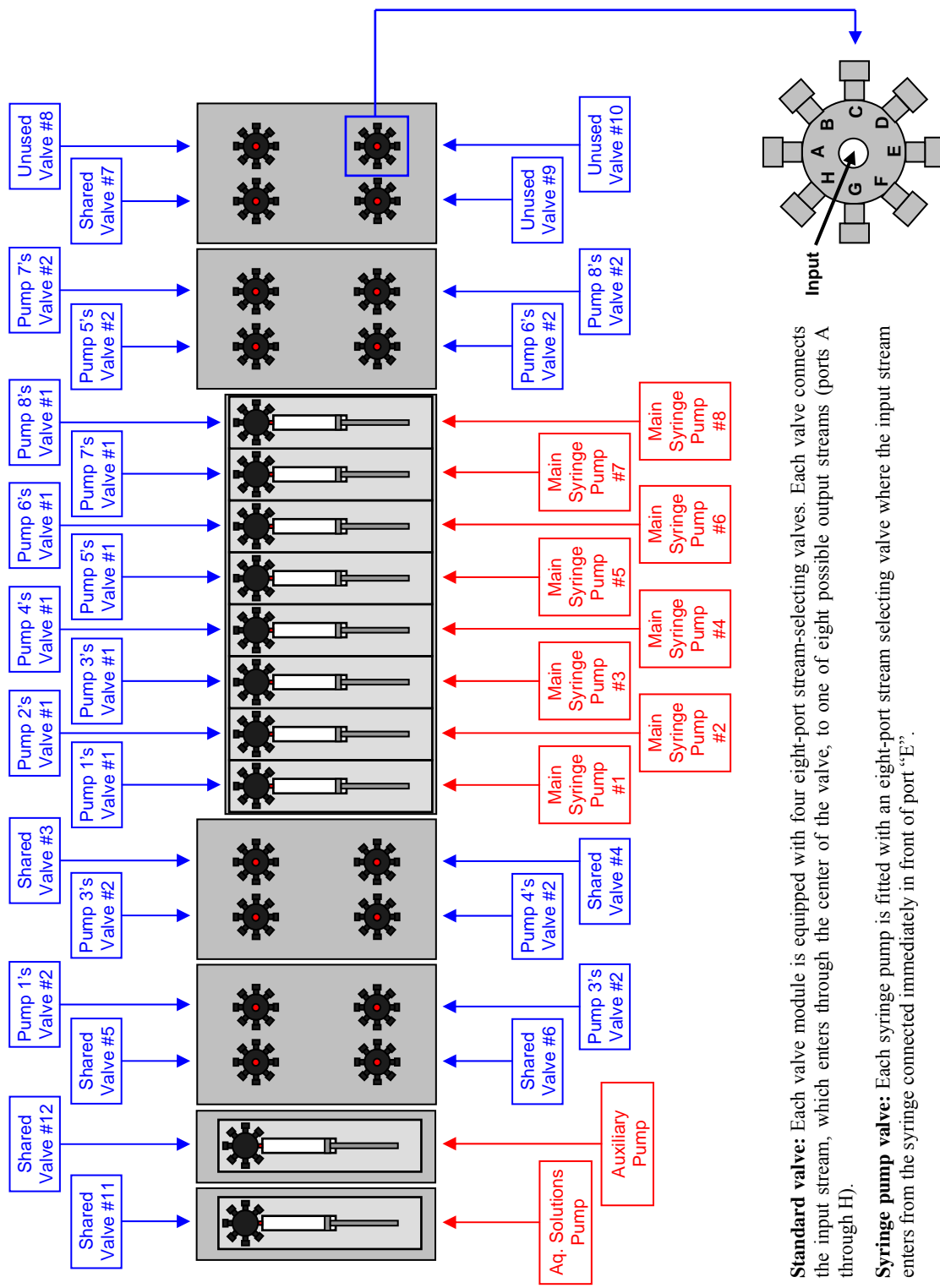
Standard valve: Each valve module is equipped with four eight-port stream-selecting valves. Each valve connects the input stream, which enters through the center of the valve, to one of eight possible output streams (ports A through H).

Syringe pump valve: Each syringe pump is fitted with an eight-port stream selecting valve where the input stream enters from the syringe connected immediately in front of port "E".

Figure 5.9. Positions of the pump, valves, and ports which comprise the automated ICC machine

274
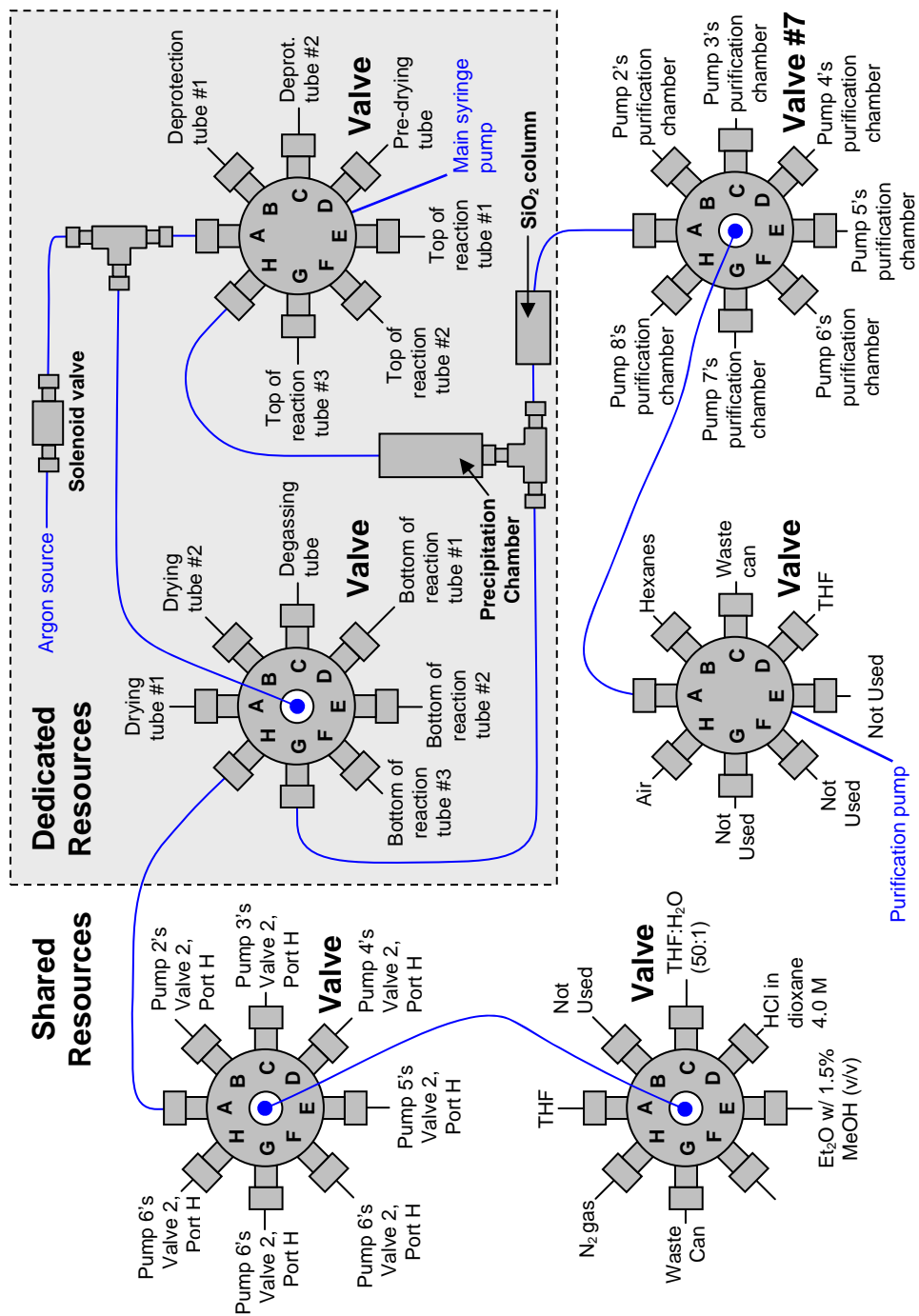
Figure 5.10. An example of the connectivity of the tubing used in the automated ICC machine. The connectivity illustrated is for main pump #1.

In the current design of the automated ICC machine, the equipment set assigned to each virtual machine is connected to two deprotection modules, three reaction modules, and one purification module. The single purification module is reused for each automated ICC cycle. Currently the two deprotection modules share the same pre-drying tube and the same degassing tube. Further, because there are only two deprotection modules per virtual machine, a three-step automated ICC sequences requires that the same deprotection module is used for the first cross-coupling and the third cross-coupling, where the reagents and tubes are cleaned and recharged manually between these coupling steps.[27] The connections between the valves on the machine and each deprotection module, reaction module and purification module are detailed in Table 5.3, and are general for each virtual machine. The port on valve #7 to which the bottom of the SiO$_2$ column in the purification module connects is specific to the virtual machine: machine #1 = port A, machine #2 = port B, machine #3 = port C, etc. For example, in order for the main syringe pump of a virtual machine to connect to the drying tube in deprotection module #1, the following valves must change: valve #1 to port A, and valve #2 to port A. In order for virtual machine #1 to access THF, the following valves must change: valve #1 to port A, valve #2 to port H, valve #3 to port A, and valve #4 to port A (Figure 5.10).

Table 5.3

	Module 1	Module 2	Module 3
Deprotection Module:			
Deprotection Tube	Valve 1, Port B	Valve 1, Port C	N/A
Pre-drying Tube	Valve 1, Port D	Valve 1, Port D	N/A
Drying Tube	Valve 2, Port A	Valve 2, Port B	N/A
Degassing Tube	Valve 2, Port C	Valve 2, Port C	N/A
Reaction Module:			
Reaction Tube Bottom	Valve 2, Port D	Valve 2, Port E	Valve 2, Port F
Reaction Tube Top Input	Valve 1, Port E	Valve 1, Port F	Valve 1, Port G
Purification Module:			
Precipitation Tube Input	Valve 1, Port H	N/A	N/A
Output	Valve 2, Port G	N/A	N/A
SiO$_2$ Column (bottom)	Pump-Specific	N/A	N/A

Software control of the machine equipment

All machine equipment is controlled by a custom software program which was written in VB.NET and is run on a Windows-based computer. As described above, the machine is designed to run eight syntheses simultaneously. Each synthesis is executed from the software environment using an independent virtual machine, and each virtual machine can be scripted and started/stopped without regard to the state of the other virtual machines. The custom software program ensures that resources are queued appropriately. Additionally, the software program is designed to interpret instructions to the machine written in a simple, custom scripting language. This enables the end-user to write very general instructions to the machine that are then read by the software and then mapped and communicated to the appropriate hardware. The commands used in this scripting language are detailed in Appendix A.

The interface of the software program at rest is shown in Figure 5.11. The buttons across the top of the window labeled "Pump 1", "Pump 2", etc., select the virtual machine that is to be modified by the user. The large text box provides an area in which the scripting commands are typed, copied and edited. When the "Run" button is pressed the software proof-reads all of the scripting commands entered into the virtual machine. If the syntax of the commands is correct the virtual machine begins operation of the actual machine equipment; if there is a syntax error, the user is alerted to the line of code that raised the error and the machine does not begin operation until the error is corrected. Figure 5.12 illustrates the interface of the software program while it is running a script on the machine. The active line of code is highlighted in blue while the lines of code that have been run are indicated in grey and the remaining lines are indicated in black. The "Break" button stops execution of the code, and the "Pump Status" label alerts the user to the current operation of the virtual machine. If the virtual machine is queued for use of shared equipment, the status of the queue is updated in the "Pump Status" label.

An important aspect of the software is that scripts which are written for one virtual machine are applicable to all of the virtual machines. That is, the script files are portable even though the actual valves that are operated by the script will differ depending on which virtual machine the code is executed from. One mechanism by which the software ensures portability of the scripts is through the use of a "header"

section (Figure 5.13). The header is a set of scripting commands that is specific to each virtual machine and contains instruction on how to operate pieces of equipment that are unique to a particular virtual machine. For example, each virtual machine is mapped to a different port on valve #3 (Figure 5.10). Therefore, scripts that are written to be portable across all virtual machines typically use a placeholder variable to refer to valve #3. The header of each virtual machine includes code which specifies the value that will be used to replace the placeholder variable if the code is executed on that specific virtual machine. The header section is typically hidden from the user but is run as the first portion of code whenever the virtual machine executes a script.
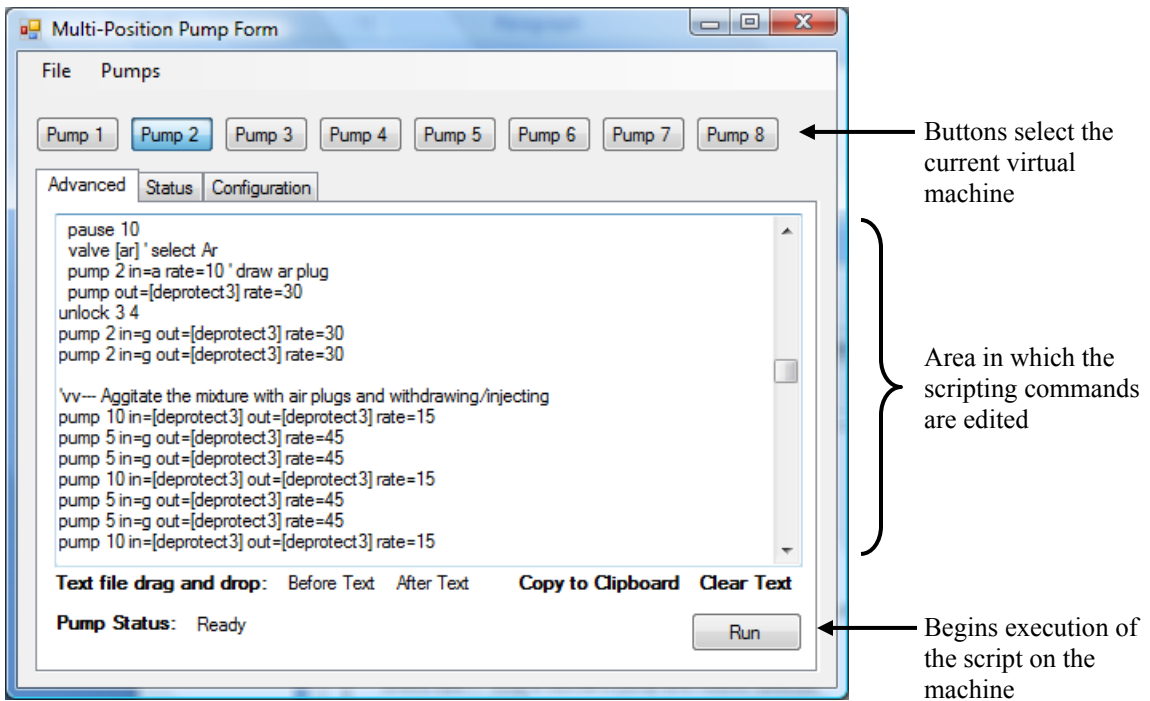
Figure 5.11. The software interface while the virtual machine is not operating. This is the screen from which the virtual machine is scripted.
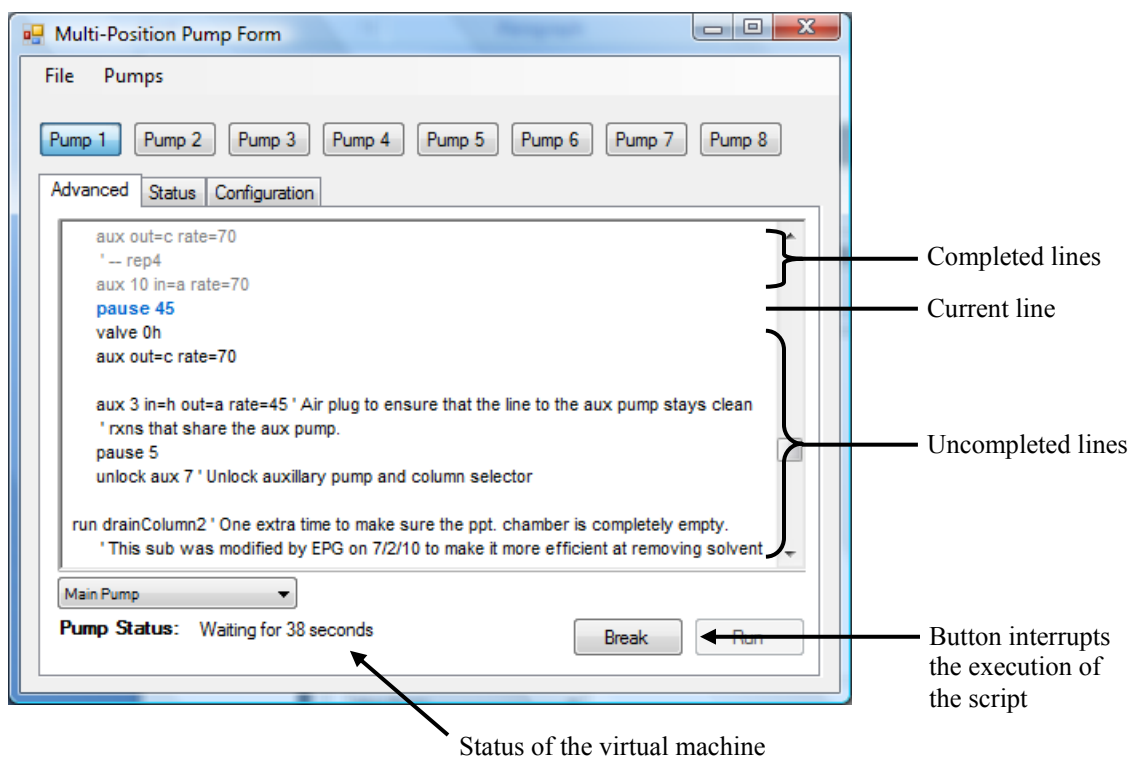
Figure 5.12. The software interface during execution of the script. This screen allows the user to monitor the progress of the script execution.
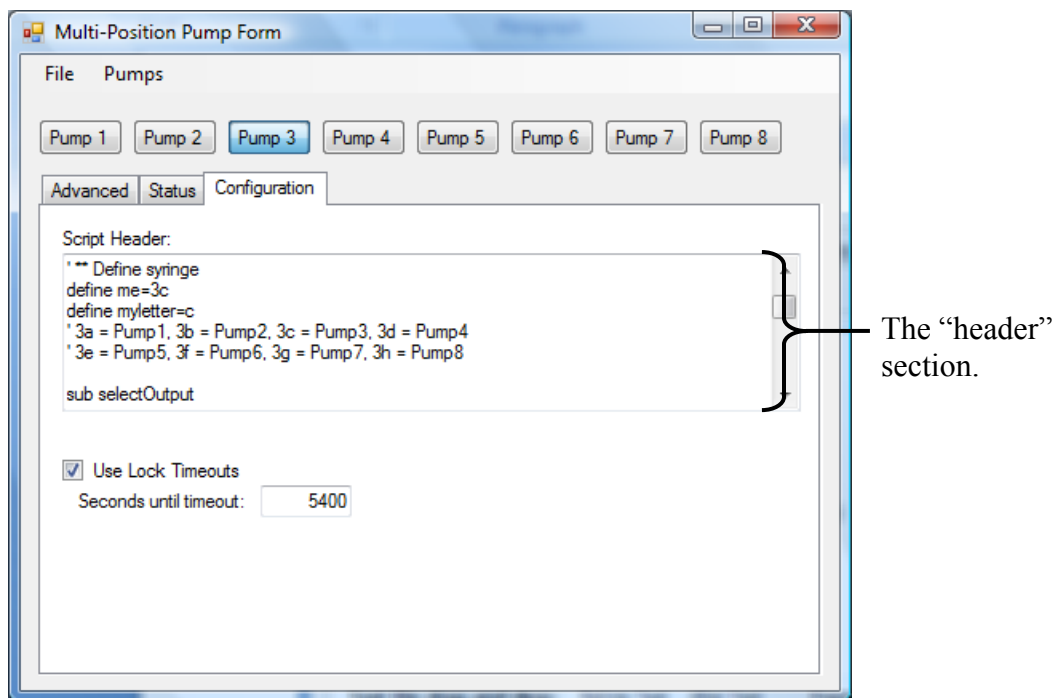
Figure 5.13. The software interface used to change the "header" section of the script.

279

From a technical stand point, the software is built from a collection of programming objects (classes). The most broadly defined object is the *virtual machine* object, which serves as a container for *equipment* objects. An equipment object comprises all of the software functions necessary to operate a single valve or syringe pump. Specifically, the equipment object translates relatively simple software instructions into the complex arrangement of ones and zeros that are understood by the hardware. The equipment object also stores information on the exact hardware address of the equipment, as well as the route by which commands must be sent to the equipment. The most elementary object is the *command* object, which interprets a single line of code to determine if the syntax of the code is correct. If the syntax is correct, the command object stores the parameters necessary to perform the requested action. Specifically, the command object stores the name of the virtual machine object and the name of the equipment object that will be required for the requested action, as well as the names of the functions that will be performed by the equipment object. When a user presses the "Run" button in the software program, each line of the script is sent to its own unique command object which interprets the code. The command objects are then organized in a list and the software program sequentially instructs each command object in the list to execute its action. To provide an example on how the software executes a script, the case in which a five line script is executed on virtual machine #2 is presented in Figure 5.14. This figure illustrates the path that the software instructions will take when the third line of the script is executed ("valve 1b"). This line of script is instructing the machine to turn virtual machine #2's valve #1 to port B. The command object first identifies the virtual machine object that is required for the operation (virtual machine #2), and then instructs the virtual machine object to pass the command to valve #1. The virtual machine then passes the command to valve #1 which reads the function "turn to port B" and translates this command into binary code which is sent to the hardware. The equipment object checks the hardware to make sure that the operation was successful, and then instructs the virtual machine object that the command is done, which in turn instructs the command object that the action is complete, which then instructs the software that the command object is done, and finally the software in turn instructs command object #4 to execute its action.
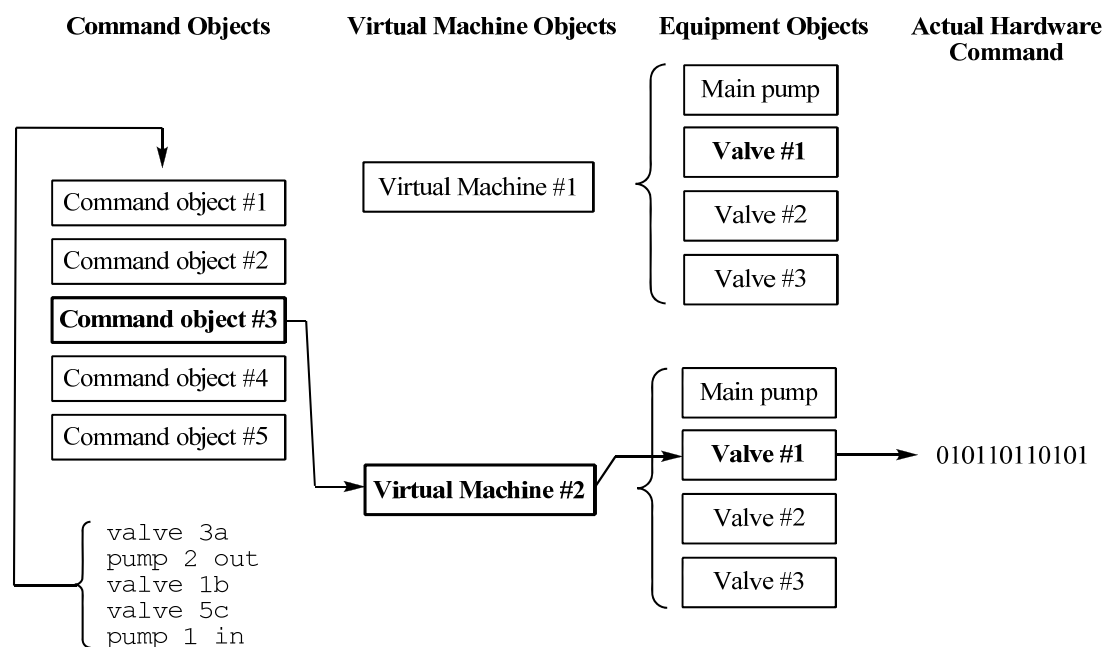
Figure 5.14. An schematic illustration of the path that the software instructions will take when line #3 of a script ("valve 1b") is executed by the software.

5-7 AUTOMATED ITERATIVE CROSS-COUPLING

The machine has been employed successfully in the synthesis of a several small molecules in two general areas: the synthesis of polyarene compounds and the synthesis of polyene compounds. In both cases the automated ICC approach has enabled the syntheses of natural products or their protected analogs. Although the development of the automated ICC machine is ongoing, these early examples demonstrate the viability of the automated approach.

Automated ICC syntheses of polyarene compounds

The first successful two-step, fully automated ICC sequence was realized in the synthesis of triaryl **5.17** as described in Scheme 5.11. Although the yield for this reaction was not determined, the ^{1}H-NMR spectrum of the crude product was relatively pure, indicating that the purification step to afford intermediate boronate **5.16** was successful (Figure 5.15). As the first example of a successful automated ICC sequence, this result served as an important foundation for further development of the machine.
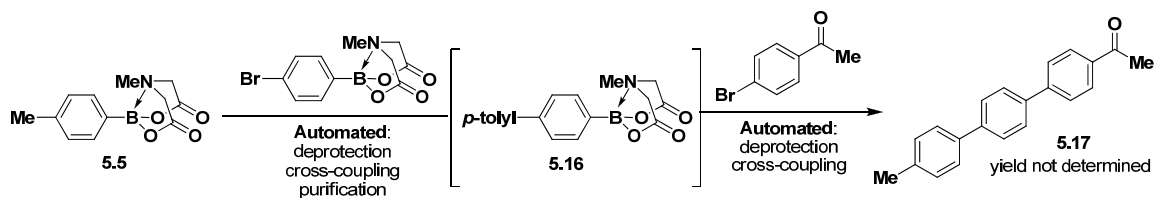
Scheme 5.11. The first example of a fully automated iterative cross-coupling sequence with MIDA boronates.
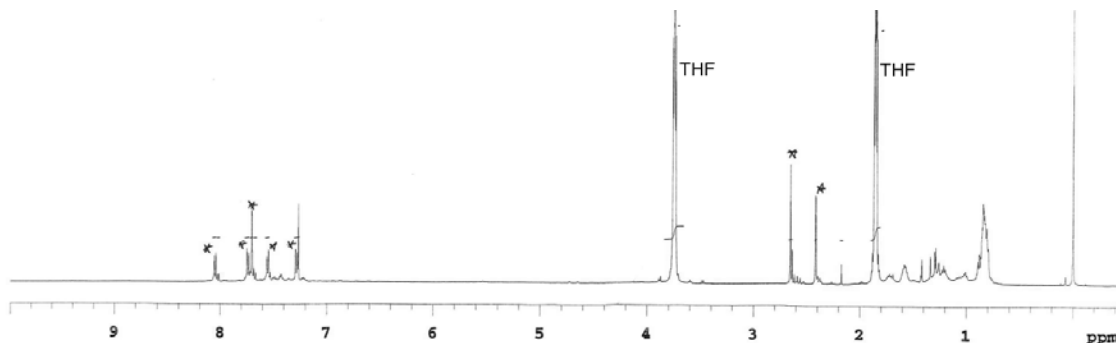
Figure 5.15. ^{1}H-NMR spectrum of 5.17 as the crude product from the first fully automated iterative cross-coupling reaction with MIDA boronates.

Following the synthesis of 5.17, efforts were taken to improve the reproducibility of the automated ICC machine. Towards this goal, the propenylation of 5.18 was studied in detail. As discussed above, the key discovery that resulted from this effort was that the stir rate in the reaction module must be greater than 500 rpm. This discovery prompted the design of a new frit for the reaction tube, as described above, in order to allow high stir rates. The coupling between 5.4 and 5.18 under automated ICC has been repeated over ten times following this method and has been found to always proceed with full conversion of the halide to afford MIDA boronate 5.14 as the pure product in a 65% to 75% yield.
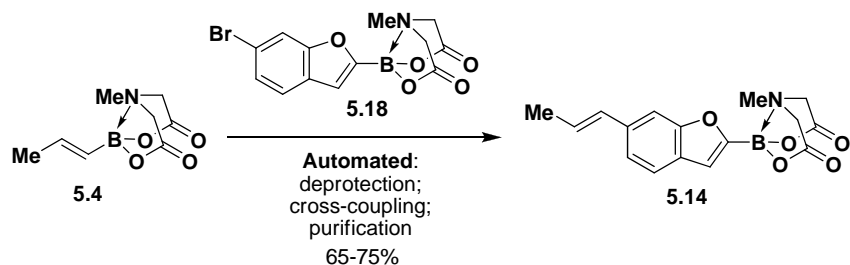
282

Deprotection: Amberlyst A26(OH); HCl.
Cross-coupling: Pd(OAc)$_2$, S-Phos, K$_3$PO$_4$, THF, 60 ºC, 6 h

Scheme 5.12. The automated SMC coupling between **5.4** and **5.18** has been found to be highly reproducible.

Following the successful synthesis of **5.14**, the automated ICC machine was applied in the synthesis of the MOM-protected analogs of the two neolignan natural products ratanhiaphenol I[28] (MOM-analog **5.20**) and 2-(2,4-dihydroxyphenyl)-5-(*E*)-propenylbenzofuran[28] (MOM-analog **5.22**) (Figure 5.12). Both products **5.20** and **5.22** were isolated in multi-milligram quantities after manual SiO$_2$ purification of the crude final reaction solutions, where the yields given in Figure 5.12 are based on the halide employed in the final SMC reaction step. Between three and four equivalents of the boronic acid are employed in all SMC reactions in automated ICC sequences in order to ensure that the boronic acid does not become the limiting reagent. For example, the automated ICC sequence that afforded **5.20** began with 197 mg of MIDA boronate **5.4** and used three equivalents of boronic acid in the first coupling step and four equivalents of boronic acid in the second coupling step. The diminution in mass that occurs in the automated ICC sequence as currently implemented makes this approach non-ideal in certain contexts. However, the syntheses of **5.20** and **5.22** demonstrate that automated ICC may be well suited towards enabling rapid access to small molecule products in quantities suitable for biological testing. The syntheses of **5.20** and **5.22** were run in parallel on the automated ICC machine and required approximately 36 hours to complete.

(A)

5.4   5.18   5.19   14.1 mg (53%)   **5.20**

Automated: deprotection; cross-coupling; purification

Automated: deprotection; cross-coupling

(B)

5.4   5.18   5.21   13.8 mg (45%)   **5.22**

Automated: deprotection; cross-coupling; purification

Automated: deprotection; cross-coupling
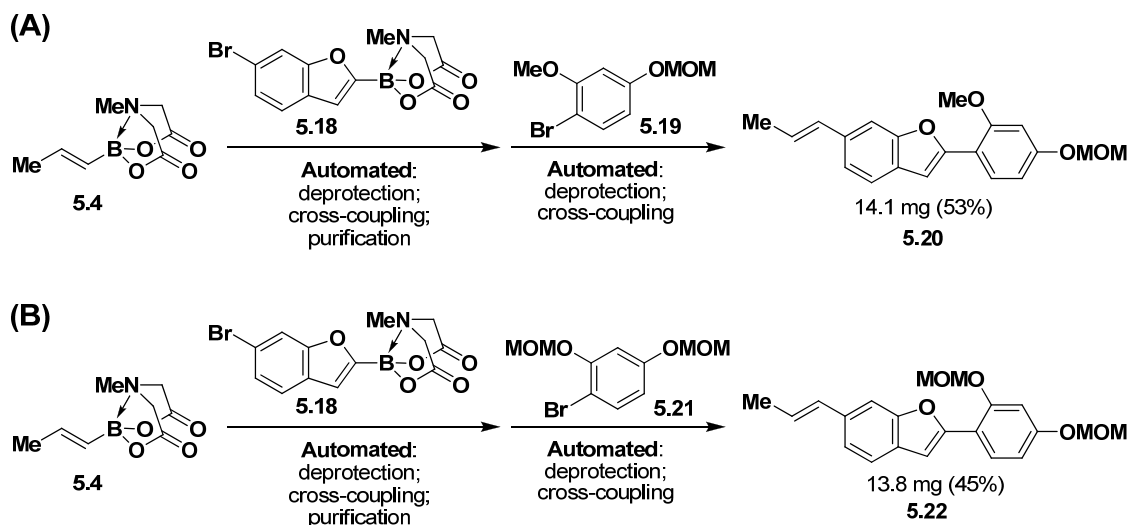
Deprotection: Amberlyst A26(OH); HCl. **Cross-coupling**: Pd(OAc)$_2$, S-Phos, K$_3$PO$_4$, THF, 60 °C, 6 h

Scheme 5.13. The MOM analogs of two natural products, ratanhiaphenol I and 2-(2,4-dihydroxyphenyl)-5-(*E*)-propenylbenzofuran, were synthesis by automated ICC.

The most complex small molecule accessed to date by automated ICC is the MOM-analog of the neolignan natural product ratanhine[29] (**5.25**) (also **2.15**, chapter 2) (Scheme 5.14). The synthesis of **5.25** was executed in a fully automated fashion without user intervention, requiring 36 hours to complete. This synthesis represented the first successful three-step automated ICC sequence; however, the product represented less than 10% of the material obtained from the final coupling as indicated by ^{1}H-NMR. At the time of this synthesis the importance of a high stir rate in the reaction module and the properties of the Amberlyst resin were poorly understood. Current efforts are being directed towards harnessing these discoveries in an improved and highly reproducible synthesis of **5.25**.

Deprotection: Amberlyst A26(OH); HCl. **Cross-coupling**: Pd(OAc)$_2$, S-Phos, K$_3$PO$_4$, THF, 60 °C, 6 h
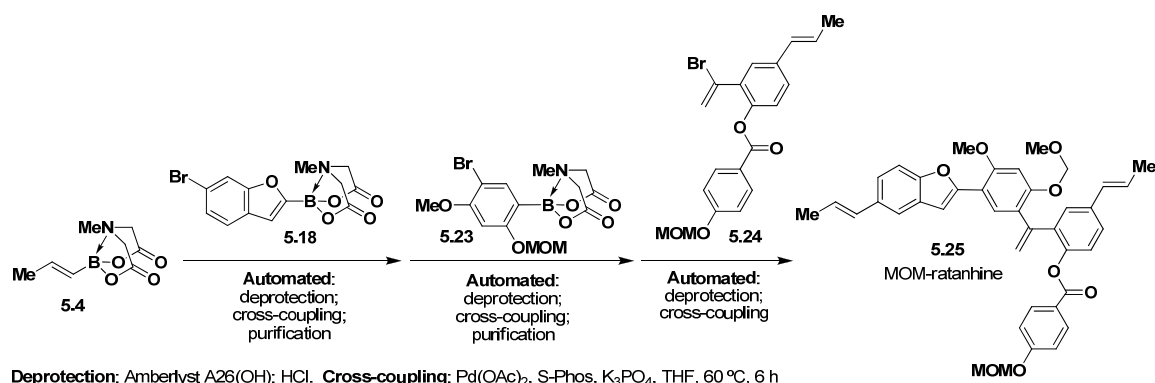
Scheme 5.14. The MOM-analog of the neolignan natural product ratanhine was synthesized in a fully automated fashion by automated ICC.

Automated ICC syntheses of polyene compounds

Previous studies have demonstrated that ICC is well suited to the synthesis of polyene compounds, particularly because the SMC reaction is stereospecific and allows precise control of *E:Z* alkene geometry.[30] In this regard, it would be advantageous to be able to access this important class of molecular architecture via an automated synthesis approach. It is known that polyene compounds, relative to polyarene structures, are typically more sensitive to decomposition and isomerization processes.[30] However, by lowering the temperature of the reaction module to 23 °C, replacing K$_3$PO$_4$ with Cs$_2$CO$_3$, and extending the SMC reaction time to 24 hours, the successful syntheses of several polyene compounds via automated ICC have been achieved. Under this modified automated ICC protocol alkenyl MIDA boronate **5.24** was converted to dienyl MIDA boronate **5.27** in 52% yield (Scheme 5.15A). This yield is based on the halide and reflects the pure material obtained from an automated purification step. Extending the automated ICC sequence by an additional iteration afforded trienyl MIDA boronate **5.28** in 76% yield (Scheme 5.15B), where the yield reflects the pure material that was isolated following an automated purification step. Further, the automated ICC sequence was extended by an additional iteration to provided access to β-parinaric acid (**5.30**)[30a] (Scheme 5.16). In this case the final coupling step was performed employing aqueous KOH as base in order to effect an in situ deprotection of MIDA boronate **5.28**. In this final coupling full conversion of **5.29** was observed by ^{1}H-NMR, although the yield of the reaction was not determined.

Scheme 5.15. (A) The automated ICC approach was successfully applied to the synthesis of dienyl MIDA boronate **5.26**. (B) The automated ICC approach was extended by an additional iteration to afford trienyl MIDA boronate **5.27**.

Scheme 5.16. The synthesis of β-parinaric acid was achieved in a three-step, fully automated synthesis.

The machine has also been applied successfully to the synthesis of the polyene natural product all-*trans*-retinal (**5.33**)[30a] (Scheme 5.17.). Specifically, the same conditions that were found to be effective for the synthesis of **5.27**, **5.28** and **5.30** were also found to be effective for the two-step synthesis of **5.33**. In fact, the automated ICC sequence used to access **5.33** differs from that of the other polyene couplings only in the identity of the building blocks that were inputted to the machine. The product, all-*trans*-retinal, was isolated in 20% yield following manual SiO_2 chromatography of the crude reaction solution that is outputted from the final coupling. Current efforts are focused on harnessing the modularity of the automated ICC approach to provide access to a number of derivatives of **5.33**.
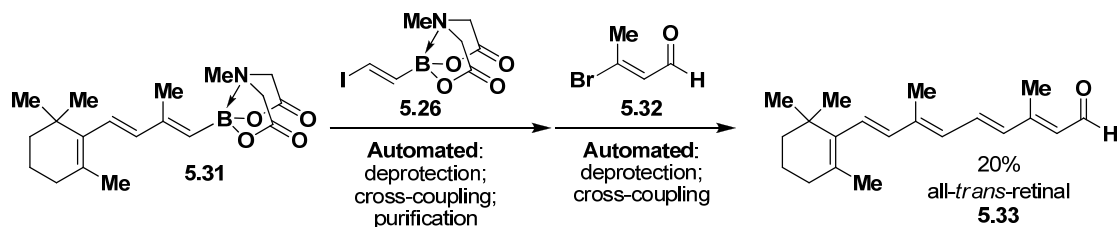
Deprotection: Amberlyst A26(OH); AcOH. **Cross-coupling**: Pd(OAc)$_2$, S-Phos, Cs$_2$CO$_3$, THF, 23 °C, 24 h

Scheme 5.17. The synthesis of *all-trans-retinal* was achieved in a fully automated fashion starting from building block **5.31**.

5-8 THESIS SUMMARY

This dissertation describes the development of a potentially general approach to small molecule synthesis based on the iterative-cross coupling (ICC) of bifunctional MIDA boronates. Critical to realizing this ICC approach in the context of small molecule synthesis was the discovery that the MIDA ligand possesses the capacity to attenuate the reactivity of boronic acids under Suzuki-Miyaura cross-coupling (SMC) conditions, yet can be cleaved from boron using mild aqueous base. Further, it was discovered that MIDA boronates are generally stable to storage under ambient air at room temperature, thus enabling MIDA boronates to serve as stable surrogates for otherwise unstable boronic acids. The rate-controlled in situ release of boronic acids from the corresponding MIDA boronates was found to offer a general approach by which otherwise unstable boronic acid can be engaged in high-yielding SMC reactions with un-activated aryl chlorides. The MIDA boronate functional group was also found to be stable to a large number of the reagents and conditions typically employed in organic synthesis. As a consequence of this unique stability, and enabled by the general compatibility of MIDA boronates with SiO$_2$ chromatography, it was found that simple MIDA boronates can be efficiently elaborated to structurally complex and/or functionally rich MIDA boronate building blocks using multi-step organic synthesis. Further, the ICC methodology was utilized in the syntheses of the natural products ratanhine and (+)-crocacin C.

Building on the collective discoveries made in the development of the ICC platform, the development of an automated small-molecule synthesizer with the capacity to perform iterative solution-phase ICC reactions with MIDA boronates was realized. The development of this machine was made possible by the additional discovery that MIDA

287

boronates are amenable to a "catch-and-release" purification protocol that is generally effective for all compounds that contain a MIDA boronate functional group. Development of the automated ICC machine involved the design and programming of a number of custom hardware components, as well as the development of a custom software program. To date, the automated ICC protocol has been applied successfully to the syntheses of five natural products or their MOM-protected analogs: MOM-ratanhiaphenol I, MOM-2-(2,4-dihydroxyphenyl)-5-(*E*)-propenylbenzofuran, MOM-ratanhine, β-parinaric acid, and all-*trans*-retinal. It is likely that with further development this automated ICC approach will become amenable to any ICC synthesis that can be performed manually. It is hoped that the discoveries presented in this dissertation will enable a more general and accessible approach to small molecule synthesis.

5-9 REFERENCES

[1] Currently over 70 MIDA boronates are commercially available: www.aldrich.com/MIDA

[2] For pioneering developments in the automated synthesis of small molecules via polymer-assistance and/or flow chemistry, see: (a) Hornung, C. H.; Mackley, M. R.; Baxendale, I. R.; Ley, V. S. *Org. Proc. Res. Dev*. **2007**, *11*, 399-405. (b) Nikbin, N.; Ladlow, M.; Ley, S. V. *Org. Process Res. Dev*. **2007**, *11*, 458–462. (c) France, S.; Bernstein, D.; Weatherwax, A.; Lectka, T. *Org. Lett*. **2005**, *7*, 3009-3012.

[3] Merrifield, R. B.; Stewart, J. M. *Nature* **1965**, *207*, 522-523.

[4] Martin, R.; Buchwald, S. L. *Acc. Chem. Res*. **2008**, *41*, 1461-1473.

[5] For an excellent review on tagging strategies for separations in organic synthesis, see: Yoshida, J.; Itami, K. *Chem. Rev*. **2002**, *102*, 3693-3716.

[6] For an excellent review on modern separation techniques in organic synthesis, see: Tzschucke, C. C.; Markert, C.; Bannwarth, W.; Roller, S.; Hebel, A.; Haag, R. *Angew. Chem. Int. Ed*. **2002**, *41*, 3964-4000.

[7] Curran, D. P. *Angew. Chem. Int. Ed*. **1998**, *37*, 1174-1196.

[8] Toy, P. H.; Janda, K. D. *Acc. Chem. Res*. **2000**, *33*, 546-554.

[9] Ley, S. V.; Massi, A.; Rodriguez, F.; Horwell, D. C.; Lewthwaite, R. A.; Pritchard, M. C.; Reid, A. M. *Angew. Chem. Int. Ed.* **2001**, *40*, 1053-1055.

[10] Brown, A. R.; Irving, S. L.; Ramage, R.; Raphy, G. *Tetrahedron* **1995**, *51*, 11815-11830.

[11] Thompson, L. A. *Curr. Opin. Chem. Bio.* **2000**, *4*, 324-337.

[12] Siegel, M. G.; Hahn, P. J.; Dressman, B. A.; Fritz, J. E.; Grunwell, J. R.; Kaldor, S. W. *Tetrahedron Lett.* **1997**, *38*, 3357-3360.

[13] For the use of catch and release type methods to purify proteins, see: Porath, J.; Carlsson, J.; Olsson, I.; Belfrage, G. *Nature* **1975**, *258*, 598.

[14] Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, VCH Publishers, 3nd ed.; **2003**, pg 473-474.

[15] Perrier, H.; Labelle, M. *J. Org. Chem.* **1999**, *64*, 2110-2113.

[16] Bosanac, T.; Wilcox, C. S. *Org. Lett.* **2004**, *6*, 2321-2324.

[17] Poupon, J. C.; Boezio, A. A.; Charette, A. B. *Angew. Chem. Int. Ed.* **2006**, *45*, 1415-1420.

[18] It was observed that in cases where the stir bar was larger and more powerful, and therefore the Celite/SiO_2 mixture was stirred for the entire time the automated ICC machine was powered, that the Celite/SiO_2 mixture would become finely ground and that portions of the solid were passed through the frit of the precipitation chamber. This resulted in clogging of downstream equipment and was especially problematic because these solids are not soluble in water or organic solvents.

[19] The deprotection sequence was executed in the absence of a MIDA boronate because boronic acids are not compatible with Karl Fisher analysis.

[20] The efficiency of the molecular sieves towards removing water was found to be strongly correlated to the temperature at which the mol. sieves were activated. Interestingly, heating the mol. sieves to the temperature of a Bunsen burner for any amount of time led to irreversible deactivation of the sieves. Rather, the sieves were best activated by heating at 300 °C under ambient pressure for at 6-8 hours with periodic mixing.

[21] Cammidge, A. N; Goddard, V. H. M.; Gopee, H.; Harrison, N. L.; Hughes, D. L.; Schubert, C. J.; Sutton, B. M.; Watts, G. L.; Whitehead, A. *J. Org. Lett.* **2006**, *8*, 4071-4074.

[22] The structure of **5.4c** was not confirmed, nor is the mechanism of MIDA boronate deprotection known.

[23] Morwick, T. M. *J. Comb. Chem.* **2006**, *8*, 649-651.

[24] Rohm and Haas Company, Philadelphia, USA: www.rohmhaas.com/ionexchange

[25] Interestingly, treatment of the Amberlyst resin with a saturated aqueous NaCl solution followed by exposure to a THF solution of *p*-tolyl MIDA boronate led to *no hydrolysis* of the MIDA boronate within 60 minutes, as observed by TLC.

[26] Mothana, S.; Grassot, J-M.; Hall, D. G. *Angew. Chem. Int. Ed.* **2010**, *49*, 2883-2887.

[27] It is planned that the machine will be updated with new equipment such that each virtual machine will have three deprotection modules, three reaction modules and two purification modules.

[28] Achenback, H.; Groß, J.; Domínguez, X. A.; Cano, G.; Verde, S. J.; Brussolo, L. C.; Muñoz, G.; Salgado, F.; Lópoz, L. *Phytochemistry* **1987**, *26*, 1159-1166.

[29] Arnone, A.; Dimodugno, V.; Nasini, G.; Depava, O. *Gazz. Chim. Ital.* **1990**, *120*, 397-401.

[30] (a) Lee, S. J.; Gray, K. C.; Paek, J. S.; Burke, M. D. *J. Am. Chem. Soc.* **2008**, *130*, 466-468. (b) Woerly, E. M.; Cherney, A. H.; Davis, E. K.; Burke, M. D. *J. Am. Chem. Soc.* **2010**, *132*, 6941-6943.

CHAPTER 5: EXPERIMENTAL SECTION

Materials. Commercial reagents were purchased from Sigma-Aldrich and were used without further purification. Solvents were dried as noted in chapter 2. The following compounds were prepared as described previously: **5.3** (chapter 2), **5.4** (chapter 4), **5.5** (chapter 2), **5.8**,[1] **5.10**,[1] **5.18** (chapter 2), **5.23** (chapter 2), **5.24** (chapter 2), **5.26**.[2] The syntheses of **5.14**, **5.19**, **5.20**, **5.21**, **5.22**, and **5.25** were performed by Steven Ballmer. MIDA boronate **5.31** was synthesized by Seiko Fujii.

Structural analysis. Structural analysis was performed and described as detailed in chapter 2.

Equipment

Syringe pumps: Syringe pumps were purchased from J-KEM Scientific (part #SYR1400-8 for P1-P8, part #SYR-1400PC for P9 and P10) and are connected to the controlling computer via a RS485 to USB connection. Each syringe pump is fitted with an eight-port stream selecting valve (J-KEM, part #SPDV8) and a 10 mL glass syringe equipped with a Teflon plunger (J-KEM, part #SPGS-10000). The syringe pump withdraws and injects at rates from 0.0 mL/min to 70.0 mL/min with a step of 0.0029 mL.

Reaction tubes: To minimize cross-contamination and allow the rapid setup of a synthesis, all chemical manipulations are performed in disposable polypropylene tubes purchased from Luknova, item #FC003012. The dimensions of the tube are 21 mm x 120 mm (ID x length). The bottom of the tube is fitted with a 21 mm diameter x 5 mm tall frit. The bottom of the tube is accessed through a male luer tip, while the top of the tube is sealed with an air-tight, threaded cap containing a female luer port. The tube holds a solvent volume of up to 25 mL.
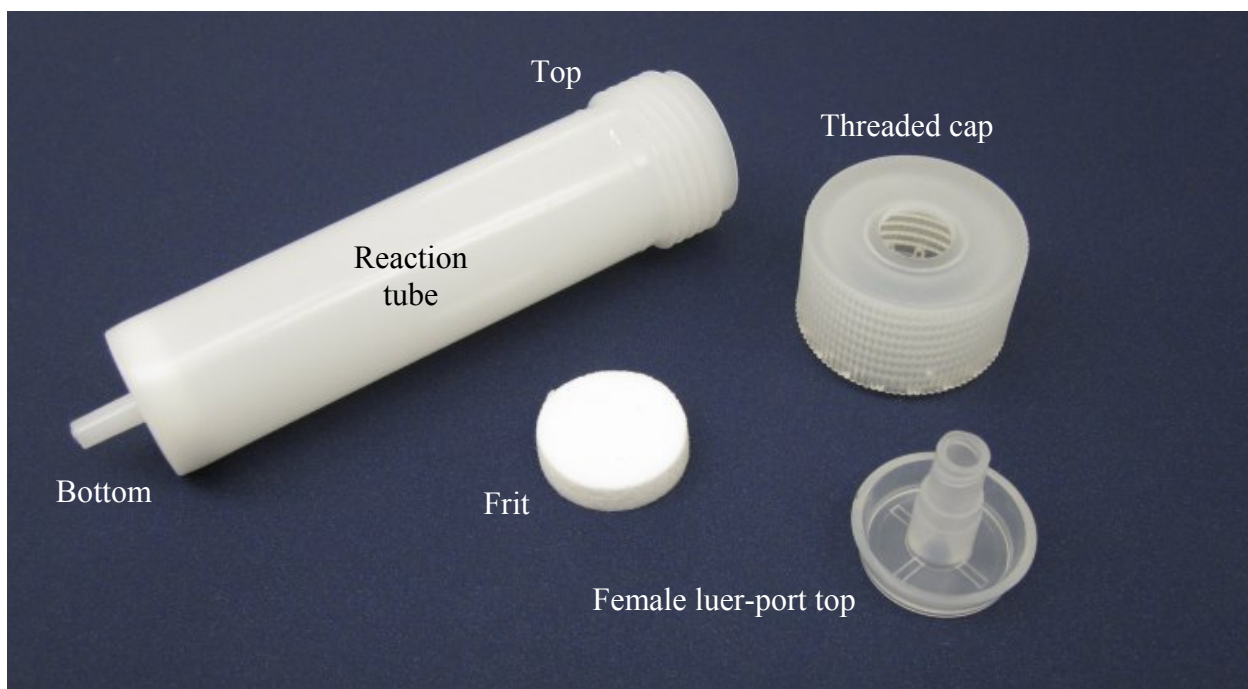
Tubing and fittings: All tubing and fittings were purchased from IDEX Health and Science. The tubing used in the machine is 0.030 inch (ID) x 1/16 inch (OD) Teflon FEP tubing (part #1520xL). All tubing connections were made with 1/16 inch ETFE flangeless ferrules (part #P-200x) and ¼-28 acetal fittings (part #P-202x). Male luer fittings (part #P-625) and female luer fittings (part #P-658) are ETFE and PEEK, respectively.
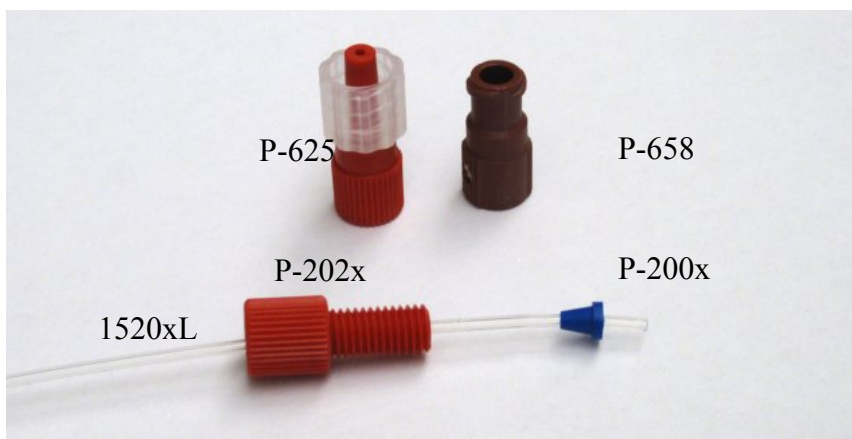
Chemical Synthesis

General procedure:

All chemical manipulations were performed in polypropylene tubes purchased from Luknova, item #FC003012 (see above).

Deprotection tubes. Amberlyst A26(OH) was purchased from Sigma-Aldrich and was stored under N_2 atm. at 4 ºC. Amberlyst A26(OH) (suspension volume of 20 mL) was twice washed with MeCN (50 mL) with vigorous agitation for 60 seconds in each wash. The residual solvent was evaporated under a fast stream of air for 5 minutes until the resin was light beige in color and was free-flowing. To a polypropylene tube was added the Amberlyst resin (2.0 g resin for every 1.0 mmol of MIDA boronate to be deprotected) and, optionally, the MIDA boronate starting material. The tube was capped and then placed on the machine where the bottom luer tip connected to the deprotection table and the top luer port is covered with aluminum foil.

Drying and degassing tubes. A polypropylene tube was charged with Celite, activated molecular sieves (4Å, 8-12 mesh) and K_2CO_3. The amounts of these reagents are proportional to the amount of Amberlyst A26 resin used in the deprotection step prior to drying/degassing, as indicated below. Onto the bed of solids was placed a plastic plunger, cut from the plunger of a 5 mL polypropylene syringe (Fisher #14-817-28, Norm-Ject). The plunger prevents the solids from lifting during the degassing step. The tube was capped and then placed on the machine where the bottom luer tip connects to the degassing table and the top luer port is connected to the gas manifold.
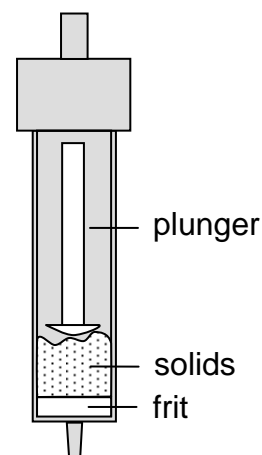
Amberlyst A26 (previous step)	Celite	Mol. sieves	K_2CO_3
2.0 g	200 mg	2.0 g	2.0 g
1.0 g	100 mg	1.0 g	1.0 g
0.5 g	50 mg	0.5 g	0.5 g

Reaction tubes. To assist in the transfer of small amounts or $Pd(OAc)_2$ and S-Phos, these reagents were adsorbed onto Cs_2CO_3 as follows:To a 40 mL glass vial was added $Pd(OAc)_2$ (22 mg) and Cs_2CO_3 (2.723 g). To the vial was added THF (10 mL), and the suspension was concentrated in vacuo to afford a pale amber powder, the *Pd-mixture*. To a 40 mL glass vial was added S-Phos (76 mg) and Cs2CO3 (2.667 g). To the vial was added THF (10 mL), and the suspension was concentrated in vacuo to afford a white powder, the *SPhos-mixture*.

To a polypropylene tube was added a stir bar (Big Science Inc., SBM-1508-REH), the halide (0.333 mmol), the Pd-mixture (488 mg, 5% Pd) and the SPhos-mixture (488 mg, 10% S-Phos). For aqueous couplings, to the tube was added a KOH pellet (75 mg, 1.7 mmol). The tube was capped with a modified cap (see detail) and was placed in a heating block. The bottom of the tube is connected the reaction table, the top of the tube is vented to the gas manifold, and the second top input is connected to the reaction table for slow addition of the boronic acid.

Automation. Each cross-coupling in the automated sequence was performed according to the following script:

Deprotection   1)   Add THF (11 mL) to deprotection tube
            2)   Agitate the mixture via gas bubbling for 60 minutes
            3)   Add HCl in dioxane (4.0 M, 5.0 mmol per 1.0 g of Amberlyst resin)
            4)   Agitate the mixture via gas bubbling for 15 minutes
            5)   Transfer the solution to the drying tube, washing the resin with THF (5 x 1.0 mL)

Degassing	6)	Sparge the mixture with Ar gas for 15 minutes
	7)	While sparging the reaction tube with Ar gas for 15 min., agitate the THF mixture via gas bubbling every 2 minutes
Cross-Coupling	8)	Add THF (3 mL) to the reaction tube and allow the mixture to stir for 10 min.
	9)	Transfer the boronic acid solution from the drying tube to the reaction tube over 120 min., washing the solids with THF (3 x 1.0 mL)
	10)	Stir the reaction mixture at 600 rpm for 22 hours.
Purification	11)	Add hexanes (12 mL) to the ppt. chamber, then add a portion of the reaction solution (3 mL) to the ppt. chamber.
	12)	Withdraw the solution in the ppt. chamber through the SiO2 plug and send to the waste can
	13)	Repeat steps 11 and 12 until all of the reaction solution has been transferred
	14)	Add Et_2O w/ MeOH (1.5 % v/v) (7.5 mL) to the ppt. chamber, withdraw the solution through the SiO_2 plug, and send to waste. Repeat an additional four times.
	15)	Add Et_2O (7.5 mL) to the ppt. chamber, withdraw the solution through the SiO_2 plug, and send to waste. Repeat an additional two times.
	16)	Flow Ar gas through the SiO_2 plug for three minutes to evaporate residual solvent.
	17)	Backflow THF (11 mL) through the SiO_2 column out to the ppt. chamber.
	18)	Stir the THF mixture for 30 minutes in the ppt. chamber.
	19)	Withdraw the THF solution into the main pump. The next coupling sequence begins at step 1.

Aqueous coupling modification:

Note: This sequence begins after step 19 from the general automation script (above).

1) Sparge the THF solution derived from the purification of the previous cross-coupling with Ar gas for 15 minutes.

2) Transfer the THF solution to the reaction tube in one portion.

3) Stir the mixture for 5 minutes.

4) Add degassed H_2O (2 mL) to the reaction tube

5) Stir the reaction mixture at room temperature for 12 hours.

6) Add aq. NH_4Cl (2.5 mL), mix for 5 minutes, then withdraw the entirety of the mixture and transfer it to the product test tube.
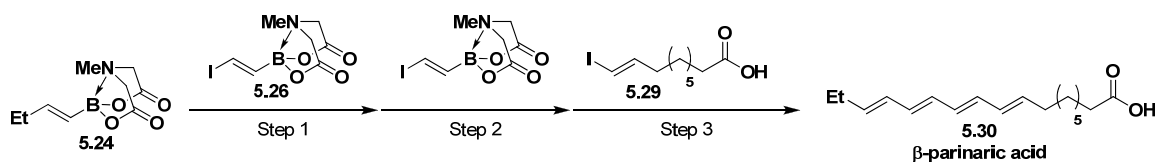
β-parinaric acid (5.30)

All steps were performed according to the general procedure. The machine was equipped with reagent tubes as follows:

Step 1. The machine was equipped with a deprotection tube charged with Amberlyst resin (2.0 g) and MIDA boronate **5.24** (211 mg, 1.0 mmol); a drying tube charged with mol. sieves (2.0 g), K_2CO_3 (2.0 g) and Celite (0.2 g); and a reaction tube charged with the Pd-mixture (488 mg), the SPhos-mixture (488 mg) and boronate **5.26** (103 mg, 0.333 mmol).

Step 2. The machine was equipped with a deprotection tube charged with Amberlyst resin (1.0 g); a drying tube charged with mol. sieves (1.0 g), K_2CO_3 (1.0 g) and Celite (0.1 g); and a reaction tube charged with the Pd-mixture (244 mg), the SPhos-mixture (244 mg), and boronate **5.26** (34 mg, 0.11 mmol).

Step 3. The machine was equipped with a deprotection tube (empty, but used for sparging the MIDA boronate solution) and a reaction tube charged with the Pd-mixture (60 mg), the SPhos-mixture (60 mg), KOH (75 mg, 1.7 mmol) and halide **5.29** (11 mg, 0.037 mmol).

Automation. The synthesis was performed in a fully automated fashion with no operator intervention. Step 1 and step 2 were performed following the standard script and step 3 was performed following the aqueous coupling modification of the standard script. The aqueous mixture that was outputted from the machine was manually purified as follows: The mixture was transferred to a 60 mL separatory funnel and was diluted with sat. aq. NH_4Cl (10 mL). The mixture was extracted twice with Et_2O (20 mL) and the combined organics were washed with brine (20 mL); dried over $MgSO_4$; filtered, then concentrated in vacuo. The ^{1}H-NMR ($CDCl_3$) spectrum of the crude product was consistent with the literature data.[3] The yield of the product was not determined.

Step 1 was repeated and the MIDA boronate solution generated in line 19 of the standard script was diverted into a test tube and then concentrated to afford pure intermediate **5.27** as a colorless solid (40 mg, 52%).

5.27
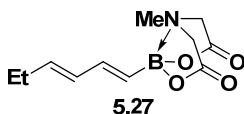
^{1}H-NMR (500 MHz, acetone-d_6): δ 6.53 (dd, *J* = 17.0, 10 Hz, 1H), 6.11 (dd, *J* = 15.5, 10.0 Hz, 1H), 5.82 (dt, *J* = 15.5, 6.5 Hz, 1H), 5.54 (d, *J* = 17.5 Hz, 1H), 4.20 (d, *J* = 17.0 Hz, 2H), 4.01 (d, *J* = 17.0 Hz, 2H), 2.98 (s, 3H), 2.10 (quint, *J* = 7.5 Hz, 2H), 0.99 (t, *J* = 7.5 Hz, 3H). ^{13}C-NMR (125 MHz, acetone-d_6): δ 196.1, 143.7, 137.8, 132.6, 62.2, 47.2, 26.1, 13.7.

Step 1 and step 2 were repeated and the MIDA boronate solution generated during the second coupling (line 19 of the standard script) was diverted into a test tube and then concentrated to afford pure intermediate **5.28** as a colorless solid (22 mg, 76%).

5.28
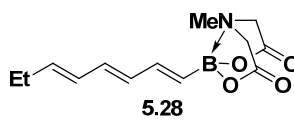
^{1}H-NMR (500 MHz, acetone-d$_6$): δ 6.58 (dd, *J* = 18.0, 10.5 Hz, 1H), 6.28 (dd, *J* = 15.0, 10.0 Hz, 1H), 6.20 (dd, *J* = 15.0, 10.0 Hz, 1H), 6.11 (ddt, *J* = 15.5, 10.5, 1.5 Hz, 1H), 5.82 (dt, *J* = 15.0, 6.5 Hz, 1H), 5.64 (d, *J* = 17.5 Hz, 1H), 4.21 (d, *J* = 17.0 Hz, 2H), 4.03 (d, *J* = 17.0 Hz, 2H), 2.99 (s, 3H), 2.12 (quint, *J* = 7.5 Hz, 2H), 0.99 (t, *J* = 7.5 Hz, 3H). ^{13}C-NMR (125 MHz, acetone-d$_6$): δ 169.0, 143.5, 138.3, 134.8, 133.5, 130.3, 62.2, 47.3, 26.4, 13.8.

5.27
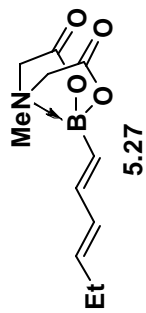
as purified by the machine
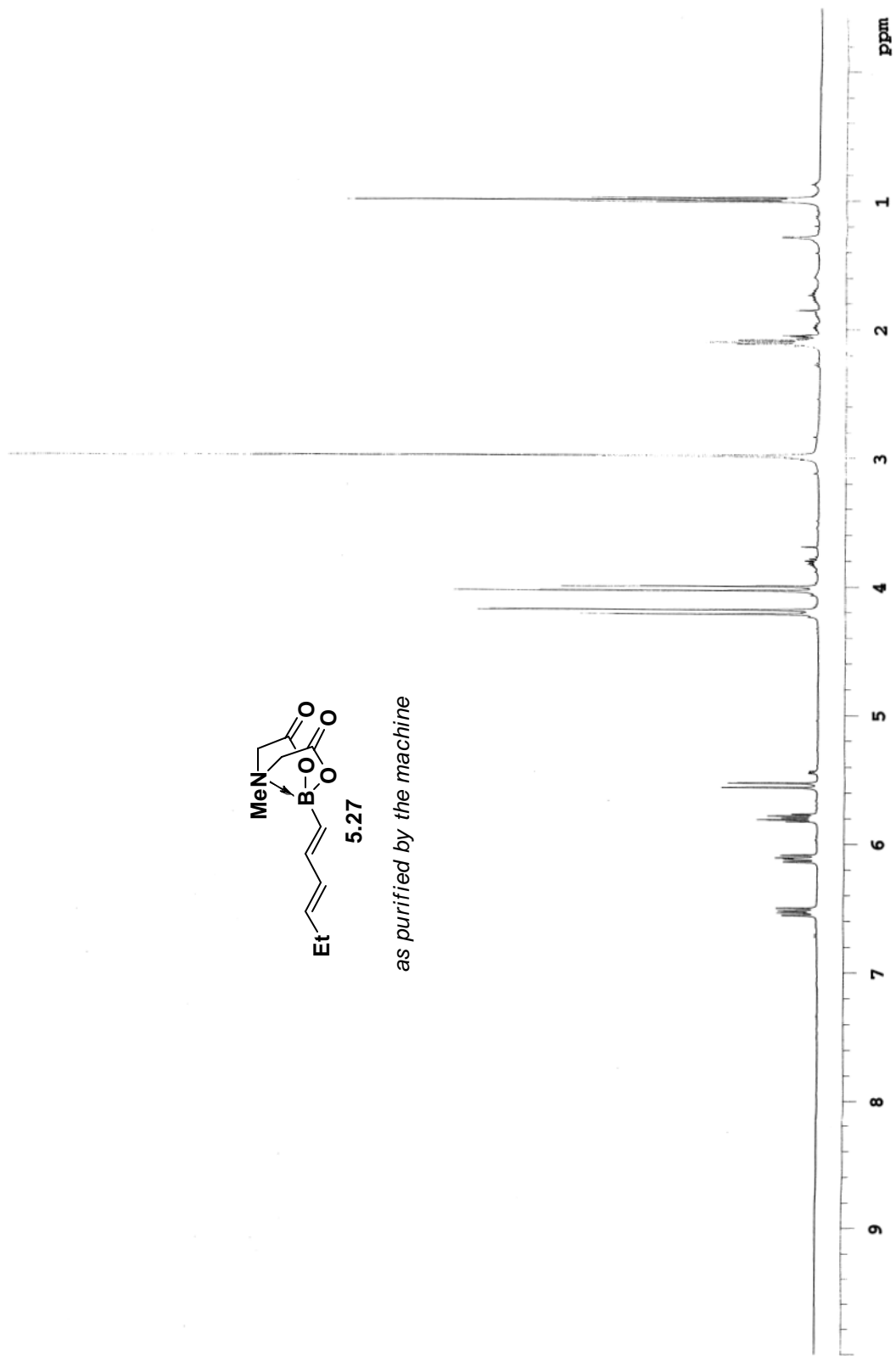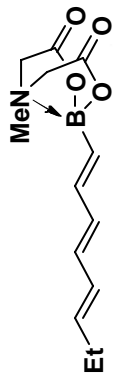
5.28

as purified by the machine
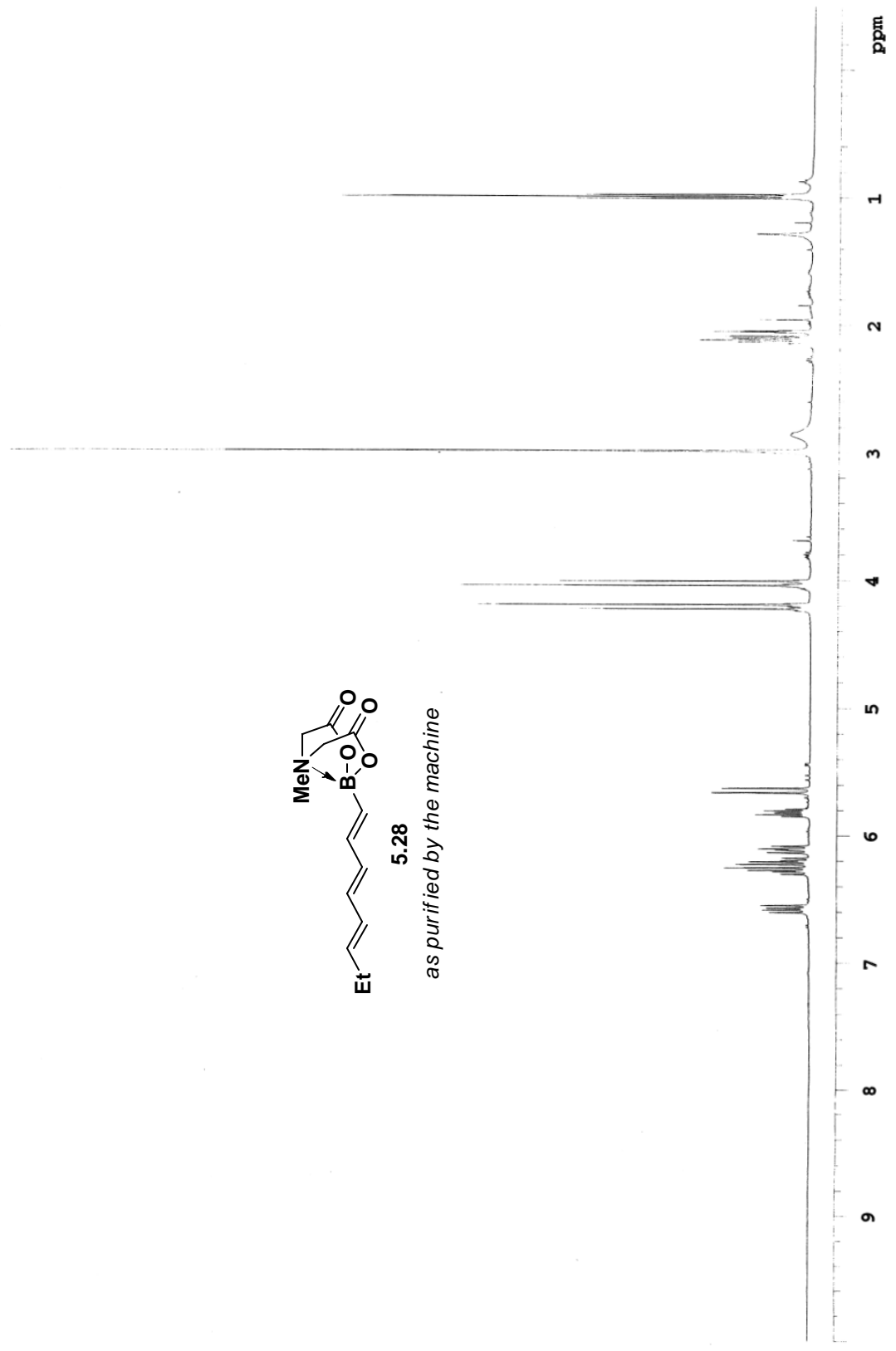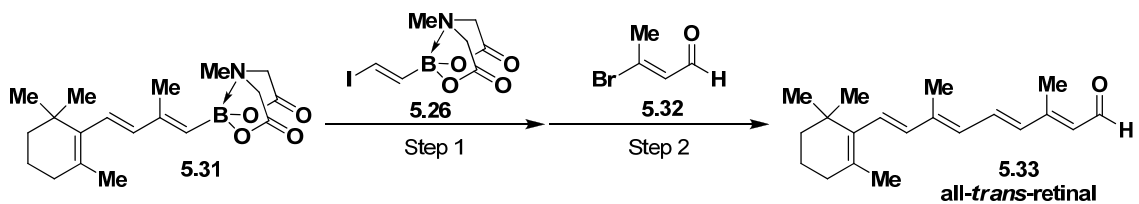
all-*trans*-retinal (5.33)

All steps were performed according to the general procedure. The machine was equipped with reagent tubes as follows:

Step 1. The machine was equipped with a deprotection tube charged with Amberlyst resin (1.0 g) and MIDA boronate **5.31** (173 mg, 0.500 mmol); a drying tube charged with mol. sieves (1.0 g), K_2CO_3 (1.0 g) and Celite (0.1 g); and a reaction tube charged with the Pd-mixture (244 mg), the SPhos-mixture (244 mg) and boronate **5.26** (52 mg, 0.111 mmol).

Step 2. The machine was equipped with a deprotection tube charged with Amberlyst resin (0.5 g); a drying tube charged with mol. sieves (0.5 g), K_2CO_3 (0.5 g) and Celite (50 mg); and a reaction tube charged with the Pd-mixture (82 mg), the SPhos-mixture (82 mg). A separate polypropylene tube was charged with a solution of halide **5.32** (0.056 mmol) in degassed THF (3 mL).

Automation. The synthesis was performed in a fully automated fashion with no operator intervention. Step 1 was performed following the standard script. Step 2 was performed following the standard script with the modification that the THF used in line 8 of the standard script was the entirety of the solution containing halide **7**. Further, the script for step 2 was stopped after line 10 and the reaction solution was outputted to a test tube. The product was manually purified as follows: The reaction solution was concentrated in vacuo and the solid yellow residue was purified by SiO_2 chromatography using an Isco-Teledyne CombiFlash system to afford all-trans-retinal as a yellow solid (3.3 mg, 20%). The ^{1}H-NMR ($CDCl_3$) spectrum of the product was consistent with the literature data.[3]

REFERENCES:

[1] Knapp, D. M.; Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2009**, *131*, 6961-6963

[2] Lee, S. J.; Anderson, T. A.; Burke, M. D. *Angew. Chem. Int. Ed.*, **2010**, *ASAP*.

[3] Lee, S. J.; Gray, K. C.; Paek, J. S.; Burke, M. D. *J. Am. Chem. Soc.*, **2008**, *130*, 466-468.

APPENDIX A

SCRIPTING COMMANDS USED TO PROGRAM THE MACHINE

This appendix describes the commands that are used in the custom scripting language that is interpreted by the software that runs the machine. All automated iterative cross-coupling procedures are written using only these fifteen commands. Each command that is described below is also accompanied by an example on the usage of the command. The scripting language is not case-sensitive.

' (apostrophe)

> Description:
>
> Used to designate a comment. The text following an apostrophe is not interpreted by the program as a command.
>
> Usage:
>
> `' [enter comment text following the apostrophe]`
>
> Example:
>
> `valve 1a 2b  ' This is a comment on the same line as a command`
> `'This is a comment on its own line.`

[ ] (brackets)

> Description:
>
> Used to designate a variable. A variable is a place-holder for a value that can be specified with a `define` command. Using variables allows the code to be more flexible.
>
> Usage:
>
> *command* [*variableName*]
>
> Executes a command, represented here generically as *command*, for which the variable *variableName* contains the instructions to be interpreted by the command. The value of *variableName* would be defined earlier in the code using the `define` command.

```
valve [Tube]
pump 5 in=[THF] out=a rate=[StdRate]
```

In the above code the variables are [Tube], [THF] and [StdRate]. Using the `define` command the values could be set at the beginning of the code, and could be changed easily before the file is executed. For example:

```
Define Tube=4a THF=b StdRate=45

valve [Tube]
pump 5 in=[THF] out=a rate=[StdRate]
pump 2 in=[THF] out=a
valve 2b [Tube]
```

In this way the code is more flexible. This same routine could be called for a number of different tube locations, and using just one line or code the entire routine could be modified for a new tube location. Also, if the location of the THF bottle changed, it would be easy to specify a new location using just one line of code, even though the routine accesses the THF bottle on several lines.

DEFINE

Description:

Used to set the value of a variable within a script.

NOTE: *Due to current code limitations, each variable should only be defined once in a procedure.*

Usage:

`define` *variable_name*=*variable_value*

variable_name represents the name of the variable to define
variable_value is the data which will now stand in the place of all instances of the variable defined by *variable_name*

```
define pumpnum=a
valve 4[pumpnum]
valve 5[pumpnum] 8[pumpnum]
```

All instances of `[pumpnum]` (the variable) will be replaced with the value *a* at runtime. That is, the program will interpret the script as follows:

```
define pumpnum=a
valve 4a
valve 5a 8a
```

Variables allow flexible code since with a few uses of the `define` command, a general script can be mapped onto any number of equipment combinations.

PAUSE

Description:
Pauses the script for a specified period of time before executing the next line.

Usage:
`pause` *[# of seconds to pause]*

Example:
`pause 5`   This pauses the script for 5 seconds

LOG

Description:
Writes a user comment to the file "MachineLog.txt" with a time and date stamp. The comment is added to the end of the file without affecting the previous text in the log file. The command is useful in logging the time and date when specific portions of code are executed or completed.

Usage:

```
log "Text Here"
```

Any text can be entered between the two quote marks.

<u>Example</u>:
```
log "Program Start"
```

Writes "5/22/09 8:32:12 AM: Program Start" to the file "cMachineLog.txt", where the system date is 5/22/09 and the system time is 8:32 AM and 12 seconds.

SUB
END SUB

<u>Description</u>:

The `SUB` and `END SUB` commands enclose scripting commands that can be executed as a sub routine. That is, a particular sequence of code can be designated as a sub routine and given a unique identifying name. Rather than retyping the code each time the routine needs to be run, the code can be executed using the RUN command. Additionally, using the `BACKGROUND` command sub routines can be executed as background processes (although care needs to taken in how the code is scripted).

<u>Usage</u>:

```
sub SubName
    enter lines of code here
end sub
```

Define a sub routine with the identifier `SubName`. The code contained within the `sub` and `end sub` lines can be executed by using the run command followed by the identifier.

NOTE: *Every sub routine within a script must have a unique identifier. If two sub routines with the same identifier are used, an error will result.*

```
sub test
  log "Start time"
  pause 30
  log "End time"
end sub
```

Defines the sub routine *test*. At this point the machine will not actually do anything. Rather, it has saved the instruction defined by the *test* routine for later use. To execute the *test* script the `run` command is used:

```
run test  ' Run the script once
run test  ' Run the script again
```

The *test* sub routine is run twice. Each time the sub routine is run it writes the line "Start time" to the log file, waits 30 seconds, and writes the line "End time" to the log file. After the above script has executed, the log file will contain four new lines.

For information on the `RUN` command, see below.

RUN

Description:
Runs a sub routine that has been specified by the `SUB` command structure.

Usage:
```
run SubName
```

Executes the code contained within the sub routine represented by the identifier *SubName*. The identifier *SubName* can refer to any sub routine defined earlier in the script using the `sub, end sub` commands.

Example:
See the above example for the `sub, end sub` command.

BACKGROUND

Begins the execution of a sub routine as a background process. After processing this initial event, the script will immediately read the next line of the main as the background process continues.

NOTE: There are important consequences to running a process in the background. It is the script writer's responsibility to ensure that the background process will not conflict with the foreground process. Specifically, appropriate use of the `lock/unlock` commands is encouraged to make sure that the same equipment is not being accessed at the same time. Additionally, the program cannot display the progress of the background process, nor can it save the progress of the background process if the code is halted. Thus, the `background` command should be used sparingly.

NOTE: Only one instance of a sub routine per pump is allowed to execute as background process at any given time.

Usage

`background` *SubName*

Begins background execution of the sub routine with the identifier *SubName*.

Example:

```
sub TestPause
  pause 15
end sub

background TestPause

pause 10
```

The `sub TestPause` portion defines a sub routine that will have the machine pause for 15 seconds. The `background` command then calls the *TestPause* routine to execute in the background while it then immediately processes the next command: `pause 10`. Thus, the total execution time for this script will be 15 seconds, since the machine will simultaneously pause for both 15 and 10 seconds.

WAIT

Halts program execution until a condition is met. Specifically, the WAIT command allows other machine processes to catch up to the script before executing the next command line. This is particularly useful in coordinating background-executed sub routines.

Usage:

```
wait SubRoutineName
```

SubRoutineName is the identifier of a sub routine that was previously executed using the `background` command. The system will wait until the process for *SubRoutineName* is complete before proceeding to the next line.

Example:

```
sub TestPause
  pause 15
end sub


background TestPause


pause 5
wait TestPause


log "Script complete"
```

Similar to the example of the `background` command, the `sub TestPause` portion defines a sub routine that will have the machine pause for 15 seconds. The `background` command then calls the *TestPause* routine to execute in the background while it then immediately processes the next command: `pause 5`. After the `pause 5` command completes (5 seconds later), the machine pauses and waits for the *TestPause* sub that is running in the background to complete. Thus, the line "Script complete" is not written to the log file until 15 seconds after the `background TestPause` command is executed. If the `wait TestPause` command was omitted, the `log` command would execute 5 seconds after the `background TestPause` command was executed

VALVE

Description:

Used to change to port position of an 8-port valve. The command can also be used to turn a selenoid valve on or off. Multiple valves can be manipulated secquentially in a single VALVE call.

Usage:

`valve` *command1 command2 commmand3*

command1, command2, commmand3, etc. describes the # of the valve being manipulated and the new state for the valve. Multiple valves can be manipulated using a single `valve` command. In fact, there is no limit to the number of manipulations that can be performed with a single `valve` command. Changes to the valves of the system are executed in the order *command1*, then *command2*, then *command3*, etc.

Example:

`valve 1a`	This moves valve #1 to position A
`valve 1b 2b`	This moves valve #1 to position A, then moves valve #2 to position B
`valve x1on`	This turns selenoid #1 on
`valve x2on x1off`	This turns selenoid #2 on, then turns selenoid #1 off

PUMP

Description:

Used to control the syringe pump. This command is used to move specific volumes of liquid from one port to another, at a rate specified by the user.

Usage:

`pump` *volume* `in=`*PortIn* `out=`*PortOut* `rate=`*RateOfWithdrawl/Infusion*
`rateIn=`*RateOfWithdrawl* `rateOut=`*RateOfInjection*

volume specifies the amount of reagent that is to be moved by the syringe pump. The volume specified can be greater than the capacity of the syringe only if the syringe is both withdrawing and injecting the reagent during the same command. The volume is expressed as a number representing mL. That is, do not include the unit when specifying the volume--it is assumed.

PortIn (optional), specifies the port from which the reagent will be withdrawn. If [port in] is not specified the program will use whatever port the syringe pump is already set to. Note: if [port out] is not specified, an equal sign does not need to follow the *in* parameter.

RateOfWithdrawl/Infusion (optional), specifies the port to which the reagent will be delivered. If [port out] is not specified the program will use whatever port the syringe pump is already set to. Note: if [port out] is not specified, an equal sign does not need to follow the *in* parameter.

RateOfWithdrawl/Infusion (optional), allows the user to specify how fast the syringe pump will handle the reagent transfer. The rate is specified as a number representing the mL/min. That is, do not include the units when specifying the rate--they are assumed.

RateOfWithdrawl (optional) (similiar to above). This implementation allows the rate of withdrawn of the syringe to be set independently of the rate of injection.

RateOfInjection (optional). Same as *RateOfWithdrawl*, but specifies the rate of injection. Note: if the rate of withdrawal is specified but the rate of injection is omitted, the default rate of injection will be used. This applies vice-versa when only the rate of injection is specified.

Excluding an out port will cause the pump to only inject the reagent already present in the syringe. If an in port is excluded, the pump will only fill the syringe with reagent.

Example:
```
pump 5 in=A out=B rate=5
```

Pumps 5 mL of reagent from port A to port B at a rate of 5 mL/min for both withdrawl and injection.

```
pump 3 in=B out=B rateIn=10 rateOut=2
```

Pumps 3 mL of reagent from port A to port B. The reagent is drawn into the syringe at 10 mL/min and is injected out at a rate of 2 mL/min.

311

```
pump 5 in=B out=C
```

Pumps 5 mL of reagent from port B to port C at the default rate for withdrawl & injection.

```
pump 4 in=A
```

Withdraws 4 mL of reagent from port A into the syringe and then waits for the next command. It is the programmer's responsibility to account for the fate of the reagent in the syringe. Note: no more than 10 mL of reagent can be withdrawn into the syringe with this command (since the syringe has a capacity of 10 mL).

```
pump 2 out=B
```

Injects 2 mL of the contents of the syringe through port B. This command assumes that the syringe contains reagent that was withdrawn with a previous command.

```
pump out=B
```

Injects the entire contents of the syringe through port B. This command assumes that the syringe contains reagents that was withdrawn with a previous command. If the syringe does not contain reagent, this command with do nothing. Note: this command can be used to ensure that the syringe is empty before executing addition code.

```
pump out
```

Similiar to above, however a port is not specified. The syringe pump injects the entire contents of the syring through the currently selected port on the syringe pump.

```
pump 0.5 in out
```

Withdraws 0.5 mL of reagent from the default port and then injects it back through this same port. This command is useful for priming the reagent lines or mixing a solution in the syringe pump.

```
pump 1 in out=C rate=2
```

Withdraws 1 mL of reagent from the currently selected port on the syringe pump and then injects the reagent through port C at a rate of 2 mL/min.

AUX

Description:

This command follows the same structure as the `pump` command, but sends its instructions to the auxiliary pump.

Usage:

Same as the `pump` command

Example:

```
aux 3 in=B out=B rateIn=10 rateOut=2
```

Uses the auxiliary pump to transfer 3 mL of reagent from port A to port B. The reagent is drawn into the syringe at 10 mL/min and is injected out at a rate of 2 mL/min.

WETPUMP

Description:

This command follows the same structure as the `pump` command, but sends its instructions to the water-handling pump.

Usage:

Same as the `pump` command

Example:

```
wetpump 3 in=B out=B rateIn=10 rateOut=2
```

Uses the water-handling pump to transfer 3 mL of reagent from port A to port B. The reagent is drawn into the syringe at 10 mL/min and is injected out at a rate of 2 mL/min.

LOCK

Description:

Used to claim a pump or valve for exclusive access by a particular module. This command is used on machines for which there are several autonomous processes that

313

share a common resource (a common valve or pump). Other processes that try to access the shared valve or pump while it is locked will get a busy signal, and will wait until the resource becomes available. The resource is freed with the UNLOCK command.

<u>Usage:</u>
```
lock #
lock aux
lock wetpump
```

# indicates the number of the valve that should be locked. To use a single lock command to lock many valves, separate each valve name with a space.
aux indicates the auxiliary pump should be locked
wetpump indicates that the water-handling pump should be locked

<u>Example:</u>
```
lock 3 5 aux
```

Locks valve #3, valve #5 and the auxiliary pump for exclusive access by the calling module.

UNLOCK

<u>Description:</u>
Used to release a pump or valve from exclusive access by a particular module (see LOCK command above).

<u>Usage:</u>
```
unlock #
unlock aux
unlock wetpump
unlock all
```

314

# indicates the number of the valve that should be unlocked. To use a single `unlock` command to unlock many valves, separate each valve number with a space.

`aux` indicates the auxiliary pump should be unlocked

`wetpump` indicates that the water-handling pump should be unlocked

`all` indicates that all resources locked by the calling module should be released

Example:

```
unlock 3 5 aux
```

Releases valve #3, valve #5 and the auxiliary pump from exclusive access by the calling module.

```
unlock all
```

Releases all resources from exclusive access by the calling module.