TOTAL SYNTHESIS AND STUDY OF THE ANTI-LIPOPEROXIDANT PERIDININ,
SYNTHESIS OF VERSATILE MIDA BORONATE BUILDING BLOCKS,
AND A GENERAL STRATEGY FOR THE SYNTHESIS OF POLYENES

BY

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DISSERTATION

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ABSTRACT

Taking advantage of the inherent modularity present in the majority of small molecule natural products, we envision that a building block based approach involving the iterative cross-coupling of MIDA boronate containing molecules can be a universal platform for the preparation of small molecules. Guided by this strategy we completed an efficient, flexible, and fully stereocontrolled synthesis of the carotenoid natural product peridinin. This natural product inspired the development of new methodology, including the stereocontrolled Suzuki-Miyaura cross-coupling of haloallenes and the transesterification of boronic esters to MIDA boronates and MIDA boronates to boronic esters. Utilizing this synthetic material, we probed the antilipoperoxidant activity of peridinin in a chemically defined liposome based system and discovered that peridinin is far more potent than the leading carotenoid gold standard astaxanthin. Detailed mechanistic studies revealed that this superior activity is derived from an early quench of chain propagating lipid peroxyl radicals.

Our work with peridinin demonstrated that synthesis is often the rate determining step in studying the function of a molecule. In order to help shift this rate determining step from synthesis to a study of function, we are interested in identifying recurring structural motifs present in small molecule natural products and transforming these motifs into MIDA boronate building blocks. Toward this goal, cis-olefins, 1,1-disubstituted olefins, and the 2-pyridyl moiety are three highly recurring motifs. To gain access to these frameworks, we have developed scalable routes to three MIDA boronate building blocks: (Z)-2-bromovinyl MIDA boronate, 1-bromovinyl MIDA boronate, and 2-pyridyl MIDA boronate. We have demonstrated that these building blocks can be readily functionalized to provide a diverse range of products.

Building on this theme, we developed a systematic approach for identifying additional recurring structural motifs present in natural products and transform them to a collection of MIDA boronate building blocks. As a case study for how this can be achieved, we have identified polyene natural products as an excellent opportunity for testing this concept. We identified a collection of just 12 bifunctional haloalkenyl MIDA boronate building blocks would be required to prepare the polyene motifs found in >75% of all polyene natural products that have ever been isolated. Applying this same approach to other classes of small molecule natural products, pharmaceuticals, and materials has the potential to provide a roadmap towards a universal approach to the synthesis of small molecules and expedite access to their functions.
To Mom, Dad, Elizabeth
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ABBREVIATIONS

Ac                acetate
Boc              \textit{t}-butoxycarbonyl
cat             catechol
CuTc         copper(I) thiophene-2-carboxylate
cy           cyclohexyl
DavePhos       2-Dicyclohexylphosphino-2′-(\textit{N},\textit{N}-dimethylamino)biphenyl
dba         dibenzylideneacetone
DBU           1,8-diazabicyclo[5.4.0]undec-7-ene
DEA           diethanolamine
DMF           \textit{N},\textit{N}-dimethylformamide
DMSO         dimethyl sulfoxide
dppf        1,1-\textit{bis}(diphenylphosphine)ferrocene
dpph \hspace{1cm} 1,6-bis(diphenylphosphino)hexane

dppp \hspace{1cm} 1,5-bis(diphenylphosphino)pentane

EYPC \hspace{1cm} egg yolk phosphatidylcholine

fur \hspace{1cm} furyl

GC \hspace{1cm} capillary gas chromatography

HPLC \hspace{1cm} high performance liquid chromatography

ICC \hspace{1cm} iterative cross-coupling

IPA \hspace{1cm} isopropyl alcohol

LOO• \hspace{1cm} lipid peroxyl radical

LOOH \hspace{1cm} lipid hydroperoxide

LUV \hspace{1cm} large unilamellar vesicle

MIDA \hspace{1cm} N-methyliminodiacetic acid

MPLC \hspace{1cm} medium pressure liquid chromatography

o-tol \hspace{1cm} ortho-tolyl

pin \hspace{1cm} pinacol

POPC \hspace{1cm} 2-Oleoyl-1-palmitoyl-sn-glycero-3-phosphocholine

PUFA = LH \hspace{1cm} polyunsaturated fatty acid

pyr \hspace{1cm} pyridyl

ROS \hspace{1cm} reactive oxygen species
SPhos  2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl

TBAF  tetrabutylammonium fluoride

TBS  tert-butyldimethylsilyl

Tf  trifluoromethanesulfonyl

THF  tetrahydrofuran

TMS  trimethylsilyl

XPhos  2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl
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CHAPTER 1
INTRODUCTION

Eric M. Woerly and Martin D. Burke

1-1 SYNTHESIS OF NATURAL PRODUCTS VIA ITERATIVE PATHWAYS

Most of the molecules found in living systems are highly modular in their constitution. This is because Nature utilizes a common strategy of iterative coupling of bifunctional building blocks to assemble the majority of these compounds. For example, polypeptides are made up of amino acids, oligonucleotides consist of nucleotide monomers, and oligosaccharides are composed of individual sugar units (Figure 1-1). This iterative approach enables the assembly of each of these important classes of biomolecules in a robust fashion, using common starting materials and biosynthetic machinery, and with outstanding flexibility.

Interestingly, Nature also uses the iterative coupling of bifunctional building blocks to biosynthesize most small molecule natural products. For example, malonyl-CoA or methylmalonyl-CoA units are assembled into polyketides, isopentenyl pyrophosphate or dimethylallyl pyrophosphate units are brought together for polyterpenes, malonyl-CoA units are recursively linked to generate fatty acids, amino acids are iteratively united for nonribosomal peptides, and a variety of other classes of small molecules, such as polyphenylpropanoids, are derived from the coupling of building blocks ultimately derived from shikimic acid (Figure 1-2).
The consequence of this shared biosynthetic logic is that, like their polypeptide, oligonucleotides, and oligosaccharide counterparts, most small molecule natural products are highly modular in their constitution.

![Diagrams of various building blocks](image)

**Figure 1-2.** Polyketides, polyterpenes, fatty acids, nonribosomal peptides, and polyphenylpropanoids are similarly derived from the iterative coupling of bifunctional building blocks.

Nature’s iterative coupling strategy has been successfully mimicked in the laboratory in a general way for the synthetic preparation of polypeptides, oligonucleotides, and oligosaccharides. In each case, a suitably protected form of a bifunctional building block is coupled to the growing end of the chain and a deprotection sequence is then executed (Figure 1-3). Such cycles of coupling and deprotection are iterated until the desired molecule is synthesized.
Figure 1-3. A general strategy for the iterative synthesis of small molecule natural products.

For example, in the solid-phase synthesis of polypeptides the C-terminus of a growing polypeptide chain is covalently linked to a solid support. Amino acid building blocks having their N-terminus protected, frequently as the Fmoc or Boc derivative, are then coupled to the resin supported peptide. A deprotection sequence reveals a free N-terminus, enabling another iteration of this process (Figure 1-4, left). Similar procedures have been developed for the efficient synthesis of oligonucleotides (Figure 1-4, middle) and oligosaccharides (Figure 1-4, right). Importantly, as in Nature, these sequences allow for the controlled construction of complex molecular frameworks. Due to the powerfully simple nature of this iterative coupling approach, these processes are now increasingly performed in a fully automated fashion. With peptides and oligonucleotides, such automation has made it possible for nonchemists to routinely prepare these types of compounds for a wide range of applications. As a result, the function, not the synthesis, of these molecules is the main focus of research in these areas.

Figure 1-4. Strategies for the iterative synthesis of peptides, nucleotides, and saccharides.
In stark contrast, it is typical for a synthetic chemist to develop a unique, highly customized strategy for each small molecule that is targeted for preparation in the laboratory. As a result, the synthesis of small molecules remains a relatively complex, unsystematized, and inflexible process that is practiced almost exclusively by highly trained specialists. However, the inherent modularity of many small molecule targets suggests that a unified strategy for their construction through the iterative assembly of bifunctional building blocks may exist. Taking advantage of the common structural motifs that appear in certain polyketide, polyterpene, fatty acid, nonribosomal peptide, and polyphenylpropanoid frameworks, customized iterative strategies have been developed for the synthesis of these five classes of small molecule natural products. This chapter will highlight classic contributions in each of these areas, as well as discuss recent advancements seeking to develop a common, general approach for the construction of most small molecules via the iterative cross-coupling of bifunctional haloboronic acids masked as the corresponding N-methyliminodiacetic acid (MIDA) boronates. This introductory chapter will provide background for the projects described in subsequent chapters, specifically the use of the MIDA boronate platform to complete a total synthesis of the carotenoid natural product peridinin, the preparation and utility of a number of MIDA boronate building blocks, and the development of a general strategy for the synthesis of polyenes. Such approaches have the potential to help shift the rate limiting step in small molecule science from synthesizing these molecules to understanding and maximally harnessing their functional potential.

1-2 ITERATIVE STRATEGIES FOR THE SYNTHESIS OF POLYKETIDE NATURAL PRODUCTS

Polyketide based small molecules are highly abundant in Nature. The structures of these compounds include both cyclic and acyclic frameworks (Figure 1-5). A number of polyketide based natural products have been identified as important pharmaceutical agents, including antibiotics, antifungals, chemotherapies, and immunosuppressants. As a result, the efficient and modular synthesis of polyketide targets is highly desirable. One approach to enable such a goal is to identify motifs that are highly conserved amongst numerous polyketides and use these motifs as building blocks around which the target can be constructed. Developing synthetic strategies to gain access to these building blocks, and demonstrating that these strategies can be utilized in
The preparation of polyketide natural products is also an important consideration. A common substructure that is highly recurring in polyketide natural products is the stereotetrad, consisting of four contiguous stereogenic centers in any diastereomeric combination. Example natural products containing the stereotetrad unit are brasilinolide A, erythromycin A, and pironetin (Figure 1-5). Numerous strategies have been developed for the synthesis of stereotetrad. Of particular interest are methodologies that allow for the iterative assembly of these building blocks, reminiscent of the approach nature takes to the preparation of polyketide natural products. Herein, the contributions of Evans and Paterson are highlighted for the construction of polypropionate units using iterative, aldol-based approaches and the application toward the synthesis of natural and unnatural polyketides.

![Figure 1-5. Structures of representative cyclic and acyclic polyketide natural products.](image)

Auxiliary based aldol reactions represent a powerful method for the construction of carbon-carbon bonds in a stereocontrolled fashion. The Evans aldol reaction utilizes an oxazolidinone based chiral auxiliary to provide syn aldol products with outstanding levels of diastereoselectivity. The absolute stereochemistry of the product is controlled by the identity of the chiral auxiliary. Commonly employed auxiliaries are derived from (S)-valinol and (1S,2R)-norephedrine. Moreover, the Evans aldol reaction has the capacity to be performed in an iterative fashion to provide access to polypropionate frameworks with outstanding levels of stereocontrol (Figure 1-6). Specifically, enolates can serve as bifunctional building blocks in this iterative aldol cycle. These building blocks have two differentiated termini; a reactive, nucleophilic enolate and an electrophilic aldehyde masked in the acid oxidation state by the chiral auxiliary.
In such an iterative cycle, first, reaction of the enolate with an aldehyde provides the aldol product. Second, reduction of the auxiliary bearing terminus, typically with protection of the newly formed hydroxyl group, can regenerate the aldehyde functionality. The newly generated aldehyde can then serve as a substrate for subsequent rounds of aldol addition reactions.

Figure 1-6. Iterative Evans aldol reaction.

Reggelin and coworkers have demonstrated the synthesis of polyketide frameworks using iterative Evans aldol reactions on a solid support. Specifically, N-propionyloxazolidinone 1.1 was converted to the Z-enolate 1.2 by treating with Bu2BOTf and Et3N. Then, reaction with a resin bound aldehyde 1.3 provided a solid supported aldol product 1.4 (Scheme 1-1). Cleavage of the oxazolidinone and conversion to a thioester 1.5 provided an intermediate that could be readily protected and converted to a new aldehyde 1.6. The newly generated aldehyde then served as a substrate for subsequent rounds of aldol addition reactions. Using this method, complex polyketide 1.7 was prepared in highly diastereomerically enriched form.

Scheme 1-1. Solid supported iterative Evans aldol reaction.
While the above example highlights the preparation of \textit{syn}-aldol products through the Evans aldol reaction, Evans and coworkers have also reported the preparation of \textit{anti}-aldol products using the same chiral auxiliary approach.\textsuperscript{19} In this method, catalytic amounts of MgCl$_2$ in the presence of Et$_3$N and chlorotrimethylsilane provided the \textit{anti}-aldol products in high diastereoselectivity. As a result, both \textit{syn}- and \textit{anti}-aldol products are accessible from the same set of \textit{N}-acyloxazolidinones. The products generated in the Evans aldol reaction are highly versatile reagents in small molecule synthesis. Following the aldol reaction, the chiral auxiliary can be removed under a variety of conditions, including hydrolysis, transesterification, transamination, or reduction.\textsuperscript{20}

Several modifications to the Evans aldol reaction have been reported.\textsuperscript{21} One such modification is the thiazolidinethione based aldol reaction developed by Crimmins and coworkers.\textsuperscript{22} In comparison to an oxazolidinone, the thiazolidinethione group can easily be removed under mild conditions, allowing facile regeneration of the aldehyde functionality in one step, thus further enabling iterative coupling cycles. An additional advancement is that this method allows for the preparation of both “Evans” or “non-Evans” \textit{syn} aldol products from a common acyloxazolidinethione precursor. Specifically, a titanium derived enolate of an acyloxazolidinethione can be used to access these products (Scheme 1-2). This is accomplished by choosing the correct stoichiometry of the amine base and titanium reagent to obtain the desired product.\textsuperscript{23} For example, acyloxazolidinethione \textbf{1.8} can yield the “Evans” \textit{syn} product \textbf{1.9} using 1.0 equivalents of TiCl$_4$ and 2.5 equivalents of (-)-sparteine. In contrast, the “non-Evans” \textit{syn} product \textbf{1.10} is obtained from the same starting material by using 2.0 equivalents of TiCl$_4$ and 1.0 equivalents of (-)-sparteine. This feature enables the synthesis of a diverse range of aldol products from a common auxiliary.

\begin{center} Scheme 1-2. Crimmins thiazolidinethione aldol reaction. \end{center}
Moreover, the modified Evans aldol reactions can also be utilized in an iterative fashion for the construction of polyketide fragments. Crimmins and coworkers utilized a combination of the “Evans” and “non-Evans” syn titanium enolate derived acyloxazolidinethione aldol reactions described above to complete a formal synthesis of the polyketide natural product 6-deoxyerythronolide B 1.11 (Scheme 1-3).24 A “non-Evans” syn aldol reaction between acyloxazolidinethione 1.12 and propionaldehyde 1.13 provided aldol product 1.14. Protection of the resulting alcohol as the silyl ether and removal of the chiral auxiliary by reductive cleavage provided aldehyde 1.15. Another iteration of the aldol reaction cycle in the form of an “Evans” syn aldol reaction was then completed between 1.12 and 1.15, providing product 1.16. Protection of the resulting alcohol and cleavage of the auxiliary provided aldehyde 1.17. This aldehyde was then reacted with 1.12 in a “non-Evans” syn aldol reaction to provide 1.18. This intermediate was further elaborated to 1.11. As demonstrated by these examples, iteration of auxiliary based aldol reactions can be harnessed to provide rapid access to the stereochemically rich polyketide motifs commonly found in many natural and unnatural polyketide frameworks.


As described above, the iterative Evans aldol reaction consists of a diastereoselective aldol reaction followed by auxiliary cleavage and regeneration of an aldehyde for repetition of the cycle. An alternative approach to the iteration of this reaction is to perform an extended Evans aldol reaction. In particular, oxidation of β-alcohol 1.19 forms β-keto imide 1.20,
providing a starting material for the efficient construction of various polypropionate frameworks. Enolization of \textbf{1.20} under different conditions enables the formation of diastereomeric products.\textsuperscript{25} For example, the enolate generated from treating \textbf{1.20} with Sn(OTf)\textsubscript{2} and Et\textsubscript{3}N can be trapped with propionaldehyde \textbf{1.13} to form the \textit{anti-syn} product \textbf{1.21} (Scheme 1-4). In contrast, enolization of \textbf{1.20} with TiCl\textsubscript{4} and \textsuperscript{3}Pr\textsubscript{2}NEt and trapping with \textbf{1.13} provides the \textit{syn-syn} product \textbf{1.22}. Additionally, boron reagents can be utilized to mediate the aldol reaction. The generation of a Z- or E-boron enolate from the corresponding ketone starting material is dependent on the identity of the electrophilic boron reagent and amine base. As demonstrated in the preparation of \textbf{1.2} and \textbf{1.19}, less sterically bulky ligands (i.e. \textit{n}-butyl) on the boron reagent combined with a good leaving group (i.e. OTf) and a hindered amine base (i.e. \textsuperscript{3}Pr\textsubscript{2}NEt) provides the Z-enolate and the \textit{syn} aldol product. In contrast, sterically bulky ligands (i.e. cyclohexyl) on the boron reagent combined with a poor leaving group on boron (i.e. Cl) and a small amine base (i.e. Et\textsubscript{3}N) provides access to the \textit{E}-enolate.\textsuperscript{26} Enolization of \textbf{1.20} under these conditions and trapping with \textbf{1.13} provides the \textit{anti-anti} product \textbf{1.23}.

![Scheme 1-4. The extended Evans aldol reaction.](image)

Furthermore, 1,3-\textit{syn} and 1,3-\textit{anti} diols can be prepared from the extended Evans aldol products \textbf{1.21}-\textbf{1.23}. For example, reduction of \textbf{1.21} with Zn(BH\textsubscript{4})\textsubscript{2}\textsuperscript{27} or LiBH\textsubscript{4}\textsuperscript{28} provides the 1,3-\textit{syn} diol product \textbf{1.24} (Scheme 1-5). In contrast, reduction with Me\textsubscript{4}NBH(OAc)\textsubscript{3} provides the 1,3-\textit{anti} diol product \textbf{1.25}.\textsuperscript{29}
Evans and Ng employed this methodology to complete a total synthesis of rutamycin B 1.26 (Scheme 1-6). In particular, an extended Evans aldol reaction between aldehyde 1.27 and 1.28 provided product 1.29. A reduction of this β-hydroxy ketone with NaBH(OAc)₃ provided anti-diol 1.30, which was further elaborated to 1.26.

As demonstrated by these examples, removable auxiliary-based aldol reactions represent powerful methods for the regio-, diastereo-, and enantioselective construction of new carbon-carbon bonds. A complementary approach is to perform an aldol reaction in which the auxiliary becomes incorporated into the desired product. The Paterson aldol reaction, which involves the boron-mediated aldol reaction between an aldehyde and a chiral ethyl ketone containing a stereogenic center bearing a methyl group, which is a very common motif in polyketide natural products, is also useful for the synthesis of β-hydroxy carbonyl compounds. Iterative applications of the Paterson aldol reaction have been used to prepare many natural and unnatural polyketide frameworks. In general, a bifunctional building block consisting of a ketone and a masked aldehyde (as a benzyl ether) are reacted with an aldehyde under aldol reaction conditions.
(Figure 1-7). Removal of the benzyl ether protecting group and oxidation of the resulting alcohol regenerates an aldehyde for another iteration of the cycle.

**Figure 1-7.** The iterative Paterson aldol reaction.

As with the Evans aldol reaction, the generation of Z- or E-boron enolates from the corresponding ketone starting material allows access to syn and anti aldol products, respectively. In addition, chiral ligands on boron (i.e. Ipc) can be used to differentiate the diastereotopic faces of the enolate.\(^3\) Furthermore, as described above, reductions of the ketones in the resulting products provides efficient access to the stereotetrad units commonly found in polyketide natural products. These points are highlighted in the Paterson aldol reactions of ketone 1.31 (Scheme 1-7).

**Scheme 1-7.** The Paterson aldol reaction.

Paterson and coworkers have prepared similar 1,3-polyol motifs on a solid support in an iterative fashion.\(^3\) In this process, E-boron enolate 1.33, generated from ketone 1.32, is reacted with resin bound aldehyde 1.34 in a Paterson aldol reaction to provide 1.35 (Scheme 1-8). A syn
reduction of the ketone, protection of the resulting diol, and PMB protecting group removal yields aldehyde 1.36, which is ready for another iteration of the aldol reaction cycle. A second Paterson aldol reaction between 1.36 and 1.33 provides 1.37. In a similar manner, a syn reduction provides 1.38, which contains 8 contiguous stereogenic centers. In theory, protection of this newly formed diol and regeneration of the aldehyde functionality could enable additional iterations of this cycle. This polypropionate framework, containing all of the hydroxyls in an all-syn relationship and a 1,3-anti methylation pattern, represents a linear, unnatural polyketide based motif. Paterson and coworkers have also prepared these motifs in an iterative fashion using solution-phase techniques.\textsuperscript{36}

\begin{center}
\textbf{Scheme 1-8.} Iterative solid phase Paterson aldol reactions.
\end{center}

In addition to the oxygenated motif described above for polyketide natural products (polypropionate), deoxypropionate natural products are also commonly found, such as (−)-dolciculide, vittatalactone, and ionomycin (Figure 1-5).\textsuperscript{37} Biosynthetically, these deoxygenated compounds are derived from the same bifunctional building blocks as their polypropionate counterparts, either malonate or methylmalonate units. In this process, a keto-reductase reduces a ketone on the growing propionate chain to a β-hydroxy group.\textsuperscript{38} Additional condensation reactions on this substrate results in polypropionate products. In contrast, if a molecule of water is eliminated from the β-hydroxy substrate an α,β-unsaturated ester results. Reduction of this olefin gives a saturated compound and provides the framework for deoxypropionate natural products.

Several synthetic methods have been developed to prepare deoxypropionate motifs in the laboratory.\textsuperscript{39} One such reaction, the Myers asymmetric alkylation, involves the alkylation of N-acylated pseudoephedrine to obtain, upon removal of the pseudoephedrine group,
enantiomerically enriched α-alkylated aldehydes, ketones, carboxylic acids, and alcohols.\(^4\) A variety of alkylating agents can be used in the reaction, including allylic, benzylic, and alkyl halides. Moreover, Myers and coworkers report that the asymmetric alkylation can be conducted in an iterative fashion (Figure 1-8).\(^4\) In this process, the N-acylated pseudoephedrine serves as a bifunctional building block. After alkylation with a halide, the chiral auxiliary can be cleaved to reveal an alcohol. Conversion of the alcohol to a halide regenerates an alkylating agent for a second iteration of the process.

![Figure 1-8. Iterative Myers asymmetric alkylations.](image)

In a specific example, Myers and coworkers have completed the synthesis of diastereomeric 1,3,5,\(n\)-(odd)-polyalkyl-substituted frameworks.\(^4\) Alkylation of N-acylated pseudoephedrine \(1.39\) followed by auxiliary cleavage and conversion of the resulting alcohol to a primary iodide generated \(1.40\) (Scheme 1-9). Alkylation of \(1.39\) with \(1.40\), followed by auxiliary cleavage and iodide formation provided an alkylating agent to be used in the completion of a third iteration of this cycle to generate \(1.41\). This same process was followed for the preparation of \(1.42, 1.43,\) and \(1.44\).
This powerful method has been utilized in an iterative fashion in the synthesis of deoxypropionate natural products. One example is the synthesis of (-)-borrelidin 1.45 by Theodorakis and coworkers. In this synthesis, alkyl iodide 1.46 was used to alkylate the enolate of (+)-pseudoephedrine 1.39 (Scheme 1-10). The auxiliary was cleaved and the resulting alcohol was converted to alkyl iodide 1.47, which served as an alkylating agent for the next iteration of the cycle. A third Myers asymmetric alkylation provided amide 1.48, which was further elaborated to 1.45.
The above examples highlight how one reaction (i.e. the Evans aldol, Paterson aldol, or Myers alkylation) can be conducted in an iterative fashion for the preparation of natural and unnatural polypropionate frameworks. In contrast to this approach, a powerful strategy for the preparation of complex molecular frameworks is to use a combination of these methods in an iterative fashion. White and coworkers took such an approach in their total synthesis of 6-deoxyerythronolide B 1.11. A Myers alkylation of ent-1.39 followed by auxiliary cleavage and oxidation to an aldehyde provides a substrate for an Evans aldol reaction with 1.49 (Scheme 1-11). Cleavage of the Evans auxiliary and conversion to an aldehyde regenerated the required functionality for a second Evans aldol reaction with 1.50. A final cycle of auxiliary cleavage and conversion to an alkyl iodide provides an alkylating agent for reaction with ent-1.39. Following auxiliary cleavage, this complex fragment was macrocyclized via C-H activation and then elaborated to 1.11 to complete the most efficient synthesis to date of this natural product.

Polyketide-derived polyene natural products, such as etnangien, roxaticin, and ansatrienine A (Figure 1-5) also represent a class of compounds that have been prepared using iterative methods.45 Several strategies have been developed to synthesize the polyene portions of such natural products, including iterative olefination reactions and iterative transition metal based reactions. One example of this concept is the iteration of the Horner-Wadsworth-Emmons reaction (Figure 1-9).
The iterative Horner-Wadsworth-Emmons strategy was used by Nicolaou and coworkers to complete a total synthesis of amphotericin B 1.51 (Scheme 1-12). In this process, aldehyde 1.52 was condensed with phosphonate 1.53 to provide triene 1.54. Reduction of the ester to an alcohol, followed by oxidation, provided aldehyde 1.55. A second iteration of this cycle with another equivalent of 1.53 provided hexaene 1.56, which was further elaborated to 1.51.

A second example is the iteration of the Wittig olefination reaction, which is the reaction of an aldehyde or ketone with a phosphonium ylide to form an alkene. In this process, a bifunctional building block consisting of a phosphonium ylide and ester enables the iteration of this reaction (Figure 1-10). After formation of the alkene, the ester functionality can be reduced, regenerating an aldehyde for another reaction cycle.
In a specific example, Pattenden and Patel have used this iterative Wittig approach to complete a total synthesis of the polyketide derived polyene natural product citreomontanin 1.57 (Scheme 1-13).\textsuperscript{47} Reaction of aldehyde 1.58 with ylide 1.59 forms diene 1.60. Reduction of the ester with lithium aluminum hydride and oxidation of the resulting alcohol with manganese oxide yields 1.61, regenerating an aldehyde for iteration of this process. Reaction with a second equivalent of 1.59 provides triene 1.62. A reduction/oxidation sequence produces aldehyde 1.63. A final Wittig reaction with 1.64 completed the synthesis of 1.57.

**Scheme 1-13.** Synthesis of polyketide-derived polyene natural product citreomontanin.

Iterative transition metal mediated reactions are an important class of reactions for both the preparation of these natural products, as well as the synthesis of polyterpene natural products. This class of reactions will be explored in the polyterpene natural product synthesis section below.
In addition to the iterative strategies developed for the polypropionate and deoxypropionate natural products described above, several iterative strategies have also been developed for the preparation of other polyketide natural products. Notably, several iterative methods have been reported for the synthesis of ladder polycyclic ether fragments, which is a motif present in a number of highly potent polyketides. Additionally, the coupling of iterative synthesis to other pathways is a powerful strategy for the installation of molecular complexity in a rapid, efficient manner. A report by Wulff and coworkers uses this approach of marrying iterative synthesis to cascading radical cyclization pathways for the preparation of polycyclic ethers. Regardless of the products that each of these strategies seeks to make, they are united by a common approach of bringing together bifunctional building blocks in an iterative fashion.

1-3 ITERATIVE STRATEGIES FOR THE SYNTHESIS OF POLYTERPENE NATURAL PRODUCTS

Polyterpene natural products are common components of living systems and contribute to vital higher-order functions, including structural support in cell membranes and light harvesting roles in bacteria. Polyterpene natural products also serve important roles as medicines and biological probes. While the terpenoids are one of the most structurally varied classes of natural products (Figure 1-11), they are united by a common biosynthetic origin; polyterpenes are biosynthesized from isoprene based building blocks that are brought together in an iterative fashion. In some cases, the inherent modularity that results from this biosynthetic origin is quite evident. In other cases, polycyclizations of initial linear polyunsaturated precursors lead to the rapid assembly of complex polycyclic cores. Synthetic access to these motifs has enabled a better understanding of the role of polyterpenes in living systems. Several strategies have been developed to gain access to these compounds, taking advantage of an iterative-based approach to efficiently and rapidly build up molecular complexity. Herein we highlight the contributions of Keinan, Negishi, and Katsumura for the construction of linear and cyclic polyterpene units using iterative approaches and the application toward the synthesis of natural products.
Transition metal mediated coupling reactions provide a rapid and efficient means for the construction of new carbon-carbon bonds. In addition to applications to the synthesis of polyterpene natural products, such reactions have found use in the synthesis of polyketide-derived polyene natural products (introduced above) and organic based materials. Applications to the preparation of organic based materials is outside the scope of this chapter, however reviews are available on the topic of iterative methods for the preparation of organic based materials.\textsuperscript{52,53,54}

One challenge to the synthesis of polyene containing natural products is maintaining the desired stereochemical relationship of the olefins throughout the course of the reaction sequence. The use of selective reactions and mild reagents is one strategy to accomplish such a goal. Using such an approach, Keinan and coworkers developed an early strategy for the iterative synthesis of polyterpene natural products.\textsuperscript{55} This strategy involves the regio- and stereoselective palladium catalyzed coupling of bifunctional building blocks in an iterative fashion (Figure 1-12). In general, geraniol derived bifunctional building blocks containing nucleophilic and masked electrophilic termini are utilized. The nucleophilic terminus consists of a methine group bearing two electron withdrawing groups, namely methoxycarbonyl and tolylsulfonyl substituents. The electrophilic terminus consists of an allylic alcohol that can be activated as a methyl carbonate leaving group. In the key bond forming process, π-allylpalladium formation from the allylic methyl carbonate followed by addition of the activated methine provides the coupled product. Activation of the pendant allyl alcohol allows for a second iteration of this process, providing extended intermediates. Removal of the activating groups provides the polyterpene framework.
Keinan and coworkers utilized this methodology to complete a total synthesis of coenzyme Q\textsubscript{10} \textbf{1.65}, an important nutritional supplement (Scheme 1-14). Coupling between allyl methyl carbonate \textbf{1.66} and bifunctional building block \textbf{1.67} provided allyl alcohol \textbf{1.68}. Activation of this substrate with methyl chloroformate and diethylaniline, followed by a second coupling sequence provided advanced intermediate \textbf{1.69}. Another such sequence, followed by activation and coupling with a capping group \textbf{1.70} provided \textbf{1.71}, the precursor to coenzyme Q\textsubscript{10}. Removal of the activating groups and oxidation of the aromatic ring to provide the quinone completed the synthesis of \textbf{1.65}. Specifically, the methoxycarbonyl substituent was cleaved under the action of 4-aminothiophenol and cesium carbonate in DMF\textsuperscript{56} and the tolylsulfonyl group was removed using lithium triethylborohydride and a palladium catalyst in THF\textsuperscript{57}.

\textbf{Scheme 1-14.} Keinan’s synthesis of coenzyme Q\textsubscript{10}.
Negishi and coworkers have also completed a total synthesis of coenzyme Q$_{10}$ using transition metal mediated iterative synthesis.$^{58}$ As an alternative to Keinan’s approach, activating groups were not required for their synthesis. In Negishi’s approach, (E)-1,4-diiodo-2-methyl-1-butene serves as a bifunctional building block (Figure 1-13). After a palladium mediated cross-coupling between the vinyl iodide terminus and a primary zinc halide species, the primary iodide is converted to a zinc halide to enable another iteration of the process. Through this sequence, a stereocontrolled total synthesis of coenzyme Q$_{10}$ was completed.

![Figure 1-13. Negishi’s iterative transition metal mediated coupling cycle.](image)

Negish and coworkers have also developed methodology based on the zirconium catalyzed carboalumination of alkynes combined with a palladium and zinc catalyzed cross-coupling reaction to provide the highly stereoselective synthesis of both symmetrical and unsymmetrical carotenoids.$^{59}$ This methodology can be conducted in an iterative fashion (Figure 1-14). Bifunctional building blocks consisting of a vinyl bromide and a protected alkyne are coupled to vinyl aluminum intermediates. Removal of the alkyne protecting group reveals a terminal alkyne, regenerating the functionality needed for another carboalumination/cross-coupling cycle.
An example of this process is the synthesis of γ-carotene 1.72 (Scheme 1-15). This unsymmetrical carotenoid was prepared in a convergent manner from vinyl bromide 1.73 and vinyl alumin ate 1.74. Each of these building blocks was prepared through an iterative sequence of carboalumination and cross-coupling reactions. Specifically, a sequence consisting of a zirconium-catalyzed carboalumination of alkyne 1.75, a palladium and zinc catalyzed cross-coupling with enyne 1.76, and alkyne deprotection provided polyen yne 1.77. A second iteration of this sequence provided intermediate 1.78, which upon carboalumination provided building block 1.74. In a similar manner, 1.73 was prepared through a series of iterative carboalumination and cross-coupling reactions. A final palladium and zinc catalyzed cross-coupling between 1.73 and 1.74 completed the synthesis of γ-carotene. Importantly, the highly stereoselective carboalumination reaction and stereospecific cross-coupling reaction provided this material in >99% stereoisomeric purity.

The methods highlighted above by Keinan and Negishi provide efficient and rapid access to linear polyterpene derived frameworks through the iterative assembly of bifunctional building blocks. Some potential challenges associated with these specific transition metal mediated methods include air sensitivity and unstable building blocks/intermediates.

Another interesting class of polyterpene natural products is cyclic terpenoids. Biosynthetically, these molecules are prepared through enzyme mediated cyclizations of the linear precursor. Synthetically, methods have been developed to convert linear polyterpene frameworks into cyclized products. However, an alternative strategy is the direct synthesis of these cyclic frameworks through the iteration of a defined set of reactions. Katsumura and coworkers have developed such an approach to prepare a series of 1,1,5-trimethyl decalin based polyterpene natural products. Specifically, a bromination-condensation-cyclization sequence of an allylic alcohol starting material provides an ester intermediate (Figure 1-15). Phosphonate formation, methylation, and ester reduction completes the sequence, regenerating the alcohol functionality for another iteration of the process.

![Figure 1-15. Iterative synthesis of cyclic terpenoids.](image)

Katsumura and coworkers have used this iterative process to complete the synthesis of the biologically active target scalarenedial. Starting from cyclogeraniol, a three step sequence involving a bromination, condensation, and cyclization reaction provided (Scheme 1-16). This bicycle then underwent a three step sequence of phosphonate formation, methylation, and ester reduction to convert to allyl alcohol. A second iteration of the bromination,
condensation, and cyclization sequence provided tricycle 1.82. Conversion of ester 1.82 to allyl alcohol 1.83, followed by a final iteration of the cyclization sequence provided 1.84, which serves as a precursor to scalarenedial.

Scheme 1-16. Iterative pathway for the synthesis of polycyclic terpenoids.

The methods developed by Keinan, Negishi, and Katsumura highlight the idea that iterative synthesis provides an effective strategy for the synthesis of a variety of polyterpene based motifs, including repeating linear polyprenoids, polyenes, and polycyclic frameworks. Collectively, these methods demonstrate that taking advantage of the inherent modularity of small molecule natural products through the power of an iterative synthetic approach can provide rapid and efficient access to a variety of molecules.

1-4 ITERATIVE STRATEGIES FOR THE SYNTHESIS OF FATTY ACID NATURAL PRODUCTS

Fatty acid natural products serve important roles in living systems, including modulation of membrane fluidity, serving as chemical energy storage units, and participation in cell signaling pathways. While many structurally diverse fatty acid natural products have been discovered (Figure 1-16), those containing eighteen carbons are the most commonly occurring. Strategies have been developed to synthesize fatty acid natural products, including several iterative-based approaches. Herein we highlight the contributions of Kim and Feringa for the construction of fatty acids in an iterative fashion.
Kim and coworkers have developed an iterative strategy for the synthesis of unsymmetrical polyyynes. In this process, a trialkylsilylacetylene serves as a bifunctional building block (Figure 1-17). Cross-coupling of the terminal alkyne with a bromoalkyne, followed by a desilylative bromination enables iteration of this reaction sequence.

Kim and coworkers have used this iterative method to complete a total synthesis of the fatty acid natural product 15,16-dihydrominquartynoic acid 1.85 (Scheme 1-17). Specifically, coupling between bromoalkyne 1.86 and TIPS-acetylene 1.87 provided diyne 1.88. A desilylative bromination afforded bromodiyne 1.89. A second iteration of this process provided triyne 1.90, which was further elaborated to 1.85.
1,3-polymethyl arrays are also present in fatty acid derived natural products. Feringa and coworkers have developed an iterative strategy to synthesize this structural motif. An iterative reaction sequence involving a stereoselective conjugate addition, palladium catalyzed reduction, and Wittig reaction regenerates the α,β-unsaturated thioester required for another iteration of this process (Figure 1-18).

Feringa and coworkers have used this iterative approach to complete a total synthesis of the fatty acid natural product mycocerosic acid 1.91 (Scheme 1-18). Enantioselective methylation of unsaturated thioester 1.92 provided 1.93. Reduction of the thioester to an aldehyde followed by a Wittig reaction with ylide 1.94 provided unsaturated thioester 1.95. Two additional iterations of this cycle furnished 1.96, which was further elaborated to mycocerosic acid.
1-5 ITERATIVE STRATEGIES FOR THE SYNTHESIS OF OTHER NATURAL PRODUCTS

In addition to the synthesis of polyketide, polyterpene, and fatty acid derived natural products via iterative strategies, nonribosomal peptide, hybrid polyketide/nonribosomal peptide, and several other classes of natural products have also been prepared using iterative approaches. This section briefly provides examples from each of these areas.

Similar to peptide based natural products, nonribosomal peptide derived natural products utilize peptide bonds to link unnatural peptide residues. As a result, the iterative peptide synthesis strategy (Figure 1-4, left) can be applied to the preparation of these compounds. An example of this can be found in Wipf and coworkers synthesis of \(N^{14}\)-desacetoxytubulysin H \(1.97\) (Scheme 1-19).\(^{65}\) \(N\)-deprotection of unnatural amino acid building block \(1.98\) followed by coupling with \(1.99\) afforded dipeptide \(1.100\). A subsequent \(N\)-deprotection regenerated the amine functionality required for a second iteration of this process. Coupling with Fmoc protected \(1.101\) provided tripeptide \(1.102\), which was further elaborated to \(1.97\).

Hybrid polyketide/nonribosomal peptide derived natural products, such as phoboxazole B \(1.103\), have been prepared using iterative strategies. Zhou, Lin, and coworkers used iterative crotylation reactions (Figure 1-19) to prepare the tetrahydropyrane-oxazole segment of \(1.103\).
(Scheme 1-20). Specifically, crotyl addition of boronic ester 1.105 to aldehyde 1.104 provided alcohol 1.106. Protection of the alcohol and ozonolysis regenerated the aldehyde functionality required for a second iteration of this process. Crotylation of 1.107 provided intermediate 1.108, which was a fragment in the synthesis of 1.103.

**Figure 1-19.** Iterative crotylation reactions.

**Scheme 1-20.** Synthesis of tetrahydropyrane-oxazole segment of phorboxazole B.

1-6.1 MIDA BORONATES: A POTENTIALLY GENERAL PLATFORM FOR THE ITERATIVE SYNTHESIS OF SMALL MOLECULE NATURAL PRODUCTS

As described above, many customized strategies and methods have been developed to access specific classes of natural products via the iterative coupling of bifunctional building blocks. It is intriguing to consider the possibility that a single platform could prove to be general for accessing many different classes of small molecules. Inspired by the building block based approach to the laboratory synthesis of polypeptides, oligonucleotides, and oligosaccharides, a
strategy for the construction of small molecules in the laboratory by the iterative coupling of bifunctional building blocks is attractive. Toward this goal, metal-mediated cross-coupling reactions provide a mild and controlled way to form new carbon-carbon and carbon-heteroatom bonds that are characteristically found in small molecules. Harnessing this synthetic potential, an idealized form of such an “Iterative Cross-Coupling” (ICC) strategy can be envisioned. In this approach, building blocks having all of the required functional groups preinstalled in the correct oxidation state and with the desired stereochemical relationships are iteratively united using only stereospecific cross-coupling reactions. In addition to being simple, efficient, and potentially amenable to automation, the modularity of this approach makes it inherently well-suited for generating diverse collections of compounds simply by substituting modified building blocks into the same synthesis pathway. Encouraging progress toward such an ICC strategy was reported by Moore and coworkers specifically for the iterative assembly of phenylacetylene oligomers. Also, contemporaneous with the results presented below, Suginome and coworkers reported the use of iterative cross-coupling reactions for the preparation of oligoarenes.

In this regard, N-methyliminodiacetic acid (MIDA) boronates also represent a highly promising platform for this type of synthesis strategy (Figure 1-20). These building blocks are remarkably convenient to prepare, analyze, purify, and store. The MIDA boronate functional group is inert to anhydrous cross-coupling conditions, yet can be readily transformed into a fully reactive boronic acid or ester using exceptionally mild conditions. As first introduced here and elaborated upon in subsequent chapters, these features have enabled the simple, efficient, and highly flexible synthesis of a wide range of small molecules, including both pharmaceuticals and complex natural products.
1-6.2 DEVELOPMENT OF ICC

The routinely automated process of iterative peptide coupling represents an inspiring benchmark for a general strategy for making small molecules in the laboratory. Peptides are often quite complex in structure. They have many different functional groups with varied oxidation states and contain a large number of stereogenic centers. However, the synthesis of many peptides simply involves the use of a single reaction to iteratively assemble a collection of amino acid building blocks having all of the required functional groups and stereochemistry preinstalled.

With the goal of developing a process for the laboratory construction of small molecules, an analogous strategy was envisioned by my colleague Dr. Eric Gillis using the Suzuki-Miyaura reaction\textsuperscript{71} and the ICC of bifunctional “haloboronic acids”.\textsuperscript{72} To avoid random oligomerization of a haloboronic acid under cross-coupling conditions, it is necessary to reversibly attenuate the reactivity of one end of this type of bifunctional reagent, in analogy to the use of a protective group to control the reactivity of the amine terminus of an amino acid.\textsuperscript{73} Toward this goal, controlling the reactivity of the boronic acid functional group is one possible strategy.

It is hypothesized that a vacant and Lewis acidic boron p orbital is required for transmetalation of a boronic acid under Suzuki-Miyaura cross-coupling conditions.\textsuperscript{74} Consistent with this, complexation of boronic acids with electron-donating, Lewis basic ligands is known to attenuate their reactivity towards cross-coupling.\textsuperscript{75} This reactivity attenuation can be attributed to the decreased Lewis acidity of the boron p orbital as a result of conjugation with the lone pairs of the ligand heteroatoms. This approach has been utilized with a variety of divalent heteroatomic
ligands, including diols and diamines. However, there is an inherent limitation with this approach that precludes its general utilization for complex small-molecule synthesis. Specifically, conjugation between the heteroatom lone pairs and boron p orbital produces relatively strong boron-heteroatom bonds, creating both a kinetic and thermodynamic barrier for bond cleavage. As a result, removing this type of ligand to regenerate the boronic acid typically requires harsh conditions and/or reagents to destroy the free divalent ligand after to prevent re-complexation. These types of conditions can be problematic in the context of small-molecule synthesis.

Recognizing the inherent limitations of this approach, an alternative strategy was envisioned. Specifically, given that the boron p orbital is predicted to be critical for the transmetalation of a boronic acid, it was hypothesized that rehybridization of the boron atom from sp² to sp³ via complexation with a trivalent heteroatomic ligand would eliminate its reactivity towards cross-coupling. Furthermore, it is known that boron-heteroatom bonds in tetrahedral adducts are weaker than those in their tricoordinate counterparts. Thus, relatively mild conditions could be used to hydrolyze this type of pyramidalized boronate and regenerate a reactive boronic acid. Testing a series of trivalent heteroatomic ligands revealed that N-methyliminodiacetic acid (MIDA) embodies all of these expectations and represents a powerful platform for ICC chemistry.

Specifically, in a competition experiment between p-(n-butyl)phenylboronic acid 1.109 and p-tolyl MIDA boronate 1.110 under Buchwald-type anhydrous Suzuki-Miyaura cross-coupling conditions with p-bromoanisaldehyde Dr. Gillis observed a >20:1 ratio of products 1.111 and 1.112, consistent with a strong preference for cross-coupling of the sp²-hybridized boronic acid (Scheme 1-21). This B-protection strategy is remarkably general, with the same ligand similarly protecting aryl, heteroaryl, alkynyl, alkenyl, and alkyl haloboronic acids, thereby enabling the highly selective coupling of the halide terminus of these building blocks. Moreover, the MIDA boronates can be hydrolyzed under mild aqueous conditions (1 N aqueous NaOH/THF, 23 °C, 10 minutes or NaHCO₃/MeOH, 23 °C, 6 hours) to generate the corresponding free boronic acid.
Having established that the MIDA ligand can attenuate the reactivity of a boronic acid, a collection of bifunctional haloboronic acid building blocks \textbf{1.113a-d} was prepared to enable the ICC strategy (Figure 1-21). These building blocks contain a halide at one terminus that can be coupled under Suzuki-Miyaura conditions. The other terminus contains a boronic acid masked as a MIDA boronate, which will be unreactive under anhydrous coupling conditions.

The potential of the MIDA ligand to enable the selective cross-coupling of these building blocks was probed by reacting each with \textit{p}-tolylboronic acid (Scheme 1-22). Although the reactivity of aryl, heteroaryl, vinyl, and alkyl boronic acids can vary dramatically, the same protective group was effective with all four classes of nucleophiles, yielding selective cross-coupling products \textbf{1.114a-d}.
With the ability to selectively couple the halide terminus of a bifunctional MIDA boronate building block, and to subsequently deprotect the resulting MIDA boronate to reveal a reactive boronic acid, Dr. Gillis utilized the iteration of this process in the synthesis of the natural product ratanhine 1.115, a neolignan isolated from the medicinal plant *Ratanhiae radix.* First, a selective coupling between propenyl boronic acid 1.116 and the halide terminus of heteroaryl MIDA boronate 1.117 provided cross-coupled product 1.118 (Scheme 1-23). Deprotection of the benzofuranyl boronate to the boronic acid generated an intermediate 1.119 for coupling with electron-rich and sterically bulky aryl bromide 1.120, providing 1.121. A final sequence of deprotection and cross-coupling, followed by cleavage of protecting groups, completed a total synthesis of 1.115 and established ICC as a viable strategy for the synthesis of complex small molecules.

**Scheme 1-22.** Selective cross-coupling of bifunctional building blocks.
1-6.3 PREPARATION OF MIDA BORONATE BUILDING BLOCKS

In order to be useful reagents for small molecule synthesis, ready access to a diverse range of MIDA boronate building blocks must be available. The MIDA ligand\textsuperscript{84} is nontoxic, biodegradable,\textsuperscript{85} and commercially available. It can also be conveniently, efficiently, and inexpensively synthesized on a large scale from the commodity chemical iminodiacetic acid.\textsuperscript{86}

Several different methods have been developed for the synthesis of MIDA boronates. Many boronic acids can be readily transformed into the corresponding MIDA boronates through condensation with MIDA. This can be accomplished under Dean-Stark conditions using a mixture of toluene and DMSO as the reaction solvent (Scheme 1-24a).\textsuperscript{87} This strategy is compatible with many aryl, heteroaryl, vinyl, and alkyl boronic acids. For example, Seed and coworkers used this approach to prepare a substituted aryl MIDA boronate building block.\textsuperscript{88} Alternatively, Hamann and coworkers report that boronic acids can be heated with MIDA in DMF to be converted to MIDA boronates in good yields.\textsuperscript{89}

Numerous methods have also been developed to access MIDA boronates without the intermediacy of a boronic acid. Brice Uno and Dr. Gillis found that haloboranes, accessed through hydroboration of alkynes or alkenes with dibromoborane or transmetalation of organotrimethylsilanes with boron tribromide, can be converted to MIDA boronates by trapping with the disodium salt of MIDA (Scheme 1-24b).\textsuperscript{90} A variety of boronic esters, including
catechol esters and pinacol esters, can be converted to MIDA boronates by heating a solution of the boronic ester with MIDA (Scheme 1-24c). This work will be described in greater detail in Chapter 2. Alternatively, as demonstrated by Piersanti and coworkers, pinacol ester boronated tryptophans can be converted to boronic acids under the action of sodium periodate. This boronic acid was then transformed into the corresponding MIDA boronate under the Dean-Stark conditions described above.

Graham Dick, Dr. David Knapp, and Dr. Gillis have found that Grignard and organolithium reagents, which can be prepared from the corresponding halide, can be converted to MIDA boronates (Scheme 1-24d). Trapping of the Grignard or lithium reagent with trimethyl or triisopropyl borate followed by transligation with MIDA in a hot solution of DMSO is an effective strategy for the preparation of a variety of alkynyl, alkenyl, aryl, and heteroaryl MIDA boronates. This work is further described in Chapters 2 and 3.

Moreover, the MIDA boronate functional group is compatible with a wide range of reaction conditions and reagents, including oxidants, reductants, electrophiles, soft nucleophiles, strong acids, and a wide range of anhydrous bases, allowing MIDA boronate building blocks to be prepared through multistep synthesis, starting from MIDA boronate containing reagents. As a demonstration of this, Hamann and coworkers have reported the synthesis of amines through a reductive amination reaction of a MIDA boronate building block containing an aldehyde followed by an additional functionalization reaction via cross-coupling of the MIDA boronate group (Scheme 1-25a). Additionally, Brice Uno and Dr. Gillis found that cross-metathesis between vinyl MIDA boronate 1,122 and a variety of olefins is a useful method for the

![Scheme 1-24. Preparation of MIDA boronate building blocks.](image-url)
preparation of trans-alkenyl MIDA boronates (Scheme 1-25b). Furthermore, cyclopropanation and epoxidation of 1.122 provides the cyclopropane and oxiranyl building blocks, respectively (Scheme 1-25b). In a similar fashion, Dr. Justin Struble and Dr. Suk Joong Lee reported that ethynyl MIDA boronate 1.123 is a versatile precursor for the preparation of MIDA boronate containing building blocks (Scheme 1-25c). For example, Hamann and coworkers have demonstrated MIDA boronate functionalized isoxazoles and triazoles can be prepared from 1.123 through cycloaddition reactions (Scheme 1-25d). Also, as described in greater detail in Scheme 1-30c below, Toste and coworkers have prepared heterocyclic MIDA boronates through a coupling/cyclization sequence.

Scheme 1-25. Preparation of MIDA boronate building blocks.

Bifunctional halo MIDA boronates can also serve as starting materials for generating MIDA boronate containing building blocks. For example, Dr. Lee, Dr. Kaitlyn Gray, and James Paek found that trans-bromo MIDA boronate 1.124 is a versatile cross-coupling partner, enabling functionalization of the halide terminus while leaving the MIDA boronate functional group intact (Scheme 1-26). Suzuki-Miyaura, Stille, and Heck couplings provide a variety of diene MIDA boronates. A series of bismetalated lynchpin-type reagents can be prepared via
Sonagashira coupling, Miyaura borylation, or a metal-selective Negishi coupling. In a similar fashion, \textit{cis}-bromo MIDA boronate 1.125 can be synthesized and functionalized to prepare a series of dienyl MIDA boronate building blocks.\textsuperscript{101} This work is described in Chapter 3.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Scheme1-25.png}
\caption{Scheme 1-25. Preparation of MIDA boronate building blocks.}
\end{figure}

In addition to 1.124 and 1.125, Dr. Lee and Dr. Tom Anderson have developed a series of MIDA protected haloalkenylboronic acid building blocks to enable stereospecific access to stereochemically complex polyene frameworks via the ICC strategy.\textsuperscript{102} A collection of iodopolyenyl MIDA boronates has been prepared by the ICC of iodide-masked bifunctional building blocks. This approach involves metal-selective cross-coupling of Sn/Ge bis-metalated olefins\textsuperscript{103} to generate polyenylgermanium intermediates, followed by stereospecific iododegermylations (Scheme 1-27a).\textsuperscript{104} Iterative cycles of this metal-selective coupling/iododegermylation strategy with building blocks 1.126 and 1.127 provided access to iodopolyenyl MIDA boronates in all possible stereoisomeric forms (Scheme 1-27b). Moreover, harnessing the iterative nature of this strategy, the more advanced trienyl halide 1.128 was also readily prepared by simply executing an additional cycle of the metal-selective coupling and stereospecific iododegermylation. This strategy and these building blocks are described in greater detail in Chapter 4.
1-6.4 DIRECT AND SLOW RELEASE CROSS-COUPLING

With ready access to MIDA boronate containing reagents and bifunctional boronate building blocks, the MIDA boronate functionality can serve as a precursor or surrogate for boronic acids in a number of different contexts. One challenge to the use of boronic acids as building blocks in the synthesis of small molecules is that many boronic acids are inherently unstable. Sensitivity to moisture and oxygen can lead to protodeborylation and/or other decomposition pathways, greatly shortening their benchtop storage time. Furthermore, the decomposition of boronic acids can be accelerated by heat, base, and/or palladium catalysts, thereby causing the in situ decomposition of boronic acids to compete kinetically with Suzuki-Miyaura cross-coupling reactions. Many of these challenges can be linked to the vacant and Lewis acidic p orbital that is present in boronic acids. Rehybridization of a boronic acid to a sp$^3$-hybridized MIDA boronate provides a solution to both of these problems.
First, MIDA boronates can serve as air-stable surrogates for many unstable boronic acids, providing a solution to the instability of boronic acids to benchtop storage. The instability of 2-heterocyclic, vinyl, and cyclopropyl boronic acids has frequently been discussed anecdotally, yet there is very little quantitative data available. Dr. Knapp and Dr. Gillis conducted a systematic evaluation of the stability of a collection of such boronic acids stored on the benchtop under air for 15 days revealed significant decomposition (Scheme 1-28). For example, with 2-furan, 2-pyrrole, 2-indole, vinyl, and cyclopropyl boronic acids, very little of the original material remained after this time. In contrast to these unstable boronic acids, MIDA boronates are uniformly stable to benchtop storage. 2-furan, 2-pyrrole, 2-indole, vinyl, and cyclopropyl MIDA boronate are indefinitely air-stable, with no decomposition detectable after more than 60 days of storage on the benchtop under air. Suginome and coworkers have reported that phenyl MIDA boronate is stable for long periods of time in a solution of wet DMSO. Furthermore, Knochel and coworkers have demonstrated that MIDA boronate containing heterocycles, in comparison to other boron containing heterocycles, are more stable and less reactive under electrophilic aromatic substitution conditions.

![Scheme 1-28. Benchtop stability of boronic acids and MIDA boronates.](image)

Second, MIDA boronates can also provide a solution to the \textit{in situ} decomposition of unstable boronic acids in several different ways. For example, MIDA boronates can serve as
precursors to boronic acids in cross-coupling reactions. The hydrolysis of MIDA boronates with aqueous NaOH is fast, typically requiring less than 10 minutes at 23 °C. As a result, a MIDA boronate can be converted to a boronic acid, enabling cross-coupling under anhydrous or aqueous conditions. This strategy has been used in the synthesis of a number of small molecule natural products, including rathanine (Scheme 1-23), all-trans-retinal, β-parinaric acid, (5Z, 8Z, 10E, 12E, 14Z)-eicosapentaenoate, and (-)-myxalamida A.112 However, as described above, complex boronic acid intermediates are often difficult to isolate, and can decompose before the desired cross-coupling reaction can be conducted. In an alternative approach, Dr. Knapp and Dr. Gillis found that MIDA boronates can serve as surrogates for boronic acids in cross-coupling reactions. This feature enables the generation of structurally complex MIDA boronates that can then be directly cross-coupled with an organic halide. The conditions that are used to deprotect a MIDA boronate are fully compatible with the Suzuki-Miyaura cross-coupling reaction, which are often conducted under aqueous basic conditions. As a result, instead of generating the boronic acid reagent from the MIDA boronate as a separate step, the boronic acid coupling partner can be directly released into the reaction solution from the corresponding MIDA boronate. This avoids the potential challenge of isolating unstable and structurally complex boronic acids. This strategy has been used as the final step in the synthesis of several small molecule natural products, including polyenes described in Chapter 4, a total synthesis of the carotenoid natural product peridinin (as described in Chapter 2), as well as the carotenoid synechoxanthin 1.129, as reported by Seiko Fujii and Stephanie Chang.113 In this process, an in situ MIDA boronate hydrolysis/two-directional double cross-coupling sequence between two equivalents of MIDA boronate 1.130 and trans-1-iodo-2-bromoethylene 1.131 yielded synechoxanthin bismethylene, which upon deprotection provided 1.129 (Scheme 1-29).

Scheme 1-29. Total synthesis of synechoxanthin.

While the direct release of a boronic acid from a MIDA boronate can be effective in many cross-coupling reactions, the in situ stability of unstable boronic acids can often lead to a
reduction in yield similar reactions. Specifically, the *in situ* decomposition of unstable boronic acids can occur at a rate that is competitive with cross-coupling reactions, resulting in an inefficient coupling process. In contrast to the rapid release of a boronic acid from a MIDA boronate using aqueous NaOH (release is complete in <10 min at 23 °C), Dr. Knapp and Dr. Gillis found that potassium phosphate in 5:1 dioxane/water at 60 °C promotes the continuous release of boronic acids from the MIDA boronates over ~3 h. This rate controlled *in situ* hydrolysis of MIDA boronates provides a “slow release” of the corresponding unstable boronic acid at a rate that is slower than the desired cross-coupling reaction. Therefore, analogous to the use of a syringe pump, successful coupling can occur before decomposition of the freshly generated boronic acid.

To demonstrate this point, the cross-coupling efficiency of freshly prepared boronic acids was compared to the corresponding MIDA boronate. Under identical reaction conditions, the coupling of a variety of heteroaryl, vinyl, and alkyl boronic acids proceeded in low to moderate yields, while the corresponding MIDA boronates provided the products in uniformly excellent yields (Scheme 1-30). Moreover, the high yields obtained when using the MIDA boronate as a coupling partner can be replicated through the syringe pump mediated addition of the boronic acid over 3 h.

![Scheme 1-30](image)

**Scheme 1-30.** Cross-coupling efficiency of boronic acids and the corresponding MIDA boronates.
Several applications of the slow-release methodology have been utilized in the synthesis of small molecules. Taylor and coworkers have demonstrated that alkenyl MIDA boronates can be coupled with alkenyl tosylates under slow-release conditions to prepare a variety of diene products (Scheme 1-31a).\textsuperscript{116} Cobb and coworkers have prepared a collection of MIDA boronate containing amino acids. They further functionalized these reagents under the slow-release cross-coupling conditions to prepare a variety of biaryl amino acids (Scheme 1-31b).\textsuperscript{117} Toste and coworkers have developed a method for the preparation of heterocyclic MIDA boronates from substituted alkynyl MIDA boronates through a gold catalyzed cycloisomerization reaction. Subsequently, these substrates were coupled to aryl bromides and chlorides under slow-release conditions to yield 2-arylheterocycles (Scheme 1-31c).\textsuperscript{118} Miller and coworkers have utilized slow-release cross-coupling in the regioselective cross-coupling of tribrominated biaryls to provide efficient access to atropisomerically defined substituted biaryl frameworks (Scheme 1-31d).\textsuperscript{119} Furthermore, slow-release cross-coupling has been used to prepare intermediates in route to the synthesis of natural products and pharmaceutical agents.\textsuperscript{120}

Monteiro, Balme, and coworkers have combined slow-release cross-coupling with ICC for the synthesis of 3,4-bisaromatic pyrazoles (Scheme 1-32).\textsuperscript{121} In this process, bifunctional MIDA boronate 1.132 was first coupled with a series of aromatic and heteroaromatic boronic acids under anhydrous Suzuki-Miyaura cross-coupling conditions. In a subsequent reaction, the resulting MIDA boronate 1.133 was hydrolyzed \textit{in situ} under slow-release conditions and coupled with a variety of aryl iodides to provide bissubstituted pyrazoles 1.134.
Slow-release cross-coupling with MIDA boronates has also provided the first general solution to “the 2-pyridyl problem”.¹²² This advance is further described in Chapter 3.

The principles behind the slow-release cross-coupling of MIDA boronates have also found applications in organic synthesis, even beyond the Suzuki-Miyaura cross-coupling reaction. For example, Ellman and coworkers have developed the asymmetric rhodium-catalyzed addition of boronic acids 1.135 and boronates 1.136 to activated imines 1.137 toward the synthesis of chiral amines 1.138 (Scheme 1-33).¹²³ They note that the efficiency of this process is hampered by the in situ decomposition of the boron reagents. Addition of pentenylboronic acid 1.135 to 1.137 proceeded in low yield, even when using an excess of boronic acid. To address this limitation, they utilized the in situ, rate controlled hydrolysis of MIDA boronate 1.136 to continuously generate the boronic acid reagent throughout the course of the reaction. This strategy greatly improved the yield of the reaction. Further optimization of the reaction solvent provided high yields of the desired amine. These same reaction conditions were compatible with the addition of a variety of vinyl MIDA boronates to substituted imines. This approach was successfully employed in the synthesis of the natural product (-)-aurantioclavine.¹²⁴
1-6.5 ICC IN SMALL MOLECULE SYNTHESIS: EFFICIENT ACCESS TO FUNCTIONAL MOLECULES

Due to their ease of synthesis, purification, characterization, storage, and reversibly attenuated capacity for cross-coupling, MIDA boronates represent a powerful platform for the development of iterative synthesis strategies. Building upon the established synthesis strategies for the preparation of MIDA boronate building blocks and the ability to couple these reagents under slow and fast release conditions, the projects described in this thesis ultimately seek to provide a path toward an ICC-based general platform for small molecule synthesis. First, Chapter 1 describes the total synthesis and study of the antilipoperoxidant activity of the carotenoid natural product peridinin. This project not only inspired and motivated the development of new methodology for small molecule synthesis, but also enabled a fundamental understanding of carotenoid antilipoperoxidant activity. Second, Chapter 2 describes the synthesis and utility of three MIDA boronate building blocks: (Z)-2-bromovinyl MIDA boronate, 1-bromovinyl MIDA boronate, and 2-pyridyl MIDA boronate. These building blocks represent motifs that are highly prevalent in natural products, pharmaceuticals, and materials. Building upon these concepts, Chapter 3 describes a generalized strategy for small molecule synthesis and its application in a specific test case toward the preparation of polyene motifs. Collectively, the overarching goal of these projects is to help shift the rate limiting step in small molecule science from synthesizing molecules to understanding and maximally harnessing their functional potential.

1-7 SUMMARY

The inherent modularity found in many small molecules can be efficiently accessed in the laboratory through iterative approaches. Analogous to Nature’s synthesis of peptides, oligonucleotides, oligosaccharides, and small molecules, these iterative strategies involve a suitably protected form of the constituent monomer that is coupled to the growing end of the chain. After executing a deprotection sequence, additional cycles can then be conducted until the desired molecule is synthesized. Customized iterative sequences have been developed for the synthesis of polyketide, polyterpene, fatty acid, and nonribosomal peptide derived natural products. The iterative cross-coupling of pre-assembled bifunctional MIDA boronate building blocks represents an evolving platform with the potential for general application to a wide range
of complex small molecules of interest. Such an approach aspires to ultimately gain more efficient and flexible access to small molecules and thereby help to shift the rate limiting step in small molecule science from synthesis to function.

1-8 REFERENCES


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37 Reference 12

38 Reference 1


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Reference 73b

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Reference 77

Reference 78

Reference 79

Reference 80

Reference 81
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Reference 83

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Reference 91


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CHAPTER 2
TOTAL SYNTHESIS AND ANTILIPOPEROXIDANT ACTIVITY OF PERIDININ


Carotenoids are promising small molecule antilipoperoxidants. Among this group, peridinin is an interesting, atypical carotenoid. Hints in the literature suggest that peridinin may have antilipoperoxidant activity. However, isolation of peridinin from its natural source is very challenging and inefficient, and thus the underpinnings of its antilipoperoxidant activity have been only minimally explored. Seeking to evaluate and understand the potential antilipoperoxidant activity of peridinin, we completed the first fully stereocontrolled total synthesis of this natural product.

The development of several important methods enabled the total synthesis of peridinin. These include the stereocontrolled Suzuki-Miyaura cross-coupling of haloallenes, which was utilized in the last carbon-carbon bond forming step in the total synthesis. Two novel transesterification reactions also enabled efficient access to peridinin: the conversion of a boronic ester to a MIDA boronate and the conversion of a MIDA boronate to a boronic ester.

Having secured ready access to peridinin via this total synthesis, the antilipoperoxidant activity of this molecule was evaluated. In comparison to the carotenoid gold standard astaxanthin, peridinin was a more effective antilipoperoxidant in a chemically defined LUV system. Analysis of the carotenoid concentration further revealed that while both peridinin and astaxanthin are consumed throughout the lipoperoxidation assay, peridinin is consumed at a much slower rate than the less effective antilipoperoxidant astaxanthin. To better understand this increased antilipoperoxidant activity but slower consumption, we have explored the role of both astaxanthin and peridinin in the lipid peroxidation process. Preliminary results indicate that peridinin exhibits this superior activity via the rapid quenching of chain propagating lipid peroxyl radicals.

Alan H. Cherney contributed to the synthesis and coupling of enantioenriched haloallenes and the preparation of building blocks for the total synthesis of peridinin. Erin K. Davis contributed to the synthesis of enantioenriched haloallenes. Hannah M. S. Haley contributed to the biophysical studies of peridinin.
2-1 CAROTENOIDS ARE PROMISING ANTILIPOPEROXIDANTS

Pathological lipid peroxidation has been linked to cancer, heart disease, and aging, among many other conditions.\(^1\) Deficiencies in antiliperoxidant proteins increase incidence of these diseases in humans.\(^2\) Small molecules have demonstrated an important role in protecting against lipid peroxidation and may serve as functional surrogates for deficient antiliperoxidant proteins, thereby protecting against disease development.\(^3\)

Evidence suggests that a diet rich in certain fruits and vegetables may help prevent the development of cancer and other diseases, presumably by reducing lipid peroxidation.\(^4\) It has been proposed that carotenoids present in these foods are responsible for protecting the lipid membrane by interacting with reactive oxygen species (ROS).\(^5\) As a class of compounds, carotenoids are promising small molecule antiliperoxidants. Among this group, astaxanthin (2.1, Figure 2-1) has emerged as a leading candidate for applications in medicine\(^6\) and is considered the current “gold standard”.\(^7\) This natural product is available as a dietary supplement, generating $200 million in sales per year.\(^8\) While these advances are highly encouraging, two important limitations stand to limit astaxanthin’s impact. First, high concentrations of astaxanthin (>5% of total lipid content in \textit{in vitro} lipid bilayers) are generally required to achieve substantial antiliperoxidant activity.\(^9\) Second, the mechanism(s) by which astaxanthin protects against lipid peroxidation have been proposed to involve free radical scavenging\(^10\) (leading to consumption of the carotenoid) and/or modulation of membrane dynamics,\(^11\) but these mechanisms are not well understood. This lack of clarity has precluded the rational optimization of astaxanthin’s activity. Encouraged by the promising activity of astaxanthin, we are interested in exploring and understanding the use of carotenoid natural products or their derivatives as substitutes for the deficient or dysfunctional antiliperoxidant proteins that underlie human disease.\(^12\)

![Figure 2-1. Structure of the carotenoid natural products astaxanthin and peridinin.](image-url)
To guide our search for molecules with advanced antilipoperoxidant capacity with the goal of better understanding the mechanism of carotenoid antilipoperoxidant activity, we have focused on carotenoids produced by organisms that thrive in environments of extreme oxidative stress. In this regard, peridinin (2.2, Figure 2-1), produced by the photosynthetic dinoflagellate responsible for “red tides”, represents an attractive candidate. As a key component of the peridinin-chlorophyll-protein complex, peridinin is thought, in part, to protect against the extensive reactive oxygen species generated during photosynthesis. However, despite being one of the most abundant carotenoids on earth, isolation of 2.2 from dinoflagellates is very challenging and inefficient, and thus its potential antilipoperoxidant activity has been only minimally explored. In vivo, peridinin has demonstrated potent skin anticarcinogenic properties in mouse studies and has been identified as the primary singlet oxygen quencher in the marine algae Gonyaulax polyedra. In vitro, peridinin has demonstrated antilipoperoxidant activity, possibly via decreasing membrane permeability to ROS. While the underpinnings of these findings have been only minimally explored, they provide hints that peridinin may be an effective antilipoperoxidant. Obviating the challenges associated with isolating peridinin, we sought to gain access to this material via a fully stereocontrolled total synthesis in order to evaluate and understand its potential antilipoperoxidant activity.

2-2 RETROSYNTHESIS OF PERIDININ

While four total syntheses of peridinin have been reported, these syntheses have not constructed the polyene core in a stereocontrolled manner (Figure 2-2). For example, the syntheses completed by Ito and Katsumura utilized stereoselective Wittig and Julia olefination reactions to construct the polyene core. As a result, a mixture of cis and trans isomers were produced and optimized isomerization protocols had to be developed to convert these isomers into the desired all-trans framework. Brückner and coworkers completed a synthesis employing two stereospecific Stille cross-coupling reactions in the construction of the polyene core. However, the final step in their route was a Julia olefination reaction which resulted in a complex mixture of isomers, with the desired all-trans peridinin representing a minor component of the mixture.
Notably, de Lera and coworkers reported an attempted synthesis of peridinin in 2005.\textsuperscript{26} Their synthetic plan involved a Julia olefination and three Stille cross-coupling reactions, one of which was between a vinyl stannane and a chiral haloallene (Scheme 2-1). The major product under optimized reaction conditions\textsuperscript{27} corresponded to net inversion at the allene center (2:1 inversion:retention) and ultimately led to the synthesis of 6'-epi-peridinin.

In addition to the strategies utilized in the reported syntheses of peridinin, several general approaches have been taken to the synthesis of carotenoids. Many of these strategies are aimed at the preparation of C\textsubscript{2}-symmetric carotenoids. Five C\textsubscript{2}-symmetric carotenoids are produced on an industrial scale via a symmetrical double Wittig coupling between a dialdehyde and a phosphonium salt.\textsuperscript{28} This approach takes advantage of the inherent symmetry of the carotenoid and can provide the carotenoid in high yield. However, the lack of stereocontrol with this method often results in a mixture of cis and trans isomers which must be isomerized or separated via specialized protocols. Ito has attempted to apply the Wittig methodology to the synthesis of peridinin, but found that the reaction conditions were incompatible with the structurally complex aldehyde and phosphonium salt building blocks.\textsuperscript{29} In general, the double Wittig strategy is
suitable for the large scale production of certain carotenoids, but this strategy can be difficult to apply to the laboratory scale production of carotenoids and their targeted derivatives.

Another strategy for the synthesis of symmetrical carotenoids is the “two-fold Stille reaction” developed by de Lera, which involves a double Stille coupling to a central pentenyl bisstannane building block. This methodology was applied to the synthesis of β-carotene and zeaxanthin. While this methodology provides an efficient preparation of these carotenoids, the synthesis of the required pentenyl bisstannane utilized a Julia olefination reaction and resulted in a mixture of isomers. As a result, this strategy does not provide a completely stereocontrolled synthesis of these carotenoids.

As first introduced in Chapter 1, Negishi and coworkers have reported a zirconium catalyzed carboalumination followed by palladium and zinc catalyzed cross-coupling strategy for the preparation of the C_2-symmetric carotenoid β-carotene and the non-C_2-symmetric carotenoid γ-carotene. While this method provides the carotenoids in >99% isomeric purity without the need for separations or isomerizations, the functional group compatibility of the carboalumination reaction has limited the application of this method to functionally simple carotenoids.

In contrast to the synthetic strategies described above, we aim to prepare peridinin via an efficient, modular, flexible, and scalable synthetic plan, using only stereospecific reactions for the construction of the polyene core. Such a modular synthesis will enable the preparation of peridinin derivatives to aid in understanding the structure/function relationships that underlie the antilipoperoxidant activity of this natural product.

Toward this end, we recognized that the iterative cross-coupling (ICC) strategy introduced in Chapter 1 could be harnessed to enable an efficient total synthesis of peridinin. This approach is attractive because the building blocks used in this strategy contain preinstalled functionality and stereochemistry which is transferred to the product through the stereospecific Suzuki-Miyaura cross-coupling reaction. This eliminates the need for post-coupling modifications (e.g. oxidations/reductions, isomerizations), except for global deprotections at the end of the synthesis. At the outset of this project, the application of this strategy to polyenes had been highly effective, as demonstrated by the synthesis of one-half of the polyene macrolide amphotericin B and polyene natural products all-trans-retinal and β-parinaric acid.
As highlighted by the previous syntheses of peridinin, the many stereochemical issues, the complex and sensitive polyene core, and a diverse array of functional groups make peridinin a challenging synthetic target. Guided by the ICC strategy, we applied only Suzuki-Miyaura\textsuperscript{35} transforms to retrosynthesize peridinin into four building blocks, 2.3-2.6, which have all of the required functional groups, oxidation states, and stereochemistry preinstalled (Scheme 2-2). We recognized, however, that the disconnection between C8'/C9' corresponded to a stereocontrolled Suzuki-Miyaura coupling with a chiral allenyl halide. Albeit potentially very useful in the preparation of allene containing natural products,\textsuperscript{36} this was an unprecedented transformation that first required development.

**Scheme 2-2.** Retrosynthesis of peridinin into four building blocks.

### 2-3 METHODOLOGY FOR THE CROSS-COUPLING OF HALOALLENES

At the start of this project, the Suzuki-Miyaura reaction had not been applied to the cross-coupling of chiral, unactivated haloallenes. Previous work in this area utilized achiral haloallene coupling partners.\textsuperscript{37} However, important precedent lies in the Negishi coupling of enantioenriched haloallenes conducted by Vermeer and Elsevier.\textsuperscript{38} In these couplings, it was observed that iodoallenes favor coupling with stereoretention, while chloro- and bromoallenes favor stereoinversion. A model involving two competing mechanisms, direct oxidative addition at C1 or indirect S\textsubscript{N}2’ oxidative addition\textsuperscript{39} at C3 followed by a suprafacial 1,3-shift of Pd, was proposed to rationalize this observation (Figure 2-3).
Based on this precedent and the assumption that the same mechanistic pathways are operative under Suzuki-Miyaura cross-coupling conditions, we generated a series of hypotheses to rationally pursue the stereoretentive Suzuki-Miyaura coupling of haloallenes. We reasoned that the use of an iodoallene should promote stereoretention via direct oxidative addition. We further hypothesized that increased steric bulk at C3 of the haloallene and the use of sterically bulky phosphine ligands would both promote stereoretention, by disfavoring $S_N2'$-like attack at the more hindered internal site.

To test these hypotheses, together with first year graduate student Erin Davis and undergraduate Alan Cherney, a series of enantioenriched haloallenes were prepared. Access to enantioenriched chloro-, bromo-, and iodoallenes was accomplished through a five step reaction sequence (Scheme 2-3). Reaction of bis(trimethylsilyl)acetylene 2.7 with a series of acid chlorides 2.8 under Friedel-Craft conditions provided the known trimethylsilyl acetylenic ketones 2.9. A Noyori transfer hydrogenation followed by desilylation provided enantioenriched propargyl alcohols 2.10. Mesylation of the alcohol provided substrates for the cuprate mediated haloallene formation to provide enantioenriched haloallenes 2.11-2.15.

**Scheme 2-3.** Synthesis of enantioenriched haloallenes.
With these substrates in hand, we set out to test our hypotheses for the stereocontrolled Suzuki-Miyaura coupling. Consistent with the Negishi coupling precedent, using conditions similar to those reported to promote the Suzuki-Miyaura coupling of achiral haloallenes, the reaction of PhB(OH)\(_2\) with enantioenriched chloro- and bromo allenes (\(R\))-2.11-2.12 demonstrated net stereoinversion to provide (\(S\))-2.16a as the major product (Table 2-1, entries 1-2). In contrast, coupling of iodoallene (\(R\))-2.13 yielded (\(R\))-2.16a with a moderate 72% stereoretention (entry 3).

![chemical structure](image)

**Table 2-1.** Conditions for the Suzuki-Miyaura cross-coupling of enantioenriched haloallenes.

<table>
<thead>
<tr>
<th>Entry</th>
<th>(\begin{array}{c}R\end{array})</th>
<th>(\begin{array}{c}X\end{array})</th>
<th>Ligand</th>
<th>Cone Angle</th>
<th>Solvent</th>
<th>2.16</th>
<th>Stereoretention</th>
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<td>1</td>
<td>((R))-2.11</td>
<td>t-Bu</td>
<td>Cl</td>
<td>PPh(_3)</td>
<td></td>
<td>THF-H(_2)O</td>
<td>((S))-2.16a</td>
</tr>
<tr>
<td>2</td>
<td>((R))-2.12</td>
<td>t-Bu</td>
<td>Br</td>
<td>PPh(_3)</td>
<td></td>
<td>THF-H(_2)O</td>
<td>((S))-2.16a</td>
</tr>
<tr>
<td>3</td>
<td>((R))-2.13</td>
<td>t-Bu</td>
<td>I</td>
<td>PPh(_3)</td>
<td>145(^\circ)</td>
<td>THF-H(_2)O</td>
<td>((R))-2.16a</td>
</tr>
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</tr>
<tr>
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<td>n-pentyl</td>
<td>I</td>
<td>PPh(_3)</td>
<td></td>
<td>THF-H(_2)O</td>
<td>((R))-2.16a</td>
</tr>
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<td>Hexane:THF-H(_2)O</td>
<td>((R))-2.16c</td>
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</table>

% stereoretention = er product/er starting material (chiral GC, average of 2 runs); negative values reflect stereoinversion. Unoptimized GC yields ranged from 10-83%.

Building on this starting point, we tested the previously unconfirmed hypothesis\(^{44}\) that maximized steric bulk at C3 of an allenyl halide could promote stereoretention, presumably by disfavoring S\(_{N2}'\)-like oxidative addition. Specifically, we evaluated a series of substrates 2.13-2.15 containing progressively smaller R groups at C3 and indeed observed decreased stereoretention (entries 3-5). Finally, we tested our third hypothesis\(^{45}\) that bulky phosphine ligands\(^{46}\) would also promote stereoretentive direct oxidative addition at the less sterically hindered C1 by surveying a series of ligands with varying cone angles. In contrast to smaller cone angles (entries 3, 6-8), >90% stereoretention was observed for phosphine ligands having
cone angles $> 180^\circ$ (entries 9-11). With air-stable XPhos, $^{48}$ optimization of the solvent led to $> 99\%$ stereoretention and 61\% isolated yield of 2.16a (entry 12).

Collectively, these findings revealed that maximized stereoretention in the Suzuki-Miyaura coupling of chiral allenyl halides can best be accomplished using allenyl iodide substrates possessing steric bulk at C3 in combination with sterically bulky phosphine ligands. Guided by these principles, we designed building block 2.6 for peridinin to include both an allenyl iodide and a sterically bulky silyl protecting group at C5’. Building block 2.6 was prepared according to literature precedent with a TBS group at C5’ (see Section 2-5).

The substrate scope of this coupling reaction was briefly explored. Using the conditions identified in entry 11 of Table 1, a variety of aryl, heteroaryl, and alkenyl boronic acids were coupled to racemic iodoallene 2.13 (Scheme 2-4). Greater than 95\% conversion was observed by crude $^1$H-NMR for all couplings. The compatibility of this methodology with a variety of boronic acid coupling partners provided encouragement that this cross-coupling reaction may be viable in the context of the peridinin synthesis.

![Scheme 2-4](image)

**Scheme 2-4.** Substrate scope for the coupling of haloallenes with various boronic acids.

### 2-4 A MODEL FOR THE HALOALLENE CROSS-COUPLING REACTION IN PERIDININ

Before pursuing the preparation of the remaining building blocks for the synthesis of peridinin, we wanted to evaluate the coupling of 2.6 using a model vinyl boronic acid to determine the stereo outcome of the coupling of our actual building block for the peridinin synthesis. With TBS protected iodoallene 2.6 in hand, the coupling with styrenyl boronic acid 2.17 was evaluated using Pd$_2$(dba)$_3$/XPhos and Ag$_2$O in THF/H$_2$O (Scheme 2-5). The crude reaction mixture contained a single cross-coupled product 2.18, which was identified as the
desired retention product through single crystal X-ray analysis. Specifically, desilylation and deacylation of 2.18 provided highly crystalline allene 2.19, of which a crystal structure was obtained. Furthermore, the importance of a bulky protecting group at C5’ was evaluated. Coupling of unprotected iodoallene 2.20 with 2.17 under identical conditions provided a 3:2 d.r. favoring the desired retention product. The structure of the inversion product 2.21 was confirmed via isolation and single crystal X-ray analysis. We hypothesize that the decreased steric bulk at C3 may be responsible for the mixture of diastereomers. Alternatively, coordination of the palladium catalyst to the tertiary alcohol in 2.20 may enable the invertive S_N2’ mechanism. Concurrent with these studies, de Lera and coworkers reported similar findings with the Stille coupling of 2.20. This model study emphasized the importance for a protecting group at C3 to favor stereoretention for the final cross-coupling in the peridinin synthesis.

Scheme 2-5. A model study for the synthesis of peridinin.

2-5 SYNTHESIS OF THE FOUR BUILDING BLOCKS FOR A TOTAL SYNTHESIS OF PERIDININ

With the methodology for a stereoretentive Suzuki-Miyaura cross-coupling of haloallenes in hand, we next sought to prepare the four building blocks for peridinin 2.3-2.6. Strategically, we utilized several guiding principles in the design and synthesis of these building blocks. First, we sought short, efficient, and scalable routes to all four molecules. We did not want our total synthetic efforts to be hampered by a lack of material and, as a result, pursued routes that could easily provide the building blocks on at least a gram scale. Taking advantage of the desirable physical properties of MIDA boronates and compatibility with a number of reagents, we
envisioned installing boron early in the synthetic routes as the MIDA boronate and carrying it through multiple steps to prepare the desired building block. Second, we sought to complete a fully stereocontrolled synthesis of peridinin. Employing the ICC strategy and the stereospecific Suzuki-Miyaura cross-coupling reaction ensures the building blocks will be united in a stereocontrolled fashion. Additionally, in order to achieve this goal, the reactions used to synthesize the building blocks need to be highly stereoselective or stereospecific.

Building blocks 2.3 and 2.6 were prepared according to literature precedent from a common precursor (Scheme 2-6). Specifically, hydroboration\(^{50}\) of alkyne 2.22, prepared from (-)-actinol 2.23\(^{51}\) in seven steps and 40% overall yield, provided pinacol ester 2.24. The structure of 2.24 was confirmed through single crystal X-ray analysis. Multiple grams (>5 g) of 2.24 could be readily prepared in one batch. Haloallene 2.6 was prepared from 2.22 according to literature precedent\(^{52}\) and the absolute configuration of the allene was confirmed through single crystal X-ray analysis (Scheme 2-4). To the best of our knowledge, this was the first example of a crystal structure of an iodoallene.\(^{53}\)

![Scheme 2-6. Synthesis of building blocks 2.24 and 2.6.](image)

As outlined in Chapter 1, the unique compatibilities of the MIDA boronate functional group with a wide range of reaction conditions and chromatography were utilized to prepare the final two building blocks. Specifically, commercially available propynyl MIDA boronate 2.25 underwent highly regio- and stereocontrolled molybdenum-catalyzed hydrostannylation\(^{54}\) to yield bis-metalated olefin 2.26 (Scheme 2-7). A subsequent metal and halide selective Stille coupling between 2.26 and lactone 2.27\(^{55}\) provided 2.4 as a single stereoisomer. The structure of 2.4 was confirmed via single crystal X-ray analysis. Multiple grams (>10 g) of 2.4 could readily
be prepared in one batch. The final building block was prepared via initial bromination of commercially available 2.28 followed by regio- and stereoselective elimination to generate the novel tri-substituted bromoalkenyl MIDA boronate 2.29 as a single stereoisomer. Two cycles of stereospecific metal-selective cross-coupling with bis-metalated olefin 2.30 followed by stereoretentive iododegermylation, as discovered by Dr. Suk Joong Lee and described in Chapter 1, provided 2.5. Gram quantities of 2.5 could be readily prepared.

Scheme 2-7. Synthesis of building blocks 2.4 and 2.5.

2-6 STEREOCONTROLLED TOTAL SYNTHESIS OF PERIDININ

The synthesis of peridinin was completed using only Suzuki-Miyaura coupling to iteratively unite the four building blocks. Initial attempts to couple pinacol ester 2.24 directly to bifunctional lactone building block 2.4 were met with incomplete conversion (<50%) and the generation of inseparable impurities (Scheme 2-8). It was hypothesized that formation of the corresponding MIDA boronate of 2.31 would permit mild hydrolysis to the boronic acid 2.32, which would allow access to additional reaction conditions for coupling with 2.4. In a novel transformation, pinacol ester 2.24 was directly transesterified under mild conditions to form air and chromatography stable, crystalline MIDA boronate 2.31. This direct transesterification from a boronic ester to a MIDA boronate avoids the intermediacy of unstable boronic acids, and as described in Section 2-7, this methodology has proven to be general for the synthesis of MIDA boronates.
Scheme 2-8. The coupling of building blocks 2.3 and 2.4 could not be accomplished in high yield. An alternative strategy involving the preparation of boronic acid 2.32 was pursued.

Hydrolysis of 2.31 followed by B-selective cross-coupling with 2.4 provided tetraenyl MIDA boronate 2.33 (Scheme 2-9). The corresponding boronic acid proved to be unstable, thus a new tactic was developed to promote the next cycle of B-activation and coupling. Specifically, in a novel transformation, 2.33 was directly converted into the corresponding pinacol ester, which was an effective intermediate for B-selective coupling with 2.5. This transesterification reaction has proven to be general and is further described in Section 2-7. The resulting highly complex heptaenyl MIDA boronate 2.34 was stable to chromatography and storage. Conversely, attempts to isolate the heptaenyl boronic acid derived from 2.34 were not fruitful. To solve this challenging problem, we hybridized the principles established above for allenyl halide coupling (Table 2-1) with in situ release of the unstable boronic acid60 (see Chapter 1) derived from MIDA boronate 2.34 to promote the final union with 2.6 in good yield and with complete stereoretention. Initially, global desilylation was attempted with both TBAF and HF pyridine. However, the sterically hindered tertiary TBS group was not removed. To solve this, building block 2.35, which contains a more labile TMS group, was utilized in the final cross-coupling reaction. This coupling also proceeded in good yield and with complete stereoretention. Global desilylation with HF pyridine concluded the first completely stereocontrolled total synthesis of 2.2.
Utilizing this efficient synthesis pathway and drawing inspiration from the proposed biosynthesis of peridinin, Erin Davis has initiated studies probing the importance of key functional groups, such as the butenolide and allene, on the molecule’s antiliperoxidant activity.

2-7 THE TRANSESTERIFICATION REACTION

As described in Section 2-6, two novel transformations were developed to complete the total synthesis of peridinin, a transesterification reaction from a boronic ester to a MIDA boronate and a transesterification reaction from a MIDA boronate to a boronic ester. Both of these reactions have proven to be general and have found utility beyond the synthesis of peridinin.

First, the transesterification of a boronic ester to a MIDA boronate was discovered because a shelf stable form of building block 2.3 that could be readily converted to a boronic acid was sought for the peridinin synthesis. While pinacol ester 2.24 was stable to storage under an inert atmosphere at -20 °C for two months, long term storage resulted in decomposition. Furthermore, attempts to convert 2.24 to boronic acid 2.32 were either sluggish or led to desilylation or opening of the epoxide. Alternative approaches to prepare MIDA boronate 2.31, including Snieckus hydroboration conditions, were not fruitful. Therefore, a direct conversion of a boronic ester intermediate was attempted.

Initially, catechol ester 2.36 was prepared from hydroboration of alkyne 2.22 (Scheme 2-10). Direct transesterification with an excess of MIDA in DMSO provided a 47% yield of the desired MIDA boronate 2.31 on small scale. The reaction provided lower yields on larger scales (>0.5 mmol). A major byproduct, identified as desilylated MIDA boronate 2.37, was also

Scheme 2-9. Total synthesis of peridinin.
isolated. We hypothesized that the acidic catechol byproduct was leading to cleavage of the silyl group and a decreased yield. As a result, transesterification of the pinacol ester intermediate 2.24 was explored. Optimized conditions revealed that an excess of MIDA (6 eq.) in DMSO at 65 °C provided a 73% isolated yield of 2.31 after three cycles. Temperatures higher than 65 °C led to partial cleavage of the TBS group. Additional equivalents of MIDA (> 6 eq.) did not provide a large increase in isolated yield.

![Scheme 2.10](image)

*Scheme 2.10.* Initial route to building block 2.31. The route suffered from low and irreproducible yields.

Formation of the MIDA boronate can be favored by using an excess of MIDA or by running the reaction at high temperature. For example, conversion of 2.24 to 2.31 was monitored with varying equivalents of MIDA (Table 2-2). This data indicates that an excess of MIDA provides better conversion. Furthermore, better conversion is observed at higher temperatures (50% conversion at 65 °C and 65% conversion at 100 °C with 6 eq. of MIDA for 7 h). This data is consistent with the reaction being under thermodynamic equilibrium. The equilibrium concentration of the two boronates can also be established starting from the MIDA boronate. Addition of pinacol, MIDA, and DMSO to a MIDA boronate reestablishes the pinacol ester:MIDA boronate equilibrium distribution. In an attempt to further drive the reaction toward the desired MIDA boronate product, a number of additives were explored. For example, destruction or sequestration of the pinacol byproduct would drive the equilibrium toward the product. Additives such as NaIO₄, CaCl₂, molecular sieves, MgSO₄, and MgCl₂ had no effect on the conversion and often led to byproduct formation. Addition of toluene as a cosolvent (to precipitate out the MIDA boronate product as it formed) did not improve conversion. Because MIDA is an inexpensive and readily available material it was decided to not pursue further optimization of this reaction.
Table 2-2. Effect of number of equivalents of MIDA on the reaction conversion.

<table>
<thead>
<tr>
<th>eq. of MIDA</th>
<th>% conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>39</td>
</tr>
<tr>
<td>4</td>
<td>58</td>
</tr>
<tr>
<td>6</td>
<td>65</td>
</tr>
<tr>
<td>8</td>
<td>71</td>
</tr>
<tr>
<td>10</td>
<td>77</td>
</tr>
</tbody>
</table>

As first discovered in the context of the peridinin synthesis, a variety of boronic esters can be transesterified to MIDA boronates. Because of the decreased thermodynamic stability of catechol esters (in comparison to pinacol esters), full conversion of a catechol ester to a MIDA boronate can be accomplished using a slight excess of MIDA (1.5 or 2.0 eq.) under mild heat (40 °C) in DMSO. Neopenylglycol esters, ethyleneglycol esters, and diethanolamine esters have also been converted to MIDA boronates.

This methodology provides the convenient and facile preparation of MIDA boronates. Beyond the Burke group, this method has also found use by the Taylor group (Scheme 2-11). A variety of substituted alkyynes were hydroborated with catechol borane and directly transesterified to provide the MIDA boronates.

![Scheme 2-11. Synthesis of MIDA boronates via transesterification of catechol esters by the Taylor group.](image)

Additionally, the conversion of MIDA boronates to pinacol esters is possible. Initial screens to convert styrenyl MIDA boronate to styrenyl pinacol ester using an excess of pinacol (25 eq.) in a variety of solvents (acetone, THF, ethyl acetate, MeCN, toluene, methylene chloride) provided low conversion at 50 °C (<5% conversion) and only slightly better conversion at elevated temperatures (~10% conversion at 100 °C). Because this methodology was to be used in the presence of the sensitive polyene core of peridinin, mild conditions were desired. Application of methanol as the reaction solvent, however, provided full conversion at 50 °C after 15 h. Additional temperatures were then explored. No conversion was obtained at 23 °C or 35 °C using 5 eq. of pinacol in methanol after 3 h, however 25% conversion was observed at 45 °C.
This improved to 70% conversion after 9 h. In an attempt to accelerate the reaction, a series of basic additives were explored, including NaOMe, NaHCO₃, and K₃PO₄. Full conversion was observed using NaHCO₃ after 3 h. These conditions (slight excess of pinacol, NaHCO₃, methanol, 45 °C, 3 h) have been established as the standard conditions to convert a MIDA boronate to a pinacol ester. Excess pinacol can be removed by stirring the crude reaction mixture with CaCl₂ in toluene.

This methodology provides the convenient and facile preparation of pinacol esters. Other boronic esters can also be prepared from this method. For example, catechol esters, ethyleneglycol esters, and neopentylglycol esters have been prepared by using the corresponding diol. Beyond the synthesis of peridinin, this methodology has also been useful in several other contexts (Scheme 2-12). Dr. Kaitlyn Gray used the transesterification reaction in order to optimize the yields in route to C35-deoxy amphotericin B 2.38 Junqi Li used the transesterification reaction to convert a PIDA boronate to a pinacol ester in the preparation of a pharmaceutical agent 2.39 Finally, Yudin and coworkers have used the transesterification reaction in the preparation of unnatural amino acids 2.40

Scheme 2-12. Application of the transesterification reaction in several different contexts.
2-8 THE ANTILOPOPEROXIDANT ACTIVITY OF PERIDININ

Having secured ready access to peridinin via a completely stereocontrolled total synthesis, we next sought to explore the antilipoperoxidant activity of this molecule. As a starting point, we compared the activity of peridinin to the “gold standard” astaxanthin in vitro.

Roughly 25% of the lipids in a mammalian cell membrane contain polyunsaturated fatty acids (PUFA) \((\text{LH, Figure 2-4})\). Upon exposure to reactive oxygen species, such fatty acids can be transformed into a lipid peroxy radical \((\text{LOO}^\bullet)\) which, in turn, can react with a neighboring unsaturated fatty acid to form a lipid hydroperoxide \((\text{LOOH})\) and a carbon-centered radical \((\text{L}^\bullet)\) with a rate constant \(k_p\). A subsequent fast reaction with \(\text{O}_2\) (diffusion-limited when \(p\text{O}_2 > 100\) Torr) generates a new lipid peroxy radical, thus closing the loop for radical chain propagation and extensive peroxidation of a lipid bilayer. The \(\text{LOO}^\bullet\) can alternatively be quenched by an antilipoperoxidant with a rate constant \(k_q\). Highly effective carotenoids may quench early in this lipoperoxidation process \((k_q > k_p)\), leading to limited propagation and minimized consumption of the carotenoid (when the carotenoid is in excess of \(\text{LOO}^\bullet\)). Alternatively, less effective carotenoids may quench later in the lipoperoxidation process \((k_q < k_p)\), leading to extensive propagation and increased consumption of the carotenoid. The mechanistic connections between lipid peroxidation and the causation of human diseases remain incompletely understood. However, it has been demonstrated that \(\text{LOO}^\bullet\) can decompose to yield highly electrophilic breakdown products, such as malondialdehyde (MDA), which can alkylate DNA, proteins, and other biomolecules and thereby cause a wide range of deleterious impacts on the cell, including mutagenesis.
Proposed mechanism of lipoperoxidation.

This lipid peroxidation process can be replicated in large unilamellar vesicles (LUVs). Specifically, as shown in Figure 2-4, when exposed to either Cu or Fe salts, pre-existing lipid hydroperoxides are broken down to generate $\text{LOO}^\cdot$ [LUVs prepared using commercial lipid mixtures isolated from natural sources, e.g., egg yolk phosphatidylcholine (EYPC), almost always contain small quantities of $\text{LOOH}$]. Following this initiation event, radical chain propagation can proceed as described above, leading to the progressive formation of MDA, which can be precisely quantified in the form of its adduct with thiobarbituric acid via HPLC or via UV at 535 nm.

Employing this established LUV-based assay we discovered that synthetic 2.2 is a much more effective antilipoperoxidant than the gold standard 2.1 (Figure 2-5) in EYPC. Consistent with literature precedent, 2.1 partially protected against lipid peroxidation when incorporated at a concentration of 1.0% of total lipid, but after 48 hours the total lipid peroxidation in the treated sample was equivalent to that observed in untreated controls. In stark contrast, a concentration of 0.9% peridinin resulted in complete protection against lipid peroxidation for more than 30 hours. Reducing the concentration to 0.5% caused a substantial loss of activity for astaxanthin, whereas peridinin maintained an outstanding level of protection, delaying the time required to achieve complete peroxidation by more than 10 hours.
Figure 2-5. Evaluating the antilipoperoxidant activity of peridinin and astaxanthin in EYPC.

As described above, evidence in the literature suggests that carotenoids exhibit antilipoperoxidant activity through the quenching of propagating \( \text{LOO}^\bullet \). This process would predict consumption of the carotenoid throughout the lipoperoxidation assay and more effective antilipoperoxidants would experience less rapid consumption. Quantitative HPLC analysis of the carotenoid concentration throughout the course of the assay revealed that both peridinin and astaxanthin are consumed throughout the assay, but peridinin is consumed at a much slower rate than the less effective antilipoperoxidant astaxanthin (Figure 2-6). To better understand the increased antilipoperoxidant activity of peridinin but slower consumption and to probe if peridinin is an early quencher, we have further explored the role of both astaxanthin and peridinin in the lipid peroxidation process.

Figure 2-6. Evaluating the consumption of peridinin and astaxanthin in EYPC.

Toward this end, we recognized that the use of EYPC to prepare LUVs for in vitro antilipoperoxidation experiments has several important limitations. First, because it is a natural
extract, the composition of EYPC can vary considerably as a function of the commercial supplier and/or even the batch number. This makes it very challenging to achieve a high degree of reproducibility. Second, because it is obtained as a mixture, it is very difficult to selectively remove individual lipid components to determine their roles in the different stages of the lipid peroxidation process and/or the consequences of their omission. Finally, while the major components of EYPC have been identified and are quantifiable by GC, there are many minor components that are typically unidentified. Thus, it is not possible to rule out potentially catalytic/important role(s) for such minor components in the lipid peroxidation process.

To circumvent all of these limitations, we developed a LUV-based lipid peroxidation assay system comprised completely of synthetic lipid components. Specifically, we found that, after treatment with the same CuCl₂ initiator, LUVs derived from a mixture of synthetic POPC (16:0-18:1, 75 mol%) and PUFA (18:0-20:4, 25 mol%) produced a lipid peroxidation profile very similar to that observed previously with EYPC LUVs (Figure 2-7). Furthermore, similar to the EYPC LUV system, 2.2 is a much more effective antilipoperoxidant than 2.1 in the chemically defined LUV system. Moreover, peridinin was also consumed at a slower rate than astaxanthin (Figure 2-8). With this very well characterized system in hand, we set out to determine the mechanistic underpinnings of the antilipoperoxidant activity of peridinin.

![Lipoperoxidation - Chemically Defined System](image_url)

**Figure 2-7.** Evaluating the antilipoperoxidant activity of peridinin and astaxanthin in a chemically defined liposome system.
To guide our mechanistic studies, we first sought to confirm that LOO• is the component of the chemically defined system that is responsible for carotenoid consumption. Incorporation of peridinin or astaxanthin into POPC liposomes lacking PUFAs and LOOH and subjection to the CuCl₂ initiated assay conditions resulted in no consumption of the carotenoids over 26 hours (Figure 2-9). Additionally, incorporation of carotenoids into POPC liposomes containing PUFAs and LOOH, but lacking CuCl₂ also resulted in no consumption of 2.1 or 2.2. Together these results indicate that the initiation components alone are not responsible for carotenoid consumption. Carotenoid consumption was not observed in samples containing PUFA and CuCl₂ but lacking LOOH, indicating that the presence of PUFA alone is not sufficient for carotenoid consumption. Next, we added CuCl₂ to the liposomes containing only the carotenoids, POPC, and LOOH (13(S)-HpOTrE, 13(S)-hydroperoxy-6Z,9Z,11E-octadecatrienoic acid) and observed time dependent consumption of 2.1 and 2.2. This data is consistent with LOO•, generated from the reaction between LOOH and CuCl₂, being responsible for carotenoid consumption. As shown in Figure 2-4, oxygen is needed for the chain propagation process to occur. As a result, it can be hypothesized that exclusion of oxygen from the system would result in minimal carotenoid consumption because the substrate for reaction with the carotenoid (LOO•) would be at a low concentration. To test this hypothesis, the carotenoid concentration was monitored in the absence of oxygen. Consistent with this mechanism, and with the importance of LOO• in the chain propagation process, only a slight decrease in the concentration of astaxanthin was observed.

Figure 2-8. Evaluating the consumption of peridinin and astaxanthin in a chemically defined liposome system.
Based on this framework, we have explored two hypotheses for the source of peridinin’s superior antilipoperoxidant activity yet minimized chemical reactivity (Figure 2-10): 1) peridinin, more effectively than astaxanthin, decreases the lateral diffusion of propagating lipid radicals,$^{85}$ thus decreasing both $k_p$ and $k_q$ and 2) for peridinin, but not for astaxanthin, $k_q$ is substantially greater than $k_p$, thus both lipid peroxidation and consumption are minimized.

To test the first hypothesis, we utilized a liposome-based solution phase NMR assay to evaluate the impact of carotenoid incorporation on the rate of lipid lateral diffusion.$^{86}$ The lateral diffusion of lipids, including $\text{LOO}^\cdot$, effects the rate of propagation in the lipoperoxidation process, as well as the rate of carotenoid quenching. A decrease in lipid lateral diffusion would result in a decrease of both $k_p$ and $k_q$. Changes in the solution phase NMR linewidths of lipid molecules contained in liposomes can be correlated to changes in lateral diffusion. Specifically, an increase in linewidth indicates a decrease in lipid lateral diffusion. This effect has been demonstrated using small molecules such as cholesterol and has been used to rationalize the
antilipoperoxidant effect of cholesterol. We have coupled this NMR assay with the antilipoperoxidant assay described above to correlate effects on lipid lateral diffusion to antilipoperoxidant activity. Using this strategy, we have demonstrated a concentration dependant correlation between cholesterol concentration, antilipoperoxidant activity, and lipid lateral diffusion (in EYPC); higher concentrations of cholesterol lead to more effective antilipoperoxidant activity and exhibit decreased levels of lipid lateral diffusion (Figure 2-11).

![Lipoperoxidation Assay - Cholesterol](image1)

**Figure 2-11.** Correlation between lipid lateral diffusion and concentration of cholesterol. Higher concentrations of cholesterol lead to more effective antilipoperoxidant activity and decreased levels of lipid lateral diffusion.

We next applied this coupled NMR/antilipoperoxidant assay to probe the role of lipid lateral diffusion in the mechanism of carotenoid antilipoperoxidant activity (in EYPC, Figure 2-12). Similar to cholesterol, astaxanthin decreased lipid lateral diffusion in a dose dependant manner. However, inconsistent with our first hypothesis, there was no distinguishable difference between the effects on lipid lateral diffusion between cholesterol and astaxanthin. Furthermore, incorporation of astaxanthin at the same concentrations as cholesterol revealed far superior antilipoperoxidant activity of the carotenoid in comparison to cholesterol, despite a similar effect
on lipid lateral diffusion. The same experiments are currently underway with peridinin. Overall, this study has revealed that, while polar carotenoids such as astaxanthin decrease lipid lateral diffusion, the magnitude of this effect is minimal and inconsistent with the large antilipoperoxidant effect that is observed.

Figure 2-12. Correlation between lipid lateral diffusion and concentration of astaxanthin, in comparison to cholesterol. Astaxanthin decreases lipid lateral diffusion but the magnitude of this effect is minimal and inconsistent with the large antilipoperoxidant effect that is observed.

The second hypothesis which could explain peridinin’s superior antilipoperoxidant activity states that the rate constant for quenching LOO• by peridinin, k_q, is both greater than the rate of propagation, k_p, as well as the rate constant for quenching by astaxanthin. To test the first part of this hypothesis, together with Hannah Haley, we have tracked the concentration of PUFA and the carotenoid over time. We hypothesized that if k_q for peridinin is greater than k_p than we would observe consumption of peridinin but no consumption of the PUFA. Incorporation of peridinin into the chemically defined liposome and tracking the concentration of the carotenoid and PUFA
revealed consumption of peridinin and no consumption of the PUFA, consistent with our hypothesis and with $k_{q,\text{peri}} > k_p$ (Figure 2-13).

![PUFA Consumption](image1)

**Figure 2-13.** PUFA and peridinin consumption in a chemically defined liposome system.

Additionally, we hypothesized that astaxanthin is a less effective antilipoperoxidant than peridinin because $k_q$ for astaxanthin is less than or equal to $k_p$. This hypothesis would predict simultaneous consumption of the PUFA and astaxanthin. Incorporation of astaxanthin into the chemically defined liposome and tracking the concentration of the carotenoid and PUFA revealed consumption of astaxanthin as well as consumption of the PUFA, consistent with our hypothesis and with $k_{q,\text{astax}} \leq k_p$ (Figure 2-14).
Finally, to test if the rate constant for quenching with peridinin ($k_{q,\text{peri}}$) is greater than the rate constant for quenching with astaxanthin ($k_{q,\text{astax}}$) we conducted a competition experiment to measure the relative rate of carotenoid consumption in the lipoperoxidation assay. Preliminary results indicate that incorporation of nearly identical concentrations of peridinin and astaxanthin into the same POPC/PUFA liposome followed by CuCl$_2$ mediated initiation leads to preferential reaction of peridinin over astaxanthin (Figure 2-15). Consistent with the hypothesis, this result demonstrates that the $k_q$ for peridinin is greater than the $k_q$ for astaxanthin. Currently, additional experiments are underway to provide further support for this hypothesis.
2-9 SUMMARY AND CONCLUSIONS

Taking advantage of a building block based strategy for small molecule synthesis, we accomplished the first completely stereocontrolled total synthesis of peridinin. This synthesis effort inspired the development of several new methodologies, including the stereocontrolled Suzuki-Miyaura cross-coupling of haloallenes and transesterification of boronic esters to MIDA boronates and MIDA boronates to boronic esters. This flexible and efficient route has enabled the preparation of derivatives of peridinin. Furthermore, we have used this synthetic material to probe the antilipoperoxidant activity of peridinin. These studies have revealed that peridinin is a more effective antilipoperoxidant than the current gold standard, astaxanthin. Mechanistic studies in a chemically defined liposome system have revealed that peridinin exhibits this excellent activity through the early quenching of lipid peroxyl radicals, quenching these radicals at a rate greater than propagation. Collectively, these studies reveal that peridinin can serve as a potent probe molecule to further understand the antilipoperoxidant mechanism of carotenoids.

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12 Palacios, D. S.; Burke, M. D. manuscript in preparation.


This result was re-explored in a later publication: Vaz, B.; Pereira, R.; Perez, M.; Alvarez, R.; de Lera, A. R. *J. Org. Chem.* 2008, 73, 6534.


Ref. 38.

The mechanism of oxidative addition with allenyl iodides is unknown. Based on leading studies with aryl iodides (Barrios-Landeros, F.; Carrow, B. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2009**, *131*, 8141-8154), oxidative addition may proceed through $L_2$Pd intermediates where sterically bulky phosphines promote reactivity at the less sterically-hindered C1. Alternatively, bulky phosphines may promote an $L_1$Pd pathway in which case the enhanced capacity of $L_1$Pd for direct OA would presumably be advantageous.


Ref 42a.

A similar result has recently been reported: Ref. 27.


(-)-actinol was kindly donated by DSM.

Ref 19c.

Search of the Cambridge Crystallographic Database on 9/14/2009.


The transesterification of aryl pinacol esters to MIDA boronates was also described by M.R. Smith, *Am. Chem. Soc. Conference*, Spring 2009.


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CHAPTER 2
EXPERIMENTAL SECTION

Materials. Commercial reagents were purchased from Sigma-Aldrich, Fisher Scientific, Alfa Aesar, TCI America, Strem Chemicals Inc., or Frontier Scientific and were used without further purification unless otherwise noted. (-)-Actinol was a generous gift from DSM Nutritional Products in Basel, Switzerland. Solvents were purified via passage through packed columns as described by Pangborn and coworkers (THF, Et₂O, CH₃CN, CH₂Cl₂: dry neutral alumina; hexane, benzene, and toluene: dry neutral alumina and Q5 reactant; DMSO, DMF: activated molecular sieves). All water was deionized prior to use. Triethylamine, diisopropylamine, pyridine, and 2,6-lutidine were freshly distilled under an atmosphere of nitrogen from CaH₂. The following compounds were prepared according to known literature procedures: iodoallene 2.6 and 2.35,² haloallenes 2.11-2.15,³ alkyne 2.22,⁴ dibromolactone 2.27,⁵ and vinyl germane 2.30.⁶ Propynyl MIDA boronate 2.25, vinyl stanane 2.26, isoprenyl MIDA boronate 2.28, and bromide 2.29 are commercially available from Sigma-Aldrich.

General Experimental Procedures. Unless noted, all reactions were performed in flame-dried round bottom or modified Schlenk flasks fitted with rubber septa under a positive pressure of argon or nitrogen. Organic solutions were concentrated via rotary evaporation under reduced pressure with a bath temperature of 35 – 40 °C. Reactions were monitored by analytical thin layer chromatography (TLC) performed using the indicated solvent on E. Merck silica gel 60 F254 plates (0.25mm). Compounds were visualized by exposure to a UV lamp (λ = 254 nm) and/or a solution of basic KMnO₄ followed by brief heating using a Varitemp heat gun. MIDA boronates are compatible with standard silica gel chromatography, including standard loading techniques. Column chromatography was performed using standard methods⁷ or on a Teledyne-Isco CombiFlash Rf purification system using Merck silica gel grade 9385 60Å (230-400 mesh). For loading, compounds were adsorbed onto non acid-washed 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.** $^1$H NMR spectra were recorded at 23 °C on one of the following instruments: Varian Unity 400, Varian Unity 500, Varian Unity Inova 500NB. 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$_3$HCN, δ = 1.94, 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, sext = sextet, 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. 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 at 23 °C on a General Electric GN300WB or a Varian Unity Inova 400 instrument and referenced to an external standard of BF$_3$•Et$_2$O. High resolution mass spectra (HRMS) were performed by Furong Sun, Dr. Steve Mullen, and Beth Eves 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, a Mattson Galaxy Series FT-IR 5000 spectrometer or a Mattson Infinity Gold FT-IR spectrometer. Absorption maxima ($\nu_{\text{max}}$) are reported in wavenumbers (cm$^{-1}$). Specific rotations were measured on a Jasco DIP-370 Digital Polarimeter. Gas chromatography analysis was conducted on an Agilent Technologies 7890A instrument. GC yields are based on a dodecane internal standard using an Agilent Technologies HP-5 column (part number 19091J-413). The stereoretention values were determined by GC analysis with an Agilent Technologies chiral β-cyclodextrin stationary phase (part number 112-2532). X-ray crystallographic analyses were carried out by Dr. Scott Wilson and Dr. Danielle Gray at the University of Illinois George L. Clark X-Ray facility.
Experimental procedures

Haloallenes 2.11-2.15.
The general reaction scheme for the synthesis of haloallenes 2.11-2.15 is shown below and reaction references are provided (Figure 2-1): 8, 9, 10, 11

![Reaction scheme for haloallene synthesis](image)

Figure 2-1. Synthesis of haloallenes 2.11-2.15.

General procedure for the synthesis of haloallenes 2.11-2.15. 5

Preparation of LiCuX₂:
The purity of copper (I) iodide was found to be critical to the enantiopurity of the products 2.11-2.15. High purity (>99.999%) copper (I) iodide was purchased from Strem or prepared by recrystallization. 12

In a glovebox, to a Schlenk flask equipped with a stir bar and charged with copper (I) halide (4 eq) was added THF (6 M with respect to the copper halide). Lithium halide (2 eq) and THF (0.6 M with respect to the lithium halide) were added to a separate vial. The Schlenk flask and vial were sealed, removed from the glovebox, and placed under an argon atmosphere. The copper (I) halide suspension was cooled to -78° C. The lithium halide solution was cannula transferred into the Schlenk flask. The mixture was stirred at -78 °C for 30 minutes and then stirred at 23 °C for 30 minutes. The resulting cuprane solution was cooled to 0 °C. A solution of enantioenriched mesylate (1 eq) in THF (0.3 M with respect to the mesylate) was added dropwise via cannula to the cuprane solution. The reaction proceeded with stirring at reflux for 1 hr 45 minutes. After
cooling the resulting mixture to 23 °C, the solution was transferred to a separatory funnel containing 1:1 NH$_4$Cl (sat. aq.):NH$_4$OH (14.8 M) and shaken. The layers were separated. The aqueous layer was extracted with Et$_2$O. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated in vacuo to afford the crude haloallene. This oil was purified via flash chromatography on silica gel (100% petroleum ether) to afford haloallenes 2.11-2.15 as oils.

(R)-1-chloro-4,4-dimethyl-1,2-pentadiene, (R)-2.11. The general procedure was followed using CuCl (1.37 g, 13.9 mmol) in THF (2 mL), LiCl (0.30 g, 6.9 mmol) in THF (11 mL) and (S)-4,4-dimethylpent-1-yn-3-yl methanesulfonate (0.66 g, 3.5 mmol, 99:1 e.r.) in THF (11 mL). The work up used NH$_4$Cl:NH$_4$OH (150 mL), Et$_2$O (2 x 125 mL), and brine (15 mL). Flash chromatography (100% petroleum ether) gave chloroallene (R)-2.11 as a clear, pale yellow oil (0.075 g, 17%).

TLC (petroleum ether)  
\[ R_f = 0.72, \text{ visualized by short wave UV} \]

$^1$H-NMR (500 MHz, CDCl$_3$)  
\[ \delta 6.05 \text{ (d, } J = 5.5 \text{ Hz, } 1\text{H}), 5.61 \text{ (d, } J = 5.5 \text{ Hz, } 1\text{H}), 1.09 \text{ (s, } 9\text{H}). \]

$^{13}$C-NMR (125 MHz, CDCl$_3$)  
\[ \delta 199.5, 113.3, 89.3, 33.0, 29.5 \]

HRMS (EI+)  
Calculated for C$_7$H$_{11}$Cl: 130.0549  
Found: 130.0543  
\[ [\alpha]_D^2 -139.8 \text{ (c } 0.9, \text{ CHCl}_3) \]

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The e.r. was determined by chiral GC using a Cyclodex B column:
t_r (major) 2.0 min, t_r (minor) 2.2 min; temperature: 80 °C; 6.5 mL/min.: 93.9:6.1 e.r.

(R)-1-bromo-4,4-dimethyl-1,2-pentadiene, (R)-2.12.\(^3\) The general procedure was followed using CuBr (1.92 g, 13.3 mmol) in THF (2 mL), LiBr (0.58 g, 6.7 mmol) in THF (11 mL) and (S)-4,4-dimethylpent-1-yn-3-yl methanesulfonate (0.64 g, 3.3 mmol, 99:1 e.r.) in THF (11 mL). The work up used NH\(_4\)Cl:NH\(_4\)OH (150 mL), Et\(_2\)O (2 x 125 mL), and brine (15 mL). Flash chromatography (100% petroleum ether) gave bromoallene (R)-2.12 as a clear, yellow oil (0.080 g, 14%).

TLC (petroleum ether)  
R_f = 0.69, visualized by short wave UV

\(^1\)H-NMR (500 MHz, CDCl\(_3\))  
δ 5.98 (d, J = 5.5 Hz, 1H), 5.36 (d, J = 5.5 Hz, 1H), 1.09 (s, 9H).

\(^{13}\)C-NMR (125 MHz, CDCl\(_3\))  
δ 199.6, 112.1, 73.1, 32.5, 29.6

HRMS (EI+)  
Calculated for C\(_7\)H\(_{11}\)Br: 174.0044  
Found: 174.0039

[\([\alpha]_D^{24}\) -183.0 (c 1.0, CHCl\(_3\))]

The e.r. was determined by chiral GC using a Cyclodex B column:  
t_r (major) 3.2 min, t_r (minor) 3.6 min; temperature: 80 °C; 6.5 mL/min.: 94.2:5.8 e.r.
(R)-1-iodo-4,4-dimethyl-1,2-pentadiene, (R)-2c. The general procedure was followed using CuI (8.03 g, 42.2 mmol) in THF (7 mL), LiI (2.86 g, 21.4 mmol) in THF (35 mL) and (S)-4,4-dimethylpent-1-yn-3-yl methanesulfonate (2.0 g, 10.5 mmol, 99:1 e.r.) in THF (35 mL). The work up used NH₄Cl:NH₄OH (400 mL), Et₂O (2 x 100 mL), and brine (100 mL). Flash chromatography (100% petroleum ether) gave iodoallene (R)-2c as a clear, yellow oil (1.98 g, 85%).

TLC (petroleum ether)

R_f = 0.74, visualized by short wave UV

_1H-NMR (500 MHz, CDCl₃)

δ 5.71 (d, J = 6 Hz, 1H), 5.06 (d, J = 6 Hz, 1H), 1.08 (s, 9H).

_13C-NMR (125 MHz, CDCl₃)

δ 203.3, 107.7, 36.5, 31.8, 29.7

HRMS (EI+)

Calculated for C₇H₁₁I: 221.9906
Found: 221.9919

[α]D²³ -264.2 (c 1.8, CHCl₃)

The e.r. was determined by chiral GC using a Cyclodex B column:

t_r (major) 2.7 min, t_r (minor) 3.0 min; temperature: 100 °C; 6.5 mL/min.: 89.5:10.5 e.r.
**(R)-1-ido-4-ethyl-1,2-hexadiene, (R)-2.14.** The general procedure was followed using CuI (7.48 g, 39.3 mmol) in THF (6.5 mL), LiI (2.58 g, 19.3 mmol) in THF (33 mL) and (S)-4-ethylhex-1-yn-3-yl methanesulfonate (1.98 g, 9.7 mmol, approximately 99:1 e.r.) in THF (33 mL). The work up used NH₄Cl:NH₄OH (400 mL), Et₂O (1 x 100 mL), and brine (100 mL). Flash chromatography (100% petroleum ether) gave iodoallene (R)-2.14 as a clear, yellow oil (2.1 g, 91%).

TLC (petroleum ether)

Rᵢ = 0.71, visualized by short wave UV

$^{1}$H-NMR (500 MHz, CDCl₃)

δ 5.67 (dd, J = 6, 1.5 Hz, 1H), 4.95 (dd, J = 8, 6 Hz, 1H), 2.03 – 1.96 (m, 1H), 1.57 – 1.43 (m, 2H), 1.41 – 1.29 (m, 2H), 0.92 (t, J = 7.5 Hz, 3H), 0.90 (t, J = 7.5 Hz, 3H).

$^{13}$C-NMR (125 MHz, CDCl₃)

δ 205.0, 100.1, 42.0, 35.7, 27.4, 27.1, 11.7, 11.5

HRMS (EI+)

Calculated for C₈H₁₃I: 236.0062

Found: 236.0048

$[α]_{D}^{25}$-309.2 (c 0.9, CHCl₃)

Absolute stereochemical assignment was made according to the Lowe-Brewster rules¹³ and by analogy to known haloallenes 2.11-2.13.³

The ee was determined by chiral GC using a Cyclodex B column:

$t_r$(major) 4.2 min, $t_r$(minor) 4.6 min; temperature: 110 °C; 6.5 mL/min.: 91.0:9.0 e.r.
(R)-1-iodo-1,2-octadiene, (R)-2.15. The general procedure was followed using CuI (5.59 g, 29.4 mmol) in THF (5 mL), LiI (1.97 g, 14.7 mmol) in THF (25 mL) and (S)-oct-1-yn-3-yl methanesulfonate (1.50 g, 7.3 mmol, approximately 97:13 e.r.) in THF (12.5 mL). The work up used NH₄Cl:NH₄OH (300 mL), Et₂O (2 x 125 mL), and brine (30 mL). Flash chromatography (100% petroleum ether) gave iodoallene (R)-2e as a clear, yellow oil (1.24 g, 74%).

TLC (petroleum ether)

R_f = 0.63, visualized by short wave UV

1H-NMR (500 MHz, CDCl₃)

δ 5.68 (ddd, J = 5.5, 2.5, 2.5 Hz, 1H), 5.11 (dt, J = 7, 6 Hz, 1H), 2.19 – 2.06 (m, 2H), 1.54 – 1.35 (m, 2H), 1.34 – 1.27 (m, 4H), 0.91 – 0.90 (m, 3H).

13C-NMR (125 MHz, CDCl₃)

δ 205.4, 96.5, 35.5, 31.2, 28.1, 27.5, 22.4, 14.0

HRMS (EI+)

Calculated for C₈H₁₃I: 236.0062
Found: 236.0045

[α]D²³ -166.9 (c 1.6, CHCl₃)

The e.r. was determined by chiral GC using a Cyclodex B column:
t_r (major) 5.6 min, t_r (minor) 6.2 min; temperature: 110 °C; 6.5 mL/min: 69.8:30.2 e.r.
General procedure for cross-coupling reactions in Table 2-I, Entries 1-11 and 13-14:

Preparation of catalyst stock solution. In a glovebox, to a 7 mL vial equipped with a stir bar and charged with phosphine ligand was added a premixed solution of Pd$_2$(dba)$_3$ in THF. The solution was stirred at 23 °C for 20 min.

The freshly prepared catalyst stock solution was used in the following reaction:

In a glovebox, to a 7 mL vial equipped with a stir bar and charged with base (0.14 mmol) was added the reaction solvent (1.2 mL). A stock solution of PhB(OH)$_2$ (125.4 mg, 1.0 mmol) in THF (3.0 mL) was prepared. An aliquot (0.20 mL, corresponding to 8.4 mg of boronic acid, 0.069 mmol) of this solution was added to the reaction vial. A stock solution of haloallene:dodecane (2:1 molar ratio) in THF (0.23 M with respect to the haloallene) was prepared. An aliquot (0.20 mL, corresponding to 0.045 mmol haloallene) was added to the reaction vial. An aliquot of the prepared catalyst stock solution (0.20 mL, corresponding to 4 mol% Pd$_2$(dba)$_3$ and 16 mol% ligand) was added to the reaction vial. The vial was sealed with a septum cap and removed from the glovebox. Degassed DI H$_2$O (0.15 mL) was added. The solution was stirred at 23 °C for 1.5 hr in a subdued light environment. Activated carbon, Darco G-60 (~50 mg) was added to the reaction solution. The solution was stirred at 23 °C under air for 20 min. The solution was dried over MgSO$_4$ and filtered through a plug of Celite. The resulting solution was analyzed by GC.

Entry 1: Synthesis of (S)-2.16a.

Following the general procedure, a stock solution of Pd$_2$(dba)$_3$ (68.0 mg, 0.074 mmol) in THF (8.0 mL) was prepared and stirred at 23 °C for 10 min. A portion (1.4 mL) of this solution was added to a vial containing recrystallized PPh$_3$ (13.8 mg, 0.053 mmol). This catalyst stock solution was stirred at 23 °C for 20 min. Ag$_2$O (32.5 mg, 0.14 mmol) was suspended in THF (1.2 mL). An aliquot (0.20 mL) of the boronic acid stock solution was added. A stock solution
of chloroallene \((R \cdot 2.11)\) (17.6 mg, 0.13 mmol) and dodecane (11.3 mg, 0.066 mmol) in THF (0.60 mL) was prepared. An aliquot (0.20 mL) of this chloroallene stock solution was added to the reaction vial. An aliquot (0.20 mL) of the prepared catalyst stock solution was added and the general procedure was followed for the remainder of the experiment.

Based on the average of two runs:
The e.r. of \((R \cdot 2.11)\) was determined by chiral GC using a Cyclodex B column: 93.9:6.1 e.r.
The e.r. of the product was determined by chiral GC using a Cyclodex B column: 15.8:84.2 e.r.
Stereoretention = -78\%, \((S \cdot 2.16a)\) was the major product, corresponding to net stereoinversion
GC yield based on the dodecane internal standard = 83\%

**Entry 2: Synthesis of \((S \cdot 2.16a).**
Following the general procedure, a stock solution of \(\text{Pd}_2(\text{dba})_3\) (68.0 mg, 0.074 mmol) in THF (8.0 mL) was prepared and stirred at 23 °C for 10 min. A portion (1.4 mL) of this solution was added to a vial containing recrystallized \(\text{PPh}_3\) (13.8 mg, 0.053 mmol). This catalyst stock solution was stirred at 23 °C for 20 min. \(\text{Ag}_2\text{O}\) (33.1 mg, 0.14 mmol) was suspended in THF (1.2 mL). An aliquot (0.20 mL) of the boronic acid stock solution was added. A stock solution of bromoallene \((R \cdot 2.12)\) (23.3 mg, 0.13 mmol) and dodecane (11.2 mg, 0.066 mmol) in THF (0.60 mL) was prepared. An aliquot (0.20 mL) of this bromoallene stock solution was added to the reaction vial. An aliquot (0.20 mL) of the prepared catalyst stock solution was added and the general procedure was followed for the remainder of the experiment.

Based on the average of two runs:
The e.r. of \((R \cdot 2.12)\) was determined by chiral GC using a Cyclodex B column: 94.2:5.8 e.r.
The e.r. of the product was determined by chiral GC using a Cyclodex B column: 15.5:84.5 e.r.
Stereoretention = -78\%, \((S \cdot 2.16a)\) was the major product, corresponding to net stereoinversion
GC yield based on the dodecane internal standard = 61\%
added to a vial containing recrystallized PPh$_3$ (13.8 mg, 0.053 mmol). This catalyst stock solution was stirred at 23 $^\circ$C for 20 min. Ag$_2$O (34.1 mg, 0.15 mmol) was suspended in THF (1.2 mL). An aliquot (0.20 mL) of the boronic acid stock solution was added. A stock solution of iodoallene ($R$)-2.13 (90.7 mg, 0.41 mmol) and dodecane (35.3 mg, 0.21 mmol) in THF (1.8 mL) was prepared. An aliquot (0.20 mL) of this iodoallene stock solution was added to the reaction vial. An aliquot (0.20 mL) of the prepared catalyst stock solution was added and the general procedure was followed for the remainder of the experiment.

Based on the average of two runs:
The e.r. of ($R$)-2.13 was determined by chiral GC using a Cyclodex B column: 89.5:10.5 e.r.
The e.r. of the product was determined by chiral GC using a Cyclodex B column: 78.4:21.6 e.r.
Stereoretention = 72%, ($R$)-2.16a was the major product, corresponding to net stereoretention
GC yield based on the dodecane internal standard = 49%

**Entry 4: Synthesis of ($R$)-2.16b.**
Following the general procedure, a solution of Pd$_2$(dba)$_3$ (15.5 mg, 0.017 mmol) in THF (2.0 mL) was prepared and stirred at 23 $^\circ$C for 10 min. This entire solution was added to a vial containing recrystallized PPh$_3$ (18.2 mg, 0.069 mmol). This catalyst stock solution was stirred at 23 $^\circ$C for 20 min. Ag$_2$O (30.1 mg, 0.13 mmol) was suspended in THF (1.2 mL). An aliquot (0.20 mL) of the boronic acid stock solution was added. A stock solution of iodoallene ($R$)-2.14 (36.5 mg, 0.15 mmol) and dodecane (13.4 mg, 0.079 mmol) in THF (0.6 mL) was prepared. An aliquot (0.20 mL) of this iodoallene stock solution was added to the reaction vial. An aliquot (0.20 mL) of the prepared catalyst stock solution was added and the general procedure was followed for the remainder of the experiment.

Based on the average of two runs:
The e.r. of ($R$)-2.14 was determined by chiral GC using a Cyclodex B column: 91.0:9.0 e.r.
The e.r. of the product was determined by chiral GC using a Cyclodex B column: 73.8:26.2 e.r.
Stereoretention = 58%, ($R$)-2.16b was the major product, corresponding to net stereoretention
GC yield based on the dodecane internal standard = 16%
Entry 5: Synthesis of (R)-2.16c.

Following the general procedure, a stock solution of Pd\textsubscript{2}(dba\textsubscript{3}) (68.0 mg, 0.074 mmol) in THF (8.0 mL) was prepared and stirred at 23 °C for 10 min. A portion (1.4 mL) of this solution was added to a vial containing recrystallized PPh\textsubscript{3} (13.8 mg, 0.053 mmol). This catalyst stock solution was stirred at 23 °C for 20 min. Ag\textsubscript{2}O (31.6 mg, 0.14 mmol) was suspended in THF (1.2 mL). An aliquot (0.20 mL) of the boronic acid stock solution was added. A stock solution of iodoallene (R)-2.15 (31.8 mg, 0.13 mmol) and dodecane (11.0 mg, 0.065 mmol) in THF (0.6 mL) was prepared. An aliquot (0.20 mL) of this iodoallene stock solution was added to the reaction vial. An aliquot (0.20 mL) of the prepared catalyst stock solution was added and the general procedure was followed for the remainder of the experiment.

Based on the average of two runs:
The e.r. of (R)-2.15 was determined by chiral GC using a Cyclodex B column: 69.8:30.2 e.r.
The e.r. of the product was determined by chiral GC using a Cyclodex B column: 55:45 e.r.
Stereoretention = 25%. (R)-2.16c was the major product, corresponding to net stereoretention GC yield based on the dodecane internal standard = 10%

Entry 6: Synthesis of (R)-2.16a.

Following the general procedure, a stock solution of Pd\textsubscript{2}(dba\textsubscript{3}) (69.4 mg, 0.076 mmol) in THF (8.0 mL) was prepared and stirred at 23 °C for 10 min. A portion (0.8 mL) of this solution was added to a vial containing trifurylphosphine (7.1 mg, 0.031 mmol). This catalyst stock solution was stirred at 23 °C for 20 min. Ag\textsubscript{2}O (30.9 mg, 0.13 mmol) was suspended in THF (1.2 mL). An aliquot (0.20 mL) of the boronic acid stock solution was added. A stock solution of iodoallene (R)-2.13 (113.5 mg, 0.51 mmol) and dodecane (38.2 mg, 0.22 mmol) in THF (2.2 mL) was prepared. An aliquot (0.20 mL) of this iodoallene stock solution was added to the reaction vial. An aliquot (0.20 mL) of the prepared catalyst stock solution was added and the general procedure was followed for the remainder of the experiment.

Based on the average of two runs:
The e.r. of (R)-2.13 was determined by chiral GC using a Cyclodex B column: 89.5:10.5 e.r.
The e.r. of the product was determined by chiral GC using a Cyclodex B column: 81.6:18.4 e.r.
Stereoretention = 80%. (R)-2.16a was the major product, corresponding to net stereoretention GC yield based on the dodecane internal standard = 59%

Entry 7: Synthesis of (R)-2.16a.
Following the general procedure, a stock solution of Pd$_2$(dba)$_3$ (68.0 mg, 0.074 mmol) in THF (8.0 mL) was prepared and stirred at 23 °C for 10 min. A portion (0.8 mL) of this solution was added to a vial containing PCy$_3$ (9.1 mg, 0.032 mmol). This catalyst stock solution was stirred at 23 °C for 20 min. Ag$_2$O (33.9 mg, 0.15 mmol) was suspended in THF (1.2 mL). An aliquot (0.20 mL) of the boronic acid stock solution was added. A stock solution of iodoallene (R)-2.13 (90.7 mg, 0.41 mmol) and dodecane (35.3 mg, 0.21 mmol) in THF (1.8 mL) was prepared. An aliquot (0.20 mL) of this iodoallene stock solution was added to the reaction vial. An aliquot (0.20 mL) of the prepared catalyst stock solution was added and the general procedure was followed for the remainder of the experiment.

Based on the average of two runs:
The e.r. of (R)-2.13 was determined by chiral GC using a Cyclodex B column: 89.5:10.5 e.r.
The e.r. of the product was determined by chiral GC using a Cyclodex B column: 69.8:30.2 e.r.
Stereoretention = 50%, (R)-2.16a was the major product, corresponding to net stereoretention GC yield based on the dodecane internal standard = 10%

Entry 8: Synthesis of (R)-2.16a.
Following the general procedure, a stock solution of Pd$_2$(dba)$_3$ (69.4 mg, 0.076 mmol) in THF (8.0 mL) was prepared and stirred at 23 °C for 10 min. A portion (0.8 mL) of this solution was added to a vial containing P^t^Bu$_2$Me (6.1 mg, 0.038 mmol). This catalyst stock solution was stirred at 23 °C for 20 min. Ag$_2$O (33.0 mg, 0.14 mmol) was suspended in THF (1.2 mL). An aliquot (0.20 mL) of the boronic acid stock solution was added. A stock solution of iodoallene (R)-2.13 (113.5 mg, 0.51 mmol) and dodecane (38.2 mg, 0.22 mmol) in THF (2.2 mL) was prepared. An aliquot (0.20 mL) of this iodoallene stock solution was added to the reaction vial. An aliquot (0.20 mL) of the prepared catalyst stock solution was added and the general procedure was followed for the remainder of the experiment.
Based on the average of two runs:
The e.r. of (R)-2.13 was determined by chiral GC using a Cyclodex B column: 89.5:10.5 e.r.
The e.r. of the product was determined by chiral GC using a Cyclodex B column: 78.0:22.0 e.r.
Stereoretention = 71%, (R)-2.16a was the major product, corresponding to net stereoretention
GC yield based on the dodecane internal standard = 15%

Entry 9: Synthesis of (R)-2.16a.
Following the general procedure, a stock solution of Pd$_2$(dba)$_3$ (68.0 mg, 0.074 mmol) in THF (8.0 mL) was prepared and stirred at 23 °C for 10 min. A portion (0.8 mL) of this solution was added to a vial containing P(o-tol)$_3$ (8.4 mg, 0.028 mmol). This catalyst stock solution was stirred at 23 °C for 20 min. Ag$_2$O (31.9 mg, 0.14 mmol) was suspended in THF (1.2 mL). An aliquot (0.20 mL) of the boronic acid stock solution was added. A stock solution of iodoallene (R)-2.13 (90.7 mg, 0.41 mmol) and dodecane (35.3 mg, 0.21 mmol) in THF (1.8 mL) was prepared. An aliquot (0.20 mL) of this iodoallene stock solution was added to the reaction vial. An aliquot (0.20 mL) of the prepared catalyst stock solution was added and the general procedure was followed for the remainder of the experiment.

Based on the average of two runs:
The e.r. of (R)-2.13 was determined by chiral GC using a Cyclodex B column: 89.5:10.5 e.r.
The e.r. of the product was determined by chiral GC using a Cyclodex B column: 85.9:14.1 e.r.
Stereoretention = 91%, (R)-2.16a was the major product, corresponding to net stereoretention
GC yield based on the dodecane internal standard = 58%

Entry 10: Synthesis of (R)-2.16a.
Following the general procedure, a stock solution of Pd$_2$(dba)$_3$ (68.0 mg, 0.074 mmol) in THF (8.0 mL) was prepared and stirred at 23 °C for 10 min. A portion (0.8 mL) of this solution was added to a vial containing P(o-tol)$_3$ (8.4 mg, 0.028 mmol). This catalyst stock solution was stirred at 23 °C for 20 min. Ag$_2$O (31.9 mg, 0.14 mmol) was suspended in THF (1.2 mL). An aliquot (0.20 mL) of the boronic acid stock solution was added. A stock solution of iodoallene (R)-2.13 (90.7 mg, 0.41 mmol) and dodecane (35.3 mg, 0.21 mmol) in THF (1.8 mL) was prepared. An aliquot (0.20 mL) of this iodoallene stock solution was added to the reaction vial. An aliquot
(0.20 mL) of the prepared catalyst stock solution was added and the general procedure was followed for the remainder of the experiment.

Based on the average of two runs:
The e.r. of (R)-2.13 was determined by chiral GC using a Cyclodex B column: 89.5:10.5 e.r.
The e.r. of the product was determined by chiral GC using a Cyclodex B column: 86.7:13.3 e.r.
Stereoretention = 93%, (R)-2.16a was the major product, corresponding to net stereoretention
GC yield based on the dodecane internal standard = 38%

Entry 11: Synthesis of (R)-2.16a.
Following the general procedure, a stock solution of Pd\textsubscript{2}(dba)\textsubscript{3} (68.0 mg, 0.074 mmol) in THF (8.0 mL) was prepared and stirred at 23 °C for 10 min. A portion (0.8 mL) of this solution was added to a vial containing XPhos\textsuperscript{15} (14.8 mg, 0.031 mmol). This catalyst stock solution was stirred at 23 °C for 20 min. Ag\textsubscript{2}O (32.2 mg, 0.14 mmol) was suspended in THF (1.2 mL). An aliquot (0.20 mL) of the boronic acid stock solution was added. A stock solution of iodoallene (R)-2.13 (90.7 mg, 0.41 mmol) and dodecane (35.3 mg, 0.21 mmol) in THF (1.8 mL) was prepared. An aliquot (0.20 mL) of this iodoallene stock solution was added to the reaction vial. An aliquot (0.20 mL) of the prepared catalyst stock solution was added and the general procedure was followed for the remainder of the experiment.

Based on the average of two runs:
The e.r. of (R)-2.13 was determined by chiral GC using a Cyclodex B column: 89.5:10.5 e.r.
The e.r. of the product was determined by chiral GC using a Cyclodex B column: 86.0:14.0 e.r.
Stereoretention = 91%, (R)-2.16a was the major product, corresponding to net stereoretention
GC yield based on the dodecane internal standard = 42%

Entry 12: Synthesis of (R)-2.16a.
Preparation of catalyst solution. In a glovebox, to a 20 mL vial equipped with a stir bar and charged with XPhos (133.1 mg, 0.28 mmol) and Pd\textsubscript{2}(dba)\textsubscript{3} (63.4 mg, 0.069 mmol) was added THF (7.5 mL). The solution was stirred at 23 °C for 20 min.
The freshly prepared catalyst solution was used in the following reaction:

In a glovebox, to a 100 mL round bottom flask equipped with a stir bar and charged with PhB(OH)$_2$ (306.5 mg, 2.5 mmol) and Ag$_2$O (1.16 g, 5.0 mmol) was added iodoallene (R)-2.13 (334.4 mg, 1.5 mmol) as a solution in hexanes (55 mL). The prepared catalyst solution was added in one portion. The flask was sealed with a septum and removed from the glovebox. Degassed DI H$_2$O (6.0 mL) was added. The solution was stirred in a subdued light environment at 23 °C for 1.5 hr. Activated carbon, Darco G-60 (800 mg) was added to the reaction solution. The solution was stirred at 23 °C under air for 20 min. The aqueous layer was removed and the organic layer was dried over MgSO$_4$ and filtered through a plug of Celite. The resulting clear, yellow solution was concentrated in vacuo, and the resulting residue was purified via flash chromatography on silica gel (100% petroleum ether) to afford the cross coupled product (R)-3a as a pale yellow oil (157.6 mg, 61%).

The e.r. of (R)-2.13 was determined by chiral GC using a Cyclodex B column: 89.5:10.5 e.r.
The e.r. of the product was determined by chiral GC using a Cyclodex B column: 89.5:10.5 e.r.
Stereoretention = >99%, (R)-2.16a was the major product, corresponding to net stereoretention

*Entry 13: Synthesis of (R)-2.16b.*

Following the general procedure, a solution of Pd$_2$(dba)$_3$ (15.5 mg, 0.017 mmol) in THF (2.0 mL) was prepared and stirred at 23 °C for 10 min. This entire solution was added to a vial containing XPhos (17.0 mg, 0.036 mmol). This catalyst stock solution was stirred at 23 °C for 20 min. Ag$_2$O (30.1 mg, 0.13 mmol) was suspended in hexanes (1.2 mL). An aliquot (0.20 mL) of the boronic acid stock solution was added. A stock solution of iodoallene (R)-2.14 (33.7 mg, 0.14 mmol) and dodecane (14.2 mg, 0.083 mmol) in hexanes (0.6 mL) was prepared. An aliquot (0.20 mL) of this iodoallene stock solution was added to the reaction vial. An aliquot (0.20 mL) of the prepared catalyst stock solution was added and the general procedure was followed for the remainder of the experiment.

Based on the average of two runs:
The e.r. of (R)-2.14 was determined by chiral GC using a Cyclodex B column: 91.0:9.0 e.r.
The e.r. of the product was determined by chiral GC using a Cyclodex B column: 91.0:9.0 e.r.
Stereoretention = >99%, \((R)-2.16b\) was the major product, corresponding to net stereoretention GC yield based on the dodecane internal standard = 64%

\textit{Entry 14: Synthesis of (R)-2.16c.}

Following the general procedure, a solution of \(\text{Pd}_2\text{(dba)}_3\) (15.5 mg, 0.017 mmol) in THF (2.0 mL) was prepared and stirred at 23 \(^\circ\)C for 10 min. This entire solution was added to a vial containing XPhos (17.0 mg, 0.036 mmol). This catalyst stock solution was stirred at 23 \(^\circ\)C for 20 min. \(\text{Ag}_2\text{O}\) (33.6 mg, 0.14 mmol) was suspended in hexanes (1.2 mL). An aliquot (0.20 mL) of the boronic acid stock solution was added. A stock solution of iodoallene \((R)-2.15\) (31.6 mg, 0.13 mmol) and dodecane (13.4 mg, 0.079 mmol) in hexanes (0.6 mL) was prepared. An aliquot (0.20 mL) of this iodoallene stock solution was added to the reaction vial. An aliquot (0.20 mL) of the prepared catalyst stock solution was added and the general procedure was followed for the remainder of the experiment.

Based on the average of two runs:
The e.r. of \((R)-2.15\) was determined by chiral GC using a Cyclodex B column: 69.8:30.2 e.r.
The e.r. of the product was determined by chiral GC using a Cyclodex B column: 66.8:33.2 e.r.
Stereoretention = 85\%, \((R)-2.16c\) was the major product, corresponding to net stereoretention GC yield based on the dodecane internal standard = 30%

\begin{figure}[h]
\centering
\includegraphics[width=0.2\textwidth]{2.16a.png}
\caption{(R)-(4,4-dimethylpenta-1,2-dien-1-yl)benzene, (R)-2.16a.}
\end{figure}

TLC (petroleum ether)
\(R_f = 0.55\), visualized by short wave UV

\(^1\text{H-NMR (500 MHz, d}_6\text{-acetone)}
\(\delta 7.35 – 7.28\) (m, 4H), 7.19 (tt, \(J = 6.5\), 2 Hz, 1H), 6.27 (d, \(J = 6.5\) Hz, 1H), 5.64 (d, \(J = 6.5\) Hz, 1H), 1.13 (s, 9H).
$^{13}$C-NMR (125 MHz, d$_6$-acetone)
\[ \delta 203.1, 136.1, 129.4, 127.5, 127.1, 107.3, 96.8, 33.2, 30.4 \]

HRMS (EI+)
Calculated for C$_{13}$H$_{16}$: 172.1252  
Found: 172.1236

$[\alpha]_D^5$ -301.8 ($c$ 1.1, CHCl$_3$)

The e.r. was determined by chiral GC using a Cyclodex B column:
$t_r$ (major) 13.3 min, $t_r$ (minor) 14.2 min; temperature: 100 °C; 6.5 mL/min: 89.5:10.5 e.r.

\[
\text{Me} \quad \text{Me} \\
\text{H} \quad \text{H} \\
\text{2.16b} \\
\quad \text{Me} \\
\text{Me} \\
\quad \text{Ph}
\]

(R)-(4-ethylhexa-1,2-dien-1-yl)benzene, (R)-2.16b.

TLC (petroleum ether)  
$R_f = 0.49$, visualized by short wave UV

$^1$H-NMR (500 MHz, CDCl$_3$)
\[ \delta 7.32 – 7.27 (m, 4H), 7.20 – 7.15 (m, 1H), 6.14 (dd, J = 6.5, 2 Hz, 1H), 5.40 (dd, J = 7, 7.5 Hz, 1H), 2.05 – 1.96 (m, 1H), 1.57 – 1.46 (m, 2H), 1.46 – 1.34 (m, 2H), 0.98 (t, J = 7.5 Hz, 3H), 0.95 (t, J = 7.5, 3H). \]

$^{13}$C-NMR (125 MHz, CDCl$_3$)
\[ \delta 204.9, 135.2, 128.5, 126.5, 98.9, 94.5, 94.5, 94.5, 43.1, 27.7, 27.4, 11.9, 11.7 \]

HRMS (EI+)
Calculated for C$_{14}$H$_{18}$: 186.1409  
Found: 186.1420
Absolute stereochemical assignment was made according to the Lowe-Brewster rules and by analogy to known haloallene 2.16a.16

The e.r. was determined by chiral GC using a Cyclodex B column:
t_r (major) 19.5 min, t_r (minor) 20.3 min; temperature: 110 °C; 6.5 mL/min: 73.8:26.2 e.r.

\[
(\text{R})\text{-octa-1,2-dien-1-ylbenzene, (R)-2.16c.}
\]

TLC (petroleum ether)

\[ R_f = 0.57, \text{ visualized by short wave UV} \]

\[^1\text{H-NMR (500 MHz, CDCl}_3\text{)}\]

\[ \delta 7.27 \text{ (d, } J = 1 \text{ Hz, } 4\text{H}), 7.16 - 7.13 \text{ (m, } 1\text{H}), 6.11 - 6.08 \text{ (m, } 1\text{H}), 5.54 \text{ (dd, } J = 7, 6.5 \text{ Hz, } 1\text{H}), 2.12 - 2.08 \text{ (m, } 2\text{H}), 1.50 - 1.44 \text{ (m, } 2\text{H}), 1.36 - 1.27 \text{ (m, } 4\text{H}), 0.88 - 0.85 \text{ (m, } 3\text{H}). \]

\[^{13}\text{C-NMR (125 MHz, CDCl}_3\text{)}\]

\[ \delta 205.1, 135.2, 128.5, 126.6, 126.6, 95.1, 94.5, 31.4, 28.8, 28.7, 22.5, 14.1 \]

HRMS (EI+)

Calculated for C_{14}H_{18}: 186.1409

Found: 186.1416

\[
[\alpha]_D^{25} -66.7 \text{ (c 1.4, CHCl}_3\text{)}
\]
Absolute stereochemical assignment was made according to the Lowe-Brewster rules and by analogy to known haloallene 2.16a.\(^\text{16}\)

The e.r. was determined by chiral GC using a Cyclodex B column:

\( t_r \) (major) 26.2 min, \( t_r \) (minor) 26.9 min; temperature: 110 °C; 6.5 mL/min: 63.0:37.0 e.r.

**Styrenyl allene 2.18.**

*Preparation of catalyst stock solution.* In a glove box, to a dry 7 mL vial charged with XPhos, (28.7 mg, 0.060 mmol) and Pd\(_2\)(dba)\(_3\) (13.3 mg, 0.014 mmol) was added THF (5 mL). The solution was stirred at 65 °C for 30 min to afford a dark orange solution.

*The prepared catalyst stock solution was used in the following reaction:* In a glovebox, to a 20 mL vial charged with Ag\(_2\)O (206.6 mg, 0.89 mmol) and styrenyl boronic acid (65.7 mg, 0.44 mmol) was added a solution of iodoallene 2.6 (134.5 mg, 0.29 mmol) in THF (6 mL). The catalyst solution was added in one portion. The vial was sealed with a septum cap and removed from the glovebox. To the vial was added degassed H\(_2\)O (0.87 mL). The solution stirred at 23 °C for 6 hr. The reaction mixture was filtered through a pad of celite and MgSO\(_4\), and concentrated *in vacuo*, dry loaded onto celite and purified via column chromatography on silica gel (Hexanes:EtOAc 100:0 → 97:3) to afford styrenyl allene 2.18 as a clear, colorless oil (89 mg, 70%).

TLC (Hexanes:EtOAc 9.5:0.5)

\( R_f = 0.42 \), visualized by short wave UV

\(^1\)H-NMR (500 MHz, CDCl\(_3\))

\( \delta \) 7.40 (d, \( J = 7.5 \) Hz, 2H), 7.31 (t, \( J = 7.5 \) Hz, 2H), 7.22 (t, \( J = 7.5 \) Hz, 1H), 6.59 – 6.48 (m, 2H), 6.08 (d, \( J = 8.5 \) Hz, 1H), 5.63 (m, 1H), 2.30 (app ddd, \( J = 12 \) Hz, 1H), 2.05 (s,
3H), 1.94 (app ddd, J = 12 Hz, 1H), 1.51 – 1.40 (m, 5H), 1.36 (s, 3H), 1.10 (s, 3H), 0.92 (s, 9H), 0.17 (s, 3H), 0.09 (s, 3H).

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

δ 204.7, 170.4, 137.3, 129.8, 128.5, 127.2, 126.1, 125.1, 116.0, 97.5, 75.0, 68.2, 47.4, 45.3, 35.5, 32.3, 30.8, 29.7, 26.1, 21.4, 18.3, -1.7, -2.3

HRMS (ESI+)

Calculated for C$_{27}$H$_{40}$O$_3$SiNa: 463.2644

Found: 463.2654

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

2958, 2929, 2895, 2858, 1936, 1739, 1598, 1471, 1362, 1246, 1159, 1076, 1034, 960, 883, 835, 775, 690, 579.

$\left[\alpha\right]_D^{24}$ -144.0 (c 1.3, CHCl$_3$)

Desilylated styrenyl allene 2.18a. To a solution of styrenyl allene 2.18 (86.0 mg, 0.20 mmol) in THF (1 mL) was added a solution of 1.0 M TBAF in THF (1 mL, 1 mmol). The solution stirred at 23 °C for 4 hr. To the resulting mixture was added saturated aqueous NaHCO$_3$ (0.50 mL). The solution stirred at 23 °C for 1 min. The organic layer was removed, dried over MgSO$_4$, and concentrated in vacuo. The resulting residue was dry loaded onto celite and purified via column chromatography on silica gel (Hexanes:EtOAc 100:0 → 75:25) to afford desilylated styrenyl allene 2.18a as a white foam (54 mg, 85%).

TLC (Hexanes:EtOAc 9:1)

$R_f = 0.09$, stained by KMnO$_4$
\(^1\)H-NMR (500 MHz, CDCl\(_3\))
\[ \delta 7.39 \text{ (d, } J = 7.5 \text{ Hz, } 2\text{H}), 7.31 \text{ (t, } J = 7.5 \text{ Hz, } 2\text{H}), 7.21 \text{ (t, } J = 7.5 \text{ Hz, } 1\text{H}), 6.58 - 6.47 \text{ (m, } 2\text{H}), 6.10 \text{ (d, } J = 7.5 \text{ Hz, } 1\text{H}), 5.38 \text{ (m, } 1\text{H}), 2.28 \text{ (app ddd, } J = 12 \text{ Hz, } 1\text{H}), 2.05 \text{ (s, } 3\text{H}), 1.98 \text{ (app ddd, } J = 12 \text{ Hz, } 1\text{H}), 1.67 \text{ (bs, } 1\text{H}), 1.59 - 1.34 \text{ (m, } 8\text{H}), 1.11 \text{ (s, } 3\text{H}). \]

\(^1^3\)C-NMR (125 MHz, CDCl\(_3\))
\[ \delta 204.2, 170.4, 137.2, 130.2, 128.5, 127.3, 126.1, 124.7, 115.9, 97.9, 72.5, 68.0, 45.2, 45.0, 35.6, 32.0, 31.1, 29.1, 21.4 \]

HRMS (ESI+)
Calculated for C\(_{21}\)H\(_{26}\)O\(_3\)Na: 349.1780
Found: 349.1774

IR (thin film, cm\(^{-1}\))
\[ 3454, 2966, 2926, 2868, 1934, 1736, 1454, 1367, 1247, 1161, 1072, 1030, 958, 858, 818, 748, 692, 590, 542. \]

\([\alpha]_D^{25} -16.9 \text{ (c 1.3, CHCl}_3\)]

**Deacylated styrenyl allene 2.19.** To a 7 mL vial containing desilylated styrenyl allene 2.18a (34.9 mg, 0.11 mmol) and finely group K\(_2\)CO\(_3\) (11.7 mg, 0.085 mmol) was added dry MeOH (1 mL). The solution stirred at 23 °C for 3.5 hr and was then poured into 10 mL H\(_2\)O. The mixture was diluted with 10 mL Et\(_2\)O and shaken. The layers were separated and the aqueous layer was extracted with Et\(_2\)O (2 x 10 mL). The combined organic phases were dried over MgSO\(_4\), filtered, and concentrated in vacuo. The resulting solid was dry loaded onto celite from an acetone solution and purified via column chromatography on silica gel (Hexanes:EtOAc 85:15 → 20:80) to afford deacylated styrenyl allene 2.19 as a white solid (26 mg, 87%).
TLC (Hexanes:EtOAc 1:1)

\[ R_f = 0.26, \text{stained by KMnO}_4 \]

\(^1\)H-NMR (500 MHz, CDCl\(_3\))

\[ \delta 7.39 (d, J = 7.5 \text{ Hz}, 2\text{H}), 7.31 (t, J = 7.5 \text{ Hz}, 2\text{H}), 7.21 (t, J = 7.5 \text{ Hz}, 1\text{H}), 6.58 – 6.47 (m, 2\text{H}), 6.09 (d, 8 \text{ Hz}, 1\text{H}), 4.31 (m, 1\text{H}), 2.25 (ddd, J = 13, 4, 2 \text{ Hz}, 1\text{H}), 1.94 (ddd, J = 13, 4, 2 \text{ Hz}, 1\text{H}), 1.51 (bs, 1\text{H}), 1.47 – 1.35 (m, 5\text{H}), 1.34 (s, 3\text{H}), 1.10 (s, 3\text{H}). \]

\(^13\)C-NMR (125 MHz, CDCl\(_3\))

\[ \delta 204.3, 137.2, 130.1, 128.6, 127.4, 126.2, 124.8, 116.2, 97.9, 72.9, 64.3, 49.2, 48.7, 35.7, 32.2, 31.2, 29.3 \]

HRMS (ESI+)

Calculated for C\(_{19}\)H\(_{25}\)O\(_2\): 285.1855

Found: 285.1842

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

3305, 2972, 2954, 1934, 1454, 1367, 1159, 1070, 1043, 964, 860, 820, 746, 690, 592, 519, 486.

\[ [\alpha]_D^{24} = -57.3 (c 1.0, \text{MeOH}) \]

X-ray quality crystals were grown by layering pentane onto a dissolved solution of \textit{10} in THF. After sitting at 23 °C for 10 hr, the sample was placed in a -20 °C freezer. Crystals formed within 3 hr.
**Iodoallene 2.35.** Iodoallene 2.35 was prepared as previously described.\(^2\) X-ray quality crystals of the unprotected iodoallene starting material 2.35 were grown by layering hexane onto a dissolved solution of the allene in Et\(_2\)O. The sample was placed in a -20 °C freezer. Crystals formed overnight. To the best of our knowledge, this is the first reported example of a crystal structure of an iodoallene.\(^{17}\)

**Pinacol ester 2.24.** In a glovebox, to a 20 mL vial equipped with a stir bar and charged with alkyne 2.22 (2.57 g, 8.7 mmol) was added solid dicyclohexylborane\(^{18}\) (203.4 mg, 1.1 mmol).\(^{19}\) The vial was sealed with a septum cap and removed from the glovebox. To the vial was added neat pinacol borane (1.4 mL, 9.6 mmol). The solution was stirred at 23 °C for 13 hr. The resulting thick white paste was dissolved in Et\(_2\)O, dry loaded onto Celite, and purified via flash chromatography on silica gel (Hexanes:EtOAc 95:5) to afford pinacol ester 2.24 as a white solid (3.0 g, 81%).
TLC (Hexanes:EtOAc 9:1)

R<sub>f</sub> = 0.50, stained by KMnO<sub>4</sub>

<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)

δ 6.68 (d, J = 18 Hz, 1H), 5.54 (d, J = 18 Hz, 1H), 3.72 (m, 1H), 2.09 (ddd, J = 14.5, 5, 1 Hz, 1H), 1.50 (dd, J = 14.5, 8 Hz, 1H), 1.36 (ddd, J = 13, 3.5, 1Hz, 1H), 1.14 (s, 12H), 1.10 (m, 1H), 1.03 (s, 3H), 1.02 (s, 3H), 0.81 (s, 3H), 0.75 (s, 9H), -0.090 (s, 3H), -0.094 (s, 3H).

<sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>)

δ 147.9, 82.9, 70.9, 66.0, 64.5, 46.9, 41.1, 34.5, 29.3, 25.7, 24.7, 24.6, 19.9, 17.9, -4.9, -4.9

<sup>11</sup>B-NMR (96 MHz, CDCl<sub>3</sub>)

δ 31.1

HRMS (ESI+)

Calculated for C<sub>23</sub>H<sub>44</sub>BO<sub>4</sub>Si: 423.3102

Found: 423.3120

IR (thin film, cm<sup>-1</sup>)

2976, 2953, 2926, 2854, 1635, 1462, 1379, 1344, 1321, 1250, 1198, 1144, 1072, 966, 922, 881, 835, 775, 667, 650, 567.

[α]<sub>D</sub><sup>27</sup> -75.6 (c 1.1, CHCl<sub>3</sub>)

X-ray quality crystals were grown by layering pentane onto a dissolved solution of 2.24 in acetone. After the layers slowly mixed, the solvent was allowed to slowly evaporate to yield crystals.
MIDA boronate 2.31. To a 250 mL round bottom flask equipped with a stir bar and charged with pinacol ester 2.24 (2.54 g, 6.0 mmol) was added N-methyliminodiacetic acid, MIDA, (5.48 g, 37.2 mmol) and DMSO (60 mL). The flask was sealed and the reaction stirred at 65 °C for 10.5 hr. The resulting solution was poured into 500 mL H₂O. The mixture was diluted with 250 mL EtOAc and shaken. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 150 mL). The combined organic phases were dried over MgSO₄, filtered, and concentrated in vacuo. The resulting residue was dry loaded onto Celite from an acetone solution and purified via flash chromatography on silica gel (Et₂O:Acetone 100:0 → 40:60) to afford MIDA boronate 2.31 as a white solid (1.18 g, 44%) and unreacted starting material (1.18 g recovered). The unreacted starting material was subjected to two additional cycles of the above procedure to afford MIDA boronate 2.31 as a white solid (1.98 g total, 73%).

TLC (Et₂O:MeCN 4:1)

\[ R_f = 0.44, \text{stained by KMnO}_4 \]
**1H-NMR (500 MHz, d$_6$-acetone)**
\[\delta 6.39 \text{ (d, } J = 18 \text{ Hz, 1H)}, 5.71 \text{ (d, } J = 18 \text{ Hz, 1H)}, 4.23 \text{ (dd, } J = 17, 2 \text{ Hz, 2H)}, 4.06 \text{ (dd, } J = 17, 4 \text{ Hz, 2H)}, 3.88 \text{ (m, 1H)}, 3.01 \text{ (s, 3H)}, 2.21 \text{ (ddd, } J = 14, 5, 1 \text{ Hz, 1H)}, 1.66 \text{ (dd, } J = 14.5, 8.5 \text{ Hz, 1H)}, 1.50 \text{ (ddd, } J = 14, 5, 1 \text{ Hz, 1H)}, 1.30 - 1.19 \text{ (m, 1H)}, 1.15 \text{ (s, 3H)}, 1.14 \text{ (s, 3H)}, 0.93 \text{ (s, 3H)}, 0.88 \text{ (s, 9H)}, 0.06 \text{ (s, 3H)}, 0.05 \text{ (s, 3H)}.

**13C-NMR (125 MHz, d$_6$-acetone)**
\[\delta 169.0, 140.7, 71.4, 66.5, 65.6, 62.3, 47.9, 47.5, 42.1, 35.4, 29.8, 26.2, 25.4, 20.4, 18.5, -4.6, -4.6

**11B-NMR (96 MHz, d$_6$-acetone)**
\[\delta 11.5

**HRMS (ESI+)**
Calculated for C$_{22}$H$_{39}$BNO$_6$Si: 452.2640

Found: 452.2657

**IR (thin film, cm$^{-1}$)**
2953, 2929, 2856, 1780, 1753, 1637, 1460, 1389, 1340, 1294, 1255, 1090, 1034, 1007, 953, 881, 858, 837, 773, 681, 588, 513.

\[\alpha_{D}^{25} -55.7 \text{ (c 1.0, CHCl}_3\text{)}

**Propynyl MIDA boronate 2.25.** To a 300 mL 3-neck round bottom flask equipped with a stir bar was added B(OMe)$_3$ (5.9 mL, 53 mmol) and THF (50 mL). The solution was cooled to -78 °C. Propynylmagnesium bromide (0.5 M in THF, 100 mL, 50 mmol) was added dropwise via cannula over 45 min. The resulting solution was stirred at -78 °C for 1.5 hr, followed by stirring at 23 °C for 2 hr. In a separate 500 mL 3-neck round bottom flask equipped with a stir bar,
internal thermometer, 500 mL addition funnel, and distillation apparatus was added MIDA (15.0 g, 102 mmol) and DMSO (50 mL). The solution was heated with an oil bath to an internal temperature of 110 - 115 °C. The borate suspension was transferred to the addition funnel and was continuously agitated with a stream of nitrogen. The borate suspension was added dropwise to the hot MIDA solution over 2 hr 50 min, keeping the internal temperature between 105 and 115 °C. After full addition of the borate suspension, the reaction solution was cooled to 60 °C and placed under vacuum (300 mTorr) to distill the reaction to dryness. The resulting foam was cooled to 23 °C and dissolved in 200 mL EtOAc, 50 mL acetone, and 75 mL H₂O and poured into 200 mL EtOAc:Acetone (1:1) and 75 mL brine. The mixture was shaken and the aqueous layer was removed and extracted with EtOAc (1 x 100 mL). The combined organic phases were washed with brine (2 x 20 mL). The brine wash was back extracted with EtOAc:Acetone (2:1, 1 x 75 mL) The combined organic phases were dried over MgSO₄, filtered, and concentrated in vacuo. The resulting yellow solid was dissolved in 100 mL THF and 1000 mL Et₂O was added to precipitate the product. The resulting solid was collected by vacuum filtration to yield propynyl MIDA boronate 2.25 as a white solid (7.48 g, 77%).

TLC (Et₂O:Acetone 2:1)

R<sub>f</sub> = 0.28, stained by KMnO₄

<sup>1</sup>H-NMR (500 MHz, d₆-acetone)

δ 4.22 (d, J = 17 Hz, 2H), 4.05 (d, J = 17 Hz, 2H), 3.18 (s, 3H), 1.83 (s, 3H).

<sup>13</sup>C-NMR (125 MHz, d₆-acetone)

δ 168.6, 62.1, 48.2, 41.1, 4.0

<sup>11</sup>B-NMR (96 MHz, d₆-acetone)

δ 6.8

HRMS (ESI+)

Calculated for C₉H₁₁BNO₄: 196.0781
Found: 196.0784
IR (thin film, cm\(^{-1}\))
3009, 2957, 2203, 1790, 1620, 1260, 1192, 1169, 1092, 994, 882, 858, 706.

MIDA boronate 2.26. In a glovebox, to a 500 mL round bottom flask equipped with a stir bar and charged with propynyl MIDA boronate 2.25 (5.65 g, 29.0 mmol) was added [Mo(allyl)Br(CO)\(_2\)(CH\(_3\)CN)\(_2\)]\(^{21}\) (705.4 mg, 1.98 mmol). The round bottom was sealed with a septum, removed from the glovebox, and placed under a nitrogen atmosphere. THF (140 mL) was added and the solution was cooled to 0 °C. To the resulting solution was added Bu\(_3\)SnH (7.6 mL, 28.2 mmol) dropwise over 45 min to give a dark brown solution. The reaction solution was recharged with a solution of [Mo(allyl)Br(CO)\(_2\)(CH\(_3\)CN)\(_2\)] (700.0 mg, 1.97 mmol) in THF (6 mL) in one portion, followed by Bu\(_3\)SnH (7.6 mL, 28.2 mmol) dropwise over 10 min. The cold bath was removed and the reaction solution was stirred at 23 °C for 2.5 hr. The resulting dark brown solution was concentrated in vacuo. The resulting foam was dissolved in hexanes and loaded onto a silica gel column. Purification via flash chromatography (Et\(_2\)O:MeCN 100:0 → 80:20) afforded MIDA boronate 2.26 as a pale yellow foam (11.8 g, 84%).

TLC (Et\(_2\)O:MeCN 4:1)
R\(_f\) = 0.70, stained by KMnO\(_4\)

\(^1\)H-NMR (500 MHz, d\(_6\)-acetone)
δ 5.74 (q, J = 1.5 Hz, 1H), 4.17 (d, J = 17 Hz, 2H), 3.98 (d, J = 17 Hz, 2H), 3.03 (s, 3H), 2.11 (d, J = 1.5 Hz, 3H), 1.64 – 1.45 (m, 6H), 1.34 (app sext, J = 7.5 Hz, 6H), 1.02 – 0.86 (m, 15H).

\(^{13}\)C-NMR (100 MHz, d\(_6\)-acetone)
δ 168.9, 161.1, 62.1, 46.9, 29.6, 27.7, 24.0, 13.7, 9.4
**11B-NMR** (96 MHz, d6-acetone)

δ 10.4

**HRMS** (ESI+)

Calculated for C20H39BNO4Sn: 488.2002

Found: 488.2008

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

3002, 2957, 2926, 2872, 2853, 1767, 1587, 1461, 1376, 1337, 1293, 1125, 1022, 922, 873, 822, 760, 733, 689, 660, 593.

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**MIDA boronate BB\(_2\)**. In a glovebox, to a 1000 mL round bottom equipped with a stir bar, MIDA boronate 2.26 (23.1 g, 47.6 mmol), and dibromolactone 2.27\(_{22}\) (13.2 g, 51.9 mmol) was added Pd\(_2\)(dba)\(_3\) (1.31 g, 1.4 mmol) and AsPh\(_3\) (878.0 mg, 2.9 mmol). The round bottom was sealed with a septum, removed from the glovebox, and placed under a nitrogen atmosphere. THF (250 mL) was added and the flask was sealed under a nitrogen atmosphere. The reaction solution was stirred at 60 °C for 3 hr and was then cooled to 23 °C. The resulting dark yellow solution was concentrated *in vacuo*. The resulting solid was dry loaded onto Celite from an acetone solution and purified via flash chromatography on silica gel (Et\(_2\)O:Acetone 100:0 → 50:50) to afford MIDA boronate 2.4 as a pale yellow solid (13.6 g, 77%).

**TLC** (Et\(_2\)O:Acetone 4:1)

R\(_f\) = 0.24, stained by KMnO\(_4\)

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**1H-NMR** (500 MHz, d6-acetone)

δ 7.96 (d, \(J = 0.5\) Hz, 1H), 6.03 (dd, \(J = 1\), 0.5 Hz, 1H), 5.92 (app quint, \(J = 1\) Hz, 1H), 4.26 (d, \(J = 17\) Hz, 2H), 4.10 (d, \(J = 17\) Hz, 2H), 3.10 (s, 3H), 2.23 (d, \(J = 1\) Hz, 3H).
$^{13}$C-NMR (125 MHz, d$_6$-acetone)
\[ \delta 168.8, 166.0, 146.6, 145.8, 145.1, 122.1, 110.6, 62.5, 47.2, 18.6 \]

$^{11}$B-NMR (96 MHz, d$_6$-acetone)
\[ \delta 11.2 \]

HRMS (ESI+)
Calculated for C$_{13}$H$_{14}$BBrNO$_6$: 370.0098
Found: 370.0089

IR (thin film, cm$^{-1}$)
3011, 2957, 2919, 2229, 1765, 1630, 1590, 1454, 1338, 1292, 1188, 1125, 891, 866, 821, 751, 710, 563.

X-ray quality crystals were grown by layering Et$_2$O onto a dissolved solution of 2.4 in acetone. The layers slowly mixed, forming crystals.
Isoprenyl MIDA boronate 2.28. To a 500 mL 3-neck round bottom flask equipped with a stir bar was added B(OMe)_3 (12.0 mL, 105 mmol) and THF (100 mL). The solution was cooled to -78 °C. Isoprenylmagnesium bromide (0.5 M in THF, 200 mL, 100 mmol) was added dropwise via cannula over 2 hr. The resulting solution was stirred at -78 °C for 1.5 hr, followed by stirring at 23 °C for 2 hr. To a separate 1000 mL 3-neck round bottom flask equipped with a stir bar, internal thermometer, 500 mL addition funnel, and distillation apparatus was added MIDA (29.9 g, 203 mmol) and DMSO (100 mL). The solution was heated with an oil bath to an internal temperature of 110 - 115 °C. The borate suspension was transferred to the addition funnel and was continuously agitation with a stream of nitrogen. The borate suspension was added dropwise to the hot MIDA solution over 2 hr, keeping the internal temperature between 100 and 115 °C. After full addition of the borate suspension, the reaction solution was cooled to 60 °C and placed under vacuum (250 mTorr) to distill the reaction to dryness. The resulting foam was cooled to 23 °C and dissolved in 400 mL EtOAc and 150 mL H_2O and poured into 400 mL EtOAc:Acetone (1:1) and 150 mL brine. The mixture was shaken and the aqueous layer was removed and extracted with EtOAc (2 x 200 mL). The combined organic phases were washed with brine (2 x 20 mL). The brine wash was back extracted with EtOAc:Acetone (2:1, 1 x 75 mL). The combined organic phases were dried over MgSO_4, filtered, and concentrated in vacuo. The resulting white solid was suspended in 150 mL THF and 1500 mL of Et_2O was added to precipitate the product. The resulting solid was collected by vacuum filtration to yield isoprenyl MIDA boronate 2.28 as a white solid (15.91 g, 81%).

TLC (Et_2O:MeCN 4:1)

R_f = 0.43, stained by KMnO_4

^1^H-NMR (500 MHz, d_6-acetone)

δ 5.45 (bs, 1H), 5.32 (d, J = 2.5 Hz, 1H), 4.21 (d, J = 17 Hz, 2H), 4.03 (d, J = 17 Hz, 2H), 3.00 (s, 3H), 1.78 (s, 3H).
\[ ^{13}\text{C-NMR} \ (100 \text{ MHz, } d_6-\text{acetone}) \]
\[ \delta 169.1, 124.4, 62.5, 47.0, 22.0 \]

\[ ^{11}\text{B-NMR} \ (128 \text{ MHz, } d_6-\text{acetone}) \]
\[ \delta 11.2 \]

**HRMS (ESI+)**
Calculated for \( \text{C}_8\text{H}_{13}\text{BNO}_4 \): 198.0938
Found: 198.0934

**IR (thin film, cm\(^{-1}\))**
3059, 2999, 2956, 2918, 1757, 1456, 1340, 1294, 1250, 1190, 1149, 1063, 1024, 993, 966, 926, 860, 741, 710, 638, 592, 567.

**MIDA Boronate 2.29.** To a 500 mL round bottom flask equipped with a stir bar and charged with isoprenyl MIDA boronate 2.28 (11.88 g, 60.3 mmol) was added CH\(_2\)Cl\(_2\) (525 mL). The resulting clear, colorless solution was cooled to 0 °C in an ice bath. Neat bromine (4.7 mL, 91.4 mmol) was added dropwise over 15 minutes to give a cloudy orange solution. The solution was warmed to 23 °C over 1 hr and then heated to reflux for 2 hr. The resulting orange solution was cooled to 23 °C and concentrated in vacuo to give a yellow solid. This solid was azeotroped with CH\(_2\)Cl\(_2\) (2 x 100 mL) to remove residual bromine.

The resulting white solid was suspended in MeCN (525 mL). 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU, 28 mL, 187.4 mmol) was added in one portion. The resulting mixture stirred at 23 °C for 1 hr to give a clear, brown solution. The solution was poured into a separatory funnel containing EtOAc:Acetone (4:1, 1000 mL) and 1 M aq. HCl (600 mL). After shaking, the layers were separated. The organic layer was washed with saturated aqueous sodium bisulfite:brine (3:2, 1 x 210 mL) and then brine (1 x 100 mL). The organic layer was dried over MgSO\(_4\),
filtered, and concentrated *in vacuo*. The resulting oil was dissolved in 60 mL EtOAc and 20 mL acetone. Et$_2$O was added in 20 mL portions to precipitate the product. The resulting solid was collected by vacuum filtration to afford MIDA boronate 2.29 as a white solid (11.03 g, 67%).

TLC (Et$_2$O:MeCN 4:1)

\[ R_f = 0.60, \text{stained by KMnO}_4 \]

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

\[ \delta 6.55 (q, J = 1.5 \text{ Hz, } 1\text{H}), 4.31 (d, J = 17 \text{ Hz, } 2\text{H}), 4.15 (d, J = 17 \text{ Hz, } 2\text{H}), 3.04 (s, 3\text{H}), 1.79 (d, J = 1.5 \text{ Hz, } 3\text{H}). \]

$^{13}$C-NMR (100 MHz, d$_6$-acetone)

\[ \delta 168.7, 115.3, 62.8, 47.3, 18.6 \]

$^{11}$B-NMR (128 MHz, d$_6$-acetone)

\[ \delta 10.9 \]

HRMS (ESI+)

Calculated for C$_8$H$_{12}$BBrNO$_4$: 276.0043

Found: 276.0040

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

3082, 3012, 2954, 2924, 2858, 1768, 1593, 1454, 1336, 1282, 1182, 1041, 891, 864, 798, 721, 694, 586.

X-ray quality crystals were grown by layering pentane onto a dissolved solution of 2.29 in acetone. The layers slowly mixed, forming crystals.
MIDA Boronate 2.41. In a glovebox, to a 500 mL round bottom flask equipped with a stir bar and charged with MIDA boronate 2.29 (5.35 g, 19.4 mmol) was added trans-bis(triphenylphosphine)palladium dichloride (680.0 mg, 0.97 mmol). The round bottom was sealed with a septum, removed from the glovebox and placed under nitrogen. THF (40 mL) and DMF (150 mL) were added to give a clear, yellow solution. (E)-triethyl(2-(tributylstannyl)vinyl)germane 2.30 (11.1 g, 23.3 mmol) was added in one portion. The round bottom was sealed under nitrogen and the solution was stirred at 60 °C for 20.5 hr. The dark brown reaction solution was cooled to 23 °C and was poured into a separatory funnel containing 400 mL H₂O:brine (1:1) and 250 mL EtOAc. After shaking, the layers were separated. The aqueous layer was extracted with EtOAc (2 x 150 mL). The combined organic layers were washed with H₂O:brine (1:1, 2 x 100 mL). The organic layer was dried over MgSO₄, filtered, and concentrated in vacuo. The resulting residue was dry loaded onto Celite from an acetone solution and purified by flash chromatography on silica gel (Et₂O:MeCN 100:0 → 70:30) to afford MIDA boronate 2.41 as a pale yellow solid (5.5 g, 74%).

TLC (Et₂O:MeCN 4:1)
Rₜ = 0.57, stained by KMnO₄

123
**H-NMR (500 MHz, d₆-acetone)**

δ 6.95 (dd, J = 18, 10.5 Hz, 1H), 6.38 (d, J = 10.5 Hz, 1H), 6.05 (d, J = 18 Hz, 1H), 4.21 (d, J = 17 Hz, 2H), 4.05 (d, J = 17 Hz, 2H), 2.99 (s, 3H), 1.82 (d, J = 1 Hz, 3H), 1.05 (t, J = 8 Hz, 9H), 0.83 (q, J = 8 Hz, 6H).

**C-NMR (125 MHz, d₆-acetone)**

δ 169.2, 141.0, 139.5, 133.3, 62.7, 47.1, 15.1, 9.2, 4.8

**B-NMR (128 MHz, d₆-acetone)**

δ 11.7

HRMS (ESI+)

Calculated for C₁₆H₂₉BGeNO₄: 384.1408

Found: 384.1430

IR (thin film, cm⁻¹)

3006, 2953, 2929, 2908, 2872, 1763, 1564, 1460, 1338, 1294, 1254, 1174, 1026, 991, 889, 850, 731, 708, 575.

**MIDA Boronate 2.43.** In a subdued light environment, to a 1000 mL round bottom flask equipped with a stir bar and charged with MIDA boronate 2.42 (6.29 g, 16.5 mmol) was added MeOH (450 mL) to give a clear, pale yellow solution. The solution was cooled to -78 °C. A solution of iodine (12.57 g, 49.5 mmol) in MeOH (150 mL) was added to the cooled reaction solution dropwise via cannula over 45 min. After stirring at -78 °C for 3 hr, 200 mL saturated aqueous sodium bisulfite and 150 mL EtOAc were added in one portion to give a clear, yellow solution. The cold bath was removed and replaced with a 23 °C water bath. The reaction solution was warmed to 23 °C over 30 min. The solution was poured into a separatory funnel containing 500 mL H₂O and 500 mL EtOAc. After shaking, the layers were separated and the
aqueous layer was extracted with EtOAc (2 x 250 mL). The combined organic layers were washed with saturated aqueous sodium bisulfite (1 x 150 mL) and brine (1 x 150 mL). The organic layer was dried over MgSO₄, filtered, and concentrated in vacuo. The resulting residue was dry loaded onto Celite from an acetone solution and purified by flash chromatography on silica gel (Et₂O:MeCN 100:0 → 80:20) to afford MIDA boronate 2.43 as a pale yellow solid (4.43 g, 77%).

TLC (Et₂O:MeCN 4:1)

Rᶠ = 0.48, visualized by short wave UV

¹H-NMR (500 MHz, d₆-acetone)

δ 7.48 (dd, J = 14.5, 11 Hz, 1H), 6.59 (d, J = 14.5 Hz, 1H), 6.34 (d, J = 11 Hz, 1H), 4.22 (d, J = 17 Hz, 2H), 4.05 (d, J = 17 Hz, 2H), 2.98 (s, 3H), 1.77 (s, 3H).

¹³C-NMR (125 MHz, d₆-acetone)

δ 169.1, 142.7, 136.3, 82.1, 62.6, 47.1, 15.3

¹¹B-NMR (128 MHz, d₆-acetone)

δ 11.5

HRMS (ESI+)

Calculated for C₁₀H₁₄BINO₄: 350.0061

Found: 350.0067

IR (thin film, cm⁻¹)

3049, 3008, 2956, 2870, 1766, 1612, 1454, 1336, 1292, 1248, 1227, 1194, 1167, 1119, 1032, 962, 889, 850, 710.
MIDA Boronate 2.44. In a glovebox, to a 300 mL round bottom flask equipped with a stir bar and charged with MIDA boronate 2.43 (4.43 g, 12.6 mmol) was added copper(I) thiophene-2-carboxylate\textsuperscript{24} (CuTc, 3.60 g, 18.9 mmol) and tetrakis(triphenylphosphine)palladium (735.6 mg, 0.64 mmol). The round bottom was sealed with a septum, removed from the glovebox and placed under nitrogen. DMF (120 mL) was added to give a dark green solution. This solution was cooled to 0 °C. (E)-triethyl(2-(tributylstanny)vinyl)germane 2.30 (7.20 g, 15.1 mmol) was added in one portion to give a dark brown solution. The 0 °C bath was removed. The round bottom was sealed under nitrogen and the solution was stirred at 23 °C in a subdued light environment for 4 hr. The dark brown reaction solution was poured into a separatory funnel containing 400 mL H\textsubscript{2}O:brine (1:1) and 400 mL EtOAc. After shaking, the layers were separated. The aqueous layer was extracted with EtOAc (2 x 200 mL). The combined organic layers were washed with H\textsubscript{2}O (2 x 200 mL) and brine (1 x 150 mL). The aqueous washes were back extracted with EtOAc (1 x 100 mL). The combined organic layers were dried over MgSO\textsubscript{4}, filtered, and concentrated \textit{in vacuo}. The resulting residue was dry loaded onto Celite from an acetone solution and purified by flash chromatography on silica gel (Et\textsubscript{2}O:MeCN 100:0 → 80:20) to afford MIDA boronate 2.44 as a pale yellow solid (2.94 g, 58\%).

TLC (Et\textsubscript{2}O:MeCN 4:1)

R\textsubscript{f} = 0.52, stained by KMnO\textsubscript{4} and visualized by short wave UV

\textsuperscript{1}H-NMR (500 MHz, d\textsubscript{6}-acetone)

\[ \delta 6.72 – 6.63 (m, 2H), 6.42 (d, J = 10.5 Hz, 1H), 6.29 (dd, J = 14.5, 10.5 Hz, 1H), 6.07 (d, J = 18.5 Hz, 1H), 4.21 (d, J = 17 Hz, 2H), 4.04 (d, J = 17 Hz, 2H), 2.97 (s, 3H), 1.82 (d, J = 1.5 Hz, 3 H), 1.04 (t, J = 8 Hz, 3H), 0.82 (q, J = 8 Hz, 6H).\]

\textsuperscript{13}C-NMR (125 MHz, d\textsubscript{6}-acetone)

\[ \delta 169.1, 145.7, 137.0, 136.6, 133.0, 129.5, 62.6, 47.1, 15.2, 9.1, 4.8 \]
$^{11}$B-NMR (128 MHz, d$_6$-acetone)

$\delta$ 11.8

HRMS (ESI+)

Calculated for C$_{18}$H$_{31}$BGeNO$_4$: 410.1558

Found: 410.1567

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

3016, 2954, 2906, 2872, 1765, 1599, 1458, 1427, 1338, 1296, 1248, 1174, 1026, 999, 968, 891, 847, 769, 708, 650, 577.

**MIDA Boronate 2.5.** In a subdued light environment, to a 500 mL round bottom flask equipped with a stir bar and charged with MIDA boronate 2.44 (2.94 g, 7.2 mmol) was added MeOH (180 mL) to give a cloudy, pale yellow solution. The solution was cooled to -78 °C. A solution of iodine (5.57 g, 21.9 mmol) in MeOH (60 mL) was added to the cooled reaction solution dropwise via cannula over 15 min. After stirring at -78 °C for 3 hr, 100 mL saturated aqueous sodium bisulfite and 100 mL EtOAc were added in one portion to give a clear, yellow solution. The cold bath was removed and replaced with a 23 °C water bath. The reaction solution was warmed to 23 °C over 30 min. The solution was poured into a separatory funnel containing 400 mL H$_2$O and 500 mL EtOAc. After shaking, the layers were separated and the aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with saturated aqueous sodium bisulfite (1 x 100 mL) and brine (1 x 100 mL). The organic layer was dried over MgSO$_4$, filtered, and concentrated *in vacuo*. The resulting residue was dissolved in a small amount of acetone and the product was precipitated with Et$_2$O. The resulting pale yellow solid was triturated with Et$_2$O (4 x 100 mL) to afford MIDA boronate 2.5 as a pale yellow solid (2.01 g, 75%).
TLC (Et₂O:MeCN 4:1)

\[ R_f = 0.50, \] stained by KMnO₄ and visualized by short wave UV

\(^1\)H-NMR (500 MHz, d₆-acetone)

\[ \delta 7.23 \text{ (ddd, } J = 14.5, 11, 0.5 \text{ Hz, 1H}), 6.75 \text{ (dd, } J = 15, 11 \text{ Hz, 1H}), 6.55 \text{ (d, } J = 14.5 \text{ Hz, 1H}), 6.38 \text{ (dd, } J = 11.5, 1.5 \text{ Hz, 1H}), 6.28 \text{ (dd, } J = 15, 11 \text{ Hz, 1H}), 4.22 \text{ (d, } J = 17 \text{ Hz, 2H}), 4.05 \text{ (d, } J = 17 \text{ Hz, 2H}), 2.98 \text{ (s, 3H)}, 1.80 \text{ (d, } J = 1.5 \text{ Hz, 3H}). \]

\(^1^3\)C-NMR (125 MHz, d₆-acetone)

\[ \delta 169.1, 146.8, 136.3, 133.5, 130.4, 79.7, 62.7, 47.1, 15.4 \]

\(^1^1\)B-NMR (128 MHz, d₆-acetone)

\[ \delta 11.7 \]

HRMS (ESI+)

Calculated for C₁₂H₁₆BINO₄:

\[ 376.0217 \]

Found:

\[ 376.0213 \]

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

3045, 3006, 2956, 2929, 2870, 1768, 1699, 1547, 1454, 1338, 1292, 1250, 1213, 1169, 1140, 1119, 1036, 989, 889, 862, 843, 710.

**MIDA boronate 2.33.** To a 20 mL vial equipped with a stir bar and charged with MIDA boronate 2.31 (500.7 mg, 1.1 mmol) was added THF (11 mL) and 1M aq. NaOH (3.3 mL). The mixture was vigorously stirred at 23 °C for 15 minutes. The reaction mixture was then poured
into aqueous sodium phosphate buffer (0.5 M, pH 7.0, 10 mL) and diluted with Et$_2$O (10 mL). The mixture was shaken and the layers were separated. The aqueous phase was extracted with THF:Et$_2$O (1:1, 2 x 10 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. Residual solvent was co-evaporated with toluene. The boronic acid 2.32 was isolated as a white solid (358.5 mg, 95%).

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

δ 6.82 (m, 3H), 5.65 (d, $J = 18$ Hz, 1H), 3.87 (m, 1H), 2.21 (ddd, $J = 14.5$, 5, 1 Hz, 1H), 1.66 (dd, $J = 14.5$, 8 Hz, 1H), 1.50 (ddd, $J = 13$, 4, 1.5 Hz, 1H), 1.30 – 1.18 (m, 1H), 1.16 (s, 3H), 1.12 (s, 3H), 0.91 (s, 3H), 0.89 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H).

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

δ 145.9, 71.5, 66.4, 65.6, 47.8, 42.0, 35.3, 29.7, 26.2, 25.4, 20.2, 18.5, -4.6, -4.6

The boronic acid 2.32 was used immediately in the following reaction:

Preparation of catalyst solution. In a glovebox, to a 7 mL vial charged with XPhos (46.3 mg, 0.10 mmol) and Pd(OAc)$_2$ (11.8 mg, 0.053 mmol) was added THF (2.5 mL). The solution was stirred at 23 °C for 20 min to afford a clear, brown solution.

The freshly prepared catalyst solution was used in the following reaction:

In a glovebox, to a 40 mL vial charged with MIDA boronate 2.4 (285.3 mg, 0.77 mmol) was added finely ground anhydrous K$_3$PO$_4$ (481.3 mg, 2.3 mmol). The prepared boronic acid (358.5 mg, 1.1 mmol) was added as a solution in THF:Toluene (1:2, 10.0 mL). The prepared catalyst solution was added in one portion. The vial was sealed with a septum cap and removed from the glovebox. The solution was stirred in a subdued light environment at 45 °C for 24.5 hr. The reaction mixture was filtered through a pad of Celite, concentrated in vacuo, dry loaded onto Celite from an acetone solution, and purified via flash chromatography on florisil (Et$_2$O:MeCN 100:0 → 80:20) to afford MIDA boronate 2.33 as a pale yellow solid (358.0 mg, 79%).
TLC (Et<sub>2</sub>O:MeCN 4:1)
R<sub>f</sub> = 0.69, visualized by short wave and long wave UV

<sup>1</sup>H-NMR (400 MHz, d<sub>6</sub>-acetone)
δ 7.52 (s, 1H), 7.19 (d, J = 15.5 Hz, 1H), 6.40 (d, J = 15.5 Hz, 1H), 5.93 (s, 1H), 5.82 (s, 1H), 4.26 (d, J = 17 Hz, 2H), 4.10 (d, J = 17 Hz, 2H), 3.89 (m, 1H), 3.09 (s, 3H), 2.28 – 2.21 (m, 4H), 1.71 (dd, J = 14.5, 8.5 Hz, 1H), 1.53 (ddd, J = 13, 3.5, 1.5 Hz, 1H), 1.35 – 1.23 (m, 1H), 1.20 (s, 3H), 1.16 (s, 3H), 0.95 (s, 3H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H).

<sup>13</sup>C-NMR (100 MHz, d<sub>6</sub>-acetone)
δ 169.2, 168.8, 147.2, 146.4, 138.7, 134.9, 126.5, 122.3, 121.0, 70.7, 67.7, 65.5, 62.5, 47.6, 47.2, 42.0, 35.7, 29.6, 26.2, 25.4, 20.1, 18.7, 18.6, -4.6, -4.6

<sup>11</sup>B-NMR (128 MHz, d<sub>6</sub>-acetone)
δ 11.1

HRMS (ESI+)
Calculated for C<sub>30</sub>H<sub>45</sub>BNO<sub>8</sub>Si: 586.3008
Found: 586.2983

IR (thin film, cm<sup>-1</sup>)
3003, 2956, 2929, 2856, 1765, 1630, 1591, 1387, 1338, 1292, 1255, 1188, 1155, 1124, 1089, 1028, 989, 893, 862, 837, 773, 735, 582.

[α]<sub>D</sub><sup>8</sup> -93.5 (c 0.85, CHCl<sub>3</sub>)
**Pinacol ester 2.45.** To a 20 mL vial equipped with a stir bar and charged with MIDA boronate 2.33 (338.2 mg, 0.58 mmol) was added pinacol (110.3 mg, 0.93 mmol) and solid NaHCO$_3$ (252.6 mg, 3.0 mmol). MeOH (5.8 mL) was added and the suspension was stirred in a subdued light environment at 45 °C for 3 hr. The mixture was filtered through a pad of Celite, eluting with EtOAc (125 mL). The collected solution was concentrated *in vacuo*. The resulting residue was azeotroped with toluene (2 x 5 mL) and was then dissolved in toluene (5.8 mL). To remove residual pinacol, finely ground CaCl$_2$ (337.8 mg, 3.0 mmol) and solid NaHCO$_3$ (252.3 mg, 3.0 mmol) were added. The suspension was stirred at 23 °C for 1.5 hr and was then filtered through a pad of Celite, eluting with EtOAc (125 mL). The collected solution was concentrated *in vacuo* to afford pinacol ester 2.45 as a deep red solid (318.3 mg, 99%).

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

δ 7.54 (s, 1H), 7.22 (d, $J = 15.5$ Hz, 1H), 6.42 (d, $J = 15.5$ Hz, 1H), 5.95 (s, 1H), 5.65 (s, 1H), 3.90 (m, 1H), 2.36 (s, 3H), 2.25 (ddd, $J = 14.5$, 5, 1 Hz, 1H), 1.72 (dd, $J = 14.5$, 8.5 Hz, 1H), 1.53 (ddd, $J = 13$, 3.5, 1 Hz, 1H), 1.34 – 1.23 (m, 13 H), 1.20 (s, 3H), 1.17 (s, 3H), 0.95 (s, 3H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H).

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

δ 168.9, 153.0, 148.8, 138.3, 135.5, 127.3, 122.2, 119.2, 83.7, 70.7, 67.7, 65.4, 47.6, 41.9, 35.6, 29.6, 26.2, 25.4, 25.1, 20.2, 20.1, 18.5, -4.5, -4.6

$^{11}$B-NMR (128 MHz, d$_6$-acetone)

δ 30.9

HRMS (ESI+)

Calculated for C$_{31}$H$_{50}$BO$_6$Si: 557.3470

Found: 557.3483
IR (thin film, cm\(^{-1}\))

2956, 2929, 2858, 1765, 1593, 1371, 1257, 1144, 1080, 1032, 976, 953, 852, 837, 775, 580.

\[ \alpha_{D}^{25} -24.4 \ (c \ 1.1, \ CHCl_{3}) \]

MIDA boronate 2.34. In a glovebox, to a 7 mL vial equipped with a stir bar and charged with pinacol ester 2.45 (105.7 mg, 0.19 mmol), MIDA boronate 2.5 (100.3 mg, 0.27 mmol), and Ag\(_2\)O (141.2 mg, 0.61 mmol) was added trans-bis(triphenylphosphine)palladium dichloride (9.0 mg, 0.013 mmol) and DMSO (2.0 mL). The vial was sealed with a cap and removed from the glovebox. The solution was stirred in a subdued light environment at 45 °C for 12 hr. The reaction mixture was poured into a separatory funnel containing EtOAc (30 mL). The organic layer was washed with H\(_2\)O:brine (5:1, 3 x 15 mL). The organic layer was dried over MgSO\(_4\), filtered, and concentrated in vacuo. The resulting residue was dry loaded onto Celite from an acetone solution, and purified via reverse phase flash chromatography on C18 silica gel (H\(_2\)O:MeCN 95:5 → 0:100) to afford MIDA boronate 2.34 as an orange solid (57.6 mg, 45%).

TLC (Et\(_2\)O:MeCN 4:1)

\( R_{f} = 0.51 \), visualized by visible light (yellow/orange)

\(^{1}\)H-NMR (500 MHz, d\(_{6}\)-acetone)

\( \delta \ 7.50 \ (s, \ 1H), \ 7.16 \ (d, \ J = 16 \ Hz, \ 1H), \ 6.81 \ (dd, \ J = 14.5, \ 11.5 \ Hz, \ 1H), \ 6.79 \ (dd, \ J = 14, \ 12 \ Hz, \ 1H), \ 6.63 \ (dd, \ J = 14, \ 11.5 \ Hz, \ 1H), \ 6.58 \ (d, \ J = 12, \ 1.5 \ Hz, \ 1H), \ 6.52 \ (d, \ J = 11 \ Hz, \ 1H), \ 6.50 \ (dd, \ J = 12, \ 11 \ Hz, \ 1H), \ 6.39 \ (d, \ J = 16 \ Hz, \ 1H), \ 6.00 \ (s, \ 1H), \ 4.23 \ (d, \ J = 17 \ Hz, \ 2H), \ 4.06 \ (d, \ J = 17 \ Hz, \ 2H), \ 3.90 \ (m, \ 1H), \ 2.98 \ (s, \ 3H), \ 2.25 \ (ddd, \ J = 9.5, \ 5, \ 1.5\ Hz)\)
Hz, 1H), 2.21 (s, 3H), 1.85 (d, J = 1.5 Hz, 3H), 1.71 (dd, J = 14.5, 8 Hz, 1H), 1.52 (ddd, J = 13, 3.5, 1.5 Hz, 1H), 1.31 (dd, J = 13, 10 Hz, 1H), 1.20 (s, 3H), 1.17 (s, 3H), 0.95 (s, 3H), 0.90 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H).

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

$\delta$ 169.1, 169.1, 148.0, 138.8, 138.2, 137.9, 137.2, 134.9, 134.5, 134.4, 131.9, 130.3, 125.4, 122.6, 119.6, 70.8, 67.8, 65.5, 62.7, 47.7, 47.1, 42.0, 35.7, 29.7, 26.2, 25.4, 20.2, 18.6, 15.5, 15.4, -4.6, -4.6

$^{11}$B-NMR (128 MHz, d$_6$-acetone)

$\delta$ 12.0

HRMS (ESI+)

Calculated for C$_{37}$H$_{53}$BNO$_8$Si: 678.3634

Found: 678.3633

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

3016, 2956, 2929, 2856, 1757, 1612, 1529, 1462, 1381, 1342, 1298, 1250, 1184, 1084, 1036, 989, 837, 775, 586.

$[\alpha]_D^{29}$ -23.2 (c 1.21, CHCl$_3$)
**Protected peridinin 2.46.**

*Preparation of catalyst stock solution.* In a glovebox, to a 7 mL vial equipped with a stir bar and charged with XPhos (30.4 mg, 0.064 mmol) and Pd(OAc)$_2$ (7.3 mg, 0.033 mmol) was added THF (degassed, inhibited with 250 ppm BHT, 2.0 mL). The solution was stirred at 23 °C for 10 min to afford a clear, brown solution.

The freshly prepared catalyst stock solution was used in the following reaction:

In a glovebox, to a 7 mL vial equipped with a stir bar and charged with MIDA boronate 2.34 (45.2 mg, 0.067 mmol) was added finely ground NaOH (18.7 mg, 0.47 mmol). Iodoallene 2.35 (37.2 mg, 0.088 mmol) was added as a solution in THF (degassed, inhibited with 250 ppm BHT, 2.0 mL). A portion of the prepared catalyst solution (0.20 mL, which contains 0.0033 mmol Pd(OAc)$_2$ and 0.0064 mmol XPhos) was added in one portion. The vial was sealed with a septum cap and removed from the glovebox. Degassed DI H$_2$O (0.45 mL) was added. The solution was stirred in a subdued light environment at 23 °C for 1.5 hr. The reaction mixture was poured into aqueous sodium phosphate buffer (0.25 M, pH 7.0, 10 mL) and diluted with Et$_2$O (20 mL). The mixture was shaken and the layers were separated. The aqueous phase was extracted with Et$_2$O (1 x 10 mL). The combined organic layers were dried over MgSO$_4$, filtered, and then concentrated *in vacuo*. The resulting residue was dry loaded onto Celite from an Et$_2$O solution, and purified via reverse phase flash chromatography on C18 silica gel (H$_2$O:Acetone 7:3 → 0:100) to afford protected peridinin 2.46 as a red solid (32.6 mg, 60%).

TLC (Hexane:EtOAc 4:1)

R$_f$ = 0.56, visualized by visible light (orange)
$^1$H-NMR (500 MHz, CDCl$_3$)
δ 7.15 (d, $J = 15.5$ Hz, 1H), 7.01 (s, 1H), 6.61 (dd, $J = 14.5$, 11.5 Hz, 1H), 6.60 (dd, $J = 14$, 11 Hz, 1H), 6.51 (dd, $J = 14$, 11 Hz, 1H), 6.43 (d, $J = 11.5$ Hz, 1H), 6.37 (dd, $J = 14$, 11 Hz, 1H), 6.34 (d, $J = 15.5$ Hz, 1H), 6.09 (d, $J = 11.5$ Hz, 1H), 5.99 (s, 1H), 5.72 (s, 1H), 5.34 (tt, $J = 11.5$, 4.5 Hz, 1H), 3.90 – 3.80 (m, 1H), 2.26 (ddd, $J = 14.5$, 5, 1 Hz, 1H), 2.23 (s, 3H), 2.03 (s, 3H), 1.96 (ddd, $J = 12.5$, 4, 2 Hz, 1H), 1.79 (s, 3H), 1.65 (dd, $J = 14.5$, 8 Hz, 1H), 1.50 (ddd, $J = 13$, 3.5, 1.5 Hz, 1H), 1.40 (m, 1H), 1.36 (s, 3H), 1.33 (s, 3H), 1.32 – 1.20 (m, 3H), 1.19 (s, 3H), 1.17 (s, 3H), 1.04 (s, 3H), 0.95 (s, 3H), 0.88 (s, 9H), 0.11 (s, 9H), 0.051 (s, 3H), 0.047 (s, 3H).

$^{13}$C-NMR (125 MHz, CDCl$_3$)
δ 202.5, 170.4, 168.7, 146.7, 138.0, 137.2, 136.2, 134.3, 133.9, 133.8, 132.7, 131.6, 128.8, 127.7, 124.8, 121.6, 119.1, 117.0, 102.7, 74.8, 70.6, 68.3, 67.5, 64.6, 47.7, 47.0, 45.7, 41.3, 35.8, 35.1, 32.3, 30.3, 29.4, 28.8, 25.9, 25.0, 21.4, 20.0, 18.1, 15.4, 14.1, 2.2, -4.7, -4.8

HRMS (ESI+)
Calculated for C$_{48}$H$_{73}$O$_7$Si$_2$: 817.4895
Found: 817.4895

IR (thin film, cm$^{-1}$)
2960, 2929, 2858, 1961, 1755, 1630, 1523, 1454, 1377, 1250, 1161, 1120, 1078, 1036, 987, 839.

$[\alpha]_D$ -40.3 (c 1.6, CHCl$_3$)
Peridinin 2.2. To a 7 mL polyethylene vial containing a stir bar was added protected peridinin 2.46 (31.3 mg, 0.038 mmol) as a solution in THF (2.0 mL). HF•pyridine (70% HF in pyridine, 0.10 mL, 5.5 mmol) was added in one portion. The solution was stirred in a subdued light environment at 23 °C for 1 hr. An additional portion of HF•pyridine (70% HF in pyridine, 0.10 mL, 5.5 mmol) was added. The solution was stirred at 23 °C for an additional 2 hr. The reaction was quenched by slow, dropwise addition of saturated aqueous NaHCO₃ until effervescence ceased (caution: slow addition is important to avoid uncontrolled effervescence). The reaction solution was then poured into saturated aqueous NaHCO₃ (10 mL) and diluted with Et₂O (20 mL). The mixture was shaken and the layers were separated. The aqueous phase was extracted with Et₂O (1 x 10 mL). The combined organics were dried over MgSO₄, filtered, and then concentrated in vacuo. The resulting residue was dry loaded onto Celite from an Et₂O solution, and purified via flash chromatography on florisil (Hexane:EtOAc 100:0 → 0:100) to afford peridinin 2.2 as a red solid (15.7 mg, 65%).

TLC (Hexane:Acetone 7:3)

Rₚ = 0.20, visualized by visible light (orange)

¹H-NMR (500 MHz, CDCl₃)

δ 7.15 (d, J = 16 Hz, 1H), 7.02 (s, 1H), 6.61 (dd, J = 14, 11.5 Hz, 1H), 6.60 (dd, J = 14, 11.5 Hz, 1H), 6.51 (dd, J = 14, 10.5 Hz, 1H), 6.43 (d, J = 11.5 Hz, 1H), 6.37 (dd, J = 14.5, 10.5 Hz, 1H), 6.35 (d, J = 15.5 Hz, 1H), 6.09 (d, J = 11.5 Hz, 1H), 6.05 (s, 1H), 5.73 (s, 1H), 5.37 (tt, J = 11.5, 4.5 Hz, 1H), 3.90 (m, 1H), 2.38 (ddd, J = 14.5, 5, 1.5 Hz, 1H), 2.27 (ddd, J = 14, 4, 2 Hz, 1H), 2.22 (s, 3H), 2.03 (s, 3H), 1.98 (ddd, J = 12.5, 4, 2 Hz, 1H), 1.80 (s, 3H), 1.69 – 1.60 (m, 2H), 1.50 (dd, J = 14, 11 Hz, 1H), 1.40 (m, 1H),
1.38 (s, 3H), 1.35 (m, 1H), 1.35 (s, 3H), 1.26 (m, 1H), 1.199 (s, 3H), 1.195 (s, 3H), 1.06 (s, 3H), 0.97 (s, 3H).

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

$\delta$ 202.6, 170.4, 168.7, 146.7, 138.0, 137.2, 136.3, 134.0, 133.9, 133.6, 133.0, 131.5, 128.9, 128.1, 124.7, 121.8, 119.2, 117.6, 103.3, 72.6, 70.4, 67.9, 67.5, 64.2, 47.1, 45.4, 45.2, 40.9, 35.8, 35.3, 32.0, 31.2, 29.5, 29.1, 24.9, 21.4, 19.8, 15.4, 14.0

HRMS (ESI+)

Calculated for C$_{39}$H$_{51}$O$_7$: 631.3635

Found: 631.3629

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

3496, 3016, 2962, 2926, 2856, 1928, 1743, 1635, 1523, 1456, 1365, 1250, 1163, 1124, 1030, 984, 908, 756.

$[\alpha]_D^{28}$ -22.9 ± 5.7 (c 1.1, MeOH)
$^1$H NMR data for peridinin: $\delta_H$/ppm

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\(^{13}\)C NMR data for peridinin: \(\delta_C/\text{ppm}\)

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**General information for lipoperoxidation assays.** Egg yolk phosphatidylcholine (EYPC) was obtained as a 20 mg/mL solution in CHCl₃ from Avanti Polar Lipids (catalog number 840051C-1g, Alabaster, AL), 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (16:0-18:1 PC, POPC) was obtained as a 25 mg/mL solution in CHCl₃ from Avanti Polar Lipids (catalog number 850457C), and 1-stearoyl-2-arachidonoyl-sn-glycero-3-phosphocholine (18:0-20:4 PC, PUFA) was obtained as a 10 mg/mL solution in CHCl₃ from Avanti Polar Lipids (catalog number 850469C) and were stored at -20°C under an atmosphere of dry nitrogen and used within 1.5 months. Prior to preparing the lipid film, the solution was warmed to ambient temperature to prevent condensation from contaminating the solution. The HPLC purity of cholesterol and carotenoids was checked prior to use and confirmed to be >95%. Cholesterol was purchased from Sigma Aldrich (catalog number C8667, >99%). Astaxanthin was a generous donation from BASF. Peridinin was synthesized as above and was HPLC purified to >95% prior to use.

**Preparation of samples for Figure 2-5.**

**Blank:**
Prepare the lipid films: To three separate 12x75 mm test tubes was added 1.0 mL EYPC solution via Hamilton syringe. The solvent was removed under a gentle stream of nitrogen and the resulting lipid film was stored under high vacuum for a minimum of 12 hours prior to use.

Prepare the liposomes: The lipid film was hydrated with 1 mL 150 mM KCl/0.5 mM HEPES pH 7.4 (K buffer) and vortexed vigorously for 1 minute (until the film no longer coated the sides of the test tube) to form a suspension of multilamellar vesicles (MLVs). The resulting lipid suspension was pulled into a Hamilton 1 mL gastight syringe and the syringe was placed in an Avanti Polar Lipids Mini-Extruder. The lipid solution was then passed through a 0.20 μm Whatman (Kent, UK) polycarbonate filter (supported by a 10 mm filter support on each side, Avanti Polar Lipids) 21 times, the newly formed large unilamellar vesicle (LUV) suspension being collected in the syringe that did not contain the original suspension of MLVs to prevent the carryover of MLVs into the LUV solution. The LUVs were purified by gel exclusion.
chromatography with a Sephadex G50-150 column (1 cm column, 1.0 g unswelled resin, swelled resin with K buffer, eluted with K buffer).

**Astaxanthin samples:**

Preparation of lipid films: To three separate 12x75 mm test tubes was added 1.0 mL EYPC solution via Hamilton syringe. The solvent was removed under a gentle stream of nitrogen and the resulting lipid film was stored under high vacuum for a minimum of 12 hours prior to use.

Preparation of liposomes: The lipid film was hydrated with 1 mL 150 mM KCl/0.5 mM HEPES pH 7.4 (K buffer) and vortexed vigorously for 1 minute (until the film no longer coated the sides of the test tube) to form a suspension of multilamellar vesicles (MLVs). The resulting lipid suspension was pulled into a Hamilton 1 mL gastight syringe and the syringe was placed in an Avanti Polar Lipids Mini-Extruder. The lipid solution was then passed through a 0.20 μm Whatman (Kent, UK) polycarbonate filter (supported by a 10 mm filter support on each side, Avanti Polar Lipids) 21 times, the newly formed large unilamellar vesicle (LUV) suspension being collected in the syringe that did not contain the original suspension of MLVs to prevent the carryover of MLVs into the LUV solution. A 25 mM solution of astaxanthin in uninhibited THF was prepared. To a vortexing solution of the newly formed LUV under a stream of dry nitrogen was dropwise added 60 μL of the carotenoid solution. The carotenoid impregnated LUVs were purified by gel exclusion chromatography with a Sephadex G50-150 column (1 cm column, 1.0 g unswelled resin, swelled resin with K buffer, eluted with K buffer).

**Peridinin samples:**

Preparation of lipid films: To three separate 12x75 mm test tubes was added 1.0 mL EYPC solution via Hamilton (Reno, NV) syringe. The solvent was removed under a gentle stream of nitrogen and the resulting lipid film was stored under high vacuum for a minimum of 12 hours prior to use.
Preparation of liposomes: The lipid film was hydrated with 1 mL 150 mM KCl/0.5 mM HEPES pH 7.4 (K buffer) and vortexed vigorously for 1 minute (until the film no longer coated the sides of the test tube) to form a suspension of multilamellar vesicles (MLVs). The resulting lipid suspension was pulled into a Hamilton 1 mL gastight syringe and the syringe was placed in an Avanti Polar Lipids Mini-Extruder. The lipid solution was then passed through a 0.20 μm Whatman (Kent, UK) polycarbonate filter (supported by a 10 mm filter support on each side, Avanti Polar Lipids) 21 times, the newly formed large unilamellar vesicle (LUV) suspension being collected in the syringe that did not contain the original suspension of MLVs to prevent the carryover of MLVs into the LUV solution. An 11 mM solution of peridinin in uninhibited THF was prepared. To a vortexing solution of the newly formed LUV under a stream of dry nitrogen was dropwise added 46 μL of the carotenoid solution. The carotenoid impregnated LUVs were purified by gel exclusion chromatography with a Sephadex G50-150 column (1 cm column, 1.0 g unswelled resin, swelled resin with K buffer, eluted with K buffer).

**Determination of phosphorus content and liposome dilution.**

Preparation of a standard curve: To 7 mL vials in triplicate was added the following amount of phosphorus standard solution (Sigma Aldrich, catalog number P3869, 0.65 mM phosphorus as KH$_2$PO$_4$): 20 μL, 40 μL, 60 μL, 80 μL, 100 μL, and 120 μL. To these vials and to a separate vial containing no phosphorus that was used as a blank, was added 450 μL of 8.9 M aq H$_2$SO$_4$. The samples were incubated open to ambient atmosphere in a 225 °C aluminum heating block for 25 min and then removed to 23 °C for 5 min. To each sample was added 150 μL of 30% w/v aqueous hydrogen peroxide and the vials were returned to the 225 °C heating block for 30 min after which the samples were removed to 23 °C for 5 min. To each sample was added 4.0 mL DI H$_2$O. To each vial was then added 500 μL of 2.5% w/v ammonium molybdate tetrahydrate. The vials were capped and the resulting mixtures were vortexed briefly and vigorously. Subsequently, 500 μL of 10% w/v L-(+)-ascorbic acid was added to each vial. The vials were capped and the resulting mixtures were vortexed briefly and vigorously. The capped vials were then placed in a 100 °C aluminum heating block for 7 min. The samples were removed to 23 °C and cooled for approximately 20 minutes to 23 °C prior to analysis by UV/Vis spectroscopy.
Total phosphorus was determined by observing the absorbance at 820 nm. A standard curve was prepared by plotting μmoles of phosphorus vs. the absorbance at 820 nm.

Analysis of liposomes: To 7 mL vials in triplicate was added 10 μL of the purified LUV suspension. To these vials and to a separate vial containing no LUVs that was used as a blank, was added 450 μL of 8.9 M aq H₂SO₄. The samples were incubated open to ambient atmosphere in a 225 °C aluminum heating block for 25 min and then removed to 23 °C for 5 min. To each sample was added 150 μL of 30% w/v aqueous hydrogen peroxide and the vials were returned to the 225 °C heating block for 30 min after which the samples were removed to 23 °C for 5 min. To each sample was added 4.0 mL DI H₂O. To each vial was then added 500 μL of 2.5% w/v ammonium molybdate tetrahydrate. The vials were capped and the resulting mixtures were vortexed briefly and vigorously. Subsequently, 500 μL of 10% w/v L-(+)-ascorbic acid was added to each vial. The vials were capped and the resulting mixtures were vortexed briefly and vigorously. The capped vials were then placed in a 100 °C aluminum heating block for 7 min. The samples were removed to 23 °C and cooled for approximately 20 minutes to 23 °C prior to analysis by UV/Vis spectroscopy. Total phosphorus was determined by observing the absorbance at 820 nm and comparing this value to the standard curve. The liposome suspension was diluted to a concentration of 1 mM.

**Determination of carotenoid content:**

To a HPLC vial was added 100 μL of the 1 mM liposome suspension and 200 μL of 4:1:1 acetone:MeOH:0.2 M BHT in EtOH. The mixture was shaken to give a clear solution. The samples were analyzed by analytical HPLC and the carotenoid content was determined by comparing the peak area to standard curves prepared from carotenoid solutions of known concentrations.

**HPLC method:**

Reverse phase, C18 column, inject 75 μL sample, flow 2 mL/min
Copper based lipoperoxidation assay:

To 7 mL vials in triplicate was added 4 mL of the 1 mM liposome suspension. To each sample was added 40 μL of 11 mM CuCl$_2$ in DI H$_2$O. The vials were capped and incubated in a 37 °C aluminum heating block. At four hour increments an aliquot was removed from each sample and analyzed for TBARS by one of the following methods:

(1) TBARS analysis. At each timepoint, a 100 μL aliquot was removed from the liposome assay sample to a 1.5 mL microcentrifuge tube containing 10 μL of 0.2 M BHT in EtOH and 400 μL of TBA solution (TBA solution = 0.375% w/v thiobarbituric acid, 0.25 M HCl, 1% Triton X-100 in MQ H$_2$O). The microcentrifuge tube was capped and incubated in a 100 °C aluminum heating block for 15 minutes. The samples were removed to 23 °C and cooled for approximately 20 minutes to 23 °C prior to analysis UV/Vis spectroscopy. TBARS formation was determined by observing the absorbance at 535 nm.

Or

(2) TBARS analysis. At each timepoint, a 100 μL aliquot was removed from the liposome assay sample to a 1.5 mL HPLC vial containing 500 μL of TBA solution (TBA solution = 0.4% w/v thiobarbituric acid in 0.1 M NaOAc, pH 3.5). The vial was capped and incubated in a 100 °C aluminum heating block for 15 minutes. The samples were removed to 23 °C and cooled for approximately 20 minutes to 23 °C prior to analysis by HPLC.

HPLC method:

Reverse phase, C18 column, inject 75 μL sample, flow 2 mL/min

TBA/MDA adduct: 72:17:11 50 mM KH$_2$PO$_4$:MeOH:MeCN; detect at 535 nm
Analysis of samples for Figure 2-6.

Carotenoid consumption: At each timepoint, a 100 μL aliquot was removed from the liposome assay sample to a HPLC vial. To each sample vial was added 200 μL of 4:1:1 acetone:MeOH:0.2 M BHT in EtOH. The mixture was shaken to give a clear solution. The samples were analyzed by analytical HPLC and the cholesterol and carotenoid consumption was determined by measuring changes to the peak area over time.

HPLC method:
Reverse phase, C18 column, inject 75 μL sample, flow 2 mL/min
astaxanthin: 90:10 MeOH:H₂O; detect at 478 nm
peridinin: 90:10 MeOH:H₂O; detect at 468 nm

Preparation of samples for Figure 2-7.

A chemically defined blank:
Preparation of lipid films: To a 12x75 mm test tube was added 0.15 mL POPC solution and 0.125 mL PUFA solution via Hamilton syringe. The solvent was removed under a gentle stream of nitrogen and the resulting lipid film was stored under high vacuum for a minimum of 12 hours prior to use.

Preparation of liposomes: The lipid film was hydrated with 0.3 mL 150 mM KCl/0.5 mM HEPES pH 7.4 (K buffer) and vortexed vigorously for 1 minute (until the film no longer coated the sides of the test tube) to form a suspension of multilamellar vesicles (MLVs). The resulting lipid suspension was pulled into a Hamilton 1 mL gastight syringe and the syringe was placed in an Avanti Polar Lipids Mini-Extruder. The lipid solution was then passed through a 0.20 μm Whatman (Kent, UK) polycarbonate filter (supported by a 10 mm filter support on each side, Avanti Polar Lipids) 21 times, the newly formed large unilamellar vesicle (LUV) suspension being collected in the syringe that did not contain the original suspension of MLVs to prevent the carryover of MLVs into the LUV solution. The LUVs were purified by gel exclusion
chromatography with a Sephadex G50-150 column (1 cm column, 1.0 g unswelled resin, swelled resin with K buffer, eluted with K buffer).

**A chemically defined astaxanthin sample:**

Preparation of lipid films: To a 12x75 mm test tube was added 0.15 mL POPC solution and 0.125 mL PUFA solution via Hamilton syringe. The solvent was removed under a gentle stream of nitrogen and the resulting lipid film was stored under high vacuum for a minimum of 12 hours prior to use.

Preparation of liposomes: The lipid film was hydrated with 0.3 mL 150 mM KCl/0.5 mM HEPES pH 7.4 (K buffer) and vortexed vigorously for 1 minute (until the film no longer coated the sides of the test tube) to form a suspension of multilamellar vesicles (MLVs). The resulting lipid suspension was pulled into a Hamilton 1 mL gastight syringe and the syringe was placed in an Avanti Polar Lipids Mini-Extruder. The lipid solution was then passed through a 0.20 μm Whatman (Kent, UK) polycarbonate filter (supported by a 10 mm filter support on each side, Avanti Polar Lipids) 21 times, the newly formed large unilamellar vesicle (LUV) suspension being collected in the syringe that did not contain the original suspension of MLVs to prevent the carryover of MLVs into the LUV solution. A 19 mM solution of astaxanthin in uninhibited THF was prepared. To a vortexing solution of the newly formed LUV under a stream of dry nitrogen was dropwise added 33 μL of the carotenoid solution. The carotenoid impregnated LUVs were purified by gel exclusion chromatography with a Sephadex G50-150 column (1 cm column, 1.0 g unswelled resin, swelled resin with K buffer, eluted with K buffer).

**A chemically defined peridinin sample:**

Preparation of lipid films: To a 12x75 mm test tube was added 0.15 mL POPC solution and 0.125 mL PUFA solution via Hamilton syringe. The solvent was removed under a gentle stream
of nitrogen and the resulting lipid film was stored under high vacuum for a minimum of 12 hours prior to use.

Preparation of liposomes: The lipid film was hydrated with 0.3 mL 150 mM KCl/0.5 mM HEPES pH 7.4 (K buffer) and vortexed vigorously for 1 minute (until the film no longer coated the sides of the test tube) to form a suspension of multilamellar vesicles (MLVs). The resulting lipid suspension was pulled into a Hamilton 1 mL gastight syringe and the syringe was placed in an Avanti Polar Lipids Mini-Extruder. The lipid solution was then passed through a 0.20 μm Whatman (Kent, UK) polycarbonate filter (supported by a 10 mm filter support on each side, Avanti Polar Lipids) 21 times, the newly formed large unilamellar vesicle (LUV) suspension being collected in the syringe that did not contain the original suspension of MLVs to prevent the carryover of MLVs into the LUV solution. A 9 mM solution of peridinin in uninhibited THF was prepared. To a vortexing solution of the newly formed LUV under a stream of dry nitrogen was dropwise added 23 μL of the carotenoid solution. The carotenoid impregnated LUVs were purified by gel exclusion chromatography with a Sephadex G50-150 column (1 cm column, 1.0 g unswelled resin, swelled resin with K buffer, eluted with K buffer).

Phosphorus determination, liposome dilution, carotenoid content measurement, and the copper based lipoperoxidation assay were performed as described above.

**Analysis of samples for Figure 2-8.** Preformed as described for Figure 2-6.

**Preparation of samples for Figure 2-9.**

Preparation of lipid films: To 12x75 mm test tubes was added the following via Hamilton syringe:

1) 0.8 mL POPC solution

2) 0.45 mL POPC solution, 0.375 mL PUFA solution, and 0.16 mL of 13(S)-HpOTre solution (0.10 mg in 1 mL EtOH), prepared in triplicate
3) 0.45 mL POPC solution, 0.375 mL PUFA solution

The solvent was removed under a gentle stream of nitrogen and the resulting lipid films were stored under high vacuum for a minimum of 12 hours prior to use.

Preparation of liposomes: The lipid films were hydrated with 1.0 mL 150 mM KCl/0.5 mM HEPES pH 7.4 (K buffer) and vortexed vigorously for 1 minute (until the film no longer coated the sides of the test tube) to form a suspension of multilamellar vesicles (MLVs). The resulting lipid suspensions were pulled into a Hamilton 1 mL gastight syringe and the syringe was placed in an Avanti Polar Lipids Mini-Extruder. The lipid solutions were then passed through a 0.20 μm Whatman (Kent, UK) polycarbonate filter (supported by a 10 mm filter support on each side, Avanti Polar Lipids) 21 times, the newly formed large unilamellar vesicle (LUV) suspension being collected in the syringe that did not contain the original suspension of MLVs to prevent the carryover of MLVs into the LUV solution. A 40 mM solution of astaxanthin in uninhibited THF was prepared. To a vortexing solution of the newly formed LUV under a stream of dry nitrogen was dropwise added 60 μL of the carotenoid solution. The carotenoid impregnated LUVs were purified by gel exclusion chromatography with a Sephadex G50-150 column (1 cm column, 1.0 g unswelled resin, swelled resin with K buffer, eluted with K buffer).

Phosphorus determination, liposome dilution, carotenoid content measurement, the copper based lipoperoxidation assay, and measurement of carotenoid consumption were performed as described above.

**Preparation of samples for Figure 2-11 and 2-12.**

Preparation of lipid films: To 15 12x75 mm test tube was added 0.40 mL EYPC solution via Hamilton syringe. A solution of 10.5 mg cholesterol in 1.0 mL CHCl₃ was prepared. To 8 of these EYPC solutions, added the following amounts of this cholesterol solution: 5 μL, 10 μL, 15 μL, 25 μL, 50 μL, 100 μL, 150 μL, and 200 μL. The solvent was removed under a gentle stream of nitrogen and the resulting lipid films were stored under high vacuum for a minimum of 12 hours prior to use.
Preparation of liposomes: The lipid films were hydrated with 0.5 mL D₂O and vortexed vigorously for 1 minute (until the film no longer coated the sides of the test tube) to form a suspension of multilamellar vesicles (MLVs). The resulting lipid suspensions were pulled into a Hamilton 1 mL gastight syringe and the syringe was placed in an Avanti Polar Lipids Mini-Extruder. The lipid solutions were then passed through a 0.20 μm Whatman (Kent, UK) polycarbonate filter (supported by a 10 mm filter support on each side, Avanti Polar Lipids) 21 times, the newly formed large unilamellar vesicle (LUV) suspension being collected in the syringe that did not contain the original suspension of MLVs to prevent the carryover of MLVs into the LUV solution. A 17 mM solution of astaxanthin in uninhibited THF was prepared. To a vortexing solution of the newly formed blank LUV (i.e. non-cholesterol samples) under a stream of dry nitrogen was dropwise added the following amounts of the carotenoid solution: 4 μL, 9 μL, 17 μL, 26 μL, 44 μL, and 85 μL. The carotenoid and cholesterol impregnated LUVs were purified by gel exclusion chromatography with a Sephadex G50-150 column (1 cm column, 0.75 g unswelled resin, swelled resin with D₂O, eluted with D₂O). At this point 15 liposome solutions had been prepared and purified: 1 blank liposome, 8 cholesterol liposomes, and 6 astaxanthin liposomes.

NMR analysis. The purified liposome solutions were transferred to NMR tubes and each sample was analyzed using a Varian Unity Inova 500NB instrument in duplicate. The following parameters were used: pw = 4.5; at = 4; d1 = 2; nt = 16. The linewidth at half height of each peak (3.1, 1.2, and 0.7 ppm) was measured and averaged for the two runs. Plots of this value vs. percent incorporation were prepared.

Following the NMR analysis, phosphorus determination, liposome dilution, carotenoid content measurement, and the copper based lipoperoxidation assay were preformed as described above. HPLC method:

Reverse phase, C18 column, inject 75 μL sample, flow 2 mL/min

Cholesterol: 90:10 MeCN:MeOH; detect at 212 nm
Preparation of samples for Figure 2-13. Preformed as described for Figures 2-6 and 2-7.

Preparation of samples for Figure 2-13.

A coincorporated (astaxanthin + peridinin) sample:

Preparation of lipid films: To a 12x75 mm test tube was added 0.15 mL POPC solution and 0.05 mL PUFA solution (25 mg/mL) via Hamilton syringe. The solvent was removed under a gentle stream of nitrogen and the resulting lipid film was stored under high vacuum for a minimum of 12 hours prior to use.

Preparation of liposomes: The lipid film was hydrated with 0.3 mL 150 mM KCl/0.5 mM HEPES pH 7.4 (K buffer) and vortexed vigorously for 1 minute (until the film no longer coated the sides of the test tube) to form a suspension of multilamellar vesicles (MLVs). The resulting lipid suspension was pulled into a Hamilton 1 mL gastight syringe and the syringe was placed in an Avanti Polar Lipids Mini-Extruder. The lipid solution was then passed through a 0.20 μm Whatman (Kent, UK) polycarbonate filter (supported by a 10 mm filter support on each side, Avanti Polar Lipids) 21 times, the newly formed large unilamellar vesicle (LUV) suspension being collected in the syringe that did not contain the original suspension of MLVs to prevent the carryover of MLVs into the LUV solution. A 2 mM stock solution of astaxanthin in uninhibited THF was prepared. A 2.8 mM stock solution of peridinin in uninhibited THF was prepared. 15 μL of the astaxanthin stock solution was added to 35 μL of the peridinin solution. To a vortexing solution of the newly formed LUV under a stream of dry nitrogen was dropwise added 50 μL of the combined carotenoid solution. The carotenoid impregnated LUVs were purified by gel exclusion chromatography with a Sephadex G50-150 column (1 cm column, 1.0 g unswelled resin, swelled resin with K buffer, eluted with K buffer).
Phosphorus determination, liposome dilution, carotenoid content measurement, the copper based lipoperoxidation assay, and measurement of carotenoid consumption were preformed as described above.

REFERENCES

14 The addition of Darco proved important in preserving the enantiopurity of the product. Working up the reaction without Darco led to a decrease in stereoretention over time. For further discussion on the use of Darco see: Molander, G.A.; Sommers, E.M.; Baker, S.R. *J. Org. Chem.* **2006**, *71*, 1563.
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CHAPTER 3
SYNTHESIS OF (Z)-2-BROMOVINYL MIDA BORONATE, 1-BROMOVINYL MIDA BORONATE, AND 2-PYRIDYL MIDA BORONATE

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Iterative cross-coupling represents a potentially general approach for the simple, efficient, and flexible construction of a wide range of functional small molecules. To advance this approach, a collection of MIDA boronate building blocks representing structural motifs commonly found in small molecules would be highly enabling. In this vein, cis-olefins, 1,1-disubstituted olefins, and the 2-pyridyl moiety are three recurring motifs in natural products, materials, and pharmaceuticals. To gain access to these frameworks, we have prepared three MIDA boronate building blocks: (Z)-2-bromovinyl MIDA boronate, 1-bromovinyl MIDA boronate, and 2-pyridyl MIDA boronate. This chapter describes the efficient and scalable synthesis of these building blocks as well as their applications in small molecule synthesis.

Dr. Justin R. Struble, Dr. Nagarjuna Palyam, and Sean P. O’Hara contributed to the synthesis and coupling of (Z)-2-bromovinyl MIDA boronate. Jonathan E. Miller contributed to the coupling of 1-bromovinyl MIDA boronate. Anthony S. Grillo contributed to the large scale synthesis of 2-pyridyl MIDA boronate. Graham R. Dick contributed to many of the results involving 2-pyridyl MIDA boronate, especially the synthesis of 2-pyridyl MIDA boronate, the development of general reaction conditions, and exploration of the cross-coupling scope.

3-1 INTRODUCTION

As exemplified by the total synthesis of peridinin (Chapter 2), a building block based strategy for the synthesis of small molecules is a powerful method for accessing targets and their derivatives in an efficient manner. Such a strategy has the potential to shift the rate limiting step in small molecule science from the synthesis of molecules to understanding and harnessing their functional potential. In general, this approach is aided by accessibility to building blocks that can be readily linked using only one reaction iteratively. To further enable this strategy, we aim to transform substructures that commonly appear in a broad range of complex natural products, pharmaceuticals, and materials into readily accessible and air-stable MIDA boronate building blocks that can be united using the Suzuki-Miyaura reaction. In this vein, cis-olefins, 1,1-disubstituted olefins, and the 2-pyridyl moiety are three motifs that are present in a diverse range of small molecules. This chapter describes the synthesis of three building blocks, (Z)-(2-bromovinyl)-MIDA boronate 3.1, (1-bromovinyl)-MIDA boronate 3.2, and 2-pyridyl MIDA boronate 3.3 (Figure 3-1) and their utility in small molecule science.

![Figure 3-1](image)

Figure 3-1. Three MIDA boronate building blocks that represent common motifs present in a large number of small molecule natural products, pharmaceuticals, and materials.

3-2 (Z)-(2-BROMOVINYL)-MIDA BORONATE

Cis-olefins are prevalent in small molecules derived from a wide range of biosynthetic pathways including polyketides, hybrid peptide/polyketides, polyterpenes, fatty acids, and phenylpropanoids (Figure 3-2).\(^1\) Controlling the stereochemistry during the formation of cis double bonds often represents a major challenge in the synthesis of these types of molecules.\(^2\) Pre-installation of this stereochemistry into a readily-accessible bifunctional olefin that can be iteratively functionalized via sequential stereospecific C-C bond forming reactions represents a very attractive goal.
Figure 3-2. cis-Olefins are found in natural products derived from all major biosynthetic classes.

Drs. Suk Joong Lee and Tom Anderson recently reported a collection of bifunctional iodoalkenyl MIDA boronates in all possible stereoisomeric forms that can provide access to a wide range of stereochemically complex polyene frameworks via selective cross-coupling of the halide terminus. An important component of this platform was \((Z)-(2\text{-iodovinyl})\)-MIDA boronate, \(\text{(Z)-I-3.1}\) (Scheme 3-1). This bifunctional building block contains the olefin geometry pre-installed in the \(\text{cis}\)-configuration to allow for the construction of a wide range of polyene motifs containing \(\text{cis}\)-olefins in a stereocontrolled fashion via stereospecific cross-coupling reactions. While the synthetic utility of \(\text{(Z)-I-3.1}\) proved to be outstanding, its synthesis was cumbersome (requiring multiple rounds of partial reduction and chromatography), low yielding, and not scalable. To enable ready access to such a building block for many diverse applications, we developed a convenient, practical, and highly scalable synthesis of an analogous reagent, \(\text{(Z)-(2-bromovinyl)}\)-MIDA boronate, \(\text{(Z)-Br-3.1}\). We further demonstrated that \(\text{(Z)-Br-3.1}\) can serve as a highly versatile building block for the preparation of a wide range of \(\text{cis}\)-alkene-containing synthetic targets.

![Scheme 3-1](image)

Scheme 3-1. \(\text{(Z)-I-3.1}\) and \(\text{(Z)-Br-3.1}\) are both prepared from alkynyl MIDA boronate 3.4.

Bromination/elimination reactions provide a convenient method for the synthesis of vinyl halides. In particular, \(\text{(E)}\)-alkenylboronic esters can be converted to \(\text{(Z)}\)-alkenyl halides via this type of transformation. We have recently reported a convenient synthesis of \(\text{bis}\)-borylated olefin
3.5 via the hydroboration of ethynyl MIDA boronate 3.4 (Scheme 3-2).\(^5\) Given the compatibility of MIDA boronates to many common synthetic reagents, we hypothesized that 3.5 would be a competent starting material for a bromination/elimination sequence, leading to an efficient synthesis of (Z)-Br-3.1. In the event, bromination of 3.5 followed by treatment of the resulting vicinal dibromide intermediate with anhydrous K\(_3\)PO\(_4\) in MeCN provides a very convenient route to (Z)-Br-3.1 in 73% overall yield. Dr. Justin Struble found that this same building block can alternatively be prepared in a one pot procedure by reacting 3.5 with CuBr\(_2\) in aqueous MeCN. Both of these pathways can be performed on the gram scale and (Z)-Br-3.1 can be isolated in pure form without the use of chromatography. Moreover, 3.4, 3.5, and (Z)-Br-3.1 are now commercially available.\(^6\)

**Scheme 3-2. Synthesis of (Z)-Br-3.1.**

With a pair of simple and readily scalable syntheses of (Z)-Br-3.1 in hand, together with Drs. Struble and Nagarjuna Palyam, we have preliminarily explored its utility in the preparation of a range of new (Z)-alkenyl MIDA boronate building blocks. Like its stereoisomeric counterpart (E)-Br-3.1,\(^7\) (Z)-Br-3.1 is a versatile cross-coupling partner, as shown in Scheme 3-3. Specifically, Suzuki-Miyaura (SM) cross-coupling with (E)-styrenylboronic acid 3.6 provided (E,Z)-diene 3.7. A Stille coupling between (Z)-Br-3.1 and vinyl stannane 3.8 provided diene 3.9. A Heck coupling with methyl acrylate 3.10 under phosphine-free conditions yielded the unsaturated methyl ester 3.11 as a single regio- and stereoisomer. Additionally, Sonogashira coupling between (Z)-Br-3.1 and TMS-acetylene 3.12 generated enyne 3.13. Finally, Negishi cross-coupling with 3.14 yielded MIDA boronate 3.15. Collectively, the diversity of coupling reactions compatible with (Z)-Br-3.1 demonstrates that this MIDA boronate possesses substantial utility in the synthesis of (Z)-alkenyl boronate building blocks for small molecule synthesis.
Scheme 3-3. (Z)-Br-3.1 can participate in Suzuki-Miyaura, Stille, Heck, Sonogashira, and Negishi couplings.

We have further determined that the scope for Suzuki-Miyaura coupling of boronic acids with (Z)-Br-3.1 is very good, enabling the preparation of a wide range of (Z)-vinyl MIDA boronates (Table 3-1). Specifically, the cross-coupling of electron neutral, rich, and deficient aryl boronic acids 3.16a-c (entries 1-3) provide the desired products 3.17a-c. Additionally, (Z)-Br-3.1 can be coupled with a series of heteroaryl boronic acids, including 2-thiophene 3.16d, 2-benzofuran 3.16e, and 2-pyrrole 3.16f (entries 4-6). Finally, trans- and cis-pentenyl boronic acid 3.16g-h can be coupled with (Z)-Br-3.1 for the synthesis of (E,Z) and (Z,Z) dienes 3.17g-h in a stereocontrolled fashion (entries 7-8).
Together with undergraduate Sean O’Hara, we further explored the utility of (Z)-Br-3.1 as a substrate for iterative SM coupling reactions. Stilbenoids are small molecule natural products that have been implicated in providing several beneficial effects on human health, including protecting against cardiovascular disease and cancer.\(^8\) (Z)-stilbenoids have demonstrated increased anticancer activity in comparison to their corresponding (E)-isomers.\(^9\) In particular, (Z)-3,5,4’-trimethoxystilbene 3.18 has been shown to be an exceptionally potent analog of the stilbenoid resveratrol (Scheme 3-4).\(^10\) We have completed an iterative cross-
coupling-based synthesis of 3.18 as shown in Scheme 3-4. The in situ hydrolysis of 3.19 followed by cross-coupling of the resulting boronic acid with aryl bromide 3.20 yielded 3.18 with complete retention of olefin stereochemistry.


Halopolyenyl MIDA boronates have also proven to be valuable building blocks for the iterative cross-coupling-based synthesis of polyene natural products, including β-parinaric acid, peridinin, and the polyene motifs of amphotericin B and vacidin A. In this vein, Dr. Lee recently reported the synthesis of all possible stereoisomeric forms of iododienyl MIDA boronates via the metal-selective cross-coupling of Sn/Ge bis-metalated olefins followed by the stereospecific iododegermylation of the resulting dienylgermanium intermediates. However, the overall efficiency of this process was limited by the low yielding preparation of key building block (Z)-I-3.1. With the development of the efficient preparation of (Z)-Br-3.1, together with Dr. Palyam, we have been able to prepare the dienylgermanium intermediates 3.21 with substantially improved overall efficiency (Scheme 3-5). Importantly, all of these products were prepared using one common set of general reaction conditions. Specifically, the Stille coupling between (Z)-Br-3.1 and (E)-3.20 yields (E,Z)-3.21 and coupling between (Z)-Br-3.1 and (Z)-3.20 provides (Z,Z)-3.21. In a similar fashion, the coupling of (E)-Br-3.1 with (E)-3.20 and (Z)-3.20 yields (E,E)-3.21 and (Z,E)-3.21, respectively. Dr. Lee has previously reported that the iododegermylation of 3.21 proceeds smoothly with I₂ in MeOH to complete the synthesis of all possible stereoisomeric forms of the iododienyl MIDA boronate building blocks 3.22.
Thus, (Z)-Br-3.1 and (E)-Br-3.1 represent a powerful pair of bifunctional haloalkenyl MIDA boronate building blocks. In addition to being versatile coupling partners themselves, they provide ready access to a collection of more complex bifunctional building blocks that have the potential to enable the synthesis of a wide range of polyene motifs via ICC. For example, iterative cross-coupling of building blocks (E,E)-3.22 and (Z,Z)-3.22 was recently shown by Dr. Lee to provide synthetic access to the highly complex (E,E,E,Z,Z,E,E)-heptaene portion of vacidin A (Scheme 3-6).\textsuperscript{3,14}

Access to a wide range of bifunctional building blocks representing motifs that commonly appear in natural products and pharmaceuticals stands to greatly increase the efficiency and flexibility of small molecule synthesis. The cis-olefin represents a very important substructure that appears in a wide range of polyenyl natural product motifs. We herein described a practical and scalable synthesis of the bifunctional building block (Z)-Br-3.1 and demonstrate its utility for the stereocontrolled synthesis of a wide range of cis-alkenes.
Collectively, these findings expand the utility of ICC with MIDA boronates as a simple and flexible platform for the efficient synthesis of a wide range of functional small molecules.

3-3 (1-BROMOVINYL)-MIDA BORONATE

1,1-disubstituted olefins are prevalent in small molecule pharmaceuticals and natural products derived from a wide range of biosynthetic pathways (Figure 3-3). In addition, they are useful synthetic intermediates. Some common strategies for the synthesis of 1,1-disubstituted olefins include the Wittig reaction of methyltriphenylphosphonium bromide and a ketone, the Heck reaction of an organohalide or triflate and monosubstituted olefin, and other metal catalyzed couplings between a halide or halide surrogate and an organometallic reagent.

![Figure 3-3. 1,1-Disubstituted olefins are abundant in pharmaceuticals and natural products.](image)

Of particular interest, the 1,1-disubstituted alkenyl boronate motif is an attractive intermediate for the preparation of 1,1-disubstituted olefins because of the versatility of the vinyl boron moiety. While methods for the synthesis of 1,2-disubstituted alkenyl boronates are abundant, the methods for the preparation of 1,1-disubstituted alkenyl boronates have been limited. Recent methods for the preparation of these motifs include the copper catalyzed hydroboration of aryl and heteroaryl substituted alkynes. Alternatively, aryl substituted vinyl boronates can be prepared from the corresponding vinyl halide via a Miyaura borylation or a lithiation/trap sequence. However, the synthesis of the requisite vinyl halide can be challenging and often uses conditions that are not compatible with acid-sensitive functionalities. To address these challenges, we envision that a B-protected 1,1-disubstituted halo boronate
building block would be extremely useful for the modular synthesis of targets containing a 1,1-disubstituted olefin motif (Scheme 3-7).

![Scheme 3-7](image)

Scheme 3-7. A 1,1-disubstituted halo boronate building block as a useful reagent for the preparation of 1,1-disubstituted olefins.

Along these lines, we are developing a platform of N-methyliminodiacetic acid (MIDA) boronate building blocks. MIDA boronates have many desirable properties that render them exceptionally useful as synthetic intermediates. They are uniformly air-stable, highly crystalline, and monomeric free-flowing solids that are fully compatible with silica gel chromatography. Many methods now exist for preparing MIDA boronates from a wide range of different starting materials, including boronic acids, haloboranes, boronic esters, trialkoxyborate salts, organohalides, organolithium reagents, and Grignard reagents. The MIDA boronate functional group is inert to anhydrous cross-coupling conditions, yet can be readily transformed into a fully reactive boronic acid or ester using mild conditions. These features enable the simple, efficient, and highly flexible synthesis of a wide range of complex small molecules via iterative cross-coupling of MIDA-protected haloboronic acids. Finally, a large and growing collection of MIDA boronates are now commercially available. Taking advantage of all of these properties, we herein report a 1,1-disubstituted halo MIDA boronate building block, which upon selective functionalization, allows ready access to a variety of 1,1-disubstituted alkenyl boronate motifs with the potential for iterative cross-coupling for the preparation of 1,1-disubstituted olefins.

Bromination-elimination reactions provide a convenient method for the synthesis of vinyl halides. In particular, 1,1-disubstituted olefins can be prepared from terminal alkenes via this type of transformation. With this strategy in mind, vinyl MIDA boronate 3.23 is an attractive starting point. This building block can easily be prepared on large scale from inexpensive starting materials (Scheme 3-8), and is now commercially available on both the gram and kilogram scales. Bromination of 3.23 followed by treatment of the resulting vicinal dibromide
intermediate with DBU in MeCN provides a convenient route to (1-bromovinyl)-MIDA boronate 3.2 in 67% overall yield. Moreover, 3.2 can be prepared on the decagram scale and isolated in pure form without the use of column chromatography. Building block 3.2 is also now commercially available.  

![Scheme 3-8. Synthesis of (1-bromovinyl)-MIDA boronate 3.2.](image)

With a readily scalable synthesis of 3.2 in hand, we have preliminarily explored its utility in the preparation of a range of new 1,1-disubstituted alkenyl boronate building blocks en route to 1,1-disubstituted olefins. In this vein, our initial attempt to couple 3.2 with phenyl boronic acid under standard anhydrous cross-coupling conditions surprisingly formed a mixture of products identified as the desired 1,1-disubstituted boronate 3.24 and the trans-1,2-disubstituted product 3.25 in a 1:4 ratio (Scheme 3-9).

![Scheme 3-9. The unoptimized coupling of building block 3.2 with phenyl boronic acid provides a mixture of products.](image)

We hypothesized that 3.25 is formed through a competitive reaction pathway involving oxidative addition of the palladium catalyst to 3.2 followed by β-hydride elimination, reinsertion of the Pd-H species to form a trans-1,2-disubstituted olefin, transmetalation with the boronic acid, and reductive elimination (Figure 3-4, pathway 2). Guided by this hypothesis, we explored reaction conditions that could limit the β-hydride elimination pathway (pathway 2) and/or accelerate the rate of the desired transmetalation reaction that leads to pathway 1 (Figure 3-4).
Along these lines, silver salts have been proposed to increase the rate of transmetalation in the Suzuki-Miyaura cross-coupling reaction.\textsuperscript{44} To test if this could favor pathway 1 over pathway 2, we employed silver oxide as the base (Table 3-2, entry 1) in combination with Pd(OAc)\textsubscript{2} and tricyclohexylphosphine (Cy\textsubscript{3}P) and observed \textit{3.24} as the major product (3:1), although with low conversion (30\%). Alternatively, the use of silver carbonate (entry 2) produced \textit{3.24} in a slightly better ratio (4:1) and with greater conversion (60\%). As a second variable, bidentate ligands, such as 1,1′-bis(diphenylphosphino)ferrocene (dppf), have been used to limit β-hydride elimination pathways in cross-coupling reactions.\textsuperscript{45} Use of PdCl\textsubscript{2}dppf (entry 3) with silver carbonate provided \textit{3.24} as the major product (4:1) with greatly improved conversion over previous reaction conditions. A survey of other bidentate phosphine ligands revealed 1,5-bis(diphenylphosphino)pentane (dppp, entry 4) as a ligand that provided \textit{3.24} in a 10:1 ratio. As a final variable, ancillary ligands were investigated. A survey of various palladium sources revealed that Pd\textsubscript{2}dba\textsubscript{3} combined with 1,6-bis(diphenylphosphino)hexane (dpph, entry 6) provided \textit{3.24} in a >20:1 ratio and with excellent conversion. Interestingly, during the course of this study, we also found that exclusive formation of the \textit{trans} product \textit{3.25} can be achieved in 85\% conversion using Pd(OAc)\textsubscript{2}, SPhos, and K\textsubscript{3}PO\textsubscript{4} in THF (entry 7).

Table 3-2. Optimization studies for the coupling of \textit{3.2}.

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|}
\hline
entry & PdLigand & base & \% conversion \textit{3.24}/\textit{3.25} \tabularnewline
\hline
1 & Pd(OAc)\textsubscript{2}/Cy\textsubscript{3}P & Ag\textsubscript{2}O & 30/3.1 \tabularnewline
2 & Pd(OAc)\textsubscript{2}/Cy\textsubscript{3}P & Ag\textsubscript{2}CO\textsubscript{3} & 60/4.1 \tabularnewline
3 & PdCl\textsubscript{2}dppf & Ag\textsubscript{2}CO\textsubscript{3} & >95/4.1 \tabularnewline
4 & Pd(OAc)\textsubscript{2}/dppp & Ag\textsubscript{2}CO\textsubscript{3} & 70/10:1 \tabularnewline
5 & Pd\textsubscript{2}dba\textsubscript{3}/dppp & Ag\textsubscript{2}CO\textsubscript{3} & 70/12:1 \tabularnewline
6 & Pd\textsubscript{2}dba\textsubscript{3}/dpph & Ag\textsubscript{2}CO\textsubscript{3} & >95/20:1 \tabularnewline
7 & Pd(OAc)\textsubscript{2}/SPhos & K\textsubscript{3}PO\textsubscript{4} & 85/0:1 \tabularnewline
\hline
\end{tabular}
\caption{Optimization studies for the coupling of \textit{3.2}.}
\end{table}
These optimized conditions for the formation of 1,1-disubstituted boronate 3.24 have proven to be scalable. On a 1 mmol scale, cross-coupled product 3.24 was obtained in 61% isolated yield as a single isomer (Scheme 3-10). We further explored the utility of 3.2 as a substrate for iterative Suzuki-Miyaura coupling reactions. The in situ hydrolysis of 3.24 followed by cross-coupling of the resulting boronic acid with aryl iodide 3.26 yielded 3.27 as a single isomer.

We next tested the generality of the optimized cross-coupling conditions with a variety of aryl, heteroaryl, and vinyl boronic acids (Table 3-3). Good to moderate conversions were observed in all cases. The coupling of boronic acids with electron neutral (entries 1-2), withdrawing (entries 3-6), and donating groups (entires 7-8) formed the desired product in all cases. Specifically, the coupling of 4-vinylphenylboronic acid 3.28a and m-tolylboronic acid 3.28b proceeded with excellent selectivity (>20:1), high conversion (>95%), and a 81% isolated yield for 3.29a and 90% isolated yield for 3.29b. However, the presence of electron withdrawing groups, including 4-methoxycarbonyl, 4-cyano, 4-fluoro, and 4-trifluoromethoxy (entries 3-6), resulted in moderate selectivities (10:1 to 4:1) albeit still with good conversions (70-90%). The electron withdrawing groups on the boronic acid may reduce the rate of the desired transmetalation reaction (Figure 3-4, pathway 1), therefore making the β-hydride elimination pathway more competitive (pathway 2). In contrast, electron donating groups, including 3,5-dimethoxy and 4-dimethylamino (entries 7-8) provided the cross-coupled products with excellent selectivity (>20:1) and a 66% isolated yield for 3.29g. Additionally, the coupling of 2-heterocyclic boronic acids, including 2-benzofuranboronic acid 3.28i and 2-thiopheneboronic acid 3.28j produced the 1,1-product in >20:1 in both cases and a 82% isolated yield for 3.29i. Finally, the coupling of vinyl boronic acids also produced the 1,1-product in >20:1 and 76% isolated yield for 3.29k and 65% isolated yield for 3.29l.
Table 3-3. Substrate scope under the optimized reaction conditions.

<table>
<thead>
<tr>
<th>entry</th>
<th>3.28</th>
<th>3.29</th>
<th>3.28:3.29</th>
<th>% conversion* (isolated yield)</th>
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</thead>
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<td><img src="image2" alt="Structure" /></td>
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<td>&gt;95 (91%)</td>
</tr>
<tr>
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<td><img src="image3" alt="Structure" /></td>
<td><img src="image4" alt="Structure" /></td>
<td>&gt;20:1</td>
<td>&gt;95 (90%)</td>
</tr>
<tr>
<td>3</td>
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<td><img src="image6" alt="Structure" /></td>
<td>10:1</td>
<td>85</td>
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<td><img src="image8" alt="Structure" /></td>
<td>8:1</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9" alt="Structure" /></td>
<td><img src="image10" alt="Structure" /></td>
<td>4:1</td>
<td>90</td>
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<td><img src="image12" alt="Structure" /></td>
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<td>85 (86%)</td>
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<td><img src="image14" alt="Structure" /></td>
<td>&gt;20:1</td>
<td>&gt;95 (92%)</td>
</tr>
<tr>
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<td><img src="image16" alt="Structure" /></td>
<td>&gt;20:1</td>
<td>50</td>
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<td>&gt;20:1</td>
<td>95 (92%)</td>
</tr>
<tr>
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<td>&gt;20:1</td>
<td>50</td>
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<td><img src="image22" alt="Structure" /></td>
<td>&gt;20:1</td>
<td>90 (76%)</td>
</tr>
<tr>
<td>12</td>
<td><img src="image23" alt="Structure" /></td>
<td><img src="image24" alt="Structure" /></td>
<td>&gt;20:1</td>
<td>80 (65%)</td>
</tr>
</tbody>
</table>

* The reaction conversion and ratio of 3.29:3.30 was determined from the crude 1H-NMR.

Similar to (Z)-Br-3.1, these findings expand the utility of ICC with MIDA boronates as a simple and flexible platform for the efficient synthesis of a wide range of functional small molecules.
3-4 2-PYRIDYL MIDA BORONATE

The 2-pyridyl subunit is one of the most prevalent and therefore important structural motifs, being found in a wide range of pharmaceuticals, natural products, unnatural nucleosides, fluorescent probes, materials, and metal-complexing ligands (Figure 3-5). Tremendous effort over the past three decades has been dedicated to the development of 2-pyridyl organometallic reagents that can be efficiently employed in cross-coupling reactions. All of these methods, however, suffer from one or more important limitations, including lack of air-stability of the 2-pyridyl building blocks, use of toxic metals, inability to isolate the building blocks in chemically pure form, and/or inefficient couplings with more challenging halide coupling partners such as deactivated aryl chlorides. Overcoming all of these limitations, we herein report the first general solution for the 2-pyridyl problem.

Figure 3-5. The 2-pyridyl unit is found in many different small molecules.
Typically, the 2-pyridyl-boron bond is exquisitely sensitive to protodeborylation, making most 2-pyridyl boranes unstable. In contrast, Drs. Eric Gillis and David Knapp recently identified 2-pyridyl MIDA boronate 3.3 (Scheme 3-11A) as the first 2-pyridyl borane that is both air stable and can be isolated in a chemically pure form. Together with Graham Dick and Anthony Grillo, we developed an inexpensive, environmentally friendly, and scalable method for preparing 3.3 and many of its derivatives (Scheme 3-11B). Importantly, all of these new building blocks are monomeric, highly crystalline, free-flowing solids that can be stored indefinitely on the bench top under air without decomposition, and several of them are now commercially available.

Scheme 3-11. a) 2-pyridyl MIDA boronate 3.3 is the first air-stable 2-pyridyl borane that can be isolated in chemically pure form. b) An inexpensive, environmentally friendly, and scalable method for preparing 2-pyridyl MIDA boronates. c) A preliminary method for cross-coupling 3.3 with activated aryl chlorides. This method is ineffective with more challenging deactivated aryl halides.

Having achieved all of these long sought after features in a collection of 2-pyridyl boranes, finding maximally general conditions to promote the cross-coupling of these building blocks became the final key goal. Kinetically competitive in situ decomposition usually hinders the effective cross-coupling of 2-pyridyl boranes. Because electronically and/or sterically deactivated aryl halides tend to react more slowly than their activated counterparts, they are especially challenging coupling partners. To overcome similar challenges with other sensitive 2-heterocyclic boronic acids, Drs. David Knapp and Eric Gillis introduced the slow-release cross-coupling strategy. Specifically, in the presence of mild bases and water as a co-solvent,
air-stable MIDA boronates undergo in situ hydrolysis to liberate the corresponding boronic acids at a rate that is slower than catalyst turnover. Analogous to utilizing a syringe pump, such conditions strongly favor cross-coupling over boronic acid decomposition.

Presumably due to the extreme lability of the 2-pyridyl-boron bond, even under these slow-release conditions the cross-coupling of 2-pyridyl MIDA boronate remained challenging. As shown in Scheme 3-11C, modified conditions employing isopropanol (IPA) instead of water as co-solvent and Cu(OAc)$_2$ as a substoichiometric additive were somewhat effective with activated, electron deficient aryl chlorides such as 3.31a. However, when we attempted to cross-couple 3.3 with more challenging deactivated aryl chlorides, such as 3.31b, very little of the desired cross-coupling product 3.32b was observed.

In collaboration with Graham Dick, an extensive survey of Pd/ligand combinations, Cu salts, bases, solvents, temperatures, and reaction times were explored, and resulted in conditions that were somewhat more effective, but the yield of 3.32b remained modest (49%, Table 3-4, entry 1). Driven by our then working hypothesis that the role of IPA in these reactions was to promote initial transligation of 3.3 to the corresponding 2-pyridyl isopropyl boronic ester, we investigated a range of different alcohols as additives. However, less (entries 2 and 3) or more (entry 4) sterically bulky alcohols were all inferior to IPA, and common diols also provided no notable advantage (entries 5-7). In contrast, addition of the trivalent ligand diethanolamine (DEA) resulted in the intriguing formation of a royal blue reaction mixture and the formation of 3.32b in a substantially increased yield of 70% (entry 8).
To enable further optimization of these reaction conditions, we sought to understand the mechanistic underpinnings of this DEA-promoted increase in efficiency. Deng and coworkers have shown that the cross-coupling of 2-pyridyl boronic esters promoted by copper(I) salts likely involves an initial C–B to C–Cu transmetallation to produce an intermediate 2-pyridyl copper species which, in turn, undergoes transmetallation with Pd(II). Starting with this general mechanistic framework, we considered two possible pathways for DEA to promote the transformation of 3.3 into a putative 2-pyridyl copper intermediate 3.33 (Scheme 3-12). In pathway 1, DEA reacts with the conformationally rigid MIDA boronate 3.3 in a novel transligation reaction to form a conformationally flexible and thereby more reactive DEA adduct 3.34, which in turn transmetallates with Cu(OAc)₂ to form 3.33. In pathway 2, DEA alternatively reacts with Cu(OAc)₂ to yield a Cu(DEA)ₙ complex and KOAc. The released KOAc then reacts with 3.3 to generate a reactive 2-pyridyl boronate intermediate 3.35 (X = acetate and/or other ion), which in turn transmetallates with Cu(DEA)₂ to form 3.33.

Table 3-4. Cross-coupling of 2-pyridyl MIDA boronate 3.3 with deactivated aryl chloride 3.31b.
Scheme 3-12. Two possible pathways for the DEA-promoted coupling of 3.3.

To determine whether pathway 1 was operative, we first mixed DEA with 3.3 in the presence of K$_3$PO$_4$ in deuterated DMF at 100 °C and monitored the reaction by $^1$H NMR. Seeming to support this mechanism, we observed the slow transligation of 3.3 to 3.34 over the course of four hours (Supporting Information) and succeeded in isolating 3.34 as a crystalline solid (Scheme 3-13). However, when we attempted to couple to 3.34 to 3.31b with or without syringe pump-mediated slow addition of 3.34 over the course of four hours to mimic the rate of its in situ formation, we observed only very low yields of 3.32b (Scheme 3-13). Thus, pathway 1 cannot account for the beneficial effects of DEA on the coupling of 3.3 and 3.32b.


To interrogate the possibility of pathway 2, we alternatively combined DEA with Cu(OAc)$_2$ in the presence of K$_3$PO$_4$ in DMF at 100 °C (Scheme 3-14). In less than 15 minutes the reaction turned royal blue, and both Cu(DEA)$_2$ and KOAc were formed. After extensive experimentation, we developed a new procedure for preparing and purifying Cu(DEA)$_2$ from CuCl$_2$, DEA, and K$_3$PO$_4$ (Supporting Information). Strikingly, when we attempted to couple 3.3 and 3.31b in the presence of purified Cu(DEA)$_2$ and KOAc under our otherwise standard conditions we observed an 84% yield of 3.32b (Scheme 3-15, entry 1). Consistent with important roles for both of these additives in achieving this result, in the absence of Cu(DEA)$_2$, without or with added KOAc, none of this cross-coupling product was observed (entries 2 and 3),
Cu(DEA)$_2$ was superior to Cu(OAc)$_2$ (entry 4), and the addition of Cu(DEA)$_2$ but not KOAc provided only a modest yield of 3.32b (entry 5).$^{70}$

\[
\text{Cu(OAc)}_2 \xrightarrow{\text{DEA}} \text{Cu(DEA)}_2 + \text{KOAc}
\]

Scheme 3-14. Synthesis of Cu(DEA)$_2$.

<table>
<thead>
<tr>
<th>entry</th>
<th>additive(s)</th>
<th>% GC yield of 3.32b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cu(DEA)$_2$ + KOAc</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>none</td>
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<tr>
<td>3</td>
<td>KOAc</td>
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<tr>
<td>4</td>
<td>Cu(OAc)$_2$ + KOAc</td>
<td>38</td>
</tr>
<tr>
<td>5</td>
<td>Cu(DEA)$_2$</td>
<td>50</td>
</tr>
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</table>

Scheme 3-15. Exploring the role of the reaction components.

To further probe the role of KOAc in this reaction, we treated 3.3 with K$_3$PO$_4$ in DMF at 100 ºC with or without adding KOAc and monitored the consumption of 3.3 via $^1$H NMR. In both the absence and presence of Cu(DEA)$_2$, the addition of KOAc to otherwise identical conditions resulted in substantially accelerated conversion of 3.3 to yield pyridine, presumably via protodemetalation of short-lived intermediates 3.35 or 3.33. Although additional studies will be needed to characterize this mechanism in further detail, all of these data are consistent with pathway 2 (Scheme 3-12).

Importantly, this mechanism also proved to be predictive for further optimizing this cross-coupling system. Specifically, the intermediacy of Cu(DEA)$_2$ predicts that the optimum ratio of DEA:Cu(OAc)$_2$ would be 2:1. We tested this hypothesis via systematically varying this ratio and found that in fact a 2:1 ratio provided the highest GC yield of 3.32b (Scheme 3-16). Employing this rationally optimized ratio of additives on a 1 mmol scale, we were able to obtain a 94% isolated yield for this very challenging cross-coupling reaction.

Scheme 3-16. The effect of the DEA/Cu(OAc)$_2$ ratio on the cross-coupling yield.
With this optimized methodology in hand, Graham Dick explored its scope with respect to both the 2-pyridyl MIDA boronate and halide coupling partners. Remarkably, the same set of reaction conditions proved to be highly general. For example, as shown in Table 3-5, a series of electron-rich and/or sterically bulky aryl chlorides were coupled with 3.3 in typically good to excellent yields (entries 1-5). Even the highly deactivated 2,6-dimethoxy chlorobenzene (3.31h) was coupled in synthetically useful yield (entry 6). Importantly, the same conditions optimized for deactivated substrates were also effective for coupling 3.3 with electronically activated aryl chlorides (entries 7-9), and a diverse series of heteroaryl chlorides (entries 10-14).
Table 3-5. General cross-coupling of air-stable 2-pyridyl MIDA boronate 3.3 with aryl and heteroaryl chlorides.

<table>
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<tr>
<th>entry</th>
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<td><img src="image" alt="3.32o" /></td>
<td>82</td>
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</tbody>
</table>

General reaction conditions: 1 equiv of aryl halide (1 mmol), 1.5 equiv of MIDA boronate 3.3, 5 mol % XPhosPdcycle, 50 mol % Cu(OAc)<sub>2</sub>, 1.0 equiv DEA, 5.0 equiv of K<sub>3</sub>PO<sub>4</sub>, 0.125 M DMF, 100 °C, 24 h. <sup>a</sup> 80 °C.
As shown in Table 3-6, these same conditions were also successfully applied to very challenging couplings with a range of other 2-pyridyl MIDA boronate derivatives. Specifically, series of both electron rich (3.3a-d) and electron deficient (3.3e-g) 2-pyridyl MIDA boronates, representing substructural motifs that appear in a wide variety of pharmaceuticals, materials, and/or ligands, were successfully coupled to a representative series of sterically and/or electronically deactivated aryl chlorides (entries 1-7).

![Diagram of reaction](image)

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<th>entry</th>
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<th>3</th>
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<th>% isolated yield</th>
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<td>3.31b</td>
<td>3.32</td>
<td>81</td>
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General reaction conditions: 1 equiv of aryl halide (1 mmol), 1.5 equiv of MIDA boronate, 5 mol % XPhosPdcyclo, K2PO4, Cu(OAc)2, DEA, DMF, 100 °C, 24 h.

Table 3-6. General cross-coupling of air-stable 2-pyridyl MIDA boronate derivatives with deactivated aryl chlorides.

Finally, it is often the case that conditions that are optimized for one class of halides or pseudohalides do not transfer to other classes. However, the exact same conditions promote the
efficient coupling of 3.3 with a diverse range of electrophilic coupling partners, including bromides (3.36a-e), iodides (3.36f-i), and triflates (3.36j-n), with all three classes of electrophiles represented as deactivated, activated, and heteroaryl variants (Table 3-7).
Table 3-7. General cross-coupling of air-stable 2-pyridyl MIDA boronate 3,3 with aryl and heteroaryl bromides, iodides, and triflates.

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General reaction conditions: 1 equiv of aryl halide (1 mmol), 1.5 equiv of MIDA boronate, 5 mol % XPhosPdCl2, 1.0 equiv DEA, 5.0 equiv of K2CO3, 0.125 M DMF, 100 °C, 24 h. * 80 °C.
The ubiquity of the 2-pyridyl subunit in a wide range of functional small molecules of substantial importance has for decades stimulated the search for an isolable 2-pyridyl borane that is both air-stable and can function as a generally effective cross-coupling partner. The Cu(DEA)$_2$/KOAc promoted cross-coupling with air-stable 2-pyridyl MIDA boronates described herein represents the first general solution to this problem. As the 2-pyridyl motif is in many ways the archetype for unstable boronic acids, this discovery has widespread implications for many other types of challenging cross-coupling processes. Moreover, this platform stands to immediately enable the more effective exploration of the functional potential of 2-pyridyl containing small molecules for a wide range of important applications in science and medicine.

3-5 SUMMARY AND CONCLUSIONS

Toward shifting the rate limiting step in small molecule science from the synthesis of molecules to the study of their function, we have identified three structural motifs that are commonly occurring in a variety of natural products, pharmaceuticals, and materials: cis-olefins, 1,1-disubstituted olefins, and the 2-pyridyl moiety. We have developed efficient and scalable syntheses of MIDA boronate building blocks that represent these three motifs. Each of these building blocks is now commercially available. Moreover, we have demonstrated that each of these building blocks can be functionalized to provide a variety of structural frameworks. Specifically, (Z)-(2-bromovinyl)-MIDA boronate 3.1, representing the cis-olefin motif, can undergo Suzuki, Stille, Heck, Sonogashira, and Negishi couplings selectively at the halide terminus. Furthermore, 3.1 is a substrate for ICC and can rapidly provide access of molecules containing cis-olefins. (1-bromovinyl)-MIDA boronate 3.2, representing the 1,1-disubstituted olefin motif, can under Suzuki-Miyaura reactions with a variety of aryl, heteroaryl, and alkenyl boronic acids to provide 1,1-disubstituted boronate building blocks that can undergo further functionalization to provide small molecules containing the 1,1-disubstituted motif. Finally, 2-pyridyl MIDA boronate 3.3 can be coupled to a variety of aryl and heteroaryl chlorides, bromides, iodides, and triflates using one common set of reaction conditions to provide a diverse range of biaryl products. Collectively these three examples stand to enable the more effective exploration of the functional potential of small molecules containing these motifs.
3-6 REFERENCES

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36 Li, J.; Burke, M. D. J. Am. Chem. Soc. 2011, 133, 13774-13777.
40 www.aldrich.com/mida
43 Sigma Aldrich: 704415; AllyChem: AC111044; BoroPharm


(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.


67 To the best of our knowledge, the use of Cu(DEA)$_2$ in a cross-coupling reaction has not been previously reported.


69 We experienced difficulties with the reported procedures for preparing Cu(DEA)$_2$. When purified Cu(DEA)$_2$ is dissolved in DMF at 100 °C, the resulting solution is royal blue.

CHAPTER 3
EXPERIMENTAL SECTION

Materials. Commercial reagents were purchased from Sigma-Aldrich, Fisher Scientific, Alfa Aesar, TCI America, Strem Chemicals Inc., or Frontier Scientific and were used without further purification unless otherwise noted. Solvents and amines were dried as noted in Chapter 2. The following compounds were prepared according to known literature procedures: ethynyl MIDA boronate 3.4,\(^1\) pinacol ester 3.5,\(^2\) (\(E\))-(2-bromovinyl)-MIDA boronate (\(E\))-Br-3.1,\(^3,4\) vinyl boronic acid 3.16h,\(^1\) vinyl stannane (\(E\))-3.20,\(^1\) vinyl stannane (\(Z\))-3.20.\(^1\)

General Experimental Procedures. The general experimental procedures followed in these studies are the same as those detailed in Chapter 2, except where noted. Gas chromatography analysis was conducted on an Agilent Technologies 7890A instrument. GC yields are based on a biphenyl internal standard using an Agilent Technologies HP-5 column (part number 19091J-413). A standard GC method was used for all analyses: the oven was held at 75 °C for 0.5 min then heated to 100 °C over 3 min followed by heating to 230 °C over 9.5 min and held at 230 °C for 1 min. \(\text{H}_2\) flow was 30 mL/min; Air flow was 400 mL/min; and \(\text{N}_2\) flow was 25 mL/min. The \(t_r\) of the biphenyl internal standard 4.96 min; the \(t_r\) of 2-(4-tertbutoxyphenyl)-pyridine was 8.01 min; and the \(t_r\) of 2-(4-acetophenone)-pyridine was 8.03 min.

Structural analysis. Structural analysis was preformed and described as detailed in Chapter 2.

Experimental Procedures.

![MIDA boronate (Z)-Br-3.1](image)

MIDA boronate (Z)-Br-3.1.

Bromination/elimination procedure:
A 300 mL round bottom flask equipped with a stir bar was charged with MIDA boronate 3.5 (3.07g, 9.9 mmol) and \(\text{CH}_2\text{Cl}_2\) (100 mL). To this solution was added dropwise neat bromine (0.75 mL, 14.6 mmol). The resulting solution was stirred at 23 °C for 1 h and then concentrated
in vacuo to afford a pale yellow solid. Residual bromine was removed by azeotroping with CH₂Cl₂ (3 x 50 mL). To the resulting pale yellow solid was added finely ground K₃PO₄ (20.02 g, 94.3 mmol) and MeCN (100 mL). The resulting suspension was stirred at 23 °C for 3.5 h. The resulting suspension was poured into 200 mL EtOAc, 100 mL pH 7 phosphate buffer (0.5 M), and 100 mL DI H₂O. The mixture was shaken and the aqueous layer was removed. The organic layer was washed with pH 7 phosphate buffer (0.5 M, 1 x 100 mL). The combined aqueous layers were back extracted with 9:1 EtOAc:Acetone (1 x 200 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated in vacuo. The resulting residue was azeotroped with CH₂Cl₂ (2 x 50 mL) and then suspended in Et₂O (100 mL). This suspension was placed in a sonicator bath for 1 h. The resulting solid was collected by vacuum filtration and rinsed with Et₂O (15 mL) to yield MIDA boronate (Z)-Br-3.1 as a colorless solid (1.91 g, 73%).

One-pot CuBr₂ procedure:
A 500-mL round bottom flask equipped with a stir bar was charged with MIDA boronate 3.5 (2.00 g, 6.47 mmol), CuBr₂ (7.23 g, 32.4 mmol) and CH₃CN:H₂O (19:1, 100 mL). The resulting solution was stirred at 23 °C for 1.75 h. The reaction was poured into a separatory funnel containing 1 M aq. HCl (150 mL). The aqueous layer was extracted with EtOAc (1 x 250 mL, 2 x 150 mL). The combined organic layers were sequentially washed with sat. aq. Na₂S₂O₃ (100 mL), half-saturated brine (100 mL), and brine (100 mL). The organic solution was vigorously stirred with an aq. solution of 2Na⁺ EDTA²⁻ (0.05 M, 150 mL) for 45 min at 23 °C. The biphasic mixture was transferred to a separatory funnel and the aqueous layer removed. The organic layer was washed with brine (100 mL) and then dried over MgSO₄ and decolorized with charcoal. Filtration and concentration of the filtrate in vacuo afforded crude (Z)-Br-3.1 as a white solid. This solid was suspended in Et₂O:Acetone (25:1, ~260 mL) and placed in a sonicator bath for 1 h. The resulting solid was collected by vacuum filtration and rinsed with Et₂O to yield MIDA boronate (Z)-Br-3.1 as a white powder (0.96 g, crop 1). The filtrate was concentrated in vacuo and the sonication process was repeated to afford (Z)-Br-3.1 as a white powder (0.13 g, crop 2; 1.09 g total, 64%).
**1H NMR (500 MHz, d₆-acetone)**

δ 7.00 (br d, J = 7.5 Hz, 1H), 6.43 (d, J = 9.0 Hz, 1H), 4.31 (d, J = 17.0 Hz, 2H), 4.10 (d, J = 17.0 Hz, 2H), 3.11 (s, 3H).

**13C NMR (125 MHz, d₆-acetone)**

δ 168.7, 120.6, 63.7, 47.9.

**HRMS (ESI⁺)**

Calculated for C₇H₁₀BBrNO₄ (M+H)⁺: 261.9886

Found: 261.9884

**IR (thin film, cm⁻¹)**

3017, 2953, 1767, 1597, 1453, 1337, 1289, 1249, 1164, 1029, 953, 896, 871.

mp 142-146 °C dec, uncorrected.

X-ray quality crystals were grown by vapor diffusion of Et₂O into a dissolved solution of (Z)-Br-3.1 in CH₂Cl₂.⁵

---

**MIDA boronate 3.7.**

*Preparation of catalyst solution.* In a glovebox, to a 7 mL vial equipped with a stir bar and charged with XPhos⁶ (9.6 mg, 0.02 mmol) and Pd(OAc)₂ (2.2 mg, 0.01 mmol) was added THF (2 mL). The solution was stirred at 23 °C for 10 min.

*The freshly prepared catalyst solution was used in the following reaction.* In a glovebox, to a 7 mL vial equipped with a stir bar and charged with MIDA boronate (Z)-Br-3.1 (52.1 mg, 0.20 mmol) and boronic acid 3.6 (45.4 mg, 0.31 mmol) was added Cs₂CO₃ (200.2 mg, 0.61 mmol). The prepared catalyst solution was added in one portion. The vial was sealed with a cap and removed from the glovebox. The solution was stirred in a subdued light environment at 23
°C for 23.5 h. The reaction mixture was filtered through a pad of Celite, concentrated \textit{in vacuo}, dry loaded onto Celite from an acetone solution, and purified via flash chromatography on silica gel (Et$_2$O:acetone 100:0 → 3:1) to afford MIDA boronate \textbf{3.7} as a pale yellow solid (40.2 mg, 71%).

\textbf{1H NMR} (400 MHz, d$_6$-acetone)

$\delta$ 7.46 (m, 3H), 7.34 (t, $J$ = 7.5 Hz, 2H), 7.25 (m, 1H), 6.87 (app t, $J$ = 12.0 Hz, 1H), 6.62 (d, $J$ = 15.5 Hz, 1H), 5.52 (d, $J$ = 14.0 Hz, 1H), 4.29 (d, $J$ = 17.0 Hz, 2H), 4.09 (d, $J$ = 17.0 Hz, 2H), 3.07 (s, 3H).

\textbf{13C NMR} (100 MHz, d$_6$-acetone)

$\delta$ 169.0, 144.3, 138.2, 135.6, 129.4, 128.7, 128.5, 127.3, 62.3, 42.3.

\textbf{HRMS (ESI$^+$)}

Calculated for C$_{15}$H$_{17}$BNO$_4$ (M+H)$^+$: 286.1251

Found: 286.1253

\textbf{General procedure: Stille coupling}

In a glovebox, to a 7 mL vial equipped with a stir bar and charged with (Z)-Br-\textbf{3.1} or (E)-Br-\textbf{3.1} (0.2 mmol) and vinyl stannane \textbf{3.8} or 1-triethylgermanium-2-tributyltin ethylene (Z)-\textbf{3.20} or (E)-\textbf{3.20} (0.22 mmol) was added Pd$_2$(dba)$_3$ (0.01 mmol) and Ph$_3$As (0.02 mmol). The vial was sealed with a PTFE-lined septum screw-cap and removed from the glovebox. At 0 °C, under a positive pressure of Ar, THF (0.5 mL) and DMF (1.5 mL) were added sequentially via syringe. The resulting mixture was stirred in a subdued light environment at 0 °C for 2 h and then slowly warmed to 23 °C and stirred for an additional 8-18 h at 23 °C. The reaction mixture was poured into brine (5.0 mL) and extracted with EtOAc (2 x 15 mL). The combined organic phases were dried over MgSO$_4$, concentrated \textit{in vacuo}, dry loaded onto Celite from an acetone solution, and purified via flash chromatography on silica gel or Florisil to afford the desired compound.
MIDA boronate 3.9. The general Stille coupling procedure was followed using (Z)-Br-3.1 (39 mg, 0.15 mmol), vinyl stannane 3.8 (53 mg, 0.17 mmol), Pd$_2$(dba)$_3$ (7.0 mg, 0.01 mmol), Ph$_3$As (4.6 mg, 0.02 mmol), THF (0.5 mL) and DMF (1.5 mL). The resulting mixture was stirred at 0 °C for 2 h and then slowly warmed to 23 °C and stirred for an additional 18 h at 23 °C. Purification via flash chromatography on Florisil (EtOAc:petroleum ether 1:1 → EtOAc → EtOAc:MeCN 9:1) afforded 3.9 as a foam (25 mg, 79%).

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

$\delta$ 6.85 (ddd, $J = 17.0, 10.0, 1.0$ Hz, 1H), 6.70 (app t, $J = 11.0$ Hz, 1H), 5.39 (d, $J = 13.5$ Hz, 1H), 5.27 (dd, $J = 17.0, 2.0$ Hz, 1H), 5.23 (ddd, $J = 10.0, 2.0, 1.0$ Hz, 1H), 3.95 (d, $J = 17.0$ Hz, 2H), 3.79 (d, $J = 17.0$ Hz, 2H), 2.79 (s, 3H).

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

$\delta$ 169.1, 145.2, 136.7, 120.6, 62.4, 47.5.

HRMS (ESI$^+$)

Calculated for C$_9$H$_{13}$BNO$_4$ (M+H)$^+$: 210.0938

Found: 210.0940

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

3006, 2954, 2852, 1767, 1577, 1458, 1288, 1022, 997, 866.

MIDA boronate 3.11. In a glovebox, to a 7 mL vial equipped with a stir bar and charged with MIDA boronate (Z)-Br-3.1 (48.3 mg, 0.18 mmol) was added Pd(OAc)$_2$ (3.4 mg, 0.05 mmol), a solution of methyl acrylate 3.10 (0.4 M in DMF, 1.0 mL), and a solution of freshly distilled Et$_3$N
(0.4 M in DMF, 1.0 mL). The vial was sealed with a cap and removed from the glovebox. The solution was stirred in a subdued light environment at 23 °C for 46.5 h. The reaction mixture was filtered through a pad of Celite, concentrated in vacuo, dry loaded onto Celite from an acetone solution, and purified via flash chromatography on Florisil (Et₂O:acetone 100:0 → 2:1) to afford MIDA boronate 3.11 as a pale yellow solid (42.4 mg, 86%).

\[ \text{MIDA boronate } 3.11 \]

\[ \begin{align*}
\text{HRMS (ESI}^+\text{)} & \quad \text{Calculated for C}_{11}\text{H}_{15}\text{BNO}_6 (M+H)^+: 268.0992 \\
& \quad \text{Found:} 268.0991
\end{align*} \]

\[ \text{1}^1\text{H NMR (500 MHz, CD}_3\text{CN)} \]
\[ \delta 7.78 (dd, J = 11.5, 15.0 \text{ Hz, 1H}), 6.81 (\text{app t, } J = 12.5 \text{ Hz, 1H}), 5.94 (d, J = 15.0 \text{ Hz, 1H}), 5.85 (d, J = 14.0 \text{ Hz, 1H}), 3.98 (d, J = 17.0 \text{ Hz, 2H}), 3.83 (d, J = 17.0 \text{ Hz, 2H}), 3.69 (s, 3H), 2.82 (s, 3H). \]

\[ \text{1}^3\text{C NMR (125 MHz, CD}_3\text{CN)} \]
\[ \delta 169.0, 168.0, 143.5, 141.4, 124.5, 62.6, 52.1, 47.6. \]

**MIDA boronate 3.13.** In a glovebox, to a 7 mL vial equipped with a stir bar and charged with (Z)-Br-3.1 (62.8 mg, 0.24 mmol) was added CuI (2.6 mg, 0.014 mmol) and PdCl₂(PPh₃)₂ (19.5 mg, 0.028 mmol). The vial was sealed with a PTFE-lined septum screw-cap and removed from the glovebox. Under a positive pressure of Ar, THF (1.2 mL), TMS-acetylene 3.12 (0.050 mL, 0.36 mmol), and Et₃N (0.10 mL, 0.72 mmol) were sequentially added via syringe. The reaction was stirred at 23 °C for 4 h. The crude reaction was transferred to a separatory funnel containing brine (10 mL) and extracted with EtOAc (2 x 15 mL). The combined organic extracts were dried over Na₂SO₄, filtered, dry loaded onto Celite and purified via flash chromatography on Florisil (Et₂O:EtOAc 3:1 → 2:1 → 1:1) to afford MIDA boronate 3.13 as a yellow solid (54 mg, 80 %). Colorless crystals could be obtained by recrystallization from Et₂O (42 mg, 63 %).
$^1$H NMR (500 MHz, CDCl$_3$)

$\delta$ 6.27 (d, $J = 14.5$ Hz, 1H), 6.05 (d, $J = 14.5$ Hz, 1H), 4.00 (d, $J = 16.5$ Hz, 2H), 3.87 (d, $J = 16.5$ Hz, 2H), 2.91 (s, 3H), 0.17 (s, 9H).

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

$\delta$ 167.7, 124.2, 103.8, 101.1, 63.0, 47.4, −0.38.

HRMS (ESI$^+$)

Calculated for C$_{12}$H$_{19}$BNO$_4$Si (M+H)$^+$: 280.1176

Found: 280.1170

MIDA boronate 3.15.

(2-methyl-1-propenyl)zinc bromide solution 3.14 was prepared as follows: A 4 mL vial equipped with a magnetic stir bar was charged with zinc bromide (68 mg, 0.31 mmol), flushed with Ar and sealed with a PTFE-lined septum screw-cap. THF (1.0 mL) was added and the solution was stirred at 0 ºC for 10 min. 2-methyl-1-propenyl magnesium bromide (0.6 mL, 0.30 mmol, 0.5 M in THF) was added and the solution was stirred at 0 ºC for 30 min.

The freshly prepared solution of 3.14 was used in the following reaction: In a glovebox, to a 7 mL vial equipped with a magnetic stir bar and charged with (Z)-Br-3.1 (39 mg, 0.15 mmol) was added Pd(OAc)$_2$ (2 mg, 0.01 mmol) and SPhos (6 mg, 0.02 mmol). The vial was sealed with a PTFE-lined septum screw-cap and removed from the glovebox. The resulting slurry was stirred for 30 min. at 23 ºC and was then cooled to 0 ºC. The freshly prepared solution of 3.14 was added dropwise to the reaction vial. The resulting mixture was stirred in a subdued light environment at 0 ºC for 2 h. The reaction mixture was poured into brine (5 mL) and extracted with EtOAc (2 × 15 mL). The combined organic phases were dried over MgSO$_4$, concentrated in vacuo, dry loaded onto Celite from an acetone solution, and purified via flash chromatography on Florisil (EtOAc:petroleum ether 1:1 → EtOAc → EtOAc:MeCN 9:1) to afford MIDA boronate 3.15 as a pale yellow solid (33 mg, 92 %).
\(^1\)H NMR (500 MHz, CD\(_3\)CN)

\(\delta 6.94\) (app t, \(J = 14.0\) Hz, 1H), \(6.25\) (d, \(J = 12.0\) Hz, 1H), \(5.18\) (d, \(J = 14.0\) Hz, 1H), \(3.94\) (d, \(J = 17.0\) Hz, 2H), \(3.77\) (d, \(J = 17.0\) Hz, 2H), \(2.78\) (s, 3H), \(1.78\) (s, 3H), \(1.75\) (s, 3H).

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

\(\delta 169.2, 140.8, 139.1, 124.7, 62.4, 47.4, 26.5, 17.7\).

HRMS (ESI\(^+\))

Calculated for C\(_{11}\)H\(_{17}\)BNO\(_4\) (M+H): 238.1251

Found: 238.1250

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

3001, 2960, 2927, 2854, 1768, 1641, 1585, 1452, 1296, 991, 861.

mp 130-132 °C dec, uncorrected.

**MIDA boronate 3.17a.**

*Preparation of catalyst solution.* In a glovebox, to a 7 mL vial equipped with a stir bar and charged with Pd\(_2\)(dba)\(_3\) (9.7 mg, 0.01 mmol) and XPhos (19.2 mg, 0.04 mmol) was added THF (2 mL). The solution was stirred at 23 °C for 10 min.

*The freshly prepared catalyst solution was used in the following reaction.* In a glovebox, to a 7 mL vial equipped with a stir bar and charged with MIDA boronate (Z)-Br-3.1 (50.5 mg, 0.19 mmol) and boronic acid 3.16a (37.9 mg, 0.31 mmol) was added finely ground K\(_3\)PO\(_4\) (129.4 mg, 0.61 mmol). The prepared catalyst solution was added in one portion. The vial was sealed with a cap and removed from the glovebox. The solution was stirred in a subdued light environment at 35 °C for 47.5 h. The reaction mixture was filtered through a pad of Celite, concentrated *in vacuo*, dry loaded onto Celite from an acetone solution, and purified via flash chromatography on silica gel (Et\(_2\)O:acetone 100:0 → 3:1) to afford MIDA boronate 3.17a as a
pale yellow solid. This solid was trituted with 0.10 mL of acetone to provide a white solid (27.5 mg, 55%).

\( ^1H \) NMR (500 MHz, CD\(_3\)CN)
\[ \delta 7.36 (d, J = 7.5 \text{ Hz}, 2H), 7.30 (t, J = 7.5 \text{ Hz}, 2H), 7.25 (d, J = 7.5 \text{ Hz}, 1H), 7.18 (\text{br d}, J = 15.0 \text{ Hz}, 1H), 5.66 (d, J = 15.0 \text{ Hz}, 1H), 3.88 (d, J = 17.0 \text{ Hz}, 2H), 3.66 (d, J = 17.0 \text{ Hz}, 2H), 2.86 (s, 3H). \]

\( ^13C \) NMR (125 MHz, CD\(_3\)CN)
\[ \delta 168.9, 145.0, 140.1, 129.4, 128.9, 128.1, 62.6, 47.4. \]

HRMS (ESI\( ^+ \))
Calculated for C\(_{13}\)H\(_{15}\)BNO\(_4\) (M+H): 260.1094
Found: 260.1088

MIDA boronate 3.17b.

Preparation of catalyst solution. In a glovebox, to a 7 mL vial equipped with a stir bar and charged with Pd\(_2\)(dba)\(_3\) (10.8 mg, 0.01 mmol) and XPhos (20.9 mg, 0.04 mmol) was added THF (2 mL). The solution was stirred at 23 °C for 10 min.

The freshly prepared catalyst solution was used in the following reaction: In a glovebox, to a 7 mL vial equipped with a stir bar and charged with MIDA boronate (Z)-Br-3.1 (50.8 mg, 0.19 mmol) and boronic acid 3.16b (72.0 mg, 0.40 mmol) was added finely ground K\(_3\)PO\(_4\) (137.7 mg, 0.65 mmol). The prepared catalyst solution was added in one portion. The vial was sealed with a cap and removed from the glovebox. The solution was stirred in a subdued light environment at 35 °C for 48 h. The reaction mixture was filtered through a pad of Celite, concentrated in vacuo, dry loaded onto Celite from an acetone solution, and purified via flash
chromatography on silica gel (Et$_2$O:acetone 100:0 → 3:1) to afford MIDA boronate **3.17b** as a pale yellow solid (52.6 mg, 85%).

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

$\delta$ 7.29 (d, $J = 2.0$ Hz, 1H), 7.07 (d, $J = 15.0$ Hz, 1H), 6.92 (dd, $J = 2.0$, 8.0 Hz, 1H), 6.86 (d, $J = 8.0$ Hz, 1H), 5.56 (d, $J = 15.0$ Hz, 1H), 4.18 (d, $J = 17.0$ Hz, 2H), 3.93 (d, $J = 17.0$ Hz, 2H), 3.83 (s, 3H), 3.79 (s, 3H), 3.04 (s, 3H).

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

$\delta$ 168.8, 149.7, 149.6, 144.7, 132.8, 122.6, 113.0, 112.0, 62.4, 55.9, 55.8, 46.9.

HRMS (ESI$^+$)

Calculated for C$_{15}$H$_{19}$BNO$_6$ (M+H)$^+$: 320.1305

Found: 320.1302

MIDA boronate **3.17c**.

*Preparation of catalyst solution.* In a glovebox, to a 7 mL vial equipped with a stir bar and charged with Pd$_2$(dba)$_3$ (10.6 mg, 0.01 mmol) and XPhos (19.5 mg, 0.04 mmol) was added THF (2 mL). The solution was stirred at 23 $^\circ$C for 10 min.

*The freshly prepared catalyst solution was used in the following reaction.* In a glovebox, to a 7 mL vial equipped with a stir bar and charged with MIDA boronate (Z)-Br-**3.1** (43.7 mg, 0.17 mmol) and boronic acid **3.16c** (63.8 mg, 0.46 mmol) was added finely ground K$_3$PO$_4$ (136.8 mg, 0.64 mmol). The prepared catalyst solution was added in one portion. The vial was sealed with a cap and removed from the glovebox. The solution was stirred in a subdued light environment at 35 $^\circ$C for 48.5 h. The reaction mixture was filtered through a pad of Celite, concentrated *in vacuo*, dry loaded onto Celite from an acetone solution, and purified via flash...
chromatography on silica gel (Et₂O:acetone 100:0 → 3:1) to afford MIDA boronate 3.17c as a pale yellow solid (29.6 mg, 64%).

³¹H NMR (400 MHz, d₆-acetone)

δ 7.47 (m, 2H), 7.27 (br d, J = 15.0 Hz, 1H), 7.09 (m, 2H), 5.71 (d, J = 15.0 Hz, 1H), 4.17 (d, J = 17.0 Hz, 2H), 3.94 (d, J = 17.0 Hz, 2H), 3.11 (s, 3H).

¹³C NMR (125 MHz, d₆-acetone)

δ 168.6, 143.3, 137.4, 131.4, 131.3, 115.4, 62.4, 47.0.

HRMS (ESI⁺)

Calculated for C₁₃H₁₄BFNO₄ (M+H)⁺: 278.1000
Found: 278.1000

MIDA boronate 3.17d.

Preparation of catalyst solution. In a glovebox, to a 7 mL vial equipped with a stir bar and charged with P(o-tolyl)₃ (12.4 mg, 0.04 mmol) and Pd₂(dba)₃ (9.8 mg, 0.01 mmol) was added THF (2 mL). The solution was stirred at 23 °C for 10 min.

The freshly prepared catalyst solution was used in the following reaction: In a glovebox, to a 7 mL vial equipped with a stir bar and charged with MIDA boronate (Z)-Br-3.1 (49.8 mg, 0.19 mmol), boronic acid 3.16d (36.8 mg, 0.29 mmol), and Ag₂O (145.0 mg, 0.63 mmol) was added the prepared catalyst solution in one portion. The vial was sealed with a cap and removed from the glovebox. The solution was stirred in a subdued light environment at 23 °C for 25 h. The reaction mixture was filtered through a pad of Celite, concentrated in vacuo, dry loaded onto Celite from an acetone solution, and purified via flash chromatography on silica gel (Et₂O:acetone 100:0 → 3:1) to afford MIDA boronate 3.17d as a pale yellow solid (36.0 mg, 72%).
$^1$H NMR (500 MHz, d$_6$-acetone)

$\delta$ 7.40 (m, 1H), 7.24 (m, 1H), 7.19 (br d, $J = 15.5$ Hz, 1H), 7.00 (dd, $J = 3.5$, 5.0 Hz, 1H), 5.54 (d, $J = 15.5$ Hz, 1H), 4.25 (d, $J = 17.0$ Hz, 2H), 4.05 (d, $J = 17.0$ Hz, 2H), 3.08 (s, 3H).

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

$\delta$ 168.8, 142.7, 136.3, 129.8, 127.8, 127.3, 62.7, 47.1.

HRMS (ESI$^+$)

Calculated for C$_{11}$H$_{13}$BNO$_4$S (M+H)$^+$: 266.0658

Found: 266.0648

MIDA boronate 3.17e.

*Preparation of catalyst solution.* In a glovebox, to a 7 mL vial equipped with a stir bar and charged with P(o-tolyl)$_3$ (11.7 mg, 0.04 mmol) and Pd$_2$(dba)$_3$ (9.3 mg, 0.01 mmol) was added THF (2 mL). The solution was stirred at 23 °C for 10 min.

*The freshly prepared catalyst solution was used in the following reaction:* In a glovebox, to a 7 mL vial equipped with a stir bar and charged with MIDA boronate (Z)-Br-3.1 (46.6 mg, 0.18 mmol), boronic acid 3.16e (66.1 mg, 0.41 mmol), and Ag$_2$O (143.5 mg, 0.62 mmol) was added the prepared catalyst solution in one portion. The vial was sealed with a cap and removed from the glovebox. The solution was stirred in a subdued light environment at 23 °C for 24 h. The reaction mixture was filtered through a pad of Celite, concentrated *in vacuo*, dry loaded onto Celite from an acetone solution, and purified via flash chromatography on silica gel (Et$_2$O:acetone 100:0 → 3:1) to afford MIDA boronate 3.17e as a pale yellow solid (49.1 mg, 92%).
$^1$H NMR (500 MHz, d$_6$-acetone)

$\delta$ 7.58 (d, $J = 8.0$ Hz, 1H), 7.42 (d, $J = 8.5$ Hz, 1H), 7.29 (t, $J = 7.5$ Hz, 1H), 7.21 (t, $J = 7.5$ Hz, 1H), 7.04 (br d, $J = 15.5$ Hz, 1H), 6.88 (s, 1H), 5.75 (d, $J = 15.5$ Hz, 1H), 4.38 (d, $J = 17.0$ Hz, 2H), 4.24 (d, $J = 17.0$ Hz, 2H), 3.11 (s, 3H).

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

$\delta$ 169.5, 156.1, 155.7, 131.2, 129.4, 125.6, 123.9, 122.0, 112.0, 108.6, 64.4, 48.9.

HRMS (ESI$^+$)

Calculated for C$_{15}$H$_{15}$BNO$_5$ (M+H)$^+$: 300.1043

Found: 300.1045

MIDA boronate 3.17f.

Preparation of catalyst solution. In a glovebox, to a 7 mL vial equipped with a stir bar and charged with Pd(OAc)$_2$ (2.3 mg, 0.01 mmol) and SPhos (9.2 mg, 0.02 mmol) was added THF (2 mL). The solution was stirred at 23 °C for 10 min.

The freshly prepared catalyst solution was used in the following reaction: In a glovebox, to a 7 mL vial equipped with a stir bar and charged with MIDA boronate (Z)-Br-3.1 (43.0 mg, 0.16 mmol) and boronic acid 3.16f (91.6 mg, 0.40 mmol) was added finely ground K$_3$PO$_4$ (136.7 mg, 0.64 mmol). The prepared catalyst solution was added in one portion. The vial was sealed with a cap and removed from the glovebox. The solution was stirred in a subdued light environment at 23 °C for 24 h. The reaction mixture was filtered through a pad of Celite, concentrated in vacuo, dry loaded onto Celite from an acetone solution, and purified via flash chromatography on silica gel (Et$_2$O:acetone 100:0 → 3:1) to afford MIDA boronate 3.17f as a pale yellow solid (39.7 mg, 70%).
1H NMR (500 MHz, d$_6$-acetone)

$\delta$ 7.24 (br d, $J = 15.5$ Hz, 1H), 7.23 (dd, $J = 2.0$, 3.5 Hz, 1H), 6.44 (m, 1H), 6.11 (t, $J = 3.5$ Hz, 1H), 5.55 (d, $J = 15.5$ Hz, 1H), 4.13 (d, $J = 17.0$ Hz, 2H), 3.84 (d, $J = 17.0$ Hz, 2H), 3.02 (s, 3H), 1.59 (s, 9H).

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

$\delta$ 168.8, 150.0, 136.2, 133.7, 122.3, 115.4, 111.3, 84.4, 62.7, 47.2, 28.0.

HRMS (ESI$^+$)

Calculated for C$_{16}$H$_{22}$BN$_2$O$_6$ (M+H)$^+$: 349.1571

Found: 349.1575

MIDA boronate 3.17g

**Preparation of catalyst solution.** In a glovebox, to a 7 mL vial equipped with a stir bar and charged with XPhos (8.6 mg, 0.02 mmol) and Pd(OAc)$_2$ (2.1 mg, 0.01 mmol) was added THF (2 mL). The solution was stirred at 23 °C for 10 min.

*The freshly prepared catalyst solution was used in the following reaction:* In a glovebox, to a 7 mL vial equipped with a stir bar and charged with MIDA boronate (Z)-Br-3.1 (46.5 mg, 0.18 mmol) and boronic acid 3.16g (53.4 mg, 0.47 mmol) was added Cs$_2$CO$_3$ (209.4 mg, 0.64 mmol). The prepared catalyst solution was added in one portion. The vial was sealed with a cap and removed from the glovebox. The solution was stirred in a subdued light environment at 23 °C for 24 h. The reaction mixture was filtered through a pad of Celite, concentrated in vacuo, dry loaded onto Celite from an acetone solution, and purified via flash chromatography on Florisil (Et$_2$O:acetone 100:0 → 3:1) to afford MIDA boronate 3.17g as a pale yellow solid (28.5 mg, 64%). For characterization of 3.17g see ref. 1.
MIDA boronate 3.17h.

Preparation of catalyst solution. In a glovebox, to a 7 mL vial equipped with a stir bar and charged with XPhos (8.6 mg, 0.02 mmol) and Pd(OAc)$_2$ (2.1 mg, 0.01 mmol) was added THF (2 mL). The solution was stirred at 23 °C for 10 min.

The freshly prepared catalyst solution was used in the following reaction: In a glovebox, to a 7 mL vial equipped with a stir bar and charged with MIDA boronate (Z)-Br-3.1 (42.8 mg, 0.16 mmol) and boronic acid 3.16h (57.5 mg, 0.50 mmol) was added Cs$_2$CO$_3$ (195.8 mg, 0.60 mmol). The prepared catalyst solution was added in one portion. The vial was sealed with a cap and removed from the glovebox. The solution was stirred in a subdued light environment at 23 °C for 24 h. The reaction mixture was filtered through a pad of Celite, concentrated in vacuo, dry loaded onto Celite from an acetone solution, and purified via flash chromatography on Florisil (Et$_2$O:acetone 100:0 → 3:1) to afford MIDA boronate 3.17h as a pale yellow solid (24.6 mg, 60%). For characterization of 3.17h see ref. 1.

MIDA boronate 3.19.

Preparation of catalyst solution. In a glovebox, to a 7 mL vial equipped with a stir bar and charged with Pd$_2$(dba)$_3$ (9.7 mg, 0.01 mmol) and XPhos (19.2 mg, 0.04 mmol) was added THF (2 mL). The solution was stirred at 23 °C for 10 min.

The freshly prepared catalyst solution was used in the following reaction: In a glovebox, to a 7 mL vial equipped with a stir bar and charged with MIDA boronate (Z)-Br-3.1 (50.0 mg, 0.19 mmol) and boronic acid (47.2 mg, 0.31 mmol) was added finely ground K$_3$PO$_4$ (131.0 mg, 0.62 mmol). The prepared catalyst solution was added in one portion. The vial was sealed with a cap and removed from the glovebox. The solution was stirred in a subdued light environment at 35 °C for 47.5 h. The reaction mixture was filtered through a pad of Celite, concentrated in vacuo,
vacuo, dry loaded onto Celite from an acetone solution, and purified via flash chromatography on silica gel (Et$_2$O:acetone 100:0 → 3:1) to afford MIDA boronate 3.19 as a pale yellow solid (52.4 mg, 95%).

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

δ 7.34 (d, $J = 8.5$ Hz, 2H), 7.08 (br d, $J = 15.0$ Hz, 1H), 6.85 (d, $J = 8.5$ Hz, 2H), 5.53 (d, $J = 15.0$ Hz, 1H), 3.89 (d, $J = 17.0$ Hz, 2H), 3.77 (s, 3H), 3.69 (d, $J = 17.0$ Hz, 2H), 2.86 (s, 3H).

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

δ 169.0, 159.9, 144.5, 132.5, 130.9, 114.2, 62.5, 55.8, 47.3.

HRMS (ESI$^+$)

Calculated for C$_{14}$H$_{17}$BNO$_5$ (M+H)$^+$: 290.1200

Found: 290.1201

mp 176-180 °C dec, uncorrected.

(Z)-3,5,4'-trimethoxystilbene 3.18.

Preparation of catalyst solution. In a glovebox, to a 7mL vial charged with SPhos (6.5 mg, 0.02 mmol) and Pd(OAc)$_2$ (2.1 mg, 0.009 mmol) was added THF (1.4 mL). The solution was stirred at 23 °C for 10 minutes.

The freshly prepared catalyst solution was used in the following reaction: In a glovebox, to a 7 mL vial equipped with a stir bar and charged with MIDA boronate 3.19 (39.2 mg, 0.14 mmol) and 1-bromo-3,5-dimethoxybenzene 3.20 (26.1 mg, 0.12) was added the prepared catalyst solution in one portion. The vial was sealed with a PTFE-lined septum screw-cap and removed from the glovebox. Under a positive pressure of Ar, 1 M aq. NaOH (0.40 mL) was added via
The solution was stirred in a subdued light environment at 23 °C for 6 h. The reaction mixture was poured into 1 M aq. phosphate buffer pH 7 (2 mL) and extracted with Et₂O (3 x 2 mL). The combined organic phases were dried over MgSO₄, filtered, and concentrated in vacuo. The crude material was dry loaded onto Celite from an acetone solution and purified via flash chromatography on Florisil (petroleum ether:CH₂Cl₂ 100:0 → 80:20) to afford the 3.18 as a pale yellow oil (28.3 mg, 76%). Spectral data for 3.18 were consistent with those previously reported.

**MIDA boronate (E,Z)-3.21.** The general Stille coupling procedure was followed using (Z)-Br-3.1 (52 mg, 0.20 mmol), (E)-3.20 (105 mg, 0.22 mmol), Pd₂(dba)₃ (9.2 mg, 0.01 mmol), Ph₃As (6.1 mg, 0.02 mmol), THF (0.5 mL), and DMF (1.5 mL). The resulting mixture was stirred at 0 °C for 2 h and then slowly warmed to 23 °C and stirred for an additional 12 h at 23 °C. Purification via flash chromatography on Florisil (EtOAc:petroleum ether 1:1 → EtOAc → EtOAc:MeCN 9:1) afforded (E,Z)-3.21 as a white solid (59 mg, 81%). The ¹H NMR of the crude product showed a single stereoisomer. Spectral data for (E,Z)-3.21 were consistent with those previously reported from our laboratories.

**MIDA boronate (Z,Z)-3.21.** The general Stille coupling procedure was followed using (Z)-Br-3.1 (52 mg, 0.20 mmol), (Z)-3.20 (105 mg, 0.22 mmol), Pd₂(dba)₃ (9.2 mg, 0.01 mmol), Ph₃As (6.1 mg, 0.02 mmol), THF (0.5 mL), and DMF (1.5 mL). The resulting mixture was stirred at 0 °C for 2 h and then slowly warmed to 23 °C and stirred for an additional 18 h at 23 °C. Purification via flash chromatography on Florisil (EtOAc:petroleum ether 1:1 → EtOAc → EtOAc:MeCN 9:1) afforded (Z,Z)-3.21 as a pale yellow solid (51.8 mg, 71%). The ¹H NMR of the crude product indicated 10% (Z,E)-3.21 as a byproduct which was inseparable by normal phase Florisil chromatography. Spectral data for (Z,Z)-3.21 were consistent with those previously reported from our laboratories.
MIDA boronate \((E,E)-3.21\). The general Stille coupling procedure was followed using \((E)-3.21\) (52 mg, 0.20 mmol), \((E)-3.20\) (105 mg, 0.22 mmol), \(\text{Pd}_2(\text{dba})_3\) (9.2 mg, 0.01 mmol), \(\text{Ph}_3\text{As}\) (6.1 mg, 0.02 mmol), THF (0.5 mL), and DMF (1.5 mL). The resulting mixture was stirred at 0 °C for 2 h and then slowly warmed to 23 °C and stirred for an additional 8 h at 23 °C. Purification via flash chromatography on silica gel (EtOAc:petroleum ether 1:1 → EtOAc → EtOAc:MeCN 9:1) afforded \((E,E)-3.21\) as a white solid (59.5 mg, 81%). The \(^1\text{H}\) NMR of the crude product showed a single stereoisomer. Spectral data for \((E,E)-3.21\) were consistent with those previously reported from our laboratories.\(^1\)

MIDA boronate \((Z,E)-3.21\). The general Stille coupling procedure was followed using \((E)-3.1\) (39 mg, 0.15 mmol), \((Z)-3.20\) (79 mg, 0.17 mmol), \(\text{Pd}_2(\text{dba})_3\) (7.0 mg, 0.01 mmol), \(\text{Ph}_3\text{As}\) (4.6 mg, 0.02 mmol), THF (0.5 mL), and DMF (1.5 mL). The resulting mixture was stirred at 0 °C for 2 h and then slowly warmed to 23 °C and stirred for an additional 12 h at 23 °C. Purification via flash chromatography on Florisil (EtOAc:petroleum ether 1:1 → EtOAc → EtOAc:MeCN 9:1) afforded \((Z,E)-3.21\) as a pale yellow solid (43 mg, 78%). The \(^1\text{H}\) NMR of the crude product showed a single stereoisomer. Spectral data for \((Z,E)-3.21\) were consistent with those previously reported from our laboratories.\(^1\)

MIDA boronate 3.23. To a 3 L 3-neck round bottom flask equipped with a stir bar was added \(\text{B(OMe)}_3\) (94 mL, 840 mmol) and THF (600 mL). The solution was cooled to -78 °C. Vinylmagnesium bromide (1.0 M in THF, 800 mL, 800 mmol) was added dropwise \(\text{via}\) cannula over 2 h 45 min. The resulting solution was stirred at -78 °C for 15 min., followed by stirring at 23 °C for 2 h 30 min. In a separate 2 L 3-neck round bottom flask equipped with a stir bar, internal thermometer, and distillation apparatus was added dry MIDA (235.0 g, 1.6 mol) and
DMSO (600 mL). The solution was heated with an oil bath to an internal temperature of 110 - 115 °C. The borate suspension was added dropwise to the hot MIDA solution via a Teflon cannula dropwise over 2 h 10 min, keeping the internal temperature between 105 and 115 °C. After full addition of the borate solution, the reaction solution was cooled to 23 °C. The resulting solution was transferred to a separatory funnel containing H₂O (1 L), brine (1 L), EtOAc (1.5 L) and acetone (1 L). The mixture was shaken and the aqueous layer was removed and extracted with EtOAc:acetone (2:1, 2 x 600 mL). The combined organic layers were washed with H₂O (2 x 500 mL). The combined water washes were back extracted with EtOAc:acetone (2:1, 2 x 300 mL). The combined organic phases were dried over MgSO₄, filtered, and concentrated in vacuo. The resulting solid was suspended in 300 mL acetone and 4 L Et₂O was added to precipitate the product. The resulting solid was collected by vacuum filtration to yield vinyl MIDA boronate 3.23 as a white solid (81.2 g, 55%). Spectral data for 3.23 were consistent with those previously reported from our laboratories.⁴

![MIDA boronate 3.2](image_url)

**MIDA boronate 3.2.** To a 2 L round bottom flask equipped with a stir bar and charged with vinyl MIDA boronate 3.23 (25.0 g, 137 mmol) was added CH₂Cl₂ (1.2 L). The resulting clear, colorless solution was cooled to 0 °C in an ice bath. Neat bromine (12.5 mL, 239 mmol) was added dropwise over 5 minutes to give a cloudy orange solution. The solution was warmed to 23 °C over 30 min. The resulting orange solution was concentrated in vacuo to give a yellow solid. Residual bromine was removed by azeotroping with CH₂Cl₂ (2 x 100 mL). The resulting solid was suspended in MeCN (1 L). 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU, 51.0 mL, 342 mmol) was added in one portion. The resulting mixture stirred at 23 °C for 1 hr. The solution was poured into 1 M aq. HCl (1 L) and diluted with EtOAc:acetone (3:1, 1 L). After shaking, the layers were separated. The organic layer was washed with saturated aqueous sodium bisulfite:brine (3:2, 1 x 500 mL) and brine (1 x 250 mL). The organic layer was dried over MgSO₄, filtered, and concentrated in vacuo. The resulting residue was passed through a plug of silica, eluting with acetone. The resulting solid was suspended in THF (50 mL) onto which Et₂O
(1.8 L) was layered to precipitate the product. The product was collected by vacuum filtration (24.0 g, 67%).

$^1$H NMR (500 MHz, $d_6$-acetone)

$\delta$ 6.39 (bs, 1H), 6.19 (bs, 1H), 4.37 (d, $J = 17.0$ Hz, 2H), 4.16 (d, $J = 17.0$ Hz, 2H), 3.16 (s, 3H).

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

$\delta$ 168.4, 129.5, 63.4, 47.2.

X-ray quality crystals were grown by vapor diffusion of Et$_2$O into a dissolved solution of 3.2 in acetone.

**General procedure for Scheme 3-9 and Table 3-2**

In a glovebox, to a 7 mL vial containing a stir bar and silver salt (0.4 mmol, 4.0 eq) was added a 0.25 mL aliquot of each of the following three stock solutions: 1) 262 mg MIDA boronate 3.2 in 2.5 mL THF (0.1 mmol, 1.0 eq of 3.2 added to each reaction); 2) 183 mg phenylboronic acid in 2.5 mL THF (0.15 mmol, 1.5 eq of boronic acid added to each reaction); 3) A solution of 0.05 mmol palladium salt and 0.2 mmol ligand in 2.5 mL THF was prepared and stirred at 23 °C for 30 min. before adding an aliquot to the reaction vials (0.005 mmol, 0.05 eq of palladium added to each reaction and 0.02 mmol, 0.2 eq of ligand added to each reaction). An additional 0.25 mL of THF was added to each reaction. The vials were capped, removed from the glovebox, and placed in a 40 °C heating block with stirring for 24 h. The crude reaction mixtures were filtered through a plug of Celite, concentrated *in vacuo*, and analyzed by $^1$H NMR.
MIDA boronate 3.24.

Preparation of catalyst solution. In a glovebox, to a 7 mL vial charged with dpph (90.9 mg, 0.20 mmol) and Pd$_2$dba$_3$ (45.8 mg, 0.05 mmol) was added THF (5.0 mL). The solution was stirred at 23 °C for 30 min.

The freshly prepared catalyst solution was used in the following reaction: In a glovebox, to a 20 mL vial with stir bar, charged with MIDA boronate 3.2 (261.9 mg, 1.0 mmol) was added Ag$_2$CO$_3$ (1.10 g, 4.0 mmol). Phenylboronic acid (182.8 mg, 1.5 mmol) was added as a solution in THF (5.0 mL). The prepared catalyst solution was added in one portion. The vial was sealed with a septum cap and removed from the glovebox. The solution was stirred at 40 °C for 24 h. The reaction mixture was filtered through a pad of Celite, concentrated in vacuo, dry loaded onto Celite from an acetone solution, and purified via flash chromatography on silica (Et$_2$O:MeCN 100:0 → 80:20) to afford MIDA boronate 3.24 (158.0 mg, 61%).

$^1$H NMR (400 MHz, d$_6$-acetone)
\[
\delta 7.42-7.38 (m, 2H), 7.33-7.28 (m, 2H), 7.26-7.21 (m, 1H), 5.73 (bd, J = 3.0 Hz, 1H), 5.69 (bs, 1H), 4.23 (d, J = 17.0 Hz, 2H), 3.85 (d, J = 17.0 Hz, 2H), 2.82 (s, 3H).
\]

1,1-disubstituted olefin 3.27. In a glovebox, to a 20 mL vial with stir bar, charged with MIDA boronate 3.24 (100.0 mg, 0.39 mmol, 1.0 eq) was added 4-idoacetephenone (113.9 mg, 0.46 mmol, 1.2 eq), 2nd gen. SPhosPd cycle (20.9 mg, 0.029 mmol, 0.075 eq), and THF (3.5 mL). The vial was sealed with a septum cap and removed from the glovebox. To the reaction solution was added 1 M aq. NaOH via syringe (2.9 mL, 2.9 mmol). The solution was stirred at 23 °C for 4 h. The reaction mixture was poured into a separatory funnel containing aqueous sodium phosphate buffer (0.5 M, pH 7.0, 10 mL) and diluted with Et$_2$O (10 mL). The mixture was shaken and the layers were separated. The aqueous phase was extracted with Et$_2$O (2 x 10 mL). The combined
organics were dried over MgSO$_4$, filtered, and then concentrated in vacuo. The crude material was dry loaded onto Celite from an acetone solution, and purified via flash chromatography on silica (hexane:EtOAc 100:0 → 90:10) to afford 1,1-disubstituted olefin 3.27 (63.5 mg, 74%). Spectral data for 3.27 were consistent with those previously reported.$^8$

**General procedure for Table 3-3.**

*Preparation of catalyst solution.* In a glovebox, to a 20 mL vial charged with dpph (136.4 mg, 0.30 mmol) and Pd$_2$dba$_3$ (68.7 mg, 0.075 mmol) was added THF (7.5 mL). The solution was stirred at 23 °C for 30 min. The freshly prepared catalyst solution was used in the following reactions: In a glovebox, to a 7 mL vial with stir bar, charged with MIDA boronate 3.2 (26.2 mg, 0.1 mmol) was added Ag$_2$CO$_3$ (110.0 mg, 0.4 mmol). Boronic acid (0.15 mmol) was added, followed by THF (0.5 mL). An aliquot of the prepared catalyst solution (0.50 mL) was added in one portion. The vial was sealed with a septum cap and removed from the glovebox. The solution was stirred at 40 °C for 24 h. The reaction mixture was filtered through a pad of Celite, concentrated in vacuo, and analyzed by $^1$H NMR. Select samples were dry loaded onto Celite from an acetone solution, and purified via flash chromatography on silica (Et$_2$O:MeCN 100:0 → 80:20) to afford the MIDA boronate 3.29.

![MIDA boronate 3.29a](image)

**MIDA boronate 3.29a.** Based on the crude $^1$H NMR, the reaction proceeded to >95% conversion and a >20:1 of 3.29:3.30 was obtained. 3.29a was isolated by column chromatography to provide 57.8 mg (0.25 mmol reaction), 81% yield.

TLC (Et$_2$O:MeCN 6:1)

\[ R_f = 0.44, \text{ visualized by short wave UV} \]

$^1$H NMR (400 MHz, d$_6$-acetone)

\[ \delta 7.71-7.33 \text{ (m, 4H), 6.85-6.68 (m, 2H), 5.90-5.68 (m, 2H), 5.29-5.17 (m, 1H), 4.25 (d, } J = 17.0 \text{ Hz, 2H), 3.88 (d, } J = 17.0 \text{ Hz, 2H), 2.81 (s, 3H).} \]
MIDA boronate 3.29b. Based on the crude $^1$H NMR, the reaction proceeded to >95% conversion and a >20:1 of 3.29:3.30 was obtained. 3.29b was isolated by column chromatography to provide 61.1 mg (0.25 mmol reaction), 90% yield.

TLC (Et$_2$O:MeCN 6:1)

$R_f = 0.44$, visualized by short wave UV

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

$\delta$ 7.24 (m, 1H), 7.21-7.18 (m, 2H), 7.10-7.05 (m, 1H), 5.73 (bd, $J = 3.0$ Hz, 1H), 5.68 (bs, 1H), 4.23 (d, $J = 17.0$ Hz, 2H), 3.83 (d, $J = 17.0$ Hz, 2H), 2.83 (s, 3H), 2.31 (s, 3H).

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

$\delta$ 168.7, 145.2, 138.3, 128.9, 128.8, 127.9, 127.6, 125.3, 62.6, 47.4, 21.4

$^{11}$B NMR (128 MHz, d$_6$-acetone)

$\delta$ 11.4

HRMS (ESI$^+$)

Calculated for C$_{14}$H$_{17}$BNO$_4$ (M+H)$^+$: 274.1251

Found: 274.1245
**MIDA boronate 3.29c.** Based on the crude $^1$H NMR, the reaction proceeded to 85% conversion and a 10:1 of 3.29:3.30 was obtained.

TLC (Et$_2$O:MeCN 6:1)

$R_f = 0.32$, visualized by short wave UV

$^1$H NMR (400 MHz, d$_6$-acetone)

$\delta$ 7.70-7.36 (m, 4H), 5.77 (bd, $J = 3.0$ Hz, 1H), 5.73 (bs, 1H), 4.25 (d, $J = 17.0$ Hz, 2H), 3.91 (d, $J = 17.0$ Hz, 2H), 3.85 (s, 3H), 2.81 (s, 3H).

HRMS (ESI$^+$)

Calculated for C$_{15}$H$_{17}$BNO$_6$ (M+H)$^+$: 318.1149

Found: 318.1143

**MIDA boronate 3.29d.** Based on the crude $^1$H NMR, the reaction proceeded to 70% conversion and a 8:1 of 3.29:3.30 was obtained.

TLC (Et$_2$O:MeCN 6:1)

$R_f = 0.32$, visualized by short wave UV

$^1$H NMR (400 MHz, d$_6$-acetone)

$\delta$ 7.79-7.52 (m, 4H), 5.82 (bd, $J = 3.0$ Hz, 1H), 5.79 (bs, 1H), 4.27 (d, $J = 17.0$ Hz, 2H), 3.95 (d, $J = 17.0$ Hz, 2H), 2.82 (s, 3H).
HRMS (ESI$^+$)

Calculated for C$_{14}$H$_{14}$BN$_2$O$_4$ (M+H)$^+$: 285.1047

Found: 285.1038

**MIDA boronate 3.29e.** Based on the crude $^1$H NMR, the reaction proceeded to 90% conversion and a 4:1 of 3.29:3.30 was obtained.

**TLC (Et$_2$O:MeCN 6:1)**

$R_f = 0.37$, visualized by short wave UV

$^1$H NMR (400 MHz, d$_6$-acetone)

$\delta$ 7.49-7.00 (m, 4H), 5.70 (bd, $J = 3.0$ Hz, 1H), 5.67 (bs, 1H), 4.23 (d, $J = 17.0$ Hz, 2H), 3.88 (d, $J = 17.0$ Hz, 2H), 2.80 (s, 3H).

HRMS (ESI$^+$)

Calculated for C$_{13}$H$_{14}$BFNO$_4$ (M+H)$^+$: 278.1000

Found: 278.0994

**MIDA boronate 3.29f.** Based on the crude $^1$H NMR, the reaction proceeded to 85% conversion and a 10:1 of 3.29:3.30 was obtained.

**TLC (Et$_2$O:MeCN 6:1)**

$R_f = 0.37$, visualized by short wave UV

$^1$H NMR (400 MHz, d$_6$-acetone)

$\delta$ 7.59-7.20 (m, 4H), 5.75 (bd, $J = 3.0$ Hz, 1H), 5.73 (bs, 1H), 4.25 (d, $J = 17.0$ Hz, 2H), 3.92 (d, $J = 17.0$ Hz, 2H), 2.82 (s, 3H).
MIDA boronate 3.29g. Based on the crude $^1$H NMR, the reaction proceeded to 85% conversion and a >20:1 of 3.29:3.30 was obtained. 3.29g was isolated by column chromatography to provide 21.1 mg (0.1 mmol reaction), 66% yield.

TLC (Et$_2$O:MeCN 6:1)

$R_f$ = 0.31, visualized by short wave UV

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

$\delta$ 6.59 (d, $J$ = 2.5 Hz, 2H), 6.38 (t, $J$ = 2.5 Hz, 1H), 5.75 (m, 2H), 4.24 (d, $J$ = 17.0 Hz, 2H), 3.84 (d, $J$ = 17.0 Hz, 2H), 3.77 (s, 6H), 2.86 (s, 3H).

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

$\delta$ 169.0, 161.7, 147.4, 127.8, 106.3, 99.7, 62.9, 55.5, 47.6.

$^{11}$B NMR (128 MHz, d$_6$-acetone)

$\delta$ 11.3

HRMS (ESI$^+$)

Calculated for C$_{15}$H$_{19}$BNO$_6$ (M+H)$^+$: 320.1305

Found: 320.1295

MIDA boronate 3.29h. Based on the crude $^1$H NMR, the reaction proceeded to 50% conversion and a >20:1 of 3.29:3.30 was obtained.
TLC (Et₂O:MeCN 6:1)
  \( R_f = 0.31 \), visualized by short wave UV

\(^1\)H NMR (400 MHz, d₆-acetone)
  \( \delta \) 7.35-7.00 (m, 4H), 5.58 (bs, 1H), 5.55 (bd, \( J = 3.0 \) Hz, 1H), 4.18 (d, \( J = 17.0 \) Hz, 2H), 3.79 (d, \( J = 17.0 \) Hz, 2H), 3.12 (s, 6H), 2.75 (s, 3H).

HRMS (ESI⁺)
  Calculated for C₁₅H₂₀BN₂O₄ (M+H)⁺: 303.1516
  Found: 303.1524

MIDA boronate 3.29i. Based on the crude \(^1\)H NMR, the reaction proceeded to 95% conversion and a >20:1 of 3.29:3.30 was obtained. 3.29i was isolated by column chromatography to provide 24.6 mg (0.1 mmol reaction), 82% yield.

\(^1\)H NMR (500 MHz, d₆-acetone)
  \( \delta \) 7.59 (d, \( J = 8.0 \) Hz, 1H), 7.47 (d, \( J = 8.0 \) Hz, 1H), 7.29 (t, \( J = 7.0 \) Hz, 1H), 7.21 (t, \( J = 7.0 \) Hz, 1H), 6.92 (s, 1H), 6.45 (s, 1H), 5.80 (d, \( J = 2.5 \) Hz, 1H), 4.41 (d, \( J = 17.0 \) Hz, 2H), 4.23 (d, \( J = 17.0 \) Hz, 2H), 3.03 (s, 3H).

\(^{13}\)C NMR (125 MHz, d₆-acetone)
  \( \delta \) 168.9, 158.4, 154.8, 129.8, 126.5, 125.0, 123.3, 121.7, 111.2, 104.5, 62.9, 47.7

\(^{11}\)B NMR (128 MHz, d₆-acetone)
  \( \delta \) 11.3
**MIDA boronate 3.29j.** Based on the crude $^1$H NMR, the reaction proceeded to 50% conversion and a >20:1 of 3.29:3.30 was obtained.

TLC (Et$_2$O:MeCN 6:1) $R_f$ = 0.39, visualized by short wave UV

$^1$H NMR (400 MHz, d$_6$-acetone)

δ 7.80-7.00 (m, 3H), 5.83 (bs, 1H), 5.56 (bs, 1H), 4.30 (d, $J = 17.0$ Hz, 2H), 4.00 (d, $J = 17.0$ Hz, 2H), 3.13 (s, 3H).

HRMS (ESI$^+$)

Calculated for C$_{11}$H$_{13}$BNO$_4$S (M+H)$^+$: 266.0658

Found: 266.0647

**MIDA boronate 3.29k.** Based on the crude $^1$H NMR, the reaction proceeded to 90% conversion and a >20:1 of 3.29:3.30 was obtained. 3.29k was isolated by column chromatography to provide 47.7 mg (0.25 mmol reaction), 76% yield.

TLC (Et$_2$O:MeCN 6:1)

$R_f$ = 0.48, visualized by short wave UV

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

δ 6.20 (d, $J = 15.0$ Hz, 1H), 5.90 (dt, $J = 15.0$ Hz, 6.5 Hz, 1H), 5.61 (bs, 1H), 5.34 (bd, $J = 3.5$ Hz, 1H), 4.25 (d, $J = 17.0$ Hz, 2H), 4.01 (d, $J = 17.0$ Hz, 2H), 2.97 (s, 3H), 2.06 (m, 2H), 1.41 (s, $J = 7.0$ Hz, 2H), 0.89 (t, $J = 7.0$ Hz, 3H).
$^{13}$C NMR (125 MHz, CDCl$_3$)

$\delta$ 167.3, 132.9, 132.8, 125.9, 61.9, 47.0, 35.4, 22.5, 13.7

$^{11}$B NMR (128 MHz, CDCl$_3$)

$\delta$ 10.7

HRMS (ESI$^+$)

Calculated for C$_{12}$H$_{19}$BNO$_4$ (M+H)$^+$: 252.1407

Found: 252.1405

MIDA boronate 3.29l. Based on the crude $^1$H NMR, the reaction proceeded to 80% conversion and a >20:1 of 3.29l:3.30 was obtained. 3.29l was isolated by column chromatography to provide 46.3 mg (0.25 mmol reaction), 65% yield.

TLC (Et$_2$O:MeCN 6:1)

$R_f$ = 0.36, visualized by short wave UV

$^1$H NMR (400 MHz, d$_0$-acetone)

$\delta$ 7.47-7.19 (m, 5H), 5.58 (d, $J$ = 2.0 Hz, 1H), 5.31 (d, $J$ = 2.0 Hz, 1H), 5.25 (d, $J$ = 2.0 Hz, 1H), 5.23 (d, $J$ = 2.0 Hz, 1H), 4.16 (d, $J$ = 17.0 Hz, 2H), 3.91 (d, $J$ = 17.0 Hz, 2H), 3.05 (s, 3H).

HRMS (ESI$^+$)

Calculated for C$_{15}$H$_{17}$BNO$_4$ (M+H)$^+$: 286.1251.

Found: 286.1244.
Scheme 3-11C⁹

Under air to a 40 mL I-CHEM vial was added K₂CO₃ (691 mg, 5.0 mmol) and 2-pyridyl MIDA boronate 3.3 (351 mg, 1.5 mmol). The vial was sealed with a septum cap and backfilled under argon. To the vial was then added the aryl chloride (1.0 mmol) via syringe. Into a separate 20 mL I-CHEM vial with septum cap and PTFE coated stirbar was added DMF (8 mL). Both vials were then brought into a glovebox. To the vial containing the chloride, K₂CO₃, and 2-pyridyl MIDA boronate was added copper (II) acetate (91 mg, 0.5 mmol) and biphenyl (154 mg, 1.0 mmol). To the vial containing DMF was added Pd₂dba₃ (14 mg, 0.015 mmol) and XPhos (29 mg, 0.06 mmol). The vial containing DMF, catalyst, and ligand was removed from the glovebox and incubated at 100 °C for 5 minutes with stirring and returned to the glovebox. This solution and the stirbar were transferred at ~40 °C to the 40 mL I-CHEM vial, and the vial was sealed. The vial was removed from the glovebox and a needle with a positive pressure of argon was inserted into the septum. To the vial by syringe was added isopropanol (2 mL, sparged with argon for 20 min and dried with 5 Å molecular sieves). The argon needle was removed from the vial and the reaction was heated to 100 °C with stirring for 4 h. The reaction was then allowed to cool to room temperature over 0.5 h. An aliquot was removed and filtered through a pad of silica gel washing with acetone into a GC vial and analyzed by gas chromatography using the biphenyl as an internal standard. GC yields were determined by the average of three injections. Each reaction was run in duplicate and the yields were averaged.

GC Yield for the coupling of 2-pyridyl MIDA boronate (3.3) to 4-chloroacetophenone (3.31a): 72%

GC Yield for the coupling of 2-pyridyl MIDA boronate (3.3) to 1-(tert-butoxy)-4-chlorobenzene (3.31b): 7%

Table 3-4

Cross-coupling of 2-pyridyl MIDA boronate to 1-(tert-butoxy)-4-chlorobenzene utilizing various alcohols and diols
Under air to a 40 mL I-CHEM vial equipped with PTFE coated stir bar was added XPhos Palladacycle, chloro(2-dicyclohexylphosphino-2’,4’,6’-tri-i-propyl-1,1’-biphenyl)2-(2-aminoethyl)phenyl] palladium(II) methyl-t-butylether adduct, (37 mg, 0.05 mmol) and 2-pyridyl MIDA boronate 3.3 (351 mg, 1.5 mmol). The vial was sealed with a septum cap and back-filled with argon. To the vial was added DMF (8 mL) and 1-(tert-butoxy)-4-chlorobenzene 3.31b (174 µL, 1.00 mmol) by syringe. The vial was brought into a glove box where K$_2$PO$_4$ (1.061 g, 5.0 mmol), biphenyl (154 mg, 1.00 mmol), and Cu(OAc)$_2$ (91 mg, 0.5 mmol) were added. At this point, solid diols with high melting points were added. The vial was sealed with a septum cap and removed from the glove box. A needle under positive pressure of argon was inserted into the septum and using a syringe, the appropriate liquid or low melting point alcohol was added. The syringe was removed and the vial was heated to 100 °C with stirring for 24 h. The reaction was then allowed to cool to room temperature over 0.5 h. An aliquot was removed and filtered through a pad of silica gel washing with acetone into a GC vial and analyzed by gas chromatography using the biphenyl as the internal standard. GC yields were determined by the average of three injections. Each reaction was run in duplicate and the yields were averaged.

<table>
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<th>Entry</th>
<th>ROH</th>
<th>Quantity</th>
<th>Equivalents</th>
<th>% GC Yield</th>
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</thead>
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<td>1</td>
<td>Isopropanol</td>
<td>229 µL</td>
<td>3</td>
<td>49</td>
</tr>
<tr>
<td>2</td>
<td>Methanol</td>
<td>121 µL</td>
<td>3</td>
<td>36</td>
</tr>
<tr>
<td>3</td>
<td>Ethanol</td>
<td>175 µL</td>
<td>3</td>
<td>39</td>
</tr>
<tr>
<td>4</td>
<td>Tert-butanol</td>
<td>285 µL</td>
<td>3</td>
<td>43</td>
</tr>
<tr>
<td>5</td>
<td>Ethylene Glycol</td>
<td>84 µL</td>
<td>1.5</td>
<td>51</td>
</tr>
<tr>
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<td>Pinacol</td>
<td>177 mg</td>
<td>1.5</td>
<td>35</td>
</tr>
<tr>
<td>7</td>
<td>Neopentyl Glycol</td>
<td>156 mg</td>
<td>1.5</td>
<td>31</td>
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<tr>
<td>8</td>
<td>Diethanolamine (DEA)</td>
<td>144 µL</td>
<td>1.5</td>
<td>70</td>
</tr>
</tbody>
</table>

Scheme 3-13

Kinetics of the transligation of 2-pyridyl MIDA boronate with diethanolamine (DEA)

Under air to a 20 mL I-CHEM vial was added 2-pyridyl MIDA boronate 3.3 (394 mg, 1.69 mmol). The vial was sealed with a septum cap and back filled under argon. To the vial was added by syringe diethanolamine (170 µL, 1.69 mmol), tert-butylbenzene (260 µL, 1.69 mmol), and DMF-d$_7$ (9 mL). This vial was brought into a glovebox along with sixteen 2 mL vials with
PTFE coated stirbars. Into each 2 mL vial was massed K$_3$PO$_4$ (66 mg, 0.31 mmol) and using a pipetman, 500 µL of the MIDA boronate containing stock solution was added to each vial. Each vial was then sealed with a PTFE lined cap and the vials were removed from the glovebox. The vials were heated to 100 °C with stirring. The remaining stock solution was transferred to a NMR tube and a $^1$H-NMR was taken (nt = 2, d$_1$ = 30) this represents t = 0. At regular intervals, two vials were removed from heating and allowed to cool to 23 °C after which the solution was transferred under air into a $^1$H-NMR tube. A $^1$H-NMR was then taken of these duplicate samples. The rate of transligation and decomposition of the MIDA boronate were determined by integration of the diastereotopic methylene protons of the MIDA boronate ($\delta$ 4.55 (d, $J$ = 17 Hz, 2H)) and of the DEA boronate ($\delta$ 3.97 (m, 2H)) and comparing them to the integration of methyl protons of the tert-butyl benzene ($\delta$ 1.29 (s, 9H)). The major decomposition product was determined to be pyridine.

Synthesis of 2-pyridyl DEA boronate

2-pyridyl DEA boronate (3.34). To a 100 mL Schlenk flask with PTFE coated stirbar was added 2-pyridyl MIDA boronate 3.3 (1.87 g, 8.00 mmol) and finely ground K$_3$PO$_4$ (8.78 g, 41.4 mmol) under positive argon pressure. The Schlenk flask was sealed with a septum and to the flask was then added acetonitrile (40 mL) and diethanolamine (1.6 mL, 17 mmol). The Schlenk
flask was then heated to 80 °C with stirring for 7 h. After 7 h while still stirring at 80 °C, the acetonitrile solution was cannulated into a tared 250 mL round bottom. The acetonitrile was then concentrated in vacuo to approximately 20 mL of solution and then allowed to cool to room temperature. A stirbar was added to the round bottom and with stirring, 100 mL of Et₂O was added to the flask over 0.5 h. After the addition was complete, the solution was allowed to stir for another 10 min before the stir bar was removed and the solution was decanted. The resulting solid was then placed under high vacuum for 10 min. To the round bottom was then added 20 mL of acetonitrile. The round bottom was sealed with a glass stopper and PTFE tape and heated to 80 °C for 15-20 min or until the solid completely dissolved. The stirbar was then removed from the round bottom and the reaction was allowed to cool to room temperature and sit overnight. The acetonitrile solution was decanted and the resulting solid was washed with small amounts of diethyl ether. The round bottom was then placed under high vacuum to remove residual acetonitrile and diethyl ether affording 3.34 as white spindly crystals (1.00 g, 65%).

![Image of molecule](image)

**3.34**

**1H-NMR (400 MHz, DMSO-d₆)**

δ 8.52 (d, J = 4.0 Hz, 1H), 7.50 (t, J = 6.0 Hz, 1H), 7.40 (d, J = 6.0 Hz, 1H), 7.09 (t, J = 4.8 Hz, 1H), 7.02 (s, br, 1H), 3.84 (m, 2H), 3.72 (m, 2H), 3.15 (m, 2H), 2.82 (m, 2H).

**13C-NMR (125 MHz, DMSO-d₆)**

δ 148.4, 133.4, 125.8, 120.9, 62.6, 50.8

**11B-NMR (128 MHz, DMSO-d₆)**

δ 9.8

**HRMS (ESI+)**

Calculated for C₉H₁₄BN₂O₂ (M+H)⁺: 193.1148

Found: 193.1147
Cross-coupling of 2-pyridyl DEA boronate to 1-(tert-butoxy)-4-chlorobenzene

Under air to a 40 mL I-CHEM vial equipped with a PTFE coated stir bar was added XPhos Palladacycle, chloro(2-dicyclohexylphosphino-2’,4’,6’-tri-i-propyl-1,1’-biphenyl)(2-(2-aminoethyl)phenyl) palladium(II) methyl-t-butylether adduct, (37 mg, 0.05 mmol). The vial was sealed with a septum cap and back-filled with argon. To the vial was added DMF (8 mL) and 1-(tert-butoxy)-4-chlorobenzene 3.31b (174 µL, 1.0 mmol) by syringe. The vial was brought into a glove box where K₃PO₄ (1.061 g, 5.0 mmol), biphenyl (154 mg, 1.0 mmol), Cu(OAc)₂ (91 mg, 0.5 mmol), and 2-pyridyl DEA boronate 3.34 (288 mg, 1.5 mmol) were added. The vial was resealed with the septum cap and removed from the glove box and heated to 100 °C with stirring for 24 h. The reaction was then allowed to cool to room temperature over 0.5 h. An aliquot was removed and filtered through a pad of silica gel washing with acetone into a GC vial and analyzed by gas chromatography using the biphenyl as the internal standard. GC yields were determined by the average of three injections. Each reaction was run in duplicate and the yields were averaged. Based on the biphenyl internal standard, the yield was 9%.

Slow addition cross-coupling of 2-pyridyl DEA boronate to 1-(tert-butoxy)-4-chlorobenzene

Under a 20 mL I-CHEM vial equipped with PTFE coated stir bar was added XPhos Palladacycle, chloro(2-dicyclohexylphosphino-2’,4’,6’-tri-i-propyl-1,1’-biphenyl)(2-(2-aminoethyl)phenyl) palladium(II) methyl-t-butylether adduct, (20 mg, 0.027 mmol). The vial was sealed with a septum cap and back-filled with argon. To the vial was added DMF (2 mL) and 1-(tert-butoxy)-4-chlorobenzene 3.31b (87 µL, 0.5 mmol) by syringe. Into a second 20 mL I-CHEM vial with septum cap was added DMF (10 mL). The vials were brought into a glove box where K₃PO₄ (555 mg, 2.61 mmol), and Cu(OAc)₂ (46 mg, 0.25 mmol) were added to the vial containing the chloride. 2-pyridyl DEA boronate 3.34 (178 mg, 0.93 mmol) was added to the vial containing just 10 mL DMF. Both vials were re-sealed with septum caps and removed from the glove box. A needle under positive pressure of argon was inserted into both vials and the vial containing the catalyst and chloride was heated to 100 °C with stirring. A 10 mL syringe with a 20 gauge steel needle was used to draw up 8 mL of the 2-pyridyl DEA boronate 3.34 solution.
This syringe was fitted into a syringe pump and the needle was inserted into the vial containing the catalyst and chloride. The 2-pyridyl DEA boronate 3.34 solution was added slowly over 4 h 15 min. The needles were then removed and the reaction was stirred for a further 20 h at 100 °C. The reaction was then allowed to cool to room temperature over 0.5 h. The reaction was transferred to a 60 mL separatory funnel, diluted with 10 mL of 2N HCl and shaken. The reaction was then diluted with 10 mL 2N NaOH and shaken. The resulting aqueous solution was extracted twice with 10 mL of diethyl ether. The organic layers were combined and washed with 5 mL of brine. The organic layers were dried using Na₂SO₄, filtered, and concentrated in vacuo. The resulting residue was adsorbed onto Celite and subjected to Florisil chromatography (EtOAc:Hexanes 5:95 → 20:80) to afford 3.32b as a pale yellow solid (15 mg, 13%).

Scheme 3-14

Preparation of Cu(DEA)₂

To a 100 mL Schlenk flask in the glovebox was added Cu(OAc)₂ (229 mg, 1.26 mmol), K₃PO₄ (2.49 g, 11.7 mmol) and a PTFE coated stirbar. The Schlenk flask was sealed with a septum and removed from the glovebox. The Schlenk flask was attached to a vacuum manifold and placed under argon maintenance. To the flask was added diethanolamine (360 µL, 3.75 mmol) and DMF (20 mL). The Schlenk flask was then heated at 100 °C with stirring for 15 min. An aliquot was removed from the crude reaction mixture and was found to contain Cu(DEA)₂ by ESI HRMS.

The reaction was then allowed to cool to room temperature and the solids were allowed to settle. The DMF solution was decanted and isopropanol (20 mL) was introduced, dissolving the product. The reaction was then air-free filtered into a tared 200 mL Schlenk flask. The filtrate was concentrated using the vacuum manifold to ¼ of its original volume. With stirring, 20 mL of dry, degassed acetone was slowly added precipitating a reddish purple solid. The solution was decanted and the solid was washed twice with 5 mL of acetone. The solid was dried on the vacuum line for 0.5 h to afford the product as a reddish purple powder with white specks (260 mg, 76%).
A NMR (in CD$_3$OD) was taken of the product which indicated that potassium acetate was contaminating the product.

HRMS (ESI+)

Calculated for C$_8$H$_{21}$CuN$_2$O$_4$ (M+H)$^+$: 272.0797

Found: 272.0793

**Synthesis and purification of Cu(DEA)$_2$**

To a 100 mL Schlenk flask in the glovebox was added CuCl$_2$ (840 mg, 6.3 mmol), K$_3$PO$_4$ (6.87 g, 32.4 mmol) and a PTFE coated stirbar. The Schlenk flask was sealed with a septum and removed from the glovebox. The Schlenk flask was attached to a vacuum manifold and placed under argon maintenance. To the flask was added diethanolamine (3.0 mL, 31.0 mmol) and isopropanol (50 mL). The Schlenk flask was then heated at 60 °C with stirring for 15 h. The reaction was then air-free filtered into a tared 200 mL Schlenk flask. The filtrate was concentrated using the vacuum manifold to ½ of its original volume. With stirring, 100 mL of dry, degassed acetone was slowly added, precipitating a reddish purple solid. The solution was decanted and the solid was washed twice with 20 mL of acetone. The solid was dried on the vacuum line for 0.5 h to afford the product as a reddish purple powder (1.38 g, 81%).

![Chemical structure of Cu(DEA)$_2$](image)

IR (nujol, cm$^{-1}$)

v 3067, 1181, 1115, 1093, 1067, 1043, 1023

CHN/ICP-MS

Calculated: C: 35.35%, H: 7.42%, N: 10.31%, Cu: 23.38%

Found: C: 35.45%, H: 7.69%, N: 9.96%, Cu: 22.60%
Cross-coupling using Cu(DEA)$_2$ and KOAc.
Under air to a 40 mL I-CHEM vial equipped with PTFE coated stir bar was added 2-pyridyl MIDA boronate 3.3 (351 mg, 1.5 mmol), XPhos Palladacycle, chloro(2-dicyclohexylphosphino-2',4',6'-tri-i-propyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl] palladium(II) methyl-t-butylether adduct, (37 mg, 0.05 mmol), and KOAc (98 mg, 1.0 mmol). The vial was sealed with a septum cap and back-filled with argon. To the vial was added DMF (8 mL) and 1-(tert-butoxy)-4-chlorobenzene 3.31b (174 µL, 1.0 mmol) by syringe. The vial was brought into a glove box where K$_3$PO$_4$ (1.061 g, 5.0 mmol), biphenyl (154 mg, 1.0 mmol), and Cu(DEA)$_2$ (136 mg, 0.5 mmol) were added. The vial was re-sealed with the septum cap and removed from the glove box and heated to 100 °C with stirring for 24 h. The reaction was then allowed to cool to room temperature over 0.5 h. An aliquot was removed and filtered through a pad of silica gel washing with acetone into a GC vial and analyzed by gas chromatography using the biphenyl as the internal standard. GC yields were determined by the average of three injections. Each reaction was run in duplicate and the yields were averaged. Based on the biphenyl internal standard, the yield was 84%.

Cross-coupling using no copper.
Under air to a 40 mL I-CHEM vial equipped with PTFE stir bar was added 2-pyridyl MIDA boronate 3.3 (351 mg, 1.5 mmol) and XPhos Palladacycle, chloro(2-dicyclohexylphosphino-2',4',6'-tri-i-propyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl] palladium(II) methyl-t-butylether adduct, (37 mg, 0.05 mmol). The vial was sealed with a septum cap and back-filled with argon. To the vial was added DMF (8 mL) and 1-(tert-butoxy)-4-chlorobenzene 3.31b (174 µL, 1.0 mmol) by syringe. The vial was brought into a glove box where K$_3$PO$_4$ (1.061 g, 5.0 mmol), biphenyl (154 mg, 1.0 mmol) were added. The vial was re-sealed with the septum cap and removed from the glove box and heated to 100 °C with stirring for 24 h. The reaction was then allowed to cool to room temperature over 0.5 h. An aliquot was removed and filtered through a pad of silica gel washing with acetone into a GC vial and analyzed by gas chromatography using
the biphenyl as the internal standard. GC yields were determined by the average of three injections. Each reaction was run in duplicate and the yields were averaged. Based on the biphenyl internal standard, the yield was <5%.

**Cross-coupling using KOAc and no copper.**

Under air to a 40 mL I-CHEM vial equipped with PTFE coated stir bar was added 2-pyridyl MIDA boronate 3.3 (351 mg, 1.5 mmol), XPhos Palladacycle, chloro(2-dicyclohexylphosphino-2',4',6'-tri-i-propyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl] palladium(II) methyl-t-butylether adduct, (37 mg, 0.05 mmol), and KOAc (98 mg, 1.0 mmol). The vial was sealed with a septum cap and back-filled with argon. To the vial was added DMF (8 mL) and 1-(tert-butoxy)-4-chlorobenzene 3.31b (174 µL, 1.0 mmol) by syringe. The vial was brought into a glove box where K$_3$PO$_4$ (1.061 g, 5.0 mmol) and biphenyl (154 mg, 1.0 mmol) were added. The vial was re-sealed with the septum cap and removed from the glove box and heated to 100 °C with stirring for 24 h. The reaction was then allowed to cool to room temperature over 0.5 h. An aliquot was removed and filtered through a pad of silica gel washing with acetone into a GC vial and analyzed by gas chromatography using the biphenyl as the internal standard. GC yields were determined by the average of three injections. Each reaction was run in duplicate and the yields were averaged. Based on the biphenyl internal standard, the yield was <5%.

**Cross-coupling using Cu(OAc)$_2$ and KOAc.**

Under air to a 40 mL I-CHEM vial equipped with PTFE coated stir bar was added 2-pyridyl MIDA boronate 3.3 (351 mg, 1.5 mmol), XPhos Palladacycle, chloro(2-dicyclohexylphosphino-2',4',6'-tri-i-propyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl] palladium(II) methyl-t-butylether adduct, (37 mg, 0.05 mmol), and KOAc (98 mg, 1.0 mmol). The vial was sealed with a septum cap and back-filled with argon. To the vial was added DMF (8 mL) and 1-(tert-butoxy)-4-chlorobenzene 3.31b (174 µL, 1.0 mmol) by syringe. The vial was brought into a glove box where K$_3$PO$_4$ (1.061 g, 5.0 mmol), biphenyl (154 mg, 1.0 mmol), and Cu(OAc)$_2$ (91 mg, 0.5 mmol) were added. The vial was re-sealed with the septum cap and removed from the glove box and heated to 100 °C with stirring for 24 h. The reaction was then allowed to cool to room temperature over 0.5 h. An aliquot was removed and filtered through a pad of silica gel washing with acetone into a GC vial and analyzed by gas chromatography using the biphenyl as the
internal standard. GC yields were determined by the average of three injections. Each reaction was run in duplicate and the yields were averaged. Based on the biphenyl internal standard, the yield was 38%.

**Cross-coupling using Cu(DEA)$_2$.**

Under air to a 40 mL I-CHEM vial equipped with PTFE coated stir bar was added 2-pyridyl MIDA boronate 3.3 (351 mg, 1.5 mmol) and XPhos Palladacycle, chloro(2-dicyclohexylphosphinopheno-2',4',6'-tri-i-propyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl] palladium(II) methyl-t-butylether adduct, (37 mg, 0.05 mmol). The vial was sealed with a septum cap and back-filled with argon. To the vial was added DMF (8 mL) and 1-(tert-butoxy)-4-chlorobenzene 3.31b (174 µL, 1.0 mmol) by syringe. The vial was brought into a glove box where K$_3$PO$_4$ (1.061 g, 5.0 mmol), biphenyl (154 mg, 1.0 mmol), and Cu(DEA)$_2$ (136 mg, 0.5 mmol) were added. The vial was resealed with the septum cap and removed from the glove box and heated to 100 °C with stirring for 24 h. The reaction was then allowed to cool to room temperature over 0.5 h. An aliquot was removed and filtered through a pad of silica gel washing with acetone into a GC vial and analyzed by gas chromatography using the biphenyl as the internal standard. GC yields were determined by the average of three injections. Each reaction was run in duplicate and the yields were averaged. Based on the biphenyl internal standard, the yield was 50%.

**2-pyridyl MIDA boronate consumption studies**

Under air, to a 20 mL I-CHEM vial was added 2-pyridyl MIDA boronate 3.3 (623 mg, 2.7 mmol), tert-butyl benzene (410 µL, 2.7 mmol), and DMF-d$_7$ (14.0 mL). The vial was sealed with a septum cap and backfilled under argon. This solution was taken into a glovebox. To six 7 mL vials containing stir bars was added K$_3$PO$_4$ (80.6 mg each, 0.38 mmol). To six 7 mL vials containing stir bars was added K$_3$PO$_4$ (80.6 mg each, 0.38 mmol) and KOAc (7.5 mg each, 0.076 mmol). To five 7 mL vials containing stir bars was added K$_3$PO$_4$ (80.6 mg each, 0.38 mmol) and Cu(DEA)$_2$ (10.2 mg each, 0.038 mmol). To five 7 mL vials containing stir bars was added K$_3$PO$_4$ (80.6 mg each, 0.38 mmol), KOAc (7.5 mg each, 0.076 mmol), and Cu(DEA)$_2$ (10.2 mg each, 0.038 mmol). A portion (0.6 mL) of the MIDA boronate containing stock solution was added to each of these vials. The vials were capped, removed from the glovebox, and heated to 100 °C with stirring. At intervals, a vial from each set was removed and cooled to room
A $^1$H-NMR was taken of the solutions taking two transients with d1=30. A $^1$H-NMR was taken of the initial stock solution. The quantity of 2-pyridyl MIDA boronate remaining was determined by integrating the diastereotopic methylene protons of the MIDA boronate ($\delta$ 4.55 (d, $J = 17$ Hz, 2H)) and comparing to the integration of the methyl protons of the tert-butyl benzene internal standard ($\delta$ 1.28 (s, 9H)).
Scheme 3-16

Under air to a 40 mL I-CHEM vial equipped with PTFE coated stir bar was added XPhos Palladacycle, chloro(2-dicyclohexylphosphino-2',4',6'-tri-i-propyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl] palladium(II) methyl-t-butylether adduct, (37 mg, 0.05 mmol) and 2-pyridyl MIDA boronate 3.3 (351 mg, 1.5 mmol). The vial was sealed with a septum cap and back-filled with argon. To the vial was added DMF (8 mL) and 1-(tert-butoxy)-4-chlorobenzene 3.31b (174 µL, 1.00 mmol) by syringe. The vial was brought into a glove box where K$_3$PO$_4$ (1.061 g, 5.0 mmol), biphenyl (154 mg, 1.00 mmol), and Cu(OAc)$_2$ (91 mg, 0.5 mmol) were added. The vial was sealed with a septum cap and removed from the glove box. A needle under positive pressure of argon was inserted into the septum and using a syringe, the appropriate alcohol was added. The syringe was removed and the vial was heated to 100 °C with stirring for 24 h. The reaction was then allowed to cool to room temperature over 0.5 h. An aliquot was removed and filtered through a pad of silica gel washing with acetone into a GC vial and analyzed by gas chromatography using the biphenyl as the internal standard. GC yields were determined by the average of three injections. Each reaction was run in duplicate and the yields were averaged.

<table>
<thead>
<tr>
<th>Entry</th>
<th>ROH</th>
<th>Quantity</th>
<th>Equivalents</th>
<th>% GC Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Diethanolamine (DEA)</td>
<td>144 µL</td>
<td>1.5</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>Diethanolamine (DEA)</td>
<td>96 µL</td>
<td>1</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>Diethanolamine (DEA)</td>
<td>2.4 mL</td>
<td>25</td>
<td>24</td>
</tr>
<tr>
<td>4</td>
<td>Diethanolamine (DEA)</td>
<td>48 µL</td>
<td>0.5</td>
<td>73</td>
</tr>
</tbody>
</table>

Cross-coupling on a 1 mmol scale.

Under air to a 40 mL I-CHEM vial equipped with PTFE coated stir bar was added XPhos Palladacycle, chloro(2-dicyclohexylphosphino-2',4',6'-tri-i-propyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl] palladium(II) methyl-t-butylether adduct, (42 mg, 0.057 mmol) and 2-pyridyl MIDA boronate 3.3 (357 mg, 1.53 mmol). The vial was sealed with a septum cap and back-filled with argon. To the vial was added DMF (20 mL), 1-(tert-butoxy)-4-chlorobenzene 3.31b (175 µL, 1.0 mmol), and diethanolamine (95 µL, 0.99 mmol) by syringe. The vial was brought into a glove box where K$_3$PO$_4$ (1.086 g, 5.1 mmol) and Cu(OAc)$_2$ (92 mg, 0.51 mmol) were added. The vial was sealed with a PTFE lined cap and removed from the glove box. The vial was heated to 100 °C with stirring for 24 h. The reaction was then allowed to cool to room 

225
temperature over 0.5 h. The reaction was transferred to a 60 mL separatory funnel, diluted with 10 mL of 2N HCl and shaken. The reaction was then diluted with 10 mL 2N NaOH and shaken. The resulting aqueous solution was extracted three times with 10 mL of diethyl ether. The organic layers were combined and washed with 10 mL of brine. The organic layers were dried using Na$_2$SO$_4$, filtered, and concentrated in vacuo. The resulting residue was adsorbed onto Celite and subjected to Florisil chromatography (EtOAc:Hexanes 5:95 → 20:80) to afford 3.32b as a pale yellow solid (215 mg, 94%).

Table 3-5.

**General procedure for the cross-coupling of 2-pyridyl MIDA boronate (Table 3-5, Table 3-6, and Table 3-7).**

Under air to a flame-dried 40 mL I-CHEM vial equipped with PTFE coated stir bar was added halide (1.0 mmol), XPhos Palladacycle, chloro(2-dicyclohexylphosphino-2',4',6'-tri-i-propyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl] palladium(II) methyl-t-butylether adduct, (37 mg, 0.05 mmol), and 2-pyridyl MIDA boronate 3.3 (351 mg, 1.5 mmol). The vial was sealed with a septum cap and back-filled with argon. To the vial was added DMF (8 mL) and diethanolamine (96 µL, 1.0 mmol) via syringe. The vial was brought into a glove box where K$_3$PO$_4$ (1.061 g, 5.0 mmol) and Cu(OAc)$_2$ (91 mg, 0.5 mmol) were added. The vial was sealed with a septum cap and removed from the glove box. The vial was heated to 100 ºC with stirring for 24 h. The vial was then cooled to 23 ºC over 0.5 h. To the vial was added 10 mL of 2N HCl and the resulting solution was shaken. To the vial was then added 10 mL of 2N NaOH and the resulting solution was shaken and transferred using ~20mL of Et$_2$O to a 100 mL separatory funnel. The mixture was shaken and the organic phase was separated. The aqueous phase was extracted twice with 10 mL of Et$_2$O. The organic fractions were combined, washed with 10 mL of brine, and dried with Na$_2$SO$_4$. The solution was then filtered and concentrated in vacuo. The resulting residue was adsorbed onto Celite and subjected to column chromatography on SiO$_2$ or Florisil to afford the purified product.
2-(4-(tert-butoxy)phenyl)pyridine (3.32b). The general procedure was followed using MIDA boronate 3.3 (360 mg, 1.54 mmol) and chloride 3.31b (175 µL, 1.00 mmol). The crude product was subjected to silica gel chromatography (EtOAc:Hexanes 5:95 → 20:80) to afford 3.32b as a pale yellow solid (199 mg, 88%).

TLC (EtOAc:Hexanes 20:80)

R_f = 0.4, visualized by UV (λ = 254 nm)

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

δ 8.61 (d, J = 5.0 Hz, 1H), 7.96 (d, J = 9.0 Hz, 2H), 7.79 (m, 2H), 7.24 (m, 1H), 7.08 (d, J = 8.5 Hz, 2H), 1.36 (s, 9H)

^13^C-NMR (125 MHz, acetone-d_6)

δ 157.6, 157.3, 150.3, 137.6, 134.9, 128.1, 124.5, 122.6, 120.3, 79.0, 29.1

HRMS (ESI+)

Calculated for C_{15}H_{18}NO (M+H)^+: 228.1388

Found: 228.1388

2-(4-methoxyphenyl)pyridine (3.32c) [Table 3-5, entry 1]. The general procedure was followed using MIDA boronate 3.3 (361 mg, 1.54 mmol) and chloride 3.31c (122.5 µL, 1.00 mmol). The crude product was subjected to Florisil chromatography (EtOAc:Hexanes 5:95 → 20:80) to afford 3.32c as an off-white solid (142 mg, 76%).
TLC (EtOAc:Hexanes 20:80)
   \( R_f = 0.29 \), visualized by UV (\( \lambda = 254 \) nm)

\(^1\)H-NMR (500 MHz, CD\(_3\)CN)
   \( \delta \): 8.59 (d, \( J = 4.5 \) Hz, 1H), 8.00 (d, \( J = 6.5 \) Hz, 2H), 7.77 (m, 2H), 7.22 (dt, \( J = 3.5, 5 \) Hz, 1H), 7.02 (d, \( J = 9.0 \) Hz, 2H), 3.38 (s, 3H).

\(^{13}\)C-NMR (125 MHz, acetone-\( d_6 \))
   \( \delta \): 161.5, 157.3, 150.3, 137.5, 132.6, 128.7, 122.3, 120.0, 114.7, 55.6

HRMS (ESI+)
   Calculated for C\(_{12}\)H\(_{12}\)NO (M+H): 186.0919
   Found: 186.0914

2-(3-methoxyphenyl)pyridine (3.32d) [Table 3-5, entry 2]. The general procedure was followed using MIDA boronate 3.3 (356 mg, 1.52 mmol) and chloride 3.31d (125 \( \mu \)L, 1.02 mmol). The crude product was subjected to Florisil chromatography (EtOAc:Hexanes 5:95 \( \rightarrow \) 20:80) to afford 3.32d as a yellow oil (182 mg, 96%).

TLC (EtOAc:Hexanes 20:80)
   \( R_f = 0.3 \), visualized by UV (\( \lambda = 254 \) nm)

\(^1\)H-NMR (500 MHz, acetone-\( d_6 \))
   \( \delta \): 8.65 (d, \( J = 5.5 \) Hz, 1H), 7.92 (dt, \( J = 1.0, 8.0 \) Hz, 1H), 7.84 (td, \( J = 2.0, 7.5 \) Hz, 1H), 7.71 (t, \( J = 2.0 \) Hz, 1H), 7.66 (dt, \( J = 1.5, 8.0 \) Hz, 1H), 7.38 (t, \( J = 8.0 \) Hz, 1H), 7.31 (ddd, \( J = 1.0, 5.0, 7.5 \) Hz, 1H), 6.99 (ddd, \( J = 0.5, 2.5, 7.5 \) Hz, 1H), 3.87 (s, 3H).
$^{13}$C-NMR (125 MHz, acetone-$d_6$)
$$\delta 161.0, 157.3, 150.3, 141.6, 137.6, 130.4, 123.2, 121.0, 119.7, 115.4, 112.8, 55.5$$

HRMS (ESI+)
- Calculated for C$_{12}$H$_{12}$NO (M+H)$^+$: 186.0919
- Found: 186.0920

![3.32e](image)

2-(2-methoxyphenyl)pyridine (3.32e) [Table 3-5, entry 3]. The general procedure was followed using MIDA boronate 3.3 (365 mg, 1.56 mmol) and chloride 3.31e (130 µL, 1.02 mmol). The crude product was subjected to Florisil chromatography (EtOAc:Hexanes 5:95 $\rightarrow$ 20:80) to afford 3.32e as a yellow oil (142 mg, 75%).

TLC (EtOAc:Hexanes 20:80)
- $R_f = 0.29$, visualized by UV ($\lambda = 254$ nm)

$^1$H-NMR (500 MHz, acetone-$d_6$)
$$\delta 8.64 \text{ (d, } J = 5.0 \text{ Hz, 1H)}, 7.92 \text{ (dt, } J = 1.0, 8.0 \text{ Hz, 1H}), 7.85 \text{ (dd, } J = 2.0, 8.0 \text{ Hz, 1H}), 7.75 \text{ (td, } J = 2.0, 8.0 \text{ Hz, 1H}), 7.38 \text{ (td, } J = 2.0, 8.0 \text{ Hz, 1H}), 7.25 \text{ (ddd, } J = 1.0, 6.0, 7.5 \text{ Hz, 1H}), 7.12 \text{ (d, } J = 8.0 \text{ Hz, 1H}), 7.05 \text{ (td, } J = 1.0, 8.0 \text{ Hz, 1H}), 3.88 \text{ (s, 3H).}$$

$^{13}$C-NMR (125 MHz, acetone-$d_6$)
$$\delta 158.1, 156.6, 150.1, 136.2, 131.9, 130.7, 129.7, 125.7, 122.4, 121.4, 112.4, 55.9$$

HRMS (ESI+)
- Calculated for C$_{12}$H$_{12}$NO (M+H)$^+$: 186.0919
- Found: 186.0914
2-(o-tolyl)pyridine (3.32f) [Table 3-5, entry 4]. The general procedure was followed using MIDA boronate 3.3 (358 mg, 1.53 mmol) and chloride 3.31f (117.5 µL, 1.01 mmol). The crude product was subjected to Florisil chromatography (EtOAc:Hexanes 5:95 → 15:85) to afford 3.32f as a yellow oil (134 mg, 79%).

TLC (EtOAc:Hexanes 17:83)
\[ R_f = 0.35, \text{ visualized by UV } (\lambda = 254 \text{ nm}) \]

\(^1\)H-NMR (500 MHz, acetone-\text{d}_6)
\[ \delta 8.65 (d, J = 5.0 \text{ Hz}, 1H), 7.85 (td, J = 2.0, 8.0 \text{ Hz}, 1H), 7.48 (dt, J = 1.0, 8.0 \text{ Hz}, 1H), 7.39 (d, J = 2.0, 7.0 \text{ Hz}, 1H), 7.29 (m, 4H), 2.35 (s, 3H). \]

\(^13\)C-NMR (125 MHz, acetone-\text{d}_6)
\[ \delta 160.7, 149.8, 141.4, 137.0, 136.5, 131.4, 130.4, 128.8, 126.5, 124.7, 122.5, 20.6 \]

HRMS (ESI+)

Calculated for C\textsubscript{12}H\textsubscript{12}N (M+H)^+: 170.0970

Found: 170.0962

2-(2,5-dimethylphenyl)pyridine (3.32g) [Table 3-5, entry 5]. The general procedure was followed using MIDA boronate 3.3 (350 mg, 1.50 mmol) and chloride 3.31g (135 µL, 1.01 mmol). The crude product was subjected to Florisil chromatography (EtOAc:Hexanes 5:95 → 15:85) to afford 3.32g as a yellow oil (134 mg, 72%).

TLC (EtOAc:Hexanes 17:83)
\[ R_f = 0.32, \text{ visualized by UV } (\lambda = 254 \text{ nm}) \]
**1H-NMR** (500 MHz, acetone-\(d_6\))

\[ \delta 8.64 \ (d, \ J = 5.0 \ Hz, \ 1H) \], \(7.83 \ (td, \ J = 2.0, 8.0 \ Hz, \ 1H) \), \(7.46 \ (dt, \ J = 1.0, 7.5 \ Hz, \ 1H) \), \(7.30 \ (ddd, \ J = 1.0, 5.0, 7.5 \ Hz, \ 1H) \), \(7.29 \ (s, \ 1H) \), \(7.19 \ (d, \ J = 20 \ Hz, \ 1H) \), \(7.10 \ (dd, \ J = 1.0, 8.0 \ Hz, \ 1H) \), \(2.32 \ (s, \ 3H) \), \(2.30 \ (s, \ 3H) \).

**13C-NMR** (125 MHz, acetone-\(d_6\))

\[ \delta 160.9, 149.8, 141.3, 136.9, 135.7, 133.4, 131.4, 131.1, 129.5, 124.7, 122.4, 20.9, 20.1 \]

**HRMS (ESI+)**

Calculated for \(C_{13}H_{14}N\) (M+H)^+: 184.1126

Found: 184.1120

2-(2,4-dimethoxyphenyl)pyridine (3.32h) [Table 3-5, entry 6]. The general procedure was followed using MIDA boronate 3.3 (355 mg, 1.52 mmol), chloride 3.31h (150 µL, 1.01 mmol), and running the reaction at 80 °C for 24 h. The crude product was subjected to Florisil chromatography (EtOAc:Hexanes 50:50) to afford 3.32h as a pale yellow oil (107 mg, 49%).

**TLC** (EtOAc:Hexanes 50:50)

\[ R_f = 0.45 \], visualized by UV (\(\lambda = 254 \text{ nm}\))

**1H-NMR** (400 MHz, acetone-\(d_6\))

\[ \delta 8.59 \ (d, \ J = 4.8 \ Hz, \ 1H) \], \(7.89 \ (t, \ J = 9.8 \ Hz, \ 2H) \), \(7.71 \ (td, \ J = 2.0, 7.4 \ Hz, \ 1H) \), \(7.18 \ (ddd, \ J = 1.4, 4.8, 7.4 \ Hz, \ 1H) \), \(6.65 \ (m, \ 2H) \), \(3.88 \ (s, \ 3H) \), \(3.85 \ (s, \ 3H) \).

**13C-NMR** (125 MHz, acetone-\(d_6\))

\[ \delta 162.4, 159.3, 156.4, 149.9, 136.2, 132.8, 125.2, 122.3, 121.8, 106.1, 99.3, 55.8, 55.6 \]
HRMS (ESI+)
   Calculated for C_{13}H_{14}NO_{2} (M+H)^{+}: 216.1025
   Found: 216.1022

\[ \text{3.32i} \]

4-(pyridin-2-yl)benzonitrile (3.32i) [Table 3-5, entry 7]. The general procedure was followed using MIDA boronate 3.3 (351 mg, 1.50 mmol) and chloride 3.31i (138 mg, 1.00 mmol). The crude product was subjected twice to silica gel chromatography (first Run, EtOAc:Hexanes 2.5:97.5 → 20:80; second Run, EtOAc:Hexanes 2.5:97.5 → 50:50) to afford 3.32i as a white crystalline solid (159 mg, 86%). Characterization was consistent with literature.9

\[ \text{3.32j} \]

2-(4-fluorophenyl)pyridine (3.32j) [Table 3-5, entry 8]. The general procedure was followed using MIDA boronate 3.3 (361 mg, 1.54 mmol) and chloride 3.31j (107.5 µL, 1.01 mmol). The crude product was subjected to silica gel chromatography (EtOAc:Hexanes 5:95 → 20:80) to afford 3.32j as a pale yellow solid (143 mg, 82%).

TLC (EtOAc:Hexanes 20:80)
\[ R_f = 0.42, \text{ visualized by UV (} \lambda = 254 \text{ nm)} \]

\[ ^1H-\text{NMR (500 MHz, CD}_3\text{CN)} \]
\[ \delta 8.63 (d, J = 4.5 \text{ Hz, 1H}), 8.08 (dq, J = 5.5, 9.0 \text{ Hz, 2H}), 7.81 (d, J = 3.5 \text{ Hz, 2H}), 7.28 (q, J = 4.5, 8.5 \text{ Hz 1H}), 7.22 (t, J = 9.0 \text{ Hz, 2H}). \]

\[ ^{13}C-\text{NMR (125 MHz, acetone-d}_6) \]
\[ \delta 164.3 (d, J = 245 \text{ Hz}), 156.6, 150.5, 137.8, 136.5, 129.5 (d, J = 8.8 \text{ Hz}), 123.1, 120.6, 116.2 (d, J = 22 \text{ Hz}) \]
HRMS (ESI+)

Calculated for C_{11}H_{9}NF (M+H)^+:
174.0719

Found:
174.0717

1-(4-(pyridin-2-yl)phenyl)ethanone (3.32a) [Table 3-5, entry 9]. The general procedure was followed using MIDA boronate 3.3 (351 mg, 1.50 mmol), chloride 3.31a (130 µL, 1.00 mmol) and running the reaction at 80 °C for 24 h. The crude product was subjected to silica gel chromatography (EtOAc:Hexanes 50:50) to afford 3.32a as an off-white crystalline solid (164 mg, 83%). Characterization was consistent with literature.9

2,5-dimethyl-3-(pyridin-2-yl)pyrazine (3.32k) [Table 3-5, entry 10]. The general procedure was followed using MIDA boronate 3.3 (359 mg, 1.53 mmol) and chloride 3.31k (120 µL, 1.00 mmol). The crude product was subjected twice to silica gel chromatography (first Run, MeCN:Et₂O 10:90; second Run, Acetone:Hexanes (with 1% Triethylamine) 65:35) to afford 3.32k as a brown oil (141 mg, 77%). Characterization was consistent with literature.9

2-(pyridin-2-yl)quinoxaline (3.32l) [Table 3-5, entry 11]. The general procedure was followed using MIDA boronate 3.3 (352 mg, 1.50 mmol) and chloride 3.31l (166 µg, 1.01 mmol). The crude product was subjected to Florisil chromatography (EtOAc:Hexanes 40:60) to afford 3.32l as an off-white crystalline solid (166 mg, 80%). Characterization was consistent with literature.9

5-(pyridin-2-yl)-1H-indole (3.32m) [Table 3-5, entry 12]. The general procedure was followed using MIDA boronate 3.3 (351 mg, 1.50 mmol) and chloride 3.31m (151 mg, 1.00 mmol). The
crude product was subjected to Florisil chromatography (EtOAc:Hexanes 50:50) and silica gel chromatography (EtOAc:Hexanes 25:75) to afford 3.32m as a brown crystalline solid (120 mg, 62%).

TLC (EtOAc:Hexanes 50:50)

\[ R_f = 0.36, \text{ visualized by UV (} \lambda = 254 \text{ nm) } \]

\(^1\)H-NMR (500 MHz, acetone-\(d_6\))

\[ \delta 10.36 (s, 1H), 8.61 (d, J = 3.5 \text{ Hz, } 1H), 8.36 (s, 1H), 7.93 (\text{ddd, } J = 1.5, 8.5, 16.5 \text{ Hz, } 2H), 7.79 (\text{td, } J = 1.5, 7.0 \text{ Hz, } 1H), 7.50 (d, J = 8.5 \text{ Hz, } 1H), 7.37 (t, J = 2.5 \text{ Hz, } 1H), 7.21 (\text{ddd, } J = 1.0, 5.0, 7.5 \text{ Hz, } 1H), 6.56 (d, J = 2.0 \text{ Hz, } 1H). \]

\(^13\)C-NMR (125 MHz, acetone-\(d_6\))

\[ \delta 159.2, 150.1, 137.8, 137.4, 131.6, 129.3, 126.5, 121.8, 121.4, 120.4, 119.8, 112.2, 103.2 \]

HRMS (ESI+)

Calculated for C\(_{13}\)H\(_{11}\)N\(_2\) (M+H): 195.0922

Found: 195.0918

\[ \text{[Table 3-5, entry 13]} \]

\[ \text{[Table 3-5, Entry 14]} \]

The general procedure was followed using MIDA boronate 3.3 (350 mg, 1.50 mmol) and chloride 3.31n (168 mg, 1.02 mmol). The crude product was subjected to silica gel chromatography (EtOAc:Hexanes 70:30) and Florisil chromatography (EtOAc:Hexanes 30:70 → 100:0) to afford 3.32n as an amber oil (135 mg, 64%). Characterization was consistent with literature.\(^9\)

\[ \text{[Table 3-5, Entry 14]} \]

The general procedure was followed using MIDA boronate 3.3 (360 mg, 1.54 mmol) and chloride 3.31o (168
mg, 1.00 mmol. The crude product was subjected to silica gel chromatography (EtOAc:Hexanes 5:95 → 75:25) to afford 3.32o as an off-white crystalline solid (173 mg, 82%).

TLC (EtOAc:Hexanes 75:25)

\[ R_f = 0.38 \], visualized by UV (\( \lambda = 254 \text{ nm} \))

\(^1\)H-NMR (500 MHz, CD\(_3\)CN)

\[ \delta 8.65 \text{ (d, } J = 4.0 \text{ Hz, } 1\text{H}), 8.26 \text{ (d, } J = 1.5 \text{ Hz, } 1\text{H}), 8.06 \text{ (dd, } J = 1.5, 8.5 \text{ Hz, } 1\text{H}), 7.89 \text{ (dt, } J = 1.0, 8.0 \text{ Hz, } 1\text{H}), 7.83 \text{ (td, } J = 2.0, 7.5 \text{ Hz, } 1\text{H}), 7.61 \text{ (d, } J = 8.5 \text{ Hz, } 1\text{H}), 7.29 \text{ (ddd, } J = 1.0, 5.0, 7.5 \text{ Hz, } 1\text{H}), 2.60 \text{ (s, } 3\text{H}). \]

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

\[ \delta 165.4, 157.3, 152.4, 150.4, 143.3, 137.7, 136.7, 124.3, 122.9, 120.9, 118.3, 110.8, 14.3 \]

HRMS (ESI+)

Calculated for C\(_{13}\)H\(_{11}\)N\(_2\)O (M+H): 211.0871

Found: 211.0874

Table 3-6

2-(4-(tertbutoxy)phenyl)-6-methylpyridine (3.32p) [Table 3-6, entry 1]. The general procedure was followed using MIDA boronate 3.3a (376 mg, 1.52 mmol) and chloride 3.31b (175 \( \mu \)L, 1.00 mmol). The crude product was subjected to Florisil chromatography (EtOAc:Hexanes 10:90). The mixed fractions were reconstituted and subject to a second Florisil column (EtOAc:Hexanes 10:90) to afford 3.32p as an amber solid (174 mg, 72%).

TLC (EtOAc: Hexanes 10:90)

\[ R_f = 0.36 \], visualized by UV (\( \lambda = 254 \text{ nm} \))
$^1$H-NMR (400 MHz, acetone-d$_6$)
$\delta$ 8.03 (d, $J = 8.4$ Hz, 2H), 7.67 (m, 2H), 7.13 (d, $J = 7.4$ Hz, 1H), 7.07 (d, $J = 8.8$ Hz, 2H), 2.53 (s, 3H), 1.37 (s, 9H).

$^{13}$C-NMR (125 MHz, acetone-d$_6$)
$\delta$ 158.7, 157.4, 156.5, 137.8, 135.0, 128.1, 124.4, 121.8, 117.2, 78.9, 29.1, 24.7

HRMS (ESI+)
Calculated for C$_{16}$H$_{20}$NO (M+H)$^+$: 242.1545
Found: 242.1539

$^{2}$-(4-(tertbutoxy)phenyl)-5-methylpyridine (3.32q) [Table 3-6, entry 2]. The general procedure was followed using MIDA boronate 3.3b (375 mg, 1.51 mmol) and chloride 3.31b (175 µL, 1.00 mmol). The crude product was subjected to Florisil chromatography (EtOAc:Hexanes 10:90) to afford 3.32q as an amber solid (197 mg, 81%).

TLC (EtOAc: Hexanes 20:80)
$R_f = 0.36$, visualized by UV ($\lambda = 254$ nm)

$^1$H-NMR (400 MHz, acetone-d$_6$)
$\delta$ 8.46 (s, 1H), 8.01 (d, $J = 8.8$ Hz, 2H), 7.76 (d, $J = 8.0$ Hz, 1H), 7.63 (dd, $J = 1.8$, 8.4 Hz, 1H), 7.07 (d, $J = 8.8$ Hz, 2H), 2.33 (s, 3H), 1.36 (s, 9H).

$^{13}$C-NMR (125 MHz, acetone-d$_6$)
$\delta$ 157.2, 154.6, 150.6, 137.9, 134.9, 131.8, 127.8, 124.4, 119.7, 78.8, 29.1, 18.0

HRMS (ESI+)
Calculated for C$_{16}$H$_{20}$NO (M+H)$^+$: 242.1545
Found: 242.1539
2-(4-tertbutoxy)phenyl-4-methylpyridine (3.32r) [Table 3-6, entry 3]. The general procedure was followed using MIDA boronate 3.3c (374 mg, 1.51 mmol) and chloride 3.31b (175 µL, 1.00 mmol). The crude product was subjected to Florisil chromatography (EtOAc:Hexanes 10:90) to afford 3.32r as an amber oil (197 mg, 81%).

TLC (EtOAc: Hexanes 10:90)

R_f = 0.22, visualized by UV (λ = 254 nm)

^H-NMR (400 MHz, acetone-d_6)

δ 8.46 (d, J = 5.0 Hz, 1H), 8.03 (d, J = 8.8 Hz, 2H), 7.71 (s, 1H), 7.08 (m, 3H), 2.39 (s, 3H), 1.36 (s, 9H).

^13C-NMR (125 MHz, acetone-d_6)

δ 157.5, 157.2, 150.0, 148.4, 135.0, 128.1, 124.4, 123.4, 121.1, 78.9, 29.1, 21.0

HRMS (ESI+)

Calculated for C_{16}H_{20}NO (M+H)^+: 242.1545

Found: 242.1539

2-(2,4-dimethoxyphenyl)-6-methoxypyridine (3.32s) [Table 3-6, entry 4]. The general procedure was followed using MIDA boronate 3.3d (340 mg, 1.29 mmol) and chloride 3.31h (127.5 µL, 0.86 mmol). The crude product was subjected to Florisil chromatography (EtOAc:Hexanes 10:90). The mixed fractions were reconstituted and subjected to silica gel chromatography (EtOAc:Hexanes 10:90) to afford 3.32s as an amber oil (162 mg, 77%).
TLC (EtOAc: Hexanes 10:90)  
\( R_f = 0.3 \), visualized by UV \((\lambda = 254 \text{ nm})\)

\(^1\)H-NMR (400 MHz, acetone-\(d_6\))  
\( \delta 8.01 (d, J = 8.4 \text{ Hz}, 1\text{H}), 7.61 (dt, J = 8.0, 16.0 \text{ Hz}, 2\text{H}), 6.63 (m, 3\text{H}), 3.93 (s, 3\text{H}), 3.90 (s, 3\text{H}), 3.85 (s, 3\text{H}). \)

\(^1^3\)C-NMR (125 MHz, acetone-\(d_6\))  
\( \delta 164.1, 162.3, 159.5, 153.5, 139.4, 132.5, 121.8, 117.9, 108.6, 106.1, 99.3, 55.9, 55.6, 53.1 \)

HRMS (ESI+)  
Calculated for \( \text{C}_{14}\text{H}_{16}\text{NO}_3 (\text{M+H})^+ \): 246.1130  
Found: 246.1130

\[ \text{2-(4-(tertbutoxy)phenyl)-6-trifluoromethylpyridine (3.32t) [Table 3-6, entry 5].} \]

The general procedure was followed using MIDA boronate \(3.3e\) (454 mg, 1.50 mmol) and chloride \(3.31b\) (175 \(\mu\)L, 1.00 mmol). The crude product was subjected to Florisil chromatography (EtOAc:Hexanes 5:95). The mixed fractions were reconstituted and subject to a second Florisil column (EtOAc:Hexanes 5:95) to afford \(3.32t\) as an amber solid (258 mg, 87%).

TLC (EtOAc: Hexanes 5:95)  
\( R_f = 0.3 \), visualized by UV \((\lambda = 254 \text{ nm})\)

\(^1\)H-NMR (400 MHz, acetone-\(d_6\))  
\( \delta 8.12 (m, 4\text{H}), 7.74 (d, J = 7.4 \text{ Hz}, 1\text{H}), 7.14 (d, J = 8.8 \text{ Hz}, 2\text{H}), 1.39 (s, 9\text{H}). \)
$^{13}$C-NMR (125 MHz, acetone-$d_6$)

$\delta$ 158.6, 158.0, 148.2 (q, $J = 34$ Hz), 139.7, 132.9, 128.6, 124.4, 123.4, 122.7 (q, $J = 272$ Hz), 119.0 (d, $J = 3$ Hz), 79.3, 29.1

HRMS (ESI$^+$)

Calculated for C$_{16}$H$_{17}$F$_3$NO (M+H)$^+$: 296.1262

Found: 296.1254

2-(4-methoxyphenyl)-5-trifluoromethylpyridine (3.32u) [Table 3-6, entry 6]. The general procedure was followed using MIDA boronate 3.3f (229 mg, 0.76 mmol) and chloride 3.31c (61 $\mu$L, 0.5 mmol). The crude product was subjected to Florisil chromatography (Et$_2$O:Hexanes 5:95). The mixed fractions were recombined and subject to a second Florisil column (Et$_2$O:Hexanes 5:95) to afford 3.32u as an off white crystalline solid (99 mg, 78%).

TLC (Et$_2$O: Hexanes 10:90)

$R_f = 0.39$, visualized by UV ($\lambda = 254$ nm)

$^1$H-NMR (500 MHz, acetone-$d_6$)

$\delta$ 8.92 (s, 1H), 8.17 (m, 3H), 8.08 (d, $J = 8.5$ Hz, 1H), 7.07 (d, $J = 8.5$ Hz, 2H), 3.88 (s, 3H).

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

$\delta$ 162.5, 161.0, 147.0 (d, $J = 4$ Hz), 134.9 (d, $J = 4$ Hz), 131.0, 129.5, 125.1 (q, $J = 269$ Hz), 124.3 (q, $J = 32$ Hz), 115.1, 55.7

HRMS (ESI$^+$)

Calculated for C$_{13}$H$_{11}$F$_3$NO (M+H)$^+$: 254.0793

Found: 254.0791
2-(4-(tertbutoxy)phenyl)-4-trifluoromethylpyridine (3.32v) [Table 3-6, entry 7]. The general procedure was followed using MIDA boronate 3.3g (464 mg, 1.54 mmol) and chloride 3.31b (175 µL, 1.00 mmol). The crude product was subjected first to florisil chromatography (EtOAc:Hexanes 2.5:97.5) and then to silica gel chromatography (EtOAc:Hexanes 5:95) to afford 3.32v as an amber oil (251 mg, 85%).

TLC (EtOAc: Hexanes 10:90)
R_f = 0.4, visualized by UV (λ = 254 nm)

1H-NMR (400 MHz, acetone-d_6)
δ 8.89 (d, J = 5.4 Hz, 1H), 8.15 (d, J = 8.8 Hz, 3H), 7.59 (d, J = 5.4 Hz, 1H), 7.13 (d, J = 8.8 Hz, 2H), 1.39 (s, 9H).

13C-NMR (125 MHz, acetone-d_6)
δ 158.9, 158.6, 151.7, 139.3 (q, J = 33 Hz), 133.2, 128.6, 124.4, 124.2 (q, J = 271 Hz), 117.8 (q, J = 4 Hz), 115.7 (q, J = 4 Hz), 79.3, 29.1

HRMS (ESI+)
Calculated for C_{16}H_{17}F_{3}NO (M+H)^+: 296.1262
Found: 296.1258

Table 3-7

2-(p-tolyl)pyridine (3.32w) [Table 3-7, entry 1]. The general procedure was followed using MIDA boronate 3.3 (355 mg, 1.52 mmol) and bromide 3.36a (122.5 µL, 1.00 mmol. The crude
product was subjected to silica gel chromatography (EtOAc:Hexanes 5:95 → 15:85) to afford **3.32w** as yellow liquid (140 mg, 83%).

TLC (EtOAc:Hexanes 17:83)

\[ R_f = 0.45, \text{ visualized by UV (} \lambda = 254 \text{ nm) } \]

**1H-NMR** (500 MHz, CD$_3$CN)

\[ \delta 8.62 (d, J = 4.5 \text{ Hz}, 1H), 7.94 (d, J = 8.5 \text{ Hz}, 2H), 7.80 (m, 2H), 7.29 (d, J = 8.0 \text{ Hz}, 2H), 7.52 (ddd, J = 2.0, 5.0, 6.5 \text{ Hz}, 1H), 2.38 (s, 3H). \]

**13C-NMR** (125 MHz, acetone-d$_6$)

\[ \delta 157.6, 150.3, 139.5, 137.5, 137.4, 130.1, 127.4, 122.8, 120.4, 21.2 \]

HRMS (ESI+)

Calculated for C$_1$H$_{12}$N (M+H)$^+$: 170.0970

Found: 170.0966

2-(4-methoxyphenyl)pyridine (**3.32c**) [Table 3-7, entry 2]. The general procedure was followed using MIDA boronate **3.3** (356 mg, 1.52 mmol) and bromide **3.36b** (125 µL, 1.00 mmol). The crude product was subjected to silica gel chromatography (EtOAc:Hexanes 5:95 → 20:80) to afford **3.32c** as an orange solid (146 mg, 79%). Characterization was consistent with previous data.

2-(4-fluorophenyl)pyridine (**3.32j**) [Table 3-7, entry 3]. The general procedure was followed using MIDA boronate **3.3** (358 mg, 1.53 mmol) and bromide **3.36c** (110 µL, 1.01 mmol). The crude product was subjected to silica gel chromatography (EtOAc:Hexanes 5:95 → 20:80) to
afford 3.32j as a pale yellow solid (145 mg, 84%). Characterization was consistent with previous data.

5-(pyridin-2-yl)pyrimidine (3.32x) [Table 3-7, entry 4]. The general procedure was followed using MIDA boronate 3.3 (353 mg, 1.51 mmol) and bromide 3.36d (159 mg, 1.00 mmol). The crude product was subjected to silica gel chromatography (EtOAc) to afford 3.32x as a white crystalline solid (74 mg, 47%).

TLC (EtOAc)

\[ R_f = 0.27, \text{ visualized by UV } (\lambda = 254 \text{ nm}) \]

\(^1\)H-NMR (500 MHz, CD\(_3\)CN)

\[ \delta \ 9.34 \text{ (s, 2H), 9.18 (s, 1H), 8.72 (d, } J = 4.5 \text{ Hz, 1H), 7.92 (m, 2H), 7.41 (ddd, } J = 2.0, \]

\[ 5.0, 7.0 \text{ Hz, 1H).} \]

\(^13\)C-NMR (125 MHz, acetone-\(d_6\))

\[ \delta \ 159.3, 155.7, 152.8, 151.1, 138.2, 133.1, 124.6, 121.5 \]

HRMS (ESI+)

Calculated for C\(_9\)H\(_8\)N\(_3\) (M+H\(^+\)): 158.0718

Found: 158.0719

1-methyl-5-(pyridin-2-yl)-1H-indole (3.32y) [Table 3-7, entry 5]. The general procedure was followed using MIDA boronate 3.3 (356 mg, 1.52 mmol) and bromide 3.36e (213 mg, 1.01 mmol). The crude product was subjected to silica gel chromatography (EtOAc:Hexanes 5:95 \(\rightarrow\)30:70) to afford 3.32y as a brown crystalline solid (117 mg, 55%).
TLC (EtOAc: Hexanes, 33:67)
\[ R_f = 0.4, \text{ visualized by UV (}\lambda = 254 \text{ nm)} \]

$^1$H-NMR (500 MHz, acetone-d$_6$)
\[ \delta 8.62 (d, J = 5.0 \text{ Hz, 1H}), 8.34 (t, J = 1.0 \text{ Hz, 1H}), 8.00 (dd, J = 2.0, 9.0 \text{ Hz, 1H}), 7.92 (dt, J = 1.0, 8.0 \text{ Hz, 1H}), 7.79 (m, 1H), 7.47 (d, J = 8.5 \text{ Hz, 1H}), 7.26 (d, J = 3.0 \text{ Hz, 1H}), 7.21 (ddd, J = 1.0, 5.0, 7.5 \text{ Hz, 1H}), 6.52, (dd, J = 1.0, 3.0 \text{ Hz, 1H}), 3.86 (s, 3H). \]

$^{13}$C-NMR (125 MHz, acetone-d$_6$)
\[ \delta 159.1, 150.2, 138.3, 137.3, 131.5, 130.8, 129.8, 121.8, 121.3, 120.3, 120.0, 110.2, 102.3, 32.9 \]

HRMS (ESI+)
\[ \text{Calculated for } C_{14}H_{13}N_2 (M+H)^+: \quad 209.1079 \]
\[ \text{Found: } \quad 209.1079 \]

2-(p-tolyl)pyridine (3.32w) [Table 3-7, entry 6]. The general procedure was followed using MIDA boronate 3.3 (354 mg, 1.52 mmol) and iodide 3.36f (130 \( \mu \)L, 1.02 mmol). The crude product was subjected to silica gel chromatography (EtOAc:Hexanes 5:95 \( \rightarrow \) 15:85) to afford 3.32w as yellow liquid (129 mg, 75%). Characterization was consistent with previous data.

2-(4-methoxyphenyl)pyridine (3.32c) [Table 3-7, entry 7]. The general procedure was followed using MIDA boronate 3.3 (355 mg, 1.52 mmol) and iodide 3.36g (235 mg, 1.00 mmol). The crude product was subjected to silica gel chromatography (EtOAc:Hexanes 5:95 \( \rightarrow \) 20:80) to afford 3.32c as a orange solid (139 mg, 75%). Characterization was consistent with previous data.
2-(4-fluorophenyl)pyridine (3.32j) [Table 3-7, entry 8]. The general procedure was followed using MIDA boronate 3.3 (360 mg, 1.54 mmol) and iodide 3.36h (115 µL, 0.995 mmol). The crude product was subjected to silica gel chromatography (EtOAc:Hexanes 5:95 → 20:80) to afford 3.32j as a pale yellow solid (139 mg, 81%). Characterization was consistent with previous data.

tert-butyl 5-(pyridin-2-yl)-1H-indole-1-carboxylate (3.32z) [Table 3-7, entry 9]. The general procedure was followed using MIDA boronate 3.3 (355 mg, 1.52 mmol), iodide 3.36i (346 mg, 1.01 mmol), and heating the reaction to 80 °C for 24 h. The crude product was subjected to silica gel chromatography (EtOAc:Hexanes 5:95 → 20:80) to afford 3.32z as a brown oil (199 mg, 67%).

TLC (EtOAc: Hexanes 20:80)

$R_f = 0.42$, visualized by UV ($\lambda = 254$ nm)

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

$\delta$ 8.64 (d, $J = 5.0$ Hz, 1H), 8.28 (d, $J = 1.5$ Hz, 1H), 8.20 (d, $J = 8.5$ Hz, 1H), 8.04 (dd, $J = 2.0$, 8.5 Hz, 1H), 7.89 (dt, $J = 1.0$, 8.0 Hz, 1H), 7.83 (td, $J = 1.5$, 8.0 Hz, 1H), 7.67 (d, $J = 3.5$ Hz, 1H), 7.27 (ddd, $J = 1.5$, 5.0, 7.5 Hz, 1H), 6.71 (d, $J = 3.5$ Hz, 1H), 1.66 (s, 9H).

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

$\delta$ 157.9, 150.3, 150.1, 137.5, 136.5, 134.9, 131.8, 127.4, 123.8, 122.6, 120.7, 120.2, 115.8, 108.5, 84.5, 28.2
HRMS (ESI+)
Calculated for C$_{18}$H$_{19}$N$_2$O$_2$ (M+H)$^+$: 295.1447
Found: 295.1446

2-(p-tolyl)pyridine (3.32w) [Table 3-7, entry 10]. The general procedure was followed using MIDA boronate 3.3 (357 mg, 1.53 mmol) and triflate 3.36j (180 µL, 1.01 mmol). The crude product was subjected to silica gel chromatography (EtOAc:Hexanes 5:95 → 15:85) to afford 3.32w as yellow liquid (138 mg, 81%). Characterization was consistent with previous data.

2-(3,5-dimethoxyphenyl)pyridine (3.32aa) [Table 3-7, entry 11]. The general procedure was followed using MIDA boronate 3.3 (352 mg, 1.50 mmol) and triflate 3.36k (202.5 µL, 1.00 mmol). The crude product was subjected to silica gel chromatography (EtOAc:Hexanes 5:95 → 30:70) to afford 3.32aa as an amber oil (187 mg, 87%).

TLC (EtOAc: Hexanes 20:80)
$R_f$ = 0.21, visualized by UV ($\lambda$ = 254 nm)

$^1$H-NMR (500 MHz, CD$_3$CN)
$\delta$ 8.63 (d, $J$ = 4.0 Hz, 1H), 7.83 (m, 2H), 7.29 (t, $J$ = 8.5 Hz, 1H), 7.20 (d, $J$ = 2.0 Hz, 2H), 6.55 (t, $J$ = 2.5 Hz, 1H), 3.84 (s, 6H).

$^{13}$C-NMR (125 MHz, acetone-d$_6$)
$\delta$ 162.1, 157.2, 150.2, 142.2, 137.6, 123.3, 121.1, 105.4, 101.7, 55.6
HRMS (ESI+)

Calculated for C\textsubscript{13}H\textsubscript{14}NO\textsubscript{2} (M+H): 216.1025
Found: 216.1023

1-(4-(pyridin-2-yl)phenyl)ethanone (3.32a) [Table 3-7, entry 12]. The general procedure was followed using MIDA boronate 3.3 (353 mg, 1.51 mmol), triflate 3.36l (190 µL, 1.00 mmol) and running the reaction at 80 °C for 24 h. The crude product was subjected to Florisil chromatography (EtOAc:Hexanes 5:95 → 50:50) to afford 3.32a as an off-white crystalline solid (103 mg, 52%). Characterization was consistent with literature.\textsuperscript{9}

2-(naphthalen-2-yl)pyridine (3.32bb) [Table 3-7, entry 13]. The general procedure was followed using MIDA boronate 3.3 (353 mg, 1.51 mmol) and triflate 3.36m (276 mg, 1.00 mmol). The crude product was subjected to silica gel chromatography (EtOAc:Hexanes 0:100 → 10:90) to afford 3.32bb as an off-white crystalline solid (185 mg, 90%).

TLC (EtOAc: Hexanes 10:90)

\( R_f = 0.27 \), visualized by UV (\( \lambda = 254 \text{ nm} \))

\(^1\)H-NMR (400 MHz, acetone-\( \text{d}_6 \))

\( \delta \) 8.71 (d, \( J = 4.0 \text{ Hz}, 1\text{H} \)), 8.65 (s, 1H), 8.30 (dd, \( J = 2, 7.4 \text{ Hz}, 1\text{H} \)), 8.10 (d, \( J = 8.0 \text{ Hz}, 1\text{H} \)), 8.02 (m, 2H), 7.92 (m, 2H), 7.54 (m, 2H), 7.35 (ddd, \( J = 1.4, 5.0, 7.4 \text{ Hz}, 1\text{H} \)).

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

\( \delta \) 157.4, 150.5, 137.7, 137.5, 134.6, 134.4, 129.5, 129.0, 128.4, 127.4, 127.1, 126.8, 125.3, 123.2, 121.1
HRMS (ESI+)
Calculated for C$_{15}$H$_{12}$N (M+H)$^+$: 206.0970
Found: 206.0967

6-(pyridin-2-yl)quinoline (3.32cc) [Table 3-7, entry 14]. The general procedure was followed using MIDA boronate 3.3 (350 mg, 1.50 mmol) and triflate 3.36n (277 mg, 1.00 mmol). The crude product was subjected to Florisil chromatography (EtOAc:Hexanes 5:95 → 70:30). The appropriate fractions were concentrated and transferred washing with 20 mL Et$_2$O to a 60 mL separatory funnel. The solution was diluted with 5 mL 2N HCl and shaken. The organic layer was separated and discarded. The aqueous layer was extracted w/ 20 mL Et$_2$O and the organic layer was again discarded. The aqueous layer was then extracted twice with 20 mL Et$_2$O. The organic fractions were combined and dried with Na$_2$SO$_4$. The solution was filtered and the filtrate was concentrated to afford 3.32cc as an off-white crystalline solid (166 mg, 80%).

TLC (EtOAc: Hexanes 30:70)
$R_f$ = 0.25, visualized by UV ($\lambda = 254$ nm)

$^1$H-NMR (500 MHz, acetone-d$_6$)
$\delta$ 8.92 (dd, $J = 1.5$, 4.0 Hz, 1H), 8.74 (d, $J = 5.0$ Hz, 1H), 8.69 (d, $J = 2.0$ Hz, 1H), 8.55 (dd, $J = 2.0$, 8.5 Hz, 1H), 8.43 (d, $J = 8$ Hz, 1H), 8.13 (m, 2H), 7.93 (td, $J = 1.5$, 7.5 Hz, 1H), 7.54 (dd, $J = 4.0$, 8.5 Hz, 1H), 7.38 (ddd, $J = 1.0$, 5.0, 7.5 Hz, 1H).

$^{13}$C-NMR (125 MHz, acetone-d$_6$)
$\delta$ 156.6, 151.7, 150.5, 149.4, 137.8, 137.2, 130.4, 129.0, 128.6, 126.7, 123.4, 122.4, 121.2, 121.2
HRMS (ESI+)

Calculated for C\textsubscript{14}H\textsubscript{11}N\textsubscript{2} (M+H): 207.0922
Found: 207.0923

**Cross-coupling of 2-pyridyl MIDA boronate without a glovebox**

This procedure was used for the coupling of 2-pyridyl MIDA boronate 3.3 to 4-chloro-tertbutoxybenzene 3.31b.

Under air to a 40 mL I-CHEM vial equipped with PTFE coated stir bar was added Cu(OAc)\textsubscript{2} (91 mg, 0.50 mmol), 2-pyridyl MIDA boronate 3.3 (351 mg, 1.50 mmol), Xphos Palladacycle, chloro(2-dicyclohexylphosphino-2',4',6'-tri-i-propyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl] palladium(II) methyl-t-butylether adduct, (42 mg, 0.057 mmol) and K\textsubscript{3}PO\textsubscript{4} (1.061g, 5.0 mmol). To the vial was added a PTFE coated stirbar. The vial was sealed with a septum cap and back-filled with argon using a 22.5 gauge needle with a gas adapter connecting to a schlenk line. To the vial was added DMF (8 mL), 1-(tert-butoxy)-4-chlorobenzene 3.31b (174 µL, 1.00 mmol), and diethanolamine (96 µL, 1.00 mmol) by syringe using 22 or greater gauge needles. The argon line was then removed from the septum and the vial was heated to 100°C with stirring for 24 h. The reaction was then allowed to cool to room temperature over 0.5 h. The reaction was transferred to a 60 mL separatory funnel, diluted with 10 mL of 2N HCl and shaken. The reaction was then diluted with 10 mL 2N NaOH and shaken. The resulting aqueous solution was extracted three times with 10 mL of diethyl ether. The organic layers were combined and washed with 10 mL of brine. The organic layers were dried using Na\textsubscript{2}SO\textsubscript{4}, filtered, and concentrated *in vacuo*. The resulting residue was adsorbed onto Celite and subjected to Florisil chromatography (EtOAc:Hexanes 5:95 → 20:80) to afford 3.32b as a pale yellow solid. This procedure was performed twice obtaining yields of 200 mg (88%), and 197 mg (87%).
Large scale synthesis of 2-pyridyl MIDA boronate

Caution! The heating of DMSO at high temperatures can lead to uncontrollable exothermic decomposition and possibly explosion. Heating DMSO should be performed by individuals trained in its proper and safe usage and necessary precautions should be taken.

2-Pyridylboronic acid MIDA ester (3.3). An oven-dried, 2-L three-necked, round-bottomed flask equipped with a 1.5” PTFE-coated football-shaped magnetic stir bar is allowed to cool to 23 °C under an inert nitrogen atmosphere (Note 1). In order, the flask is charged with anhydrous tetrahydrofuran (500 mL) (Note 2), 2-bromopyridine (25.5 mL, 42.25 g, 267.4 mmol, 1.1 eq) (Note 3), and triisopropylborate (54.2 mL, 44.17 g, 234.9 mmol, 1.0 eq) (Note 4). The resulting clear, colorless solution is cooled to -78 °C in a dry ice/acetone bath with stirring (600 rpm). To the cooled solution is slowly added via cannula n-butyllithium (100.0 mL, 2.50 M in hexanes, 250.0 mmol, 1.1 eq) dropwise over 2 hours (~0.8 mL/min) with stirring (Note 5). The opaque, brown suspension (Note 6) is stirred for an additional 1.5 hours at -78 °C. It is then removed from the dry ice bath and allowed to warm to 23 °C and stirred under nitrogen for an additional 18 hours giving an opaque, green suspension (Note 7).

An oven-dried, 2-L three-necked, round-bottomed flask equipped with a 1.5” PTFE-coated football-shaped magnetic stir bar is cooled to 23 °C under an inert nitrogen atmosphere (Note 1). The flask is charged with dry N-methyliminodiacetic acid (MIDA) (70.60 g, 479.8 mmol, 2.0 eq) (Note 8) and then anhydrous DMSO (500 mL) (Note 9). The flask is placed in a heating mantle and fitted with a water-cooled distillation train connected to an oven-dried 1-L round-bottomed flask in one side neck, and a thermometer in the other side neck via a PTFE-coated thermometer adapter. With stirring (600 rpm), the contents are heated to an internal temperature of 120 °C to give a clear, pale yellow solution (Note 10). The prepared borate suspension is then transferred dropwise via cannula to the hot MIDA/DMSO solution over 1 hour (~10 mL/min), maintaining the internal temperature between 115°C and 120°C (Note 11). A dark brown suspension results (Note 12). Additional anhydrous tetrahydrofuran (2 x 50 mL) is used to quantitatively transfer the borate suspension to the MIDA/DMSO solution. After addition, the suspension is removed from the heating mantle and allowed to cool to 23 °C with stirring (2 hours). The suspension is filtered through a pad of Celite (Note 13), and the filter cake
is washed with DMSO (2 x 125 mL, then 1 x 50 mL). To the combined filtrate is added freshly ground, oven-dried, anhydrous potassium phosphate tribasic (200.0 g, 942.2 mmol, 4.0 eq) (Note 14), and the suspension is stirred (700 rpm) for 1.5 hours at 23 °C. The suspension is then filtered through a pad of Celite (Note 15) into a 2-L round-bottomed flask. The filter cake is rinsed with anhydrous acetonitrile (3 x 200 mL) (Note 16). The acetonitrile is then removed in vacuo (Note 17) and the flask is equipped with a 1.5” PTFE-coated football-shaped magnetic stir bar. A water-cooled distillation train connected to a 1-L round-bottomed flask is attached to the flask, and the DMSO is removed by vacuum distillation (Note 18) at 60 °C (Note 19) with stirring (600 rpm) over 16 hours.

To the resulting thick, brown oil is added acetonitrile (200 mL) and Celite (10 g) (Note 20). The suspension is filtered through a pad of silica gel and Celite (Note 21), and the filter cake is washed with additional acetonitrile (2 x 200 mL, then 1 x 50 mL) to ensure quantitative transfer (Note 22). The solvent is removed in vacuo (Note 17) yielding a dark brown oil. This oil is dissolved in anhydrous acetonitrile (70 mL), and transferred to a 4-L Erlenmeyer flask equipped with a 3” PTFE-coated octagonal stir bar. Additional acetonitrile (70 mL) and dichloromethane (2 x 200 mL) is used to transfer the oil. Diethyl ether (1.9 L) is added dropwise over 12 hours (~2.6 mL/min) with stirring (300 rpm) (Note 23). The suspension is stirred (700 rpm) for an additional 12 hours after Et₂O addition. The resulting solid is collected by vacuum filtration, rinsed with diethyl ether (3 x 200 mL), and residual solvent is removed from the collected solid under high vacuum (200 mTorr) for 4 hours. The obtained solid is transferred to a 500-mL Erlenmeyer flask equipped with a 1.5” PTFE-coated octagonal stir bar. Anhydrous acetonitrile (300 mL) is added to give a tan suspension, to which activated carbon (1.0 g) (Note 24) is added. The suspension is stirred (400 rpm) for 10 minutes at 23 °C, and then filtered over a pad of silica gel (Note 25) into a tared 1-L round-bottomed flask. The filter cake is rinsed with additional acetonitrile (3 x 100 mL) into the same flask. The solution is concentrated in vacuo (Note 26), azeotroped with acetone (2 x 100 mL) (Note 17), and residual solvent is removed under high vacuum (200 mTorr) at 23 °C for 16 hours to yield 2-pyridylboronic acid MIDA ester (3.3) as an off-white, free-flowing solid (26.01 g, 111.1 mmol, 47.2% yield, >95% pure) (Notes 26-30).
Notes

1. The glassware is dried in a 120 °C oven for 16 hours. The three-necked flask is capped with a gas inlet adapter in one side neck, a thermometer and PTFE-coated thermometer adapter in the second neck, a rubber septum in the remaining neck, and cooled under a stream of nitrogen for 30 minutes venting through an 18-gauge needle.

2. Tetrahydrofuran was obtained from a Solvent Delivery System, purified via passage through packed dry neutral alumina columns as described by Pangborn and coworkers. It is added under nitrogen via cannula from an oven-dried, 1-L round-bottomed flask.

3. 2-Bromopyridine (1, 99%) was obtained from Sigma-Aldrich (Cat. No. B80100, Lot No. 06596LMV) and used as received. It is added via an anhydrous 60-mL polypropylene syringe.

4. Triisopropylborate (≥98%) was obtained from Sigma-Aldrich (Cat. No. 197335, Lot No. SHBB2938V) and used as received. It is added via an anhydrous 60-mL polypropylene syringe.

5. n-Butyllithium (2.50 M in hexanes) was obtained from Sigma-Aldrich (Cat. No. 230707, Lot No. SHBB8936V) and used as received. It is important to keep the internal temperature below -70 °C.

6. During the addition, the solution first turns yellow then becomes a strong yellow/orange and finally brown.

7. The suspension may be brown.

8. N-methyliminodiacetic acid (MIDA) is commercially available (Sigma-Aldrich M51008), or can be prepared according to Dick et al. MIDA is a snow-white, free-flowing powder. MIDA (500 g) can be recrystallized by dissolving in water (500 mL) and precipitating by adding acetone (4 L) with stirring at 23 °C. It is dried in a vacuum oven (15 Torr, 150 °C) for 24 hours immediately prior to use. The use of pure, dry MIDA is crucial to the success of this procedure. The use of impure or wet MIDA will result in impure product with diminished yields. The MIDA used in this procedure was prepared by the submitters according to Dick et al., and was consistent with physical and spectral data as described by Ballmer et al.

9. DMSO was obtained from a Solvent Delivery System, purified by passage through packed molecular sieves as described by Pangborn and coworkers. It is added under nitrogen via cannula through an oven-dried 1-L round-bottomed flask.
10. The use of pure MIDA will result in a clear, colorless or pale yellow solution. The use of impure MIDA will result in a dark yellow or brown solution. This has led to the product with reduced yields.

11. The borate suspension is added via large bore PTFE cannula (1/4” ID x 1/32” W) at a constant rate to control the internal temperature of the solution. The distillation train and collection flask are left open to atmospheric pressure. Nitrogen pressure is used to cannulate the borate suspension. Careful control of the internal temperature is important. It should not exceed 120 °C. Distillation is continuously observed throughout addition of the borate suspension. Heating is continued until completion of the THF (2 x 50 mL) transfer. An image displaying the distillation setup can be found at the end of this document.

12. The clear, colorless distillate contains THF, isopropanol, hexanes, and 2-bromopyridine. The crude product remains in the three-necked flask.

13. Celite 545 filter aid (non-acid washed) is used throughout this procedure. A 600-mL glass fritted funnel is packed with 50 g of Celite. The filtrate is collected via vacuum filtration into a 2-L Erlenmeyer flask equipped with a 3” PTFE-coated octagonal stir bar.

14. Anhydrous potassium phosphate tribasic (≥98%) was obtained from Sigma-Aldrich (Cat. No. P5629, Lot No. 031M0077V). It is freshly ground with mortar and pestle to a very fine powder and dried at 120°C for 3 hours directly prior to use.

15. A 600-mL glass fritted funnel is packed with 50 g of Celite.

16. Anhydrous acetonitrile was obtained from Sigma-Aldrich (Lot No. 68996APV) and used as received. The sure-seal is removed directly prior to use.

17. The solvent is removed by rotary evaporation at 40 °C and 30 Torr. The vacuum pressure is monitored to avoid vigorous bumping.

18. Vacuum distillation occurs at 150 mTorr with stirring (600 rpm). Two dry ice/acetone traps were placed in line between the flask and the vacuum pump. The solvent levels in these traps were monitored and emptied periodically. All ground glass joints were sealed with Apiezon H high vacuum grease and secured with Keck clips. The vacuum pressure was monitored to avoid vigorous bumping. It is important to maximally remove DMSO and failure to do so will complicate the remainder of the procedure.

19. The flask is heated with an oil bath at a bath temperature of 60 °C.
20. After addition of acetonitrile, the solution is placed in a 60 °C water bath with agitation for 20 minutes to give a light-brown suspension. The Celite is then added, and the suspension is mixed and allowed to settle before filtration.

21. A 600-mL glass fritted funnel is packed with 40 g of silica gel and 25 g of Celite is then layered on top of the silica gel.

22. The indicated product is in the filtrate. $^1$HNMR of the celite/silica mix indicated the absence of product, ensuring quantitative transfer.

23. Diethyl ether is added (slowly down the side of the Erlenmeyer flask) from a 2-L separatory funnel. Adding the diethyl ether too quickly will result in formation of an oil.

24. Activated carbon (100 mesh size) was obtained from Sigma-Aldrich (Lot No. MKBH7471V) and used as received.

25. A 150-mL glass fritted funnel is packed with 30 g of silica gel. After rinsing with acetonitrile, $^1$HNMR of the obtained silica gel/charcoal mix indicated absence of product.

26. The physical and spectral data for 3.3 are as follows: mp 176-180 °C, uncorrected; TLC (MeCN) $R_f = 0.41$, visualized by UV ($\lambda = 254$ nm) and KMnO$_4$ stain; $^1$HNMR (500 MHz, CD$_3$CN) $\delta$ 8.67 (ddd, $J = 4.8, 1.6, 1.1$ Hz, 1H), 7.70 (td, $J = 7.6, 1.7$ Hz, 1H) 7.63 (dt, $J = 7.6, 1.1$ Hz, 1H), 7.28 (ddd, $J = 7.6, 4.8, 1.4$ Hz, 1H), 4.11 (d, $J = 16.8$ Hz, 2H), 4.00 (d, $J = 16.8$ Hz, 2H), 2.56 (s, 3H); $^{13}$CNMR (125 MHz, CD$_3$CN) $\delta$ 169.6, 150.9, 135.8, 128.1, 124.3, 63.0, 47.6; $^{11}$BNMR (96 MHz, CD$_3$CN) $\delta$ 10.3; HRMS (CI+) Calculated for C$_{10}$H$_{12}$BN$_2$O$_4$ (M+H)$^+$ : 235.0890 Found : 235.0895; FTIR (KBr, cm$^{-1}$) 3004, 2956, 1774, 1749, 1663, 1590, 1466, 1340, 1289, 1279, 1214, 1152, 1095, 1054, 1045, 998, 964, 894, 866, 775, 754, 708, 683. Anal. calcd. for C$_{10}$H$_{11}$BN$_2$O$_4$ : C, 51.32; H, 4.74; N, 11.97; Found : C, 51.07; H, 4.52; N, 11.63 (Note 27, Part A).

27. An analytically pure sample for CHN analysis can be obtained via any of three methods. A) Recrystallization through vapor diffusion: 2-pyridylboronic acid MIDA ester (70 mg) in a 7 mL scintillation vial is partially dissolved with anhydrous acetone (2 mL), and the suspension swirled for 10 minutes. The saturated solution is then taken up into a 5 mL polypropylene syringe, and filtered through a 0.45 μm Iso-Disc™ filter into a 7 mL scintillation vial. The vial is then placed into a 40 mL scintillation vial containing anhydrous diethyl ether (9 mL), and the 40 mL vial capped. The system is allowed to sit undisturbed for 24 hours, upon which white crystals form. The remaining solvent is removed and the product is dried over P$_2$O$_5$
at 150 mTorr overnight immediately before analysis. B) Recrystallization through liquid/liquid diffusion: To 2-pyridylboronic acid MIDA ester (70 mg) in a 7 mL scintillation vial is added anhydrous acetone (2 mL), and the saturated suspension swirled for 10 minutes. The suspension is then taken up into a 5 mL polypropylene syringe, and filtered through a 0.45 μm Iso-Disc™ filter into a 7 mL scintillation vial. Then anhydrous diethyl ether (4 mL) is slowly added on top of the acetone layer, and the vial is capped. The solution is allowed to sit undisturbed for 24 hours, upon which white crystals form. The remaining solvent is removed and the product is dried over P₂O₅ at 150 mTorr overnight immediately before analysis. C) Column chromatography: 2-pyridylboronic acid MIDA ester (140 mg) is purified by flash column chromatography (10.0 g silica gel) with anhydrous acetonitrile as eluent. The fractions containing product (as indicated by TLC) are collected into a 100 mL round-bottomed flask, and concentrated in vacuo. The product is transferred via acetonitrile (4 mL) into a 7 mL scintillation vial, and concentrated in vacuo. The white crystals are then dried over P₂O₅ at 150 mTorr overnight immediately before analysis.

28. If the method is not performed effectively, a pyridinium species may form: ¹HNMR (500 MHz, CD₃CN): δ 8.81 (ddd, J = 5.8, 1.4, 0.7 Hz, 1H), 8.48 (td, J = 7.8, 1.5 Hz, 1H), 8.17 (d, J = 7.8 Hz, 1H), 8.02 (ddd, J = 7.2, 5.8, 1.4 Hz, 1H), 4.34 (d, J = 17.2 Hz, 2H), 4.23 (d, J = 17.2, 2H), 2.96 (s, 3H). Other shifts have been observed, however they are always downfield from the expected shifts (Note 23). A free-base procedure can be performed to convert this material into 2-pyridyl MIDA boronate. This involves stirring the isolated material with anhydrous K₂CO₃ (1.5 g/g) in boiling acetonitrile (20 mL/g) for 20 minutes, then adding activated carbon (50 mg/g) and MgSO₄ (200 mg/g). The suspension is then stirred for 20 minutes, and filtered while hot through a pad of Celite. The solvent is then removed in vacuo to yield pure 2-pyridylboronic acid MIDA ester.

29. Additional 2-pyridylboronic acid MIDA ester (5% additional product) can be obtained from the final filtrate. Diethyl ether (1 L) is carefully layered on top of the filtrate and this biphasic solution is allowed to sit undisturbed for 48 hours. The suspension is stirred, and the resulting solid is collected by vacuum filtration.

30. The purity of the product is found to be >95% by ¹HNMR. The impurity (<5%) is n-butyl MIDA boronate. Higher purity material can be obtained by trituration with acetone/ether with a loss of yield or through column chromatography.
REFERENCES


5 CCDC 820377 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.


In order to expedite synthetic access to functional molecules, we aim to identify common substructural motifs that are prevalent in a wide range of natural products and transform them into shelf-stable building blocks that are compatible with iterative assembly using, ideally, a single reaction and a general set of reaction conditions. We identified polyene natural products as an excellent opportunity for testing this concept, because of their prevalence across a wide range of biosynthetic classes of natural products. We specifically decided to ask the question: if restricted to the use of only the Suzuki-Miyaura reaction, how many bifunctional MIDA boronate building blocks would be required to make most polyene natural product motifs? To address this question, we devised an algorithm for systematically retrosynthesizing polyene core motifs into bifunctional building blocks. Remarkably, this analysis resulted in a collection of just 12 bifunctional haloalkenyl MIDA boronate building blocks with which >75% of all polyene motifs found in Nature can be prepared using a single reaction iteratively. Applying this same approach to other classes of small molecule natural products, pharmaceuticals, and materials represents a promising roadmap towards a universal approach to the synthesis of small molecules.

Jahnabi Roy contributed to the synthesis of building blocks and to the preparation of polyene motifs.

Adapted from Woerly, E. M.; Roy, J.; Burke, M. D. manuscript in preparation.
4-1 INTRODUCTION

The vast majority of molecules found in living systems are biosynthesized via a common systematic strategy involving the iterative assembly of bifunctional building blocks.\(^1\) In the case of polypeptides, oligonucleotides, and increasingly oligosaccharides, this strategy has been successfully replicated in the laboratory to enable efficient, flexible, and even fully-automated access to these molecules.\(^2\) As a result, the function, not the synthesis, of these molecules is now the main focus of research in these areas.

In contrast, despite also being biosynthesized primarily via iterative building block assembly, the laboratory synthesis of small molecule natural products remains a relatively inefficient, inflexible, and unsystematized process practiced almost exclusively by specialists.\(^3\) The substantial level of inherent modularity that results from the common biosynthetic origins of most natural products suggests that a generalized building block based approach may also be applicable to the laboratory synthesis of many of these compounds. Customized iterative strategies have been developed for the synthesis of substructures of particular biosynthetic origins (see Chapter 1). However, a generalized strategy that is potentially applicable to most classes of natural products has yet to emerge. As a result, synthesis remains the rate-limiting step in small molecule science, and the functional capacity of many small molecules remains untapped.

As a roadmap for creating a general strategy for small molecule synthesis, we aim to identify common substructural motifs that are prevalent in a wide range of natural products and transform them into shelf-stable building blocks that are compatible with iterative assembly using, ideally, a single reaction and a general set of reaction conditions. As described throughout this thesis, iterative cross-coupling (ICC) with N-methyliminodiacetic acid (MIDA) boronates has emerged as a potentially general platform for enabling such an approach.\(^4\) In this type of synthesis, MIDA boronate building blocks having all of the required functional groups preinstalled in the correct oxidation states and with the desired stereochemical relationships are iteratively united using only the stereospecific Suzuki-Miyaura cross-coupling reaction. These building blocks are remarkably convenient to prepare, analyze, purify, and store and more than 130 are now commercially available.\(^5\) The MIDA boronate functional group is inert to anhydrous cross-coupling conditions, yet can be readily transformed into a fully reactive boronic acid using mild reagents. These features have enabled the simple, efficient, and flexible synthesis of a range
of complex small molecules, including polyketide, polyterpene, fatty acid, and phenylpropanoid derived natural products, as well as pharmaceutical agents, via the ICC of MIDA protected haloboronic acids.⁴

Emboldened by the accelerating success of the ICC strategy, we have begun to question whether this approach could provide a pathway to systematize and ultimately automate the total synthesis of most natural products. We identified polyene natural products as an excellent opportunity for testing this concept, because of their prevalence across a wide range of biosynthetic classes of natural products (Figure 4-1).⁶ The synthesis of polyenes is challenging due to sensitivities to light, oxygen, and many common reagents including protic and Lewis acids.⁷ Controlling the stereochemistry during the formation of each double bond is also a critical issue. Common strategies for the synthesis of polyenes include olefination reactions (Wittig, Horner-Wadsworth-Emmons, Julia), which suffer from lack of stereocontrol, and transition metal based reactions (organozinc and organostannane cross-couplings), which often suffer from challenges in synthesis, instability to long-term storage, difficulty in handing, and the generation of toxic byproducts.⁸ Due to the instability of polyenylboronic acid intermediates, it had been challenging to similarly prepare polyenes via organoboron cross-couplings, yet some progress has been made using the MIDA boronate platform. However, none of these approaches have previously proven to be universally applicable to most polyene frameworks found in Nature.

Figure 4-1. The polyene motif is present in natural products across a range of biosynthetic classes.
With this goal in mind, together with Jahnabi Roy, we specifically decided to ask the question: if restricted to the use of only the Suzuki-Miyaura reaction, how many bifunctional MIDA boronate building blocks would be required to make most polyene natural product motifs? To address this question, we devised an algorithm for systematically retrosynthesizing polyene core motifs into bifunctional building blocks. Remarkably, this analysis resulted in a collection of just 12 bifunctional haloalkenyl MIDA boronate building blocks with which >75% of all polyene motifs found in Nature can be prepared using a single reaction iteratively. Applying this same approach to other classes of small molecule natural products, pharmaceuticals, and materials represents a promising roadmap towards a universal approach to the synthesis of small molecules.

4-2 IDENTIFYING POLYENE NATURAL PRODUCTS

We first utilized the CRC Dictionary of Natural Products, a comprehensive searchable database of over 238,000 compounds, to identify all known polyene natural products. Specifically, a substructure search for a polyene motif, which we defined as three or more carbon-carbon double bonds in conjugation, none of which are contained in a <12-membered ring, returned 2,839 compounds, or 1.2% of all known natural products. Importantly, this set includes natural products derived from all major biosynthetic classes, including polyterpenes, polyketides, hybrid peptide/polyketides, fatty acids, and polyphenylpropanoids.

4-3 A SYSTEMATIC RETROSYNTHESIS OF POLYENE NATURAL PRODUCTS

To determine how many bifunctional MIDA boronate building blocks would be required to access the core polyene motif found in >75% of these natural products, we developed an algorithm for systematically retrosynthesizing these motifs into a collection of bifunctional haloalkenyl MIDA boronate building blocks (Figure 4-2). Based on a wide range of experiences with MIDA boronates in our own laboratories, this algorithm was designed to maximize the potential that the resultant forward synthetic pathways would prove to be viable in the laboratory. To achieve this goal, the following specific guidelines were employed: First, the polyenyl halo MIDA boronate building blocks cannot be longer than a triene. Our experience has shown that increasing the polyene length in a single building block beyond a triene leads to increased challenges in stereospecific synthesis and/or decreased ICC efficiency. Second, using
mono-, di-, and triene building blocks, the polyene cores are dissected into the number of building blocks such that the fewest number of couplings would be needed for the targeted synthesis, thus maximizing the overall efficiency. Third, disconnections are chosen such that the length of the longest polyenyl borane intermediate in each pathway is minimized. This is because increasing the length of polyenyl borane intermediates can decrease their stability. Applying this algorithm to the polyene motifs found in >75% of all polyene natural products yielded a collection of just 12 bifunctional MIDA boronate building blocks (4.1 – 4.12) from which, in theory, any of these polyene motifs can be prepared via ICC (Figure 4-3).

**Guideline 1**
*No building blocks longer than a triene.*

![Guideline 1 Diagram](image)

**Guideline 2**
*Dissect the core motif into the fewest number of building blocks.*

![Guideline 2 Diagram](image)

**Guideline 3**
*Minimize the length of polyenyl borane intermediates.*

![Guideline 3 Diagram](image)

*Figure 4-2.* A set of guidelines to systematically retrosynthesize polyene natural products into a collection of bifunctional MIDA boronate building blocks.

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The following three examples demonstrate the systematic application of this algorithm. First, the hybrid polyketide/polyphenylpropanoid derived natural product asnipyrone A was originally isolated and structurally assigned in 1989 by Li and coworkers and reisolated in 2011 by Liu and coworkers (Figure 4-4).\textsuperscript{10} Detailed NMR analysis led Liu to reassign the structure of asnipyrone A to \textbf{4.13}. Applying the algorithm, the polyene core, defined as the polyene motif minus the terminal olefins, was identified as a monoene. As a result, three building blocks \textbf{4.14, 4.3, and 4.15} were identified as being required to complete the synthesis of this natural product.

**Figure 4-4.** Systematic retrosynthesis of asnipyrone A.
Second, the fatty acid derived natural product α-parinaric acid 4.16 was first discovered in 1933 by Tsujimoto and Koyanagi (Figure 4-5).\textsuperscript{11} This tetraene has important fluorescent properties and is commonly used for the study of biomembranes. The polyene core of α-parinaric acid was identified as a diene. Following our second guideline, this motif can be accessed with one building block (4.5) instead of dissecting into two building blocks (4.1 + 4.1). Therefore, three building blocks 4.17, 4.5, and 4.18 were identified as being required to complete the synthesis of this natural product.

\begin{figure}
\centering
\includegraphics[width=0.7\textwidth]{figure4-5.png}
\caption{Systematic retrosynthesis of α-parinaric acid.}
\end{figure}

Third, the polyterpene derived natural product neurosporaxanthin β-D-glucopyranoside 4.19 was isolated by Sakaki and coworkers in 2002 (Figure 4-6).\textsuperscript{12} In order to determine the building blocks that would be necessary to complete the synthesis of 4.19, we applied the standardized retrosynthetic algorithm. First, the polyene core for 4.19 was identified as an octaene. Second, we dissected this octaene core into the fewest number of building blocks, a diene and two trienes. In order to minimize the length of the polynyl borane intermediates, we would first couple the diene building block, followed by couplings of the trienes. As a result, five building blocks 4.20, 4.6, 4.11, 4.9, and 4.21 were identified from this analysis.
4-4 SYNTHESIS OF THE TWELVE MIDA BORONATE BUILDING BLOCKS

Efficient access to these 12 building blocks was accomplished by taking advantage of many of the enabling features of the MIDA boronate platform, including the capacity to carry MIDA boronates through multistep synthesis pathways. We recognized that many of the di- and trienyl building blocks can be prepared using the monoene building blocks as a starting material. Thus, we first developed robust and scalable syntheses of each of these single olefin building blocks 4.1, 4.2, 4.3, and 4.4 (Figure 4-7).
Our group has developed several routes to building block 4.1. First reported by Dr. Suk Joong Lee and Dr. Kaitlyn Gray, the bromoborylation of acetylene followed by complexation with MIDA provided a first generation route to 4.1.\(^{13}\) Later, Brice Uno and Dr. Eric Gillis reported that 4.1 can be prepared from the silane precursor through a transmetalation/trap sequence with boron tribromide and the bis-sodium salt of MIDA (MIDA\(^2^-\) Na\(^+\)).\(^{14}\) Alternatively, 4.1 can be accessed through a bromodestannylation reaction from commercially available trans-2-((tributyltin)vinyl MIDA boronate.\(^{15}\)

As described in Chapter 3, MIDA boronate 4.2 can be obtained from a bromination/elimination sequence starting from commercially available trans-2-(pinacol boronate)vinyl MIDA boronate.\(^{16}\)

As described in Chapter 2 in the context of the total synthesis of peridinin, MIDA boronate 4.3 can be synthesized from a bromination/elimination sequence starting from commercially available isoprenyl MIDA boronate.\(^{17}\)

Finally, as originally developed in collaboration with undergraduate Sean O’Hara, MIDA boronate 4.4 can be prepared through a bromination/elimination sequence starting from 4.5. Building block 4.5, in turn, is obtained from a Miyaura borylation of 4.3. All of these building blocks (4.1-4.4) can be readily accessed on larger than 10 gram scale without the need for
puriﬁcation by column chromatography. Moreover, all four of these building blocks are now commercially available.

The di- and triene building blocks 4.6-4.12 were accessed through couplings with a range of different bis-metalated fragments followed by halodemetalation of the resulting polyenylgermanium or polyenylsilicon precursors (Figure 4-8). While halodesilylation reactions have been used on dienylsilane systems,\textsuperscript{18} to the best of our knowledge, the halodesilylation of a trienylsilane has not been reported. The development of this methodology was instrumental in the preparation of building blocks 4.10 and 4.11. Interestingly, in contrast to halodegermylation and halodestannylation reactions, the methyl substitution pattern of the polyene plays an important role in the stereo outcome of the halodesilylation reaction. For example, while 4.11 can be prepared by treating the silane precursor with NIS in MeCN, building block 4.12 could not be prepared by this method. Specifically, treatment of the silane precursor with NIS in MeCN produced trace amounts of the desired product and numerous decomposition products. As a result, an alternative route to 4.12 was developed involving the iododegermylation of the germane precursor. In all, the halodegermylation and halodesilylation approach provides a mild and highly stereocontrolled way to access a variety of substituted polyene frameworks.

\textbf{Figure 4-8.} Preparation of building blocks 4.5-4.12 from 4.1-4.4.
With building blocks 4.1-4.12 in hand we sought to combine them in an iterative fashion to prepare a collection of common polyene motifs that collectively represent those found in 2,131 natural products, or >75% of all polyene natural products that have been isolated and characterized to date (Figure 4-9). This collection of motifs include both trans- and cis-olefins, various methyl substituted olefins, as well as a variety of chain lengths, from three to ten olefins. Thus, this diverse collection of targets represents a substantial challenge for the development of a general synthesis strategy, especially one that is restricted to only the use of common reaction conditions.

![Frequency of Core Polyene Motifs](image)

**Figure 4-9.** The polyene motifs that are present in >75% of all known polyene natural products.

In this vein, we encountered important limitations when we first attempted to apply our established ICC strategy (Chapters 1-3) to the synthesis of some of the more complex members
of our collection of targeted polyene motifs. Specifically, instability of the polyenyl boronic acid intermediates required for the synthesis of the longer motifs resulted in poor yields of the desired final products. As described above, polyenylboronic acids are notoriously unstable, and this precluded their general utilization to achieve our stated goals.

In contrast, polyenylboronic esters are typically more stable than their boronic acid counterparts. Moreover, we have found that when using DMSO as the solvent, polyenyl boronic esters can be cross-coupled under anhydrous Suzuki-Miyaura cross-coupling reaction conditions, as required for ICC with MIDA boronates. We envisioned a new ICC cycle involving the coupling of a pinacol ester to a bifunctional MIDA boronate building block under anhydrous conditions followed by a transesterification of the resulting MIDA boronate to a pinacol ester, thus generating a new boronic ester to continue the cycle (Figure 4-10).

**Figure 4-10.** A new ICC cycle involving the coupling of pinacol esters and bifunctional MIDA boronate building blocks.

With the goal of developing a general platform, we further sought to identify a single set of reaction conditions for both the coupling of polyenyl pinacol esters with polyenyl bifunctional MIDA boronate building blocks and for deprotection of MIDA boronates to pinacol esters. Such general conditions can greatly enable utilization of the ICC approach, removing the need for ad hoc optimization and potentially facilitating automation of the synthesis process. In this vein, we found that a wide range of polyenyl MIDA boronates of varying length and with varying methyl substitution patterns can be transesterified to the corresponding pinacol ester using the same set of general conditions: pinacol (1.5 eq.) and NaHCO₃ (5.0 eq.) in MeOH at room temperature for
3 h. The resulting pinacol esters were found to be quite stable, and could be isolated without special precautions. Moreover, we found that these polyenyl pinacol esters of varying length, stereochemistry, and methyl substitution patterns can be coupled to mono-, di- and trienyl chloride, bromide, and iodide bifunctional MIDA boronate building blocks using a general set of cross-coupling conditions: 2nd generation XPhos palladacycle pre-catalyst (10 mol%), Cs₂CO₃ (4 eq.), and DMSO. Furthermore, a final coupling between the polyenyl MIDA boronate and a capping group, also under a common set of conditions (2nd generation XPhos palladacycle catalyst, NaOH, and THF:H₂O), provides the final polyene motifs. These conditions promote the in situ release of unstable polyenyl boronic acids directly from the corresponding much more stable polyenyl MIDA boronates and thereby promote the final coupling reactions in the ICC sequence with maximized efficiency.

4-6 ACCESSING >75% OF KNOWN POLYENE NATURAL PRODUCTS

With this new ICC cycle in hand, we attempted to synthesize all of the targeted polyene motifs 4.22-4.36, representing the structures found in >75% of all polyene natural products, using only our twelve building blocks and the general set of cross-coupling conditions in an iterative fashion (Figure 4-11). MIDA boronate 4.37 and vinyl iodide 4.38 were chosen as representative natural product-like capping groups for the polyene motifs. Remarkably, without any optimizations to the general reaction conditions described above, all of the targeted polyene motifs were successfully prepared in multimilligram quantities. These syntheses ranged from a single iteration of ICC to generate triene 4.22 to four iterations to generate highly complex decaene 4.36. Moreover, all of the targets, including those that contain cis-olefins (4.23 and 4.24) were formed with complete stereocontrol. The successful preparation of all of these targets validates the effectiveness and scope for this systematized approach for polyene synthesis.
Figure 4-11. The synthesis of motifs that are present in >75% of all polyene natural products from a collection of 12 building blocks and a common set of reaction conditions. The isolated yields for the deprotection and cross-coupling reactions are located below the corresponding bolded bond.
4-7 TOTAL SYNTHESIS OF NEUROSPORAXANTHIN β-D-GLUCOPYRANOSIDE

As a final test of this platform, we targeted the first total synthesis of the complex polyene natural product neurosporaxanthin β-D-glucopyranoside 4.19 (Figure 4-12). Using the
general set of deprotection and cross-coupling reactions identified above, the synthesis commenced with the deprotection of 4.20 and coupling with diene 4.6 to provide tetraene 4.39. Deprotection of 4.39 and coupling with 4.11 provided heptaene 4.40. This framework could be accessed using the general reaction conditions despite the varying methyl substitution pattern. A third iteration of deprotection and coupling with 4.9 provided decaene 4.41. Importantly, the polyenyl pinacol ester intermediate could be isolated without difficulty. Furthermore, the general reaction conditions are compatible with the coupling of this pinacol ester with a polyenyl bromide without modification, providing access to the very complex boronate framework of 4.41. A final coupling with 4.21 utilizing the general in situ deprotection/coupling conditions provided 4.42. Current efforts are focused on global deprotection to complete the first total synthesis of 4.19.

Figure 4.12. The first total synthesis of neurosporaxanthin β-D-glucopyranoside.

4-8 SUMMARY AND CONCLUSIONS

Although natural products are very diverse at their cores, they are inherently modular and lend themselves to iterative synthesis. We envision that the systematic and automated synthesis of most natural products can be achieved using a limited number of building blocks that are united under common reaction conditions. Toward this broader goal, we have demonstrated that the polyene motifs present in >75% of all polyene natural products can be generated from a collection of just 12 bifunctional MIDA boronate building blocks that are united using one reaction and a general set of reaction conditions. Furthermore, these building blocks and general conditions were applied en route to the first total synthesis of the polyene natural product neurosporaxanthin β-D-glucopyranoside.

The identification of general reaction conditions is central to the execution of this synthesis strategy. A robust and general set of conditions that can reliably provide the targeted
product is highly amenable to automation and removes the need for a specialist to perform screening and optimization studies.

Ultimately, we envision that this same strategy may represent a general approach to the preparation of other classes of small molecule natural products, pharmaceuticals, and materials. For example, polyketide derived natural products contain the stereotetrad substructural motif, consisting of four contiguous stereogenic centers in any diastereomeric combination. Recent advances in sp²-sp³ and sp³-sp³ Suzuki-Miyaura cross-coupling methodology would enable the iterative union of building blocks containing these motifs, potentially using a general set of reaction conditions.

Furthermore, cyclic natural products (for example amphotericin B and steroids) are biosynthesized via the covalent folding of linear precursors. A single cyclization can lead to macrocycles, which often have superior physical and/or functional properties relative to their linear counterparts. Moreover, in the same fashion, linear frameworks can be constructed through the iterative assembly of bifunctional building blocks and then cyclized to form complex molecular frameworks.

It is interesting to consider how many building blocks would be required to access most of the structural motifs found in known natural products. Collectively, such a synthesis strategy seeks to promote a move away from specialized synthesis routes and reaction conditions toward a more systematic approach that has the potential to enable the efficient, flexible, and even fully automated access to many classes of small molecules.

4-9 REFERENCES


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4 (a) see Chapter 1. (b) Gillis, E. P.; Burke, M. D. Aldrichimica Acta 2009, 42, 17-27.
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CHAPTER 4
EXPERIMENTAL SECTION

Materials. Commercial reagents were purchased from Sigma-Aldrich, Fisher Scientific, Alfa Aesar, TCI America, Strem Chemicals Inc., or Frontier Scientific and were used without further purification unless otherwise noted. Solvents and amines were dried as noted in Chapter 2.

General Experimental Procedures. The general experimental procedures followed in these studies are the same as those detailed in Chapter 2, except where noted.

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

Experimental Procedures.

MIDA boronate 1. MIDA boronate 4.1 was prepared according to literature precedent.¹ MIDA boronate 4.1 is commercially available from Sigma-Aldrich (product number 703478).

MIDA boronate 4.2. MIDA boronate 4.2 was prepared according to literature precedent.²

MIDA boronate 4.3. MIDA boronate 4.3 was prepared according to literature precedent³ by the following modified procedure:

To a 2 L round bottom flask equipped with a stir bar and charged with isoprenyl MIDA boronate 4.43 (25.12 g, 127.5 mmol) was added CH₂Cl₂ (1.2 L). The resulting clear, colorless
solution was cooled to 0 °C in an ice bath. Neat bromine (13.0 mL, 253.8 mmol) was added dropwise over 10 minutes to give a cloudy orange solution. The solution was warmed to 23 °C over 1 hr. An aliquot was removed, concentrated *in vacuo*, and analyzed by NMR to ensure full conversion of the isoprenyl MIDA boronate starting material. If full conversion is not observed, an additional 0.5 eq. of neat bromine can be added. Ensuring full conversion, the resulting orange solution was concentrated *in vacuo* to give a yellow solid. This solid was azeotroped with CH₂Cl₂ (2 x 100 mL) to remove residual bromine.

The resulting white solid was suspended in MeCN (1 L). 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU, 56.9 mL, 380.7 mmol) was added in one portion. The resulting mixture stirred at 23 °C for 1 hr to give a clear, yellow/brown solution. The solution was poured into a separatory funnel containing EtOAc:acetone (4:1, 1 L) and 1 M aq. HCl (1 L). After shaking, the layers were separated. The organic layer was washed with saturated aqueous sodium bisulfite:brine (3:2, 1 x 500 mL) and then brine (1 x 250 mL). The organic layer was dried over MgSO₄, filtered, and concentrated *in vacuo*. The resulting crude material was pushed through a plug of silica, eluting with acetone. The filtrate was concentrated and resuspended in a minimum volume of 3:1 EtOAc:acetone. Et₂O was added in portions to precipitate the product. The resulting solid was collected by vacuum filtration to afford MIDA boronate 4.3 as a white solid (24.58 g, 70%).

**MIDA Boronate 4.44.** To a 40 mL vial containing brominated MIDA boronate 4.3 (1.04 g, 3.8 mmol) and a stir bar, in a glovebox, was added B₂pin₂ (1.37 g, 5.4 mmol), KOAc (1.20 g, 12.2 mmol), and PdCl₂dpff•CH₂Cl₂ (151.8 mg, 0.19 mmol). The vial was capped with a septum cap, removed from the glovebox, and placed under N₂. DMSO (30 mL) was added in one portion. The reaction was sealed under N₂ and stirred at 75 °C for 25 h. The solution was poured into a separatory funnel containing EtOAc (200 mL) and H₂O (150 mL). After shaking, the layers were separated. The organic layer was washed with H₂O (2 x 150 mL). The aqueous layer from the initial extraction was back extracted with EtOAc (100 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated *in vacuo*. The resulting residue was dry
loaded onto celite and purified by column chromatography on silica gel (Et₂O:Acetone 100:0 → 3:1) to afford bis-borylated 4.44 as a pale yellow solid (537.6 mg, 44%).

TLC (Et₂O:MeCN 4:1)

R_f = 0.47, stained by KMnO₄

¹H-NMR (500 MHz, d₆-acetone)

δ 5.78 (s, 1H), 4.21 (d, J = 17.0 Hz, 2H), 4.05 (d, J = 17.0 Hz, 2H), 2.97 (s, 3H), 2.01 (s, 3H), 1.25 (s, 12H).

¹³C-NMR (125 MHz, d₆-acetone)

δ 169.1, 83.2, 62.6, 47.0, 25.1, 20.2

¹¹B-NMR (128 MHz, d₆-acetone)

δ 30.0, 11.1

HRMS (ESI+)

Calculated for C₁₄H₂₄B₂NO₆ (M+H)⁺: 324.1790

Found: 324.1788

**MIDA Boronate 4.4.** To a 100 mL round bottom flask containing bis-borylated MIDA boronate 4.44 (537 mg, 1.66 mmol) and a stir bar, was added CH₂Cl₂ (20 mL) followed by neat bromine (0.13 mL, 2.5 mmol). The solution was stirred at 23 °C for 1 h and then concentrated in vacuo to give a yellow solid. This solid was azeotroped with CH₂Cl₂ (3 x 20 mL) to remove residual bromine. To the resulting solid was added finely ground K₃PO₄ (3.68 g, 17.3 mmol) and MeCN (20 mL). The resulting suspension was stirred at 23 °C for 4.5 h. The resulting suspension was poured into 35 mL EtOAc and 30 mL pH 7 phosphate buffer (0.5 M). The mixture was shaken and the aqueous layer was removed. The organic layer was washed with pH 7 phosphate buffer (0.5 M, 1 x 35 mL). The combined aqueous layers were back extracted with 9:1 EtOAc:Acetone (1 x 50 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated in vacuo. The resulting residue was azeotroped with CH₂Cl₂ (2 x 50 mL) and then suspended in
Et₂O (75 mL). This suspension was placed in a sonicator bath for 30 min. The resulting solid was collected by vacuum filtration and rinsed with Et₂O (15 mL) to yield MIDA boronate 4.4 as a tan solid (369.7 mg, 81%).

TLC (Et₂O:MeCN 4:1)

\[ R_f = 0.53, \text{stained by KMnO}_4 \]

\(^1\)H-NMR (500 MHz, d\textsubscript{6}-acetone)

\[ \delta 6.71 (s, 1H), 4.31 (d, J = 17.0 \text{ Hz}, 2H), 4.11 (d, J = 17.0 \text{ Hz}, 2H), 3.19 (s, 3H), 1.83 (d, J = 1.5 \text{ Hz}, 3H). \]

\(^{13}\)C-NMR (125 MHz, d\textsubscript{6}-acetone)

\[ \delta 168.9, 112.0, 64.5, 47.9, 24.4 \]

\(^{11}\)B-NMR (128 MHz, d\textsubscript{6}-acetone)

\[ \delta 11.1 \]

HRMS (ESI+)

Calculated for C\textsubscript{8}H\textsubscript{12}BBrNO\textsubscript{4} (M+H)\textsuperscript{+}: 276.0043

Found: 276.0045

X-ray quality crystals were grown by layering petroleum ether onto a dissolved solution of 4.4 in acetonitrile.

MIDA boronate 4.5. MIDA boronate 4.5 was prepared according to literature precedent.\textsuperscript{4}
Aldehyde 4.46. To a 500 mL round bottom flask charged with a stir bar and allylic alcohol 4.45\(^5\) (10.0 g, 69.3 mmol) was added CH\(_2\)Cl\(_2\) (270 mL). To the stirring solution, at 23 °C was added activated MnO\(_2\) (122.1 g, 1404 mmol). The suspension was stirred vigorously at 23 °C under air for 30 min. The suspension was filtered through celite, rinsing the filter cake with CH\(_2\)Cl\(_2\) (4 x 50 mL then 1 x 100 mL). The filtrate was concentrated in vacuo (the bath was maintained at 23 °C because the product is volatile) to yield aldehyde 4.46 (9.9 g, 99%) as a pale yellow oil. This material was used immediately in the next reaction.

TLC (hexane:EtOAc 4:1)
\[ R_f = 0.66, \text{stained by KMnO}_4 \]

\(^1\)H-NMR (500 MHz, CDCl\(_3\))
\[ \delta 10.12 (d, J = 8.0 \text{ Hz}, 1H), 6.21 (dq, J = 8.0, 2.0 \text{ Hz}, 1H), 2.26 (d, J = 2.0 \text{ Hz}, 3H), 0.15 (s, 9H). \]

\(^13\)C-NMR (125 MHz, CDCl\(_3\))
\[ \delta 190.2, 165.8, 136.5, 15.5, -2.8 \]

HRMS (EI+)
Calculated for C\(_7\)H\(_{14}\)OSi: 142.0814
Found: 142.0814

Alkyne 4.47. To a 500 mL Schlenk flask charged with a stir bar was added TMS diazomethane solution (2.0 M in Et\(_2\)O, 52 mL, 104 mmol). The solution was cooled to -78 °C. To the stirring solution was dropwise added nBuLi solution (2.5 M in hexanes, 36 mL, 90 mmol) over 45 min. After the addition was complete, the solution was stirred at -78 °C for an additional 30 min. A
solution of aldehyde 4.46 (9.9 g, 69.3 mmol) in THF (120 mL) was prepared and dropwise added to the cooled reaction solution over 1 h 15 min. After the addition was complete, the solution was stirred at -78 °C for an additional 1 h then at 0 °C for 30 min. The solution was transferred to a separatory funnel and diluted with saturated aqueous NH₄Cl (200 mL), H₂O (200 mL) and Et₂O (100 mL). After shaking, the layers were separated and the aqueous layer was extracted with Et₂O (2 x 100 mL). The combined organics were dried over MgSO₄, filtered, and concentrated in vacuo (the bath was maintained at 23 °C because the product is volatile) to provide a brown oil. The resulting residue was purified by column chromatography on silica gel (petroleum ether) to afford alkyne 4.47 as a pale orange oil (6.6 g, 69%). This material was used immediately in the next reaction.

TLC (hexane)
\[ R_f = 0.68 \], stained by KMnO₄

¹H-NMR (500 MHz, d₆-acetone)
\[ \delta 5.76 \text{ (s, 1H)}, 3.69 \text{ (s, 1H)}, 1.96 \text{ (s, 3H)}, 0.10 \text{ (s, 9H)} \].

**MIDA boronate 4.48.** To a 300 mL round bottom flask charged with a stir bar and dicyclohexylborane (900 mg, 5.0 mmol), under an inert atmosphere, was added THF (25 mL). The solution was cooled to 0 °C and catecholborane (5.1 mL, 47.6 mmol) was added in one portion. The solution was stirred at 0 °C for an additional 5 min. A solution of alkyne 4.47 (6.58 g, 47.6 mmol) in THF (25 mL) was prepared and dropwise added to the cooled reaction solution over 15 min. The solution was warmed to 23 °C and stirred at this temperature for 4 h. After this time, to the solution was added N-methyliminodiacetic acid (MIDA, 10.5 g, 71.3 mmol) and DMSO (90 mL). The suspension was sealed under N₂ and placed in a 60 °C oil bath with stirring for 16 h. After this time, the solution was cooled to 23 °C and transferred to a separatory funnel and diluted with H₂O (400 mL) and EtOAc:acetone (4:1, 500 mL). After shaking, the layers were separated and the organic layer was washed with brine:H₂O (1:1, 2 x 400 mL). The combined aqueous layers were back extracted with EtOAc:acetone (3:1, 2 x 400 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated in vacuo. The resulting residue
was dry loaded onto celite and purified by column chromatography on silica gel (Et₂O:MeCN 100:0 → 50:50) to afford MIDA boronate 4.48 as a white solid (6.84 g, 49%).

TLC (Et₂O:MeCN 4:1)
R_f = 0.39, stained by KMnO₄

¹H-NMR (500 MHz, d₆-acetone)
δ 7.00 (dd, J = 17.0, 11.0 Hz, 1H), 6.39 (d, J = 11 Hz, 1H), 5.72 (d, J = 17.0 Hz, 1H), 4.22 (d, J = 17.0 Hz, 2H), 4.05 (d, J = 17.0 Hz, 2H), 3.01 (s, 3H), 1.85 (d, J = 2.0 Hz, 3H), 0.09 (s, 9H).

¹³C-NMR (125 MHz, d₆-acetone)
δ 169.0, 140.5, 140.0, 138.3, 62.3, 47.3, 15.2, -2.2

¹¹B-NMR (128 MHz, d₆-acetone)
δ 11.5

HRMS (ESI+)
Calculated for C₁₃H₂₃BNO₄Si (M+H)^+: 296.1489
Found: 296.1486

**MIDA boronate 4.6.** To a 40 mL vial charged with a stir bar and MIDA boronate 4.48 (600 mg, 2.0 mmol) was added MeCN (10 mL). The solution was cooled to 0 °C. To a second 40 mL vial charged with a stir bar and N-iodosuccinimide (NIS, 915 mg, 4.1 mmol) was added MeCN (10 mL). The solution was cooled to 0 °C. The cooled NIS solution was transferred to the cooled reaction solution in one portion. The solution continued to stir at 0 °C for 4 h 30 min. After this time, saturated aq. Na₂S₂O₃ (10 mL) and EtOAc (10 mL) were added to the reaction solution. The reaction solution was warmed to 23 °C with vigorous stirring. The solution was poured into a separatory funnel and diluted with saturated aq. Na₂S₂O₃ (50 mL) and EtOAc (50 mL). After shaking, the layers were separated and the aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated *in vacuo*. The
resulting residue was dry loaded onto celite and purified by column chromatography on silica gel (hexanes:EtOAc 100:0 → 0:100) to afford MIDA boronate 4.6 as a white solid (534 mg, 76%).

TLC (Et₂O:MeCN 4:1)

\[ R_f = 0.53, \text{stained by KMnO}_4 \]

\(^1\text{H-NMR} (500 \text{ MHz, } \text{d}_6-\text{acetone})\]

\[ \delta 6.89 \text{ (d, } J = 11.0 \text{ Hz, } 1\text{H}), \ 6.74 \text{ (dd, } J = 17.0, 11.0 \text{ Hz, } 1\text{H}), \ 5.71 \text{ (d, } J = 17.0 \text{ Hz, } 1\text{H}), \ 4.23 \text{ (d, } J = 17.0 \text{ Hz, } 2\text{H}), \ 4.05 \text{ (d, } J = 17.0 \text{ Hz, } 2\text{H}), \ 3.02 \text{ (s, } 3\text{H}), \ 2.56 \text{ (d, } J = 1.5 \text{ Hz, } 3\text{H}). \]

\(^{13}\text{C-NMR} (125 \text{ MHz, } \text{d}_6-\text{acetone})\]

\[ \delta 169.0, 143.6, 137.3, 99.6, 62.2, 47.4, 28.5 \]

\(^{11}\text{B-NMR} (128 \text{ MHz, } \text{d}_6-\text{acetone})\]

\[ \delta 11.1 \]

HRMS (ESI+)

Calculated for C\(_{10}\)H\(_{14}\)BINO\(_4\) (M+H)

\[ \text{Calculated: } 350.0061 \]

\[ \text{Found: } 350.0070 \]

**MIDA boronate 4.51.** In a glovebox, to a 20 mL vial charged with a stir bar, 1-triethylgermanium-2-tributytin ethylene 4.50 (443 mg, 0.93 mmol) and vinyl iodide 4.49 (200 mg, 0.62 mmol) was added Pd\(_2\)dba\(_3\) (14 mg, 0.016 mmol), Ph\(_3\)As (18.0 mg, 0.059 mmol), DMF (9.3 mL), and THF (3.0 mL). The vial was sealed with a PTFE-lined cap, removed from the glovebox, and placed in a 60 °C heating block and maintained at that temperature with stirring for 15 h. The reaction was cooled to 23 °C and transferred to a separatory funnel, diluted with EtOAc (20 mL) and brine (20 mL). After shaking, the layers were separated. The aqueous layer
was extracted with EtOAc (3 x 20 mL), dried over MgSO\(_4\), filtered and concentrated in vacuo. The resulting residue was dry loaded onto celite and purified by column chromatography on silica gel (1:1 petroleum ether:EtOAc \(\rightarrow\) EtOAc \(\rightarrow\) 9:1 EtOAc:MeCN) to afford MIDA boronate 4.51 as a white solid (205 mg, 86%).

TLC (EtOAc)
\[
R_f = 0.38, \text{stained by KMnO}_4
\]

\(^1\)H-NMR (500 MHz, d\(_6\)-acetone)
\[
\begin{align*}
\delta & 6.61 \text{ (d, } J = 18.5 \text{ Hz, 1H)}, \ 6.04 \text{ (d, } J = 18.5 \text{ Hz, 1H)}, \ 5.42 \text{ (s, 1H)}, \ 4.21 \text{ (d, } J = 17.0 \text{ Hz, 2H)}, \ 4.05 \text{ (d, } J = 17.0 \text{ Hz, 2H)}, \ 3.03 \text{ (s, 3H)}, \ 1.92 \text{ (s, 3H)}, \ 1.03 \text{ (t, } J = 8.0 \text{ Hz, 9H)}, \ 0.88 \text{ (q, } J = 8.0 \text{ Hz, 6H}).
\end{align*}
\]

\(^1\)C-NMR (125 MHz, d\(_6\)-acetone)
\[
\begin{align*}
\delta & 169.1, \ 152.0, \ 149.5, \ 126.5, \ 62.6, \ 47.2, \ 15.1, \ 9.4, \ 5.1
\end{align*}
\]

\(^{11}\)B-NMR (128 MHz, d\(_6\)-acetone)
\[
\begin{align*}
\delta & 10.9
\end{align*}
\]

HRMS (ESI+)
Calculated for C\(_{16}\)H\(_{29}\)BGeNO\(_4\) (M+H): 384.1401
Found: 384.1404

**MIDA boronate 4.7.** To a 250 mL round bottom flask charged with a stir bar and MIDA boronate 4.51 (1.41 g, 3.7 mmol) was added MeCN (70 mL). The solution was cooled to 0 °C. A solution of \(N\)-iodosuccinimide (NIS, 2.49 g, 11.1 mmol) in MeCN (60 mL) was prepared and this solution was added dropwise to the cooled reaction solution over 30 min. After the addition was complete, the mixture was stirred at 0 °C for an additional 2 h. After this time, saturated aqueous Na\(_2\)S\(_2\)O\(_3\) (100 mL) was added to the reaction solution. The reaction solution was warmed to 23 °C with vigorous stirring. The solution was transferred to a separatory funnel and diluted with EtOAc (100 mL). After shaking, the layers were separated and the aqueous layer
was extracted with EtOAc (2 x 100 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated in vacuo. The resulting residue was dry loaded onto celite and purified by column chromatography on silica gel (1:1 petroleum ether:EtOAc → EtOAc) to afford MIDA boronate 4.7 as a white solid (1.07 g, 83%).

TLC (EtOAc)

R_f = 0.38, stained by KMnO₄

H-NMR (500 MHz, d₆-acetone)

δ 7.16 (d, J = 15.0 Hz, 1H), 6.56 (d, J = 15.0 Hz, 1H), 5.42 (s, 1H), 4.24 (d, J = 17.0 Hz, 2H), 4.05 (d, J = 17.0 Hz, 2H), 3.04 (s, 3H), 1.92 (s, 3H).

C-NMR (125 MHz, d₆-acetone)

δ 168.7, 152.8, 148.3, 77.6, 62.2, 46.9, 14.8

B-NMR (128 MHz, d₆-acetone)

δ 10.5

HRMS (ESI+)

Calculated for C₁₀H₁₄BINO₄ (M+H)^+: 350.0061

Found: 350.0066

MIDA boronate 8. MIDA boronate 8 was prepared according to literature precedent.⁴
**Pinacol ester 4.53.** To a 40 mL vial charged with a stir bar and MIDA boronate 4.52 (998 mg, 2.6 mmol) was added solid NaHCO₃ (1.27 g, 15.1 mmol), pinacol (500 mg, 4.2 mmol), and MeOH (13 mL). The suspension was stirred at 45 °C for 3 h. The suspension was cooled to 23 °C and filtered through celite, eluting with acetone. The solution was concentrated *in vacuo* and residual MeOH was azeotropically removed with toluene (1 x 10 mL). To the resulting residue was added solid NaHCO₃ (1.11 g, 13.1 mmol), finely ground CaCl₂ (1.49 g, 13.4 mmol), and toluene (13 mL). The suspension was stirred at 23 °C for 1 h. The suspension was filtered through celite, eluting with acetone. The solution was concentrated *in vacuo* and residual toluene was azeotropically removed with MeCN (3 x 10 mL) to provide pinacol ester 4.53 as a clear, colorless oil (920.5 mg, 99%) that was used immediately in the next reaction.

**1H-NMR (500 MHz, d6-acetone)**

δ 6.95 (dd, J = 18.0, 11.0 Hz, 1H), 6.73 (d, J = 11.0 Hz, 1H), 6.24 (d, J = 18.0 Hz, 1H), 1.80 (d, J = 1.5 Hz, 3H), 1.25 (s, 12H), 1.05 (t, J = 8.0 Hz, 9H), 0.85 (q, J = 8.0 Hz, 6H).

**13C-NMR (125 MHz, d6-acetone)**

δ 144.9, 140.6, 136.5, 83.9, 25.1, 14.4, 9.2, 4.8

**11B-NMR (128 MHz, d6-acetone)**

δ 31.1

HRMS (EI+)

Calculated for C₁₇H₃₃BGeO₂: 354.1786

Found: 354.1790
**MIDA boronate 4.54.** In a glovebox, to a 40 mL vial charged with a stir bar, pinacol ester 4.53 (920 mg, 2.6 mmol), and MIDA boronate 4.1 (559 mg, 2.1 mmol) was added 2\textsuperscript{nd} generation XPhosPd cycle (170 mg, 0.22 mmol), Cs\textsubscript{2}CO\textsubscript{3} (2.5 g, 7.7 mmol), and DMSO (15 mL). The vial was capped, removed from the glovebox, and stirred at 45 °C for 14.5 h. After this time, the solution was cooled to 23 °C and poured into a separatory funnel. The solution was diluted with H\textsubscript{2}O:brine (1:1, 60 mL) and EtOAc (60 mL). After shaking, the layers were separated, and the aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with H\textsubscript{2}O:brine (1:1, 1 x 50 mL). The organic layer was dried over MgSO\textsubscript{4}, filtered, and concentrated in vacuo. The resulting residue was dry loaded onto celite and purified by reverse phase column chromatography on C18 silica gel (H\textsubscript{2}O:MeCN 90:10 → 0:100) to afford MIDA boronate 4.54 as a pale yellow solid (402 mg, 46%).

TLC (Et\textsubscript{2}O:MeCN 6:1)

\( R_f = 0.30 \), stained by KMnO\textsubscript{4}

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

\( \delta \) 6.94 (dd, \( J = 18.0, 11.0 \text{ Hz, 1H} \)), 6.23 (d, \( J = 18.0 \text{ Hz, 1H} \)), 6.17 (d, \( J = 11.0 \text{ Hz, 1H} \)), 6.16 (d, \( J = 18.0 \text{ Hz, 1H} \)), 5.79 (d, \( J = 18.0 \text{ Hz, 1H} \)), 4.22 (d, \( J = 17.0 \text{ Hz, 2H} \)), 4.04 (d, \( J = 17.0 \text{ Hz, 2H} \)), 3.01 (s, 3H), 1.92 (d, \( J = 1.0 \text{ Hz, 3H} \)), 1.05 (t, \( J = 8.0 \text{ Hz, 9H} \)), 0.85 (q, \( J = 8.0 \text{ Hz, 6H} \)).

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

\( \delta \) 169.2, 147.3, 141.1, 136.0, 135.0, 134.3, 62.1, 47.2, 12.6, 9.1, 4.8

\(^{11}\text{B}-\text{NMR} (128 \text{ MHz, d}_6\text{-acetone})\)

\( \delta \) 11.7

HRMS (ESI+)

Calculated for C\textsubscript{18}H\textsubscript{31}BGeNO\textsubscript{4} (M+H): 410.1558

Found: 410.1557
MIDA boronate 4.9. To a 40 mL vial charged with a stir bar and MIDA boronate 4.54 (400 mg, 0.98 mmol) was added MeCN (10 mL). The solution was cooled to 0 °C. To a second 40 mL vial charged with a stir bar and N-bromosuccinimide (NBS, 265 mg, 1.5 mmol) was added MeCN (10 mL). The solution was cooled to 0 °C. The cooled NBS solution was dropwise transferred to the cooled reaction solution. The solution continued to stir at 0 °C for 1 h. After this time, saturated aq. Na$_2$S$_2$O$_3$ (8 mL) and EtOAc (8 mL) were added to the reaction solution. The reaction solution was warmed to 23 °C with vigorous stirring. The solution was poured into a separatory funnel and diluted with saturated aq. Na$_2$S$_2$O$_3$·H$_2$O (1:1, 30 mL) and EtOAc (30 mL). After shaking, the layers were separated and the aqueous layer was extracted with EtOAc (30 mL). The combined organic layers were dried over MgSO$_4$, filtered and concentrated in vacuo. The resulting residue was dry loaded onto celite and purified by reverse phase column chromatography on C18 silica gel (H$_2$O:MeCN 95:5 → 0:100) to afford MIDA boronate 4.9 as a pale yellow solid (238 mg, 74%).

TLC (Et$_2$O:MeCN 6:1)  
R$_f$ = 0.30, stained by KMnO$_4$

$^1$H-NMR (500 MHz, d$_6$-acetone)  
δ 7.16 (dd, $J$ = 13.0, 11.0 Hz, 1H), 6.63 (d, $J$ = 13.0 Hz, 1H), 6.60 (d, $J$ = 18.0 Hz, 1H), 6.16 (d, $J$ = 11.0 Hz, 1H), 5.89 (d, $J$ = 18.0 Hz, 1H), 4.23 (d, $J$ = 17.0 Hz, 2H), 4.05 (d, $J$ = 17.0 Hz, 2H), 3.01 (s, 3H), 1.89 (d, $J$ = 1.0 Hz, 3H).

$^{13}$C-NMR (125 MHz, d$_6$-acetone)  
δ 169.1, 146.5, 137.9, 135.2, 129.5, 110.5, 62.2, 47.3, 12.6

$^{11}$B-NMR (128 MHz, d$_6$-acetone)  
δ 11.5

HRMS (ESI+)
Calculated for C$_{12}$H$_{15}$BBrNaNO$_4$ (M+Na)$^+$: 350.0175  
Found: 350.0180
MIDA boronate 4.55. In a glovebox, to a 500 mL Schlenk flask charged with a stir bar and MIDA boronate 4.1 (15.3 g, 58.3 mmol) was added Pd₂dba₃ (2.7 g, 2.9 mmol) and Ph₃As (1.8 g, 5.8 mmol). The flask was sealed, removed from the glovebox, and placed under a N₂ atmosphere. THF (300 mL) was added to the reaction flask, followed by stannane 4.56⁹ (30.6 g, 75.8 mmol). The solution was stirred at 50 °C for 13.5 h. After this time, the reaction solution was cooled to 23 °C and filtered through a pad of celite/silica, rinsing the filter cake with acetone. The filtrate was concentrated in vacuo and the resulting residue was dry loaded onto celite and purified by column chromatography on silica gel (Et₂O:MeCN 100:0 → 6:1 → 5:1 → 3:1) to afford MIDA boronate 4.55. This material was dissolved in acetone and the product was precipitated by addition of Et₂O. The material was collected by vacuum filtration to provide MIDA boronate 4.55 as a white solid (5.23 g, 30%).

TLC (Et₂O:MeCN 4:1)

R<sub>f</sub> = 0.64, stained by KMnO₄

<sup>1</sup>H-NMR (500 MHz, d₆-acetone)

δ 6.60 (d, J = 18.0 Hz, 1H), 5.71 (d, J = 18.0 Hz, 1H), 5.59 (s, 1H), 4.22 (d, J = 17.0 Hz, 2H), 4.05 (d, J = 17.0 Hz, 2H), 3.01 (s, 3H), 1.94 (s, 3H), 0.14 (s, 9H).

<sup>13</sup>C-NMR (125 MHz, d₆-acetone)

δ 169.1, 149.3, 133.0, 62.3, 47.3, 17.5, 2.0, 0.0

<sup>11</sup>B-NMR (128 MHz, d₆-acetone)

δ 11.6
Pinacol ester 4.57. To a 20 mL vial charged with a stir bar and MIDA boronate 4.55 (120 mg, 0.41 mmol) was added solid NaHCO$_3$ (171 mg, 2.0 mmol), pinacol (72 mg, 0.6 mmol), and MeOH (4 mL). The suspension was stirred at 45 °C for 3 h. The suspension was cooled to 23 °C and filtered through celite, eluting with acetone. The solution was concentrated in vacuo and residual MeOH was azeotropically removed with toluene (1 x 5 mL). To the resulting residue was added solid NaHCO$_3$ (172 mg, 2.0 mmol), finely ground CaCl$_2$ (225 mg, 2.0 mmol), and toluene (4 mL). The suspension was stirred at 23 °C for 1 h. The suspension was filtered through celite, eluting with acetone. The solution was concentrated in vacuo and residual toluene was azeotropically removed with MeCN (3 x 10 mL) to provide pinacol ester 4.57 as a clear, colorless oil (107 mg, 99%) that was used immediately in the next reaction.

$^1$H-NMR (400 MHz, d$_6$-acetone)
\[
\delta 6.98 (d, J = 18.0 \text{ Hz}, 1\text{H}), 5.76 (s, 1\text{H}), 5.49 (d, J = 18.0 \text{ Hz}, 1\text{H}), 1.92 (s, 3\text{H}), 1.24 (s, 12\text{H}), 0.15 (s, 9\text{H}).
\]

$^{13}$C-NMR (100 MHz, d$_6$-acetone)
\[
\delta 156.2, 151.6, 136.7, 83.7, 25.1, 17.0, -0.2
\]

$^{11}$B-NMR (128 MHz, d$_6$-acetone)
\[
\delta 30.8
\]

HRMS (ESI+)
Calculated for C$_{13}$H$_{23}$BNO$_4$Si (M+H)$^+$: 296.1489
Found: 296.1488

MIDA boronate 4.58. In a glovebox, to a 20 mL vial charged with a stir bar, pinacol ester 4.57 (134 mg, 0.5 mmol), and MIDA boronate 4.3 (116 mg, 0.42 mmol) was added 2$^{nd}$ generation
XPhosPd cycle (33 mg, 0.04 mmol), Cs₂CO₃ (547 mg, 1.7 mmol), and DMSO (8 mL). The vial was capped, removed from the glovebox, and stirred at 40 °C for 14 h. After this time, the solution was cooled to 23 °C and poured into a separatory funnel. The solution was diluted with H₂O:brine (1:1, 20 mL) and EtOAc (20 mL). After shaking, the layers were separated, and the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with H₂O:brine (1:1, 1 x 20 mL). The organic layer was dried over MgSO₄, filtered, and concentrated in vacuo. The resulting residue was dry loaded onto celite and purified by column chromatography on florisil (hexanes:EtOAc 95:5 → 0:100) to afford MIDA boronate 4.58 as a pale yellow solid (102 mg, 73%).

TLC (Et₂O:MeCN 4:1)

Rf = 0.63, stained by KMnO₄

^1^H-NMR (400 MHz, d₆-acetone)

δ 6.67 (dd, J = 15.5, 11.0 Hz, 1H), 6.45 (d, J = 11.0 Hz, 1H), 6.34 (d, J = 15.5 Hz, 1H), 5.61 (s, 1H), 4.23 (d, J = 17.0 Hz, 2H), 4.06 (d, J = 17.0 Hz, 2H), 2.97 (s, 3H), 1.98 (s, 3H), 1.83 (d, J = 1.0 Hz, 3H), 0.14 (s, 9H).

^1^C-NMR (100 MHz, d₆-acetone)

δ 169.2, 151.4, 140.6, 137.2, 133.1, 125.4, 62.6, 47.1, 17.9, 15.3, 0.1

^1^B-NMR (128 MHz, d₆-acetone)

δ 11.6

HRMS (ESI+)

Calculated for C₁₆H₂₇BNO₄Si (M+H)^+: 336.1802

Found: 336.1813

**MIDA boronate 4.10.** To a 40 mL vial charged with a stir bar and MIDA boronate 4.58 (102 mg, 0.3 mmol) was added EtCN (4 mL). The solution was cooled to -78 °C. To a second 40 mL vial charged with a stir bar and N-iodosuccinimide (NIS, 137 mg, 0.6 mmol) was added EtCN (4
mL). The solution was cooled to -78 °C. The cooled NIS solution was dropwise transferred to the cooled reaction solution. The solution continued to stir at -78 °C for 5 h 30 min. After this time, saturated aq. Na₂S₂O₃ (10 mL) and EtOAc (10 mL) were added to the reaction solution. The reaction solution was warmed to 23 °C with vigorous stirring. The solution was poured into a separatory funnel and diluted with saturated aq. Na₂S₂O₃ (10 mL) and EtOAc (10 mL). After shaking, the layers were separated and the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated in vacuo. The resulting residue was dry loaded onto celite and purified by reverse phase column chromatography on C18 silica gel (H₂O:MeCN 95:5 → 0:100) to afford MIDA boronate 4.10 as a pale yellow solid (99 mg, 83%).

TLC (Et₂O:MeCN 4:1)
Rₛ = 0.47, stained by KMnO₄

¹H-NMR (500 MHz, d₆-acetone)
δ 6.78 (dd, J = 15.0, 11.0 Hz, 1H), 6.57 (s, 1H), 6.47 (d, J = 15.0 Hz, 1H), 6.42 (d, J = 11.0 Hz, 1H), 4.23 (d, J = 17.0 Hz, 2H), 4.06 (d, J = 17.0 Hz, 2H), 2.97 (s, 3H), 2.03 (d, J = 1.0 Hz, 3H), 1.82 (d, J = 1.0 Hz, 3H).

¹³C-NMR (125 MHz, d₆-acetone)
δ 169.1, 146.5, 136.8, 134.7, 126.3, 84.5, 62.6, 47.1, 20.1, 15.4

¹¹B-NMR (128 MHz, d₆-acetone)
δ 11.6

HRMS (ESI+)
Calculated for C₁₃H₁₈BINO₄ (M+H)⁺: 390.0374
Found: 390.0381
Pinacol ester 4.59. To a 40 mL vial charged with a stir bar and MIDA boronate 4.48 (1.4 g, 4.7 mmol) was added solid NaHCO₃ (2.0 g, 23.7 mmol), pinacol (841 mg, 7.1 mmol), and MeOH (24 mL). The suspension was stirred at 45 °C for 3 h. The suspension was cooled to 23 °C and filtered through celite, eluting with acetone. The solution was concentrated in vacuo and residual MeOH was azeotropically removed with toluene (1 x 10 mL). To the resulting residue was added solid NaHCO₃ (2.0 g, 23.7 mmol), finely ground CaCl₂ (2.6 g, 23.7 mmol), and toluene (24 mL). The suspension was stirred at 23 °C for 1 h. The suspension was filtered through celite, eluting with acetone. The solution was concentrated in vacuo and residual toluene was azeotropically removed with MeCN (3 x 10 mL) to provide pinacol ester 4.59 as a clear, colorless oil (1.22 g, 97%) that was used immediately in the next reaction.

¹H-NMR (500 MHz, d₆-acetone)
δ 7.37 (dd, J = 18.0, 11.0 Hz, 1H), 6.40 (d, J = 11.0 Hz, 1H), 5.53 (d, J = 18.0 Hz, 1H), 1.91 (d, J = 1.5 Hz, 3H), 1.25 (s, 12H), 0.10 (s, 9H).

¹³C-NMR (125 MHz, d₆-acetone)
δ 145.1, 144.9, 139.5, 83.7, 25.1, 15.5, -2.3

¹¹B-NMR (128 MHz, d₆-acetone)
δ 30.7

HRMS (ESI+)
Calculated for C₁₄H₂₈BO₂Si (M+H)^+: 267.1952
Found: 267.1964
MIDA boronate 4.60. In a glovebox, to a 40 mL vial charged with a stir bar, pinacol ester 4.59 (532 mg, 2.0 mmol), and MIDA boronate 4.3 (459 mg, 1.7 mmol) was added 2nd generation XPhosPd cycle (65.5 mg, 0.08 mmol), Cs₂CO₃ (2.2 g, 6.7 mmol), and DMSO (30 mL). The vial was capped, removed from the glovebox, and stirred at 35 °C for 14 h. After this time, the solution was cooled to 23 °C and poured into a separatory funnel. The solution was diluted with H₂O:brine (1:1, 100 mL) and EtOAc (100 mL). After shaking, the layers were separated, and the aqueous layer was extracted with EtOAc (100 mL). The combined organic layers were washed with H₂O:brine (1:1, 100 mL). The organic layer was dried over MgSO₄, filtered, and concentrated in vacuo. The resulting residue was dry loaded onto celite and purified by column chromatography on florisil (hexanes:EtOAc 90:10 → 0:100) to afford MIDA boronate 4.60 as a pale yellow solid (459 mg, 82%).

TLC (Et₂O:MeCN 6:1)
Rₓ = 0.39, stained by KMnO₄

¹H-NMR (400 MHz, d₆-acetone)
δ 6.70-6.62 (m, 2H), 6.52-6.42 (m, 2H), 4.22 (d, J = 17.0 Hz, 2H), 4.04 (d, J = 17.0 Hz, 2H), 2.96 (s, 3H), 1.86 (d, J = 1.0 Hz, 3H), 1.81 (d, J = 1.0 Hz, 3H), 0.08 (s, 9H).

¹³C-NMR (125 MHz, d₆-acetone)
δ 169.2, 140.8, 138.3, 137.5, 130.4, 129.9, 62.7, 47.1, 15.3, 15.2, -2.1

¹¹B-NMR (128 MHz, d₆-acetone)
δ 11.7

HRMS (ESI+)
Calculated for C₁₆H₂₇BNO₄Si (M+H)+: 336.1802
Found: 336.1805

MIDA boronate 4.11. To a 40 mL vial charged with a stir bar and MIDA boronate 4.60 (500 mg, 1.5 mmol) was added EtCN (7.5 mL). The solution was cooled to -78 °C. To a second 40
mL vial charged with a stir bar and N-iodosuccinimide (NIS, 670 mg, 3.0 mmol) was added EtCN (7.5 mL). The solution was cooled to -78 °C. The cooled NIS solution was dropwise transferred to the cooled reaction solution. The solution continued to stir at -78 °C for 6 h. After this time, the solution was poured into a separatory funnel and diluted with saturated aq. Na2S2O3 (50 mL) and EtOAc (50 mL). After shaking, the layers were separated and the organic layer was washed with saturated aq. Na2S2O3 (50 mL). The combined aqueous layers were extracted with EtOAc (50 mL). The combined organic layers were dried over MgSO4, filtered and concentrated in vacuo. The resulting residue was dry loaded onto celite and purified by column chromatography on silica gel (hexanes:EtOAc 90:10 → 0:100) to afford MIDA boronate 4.11 as a pale yellow solid (456 mg, 79%).

TLC (Et2O:MeCN 4:1)
Rf = 0.47, stained by KMnO4

1H-NMR (500 MHz, d6-acetone)
δ 6.92 (d, J = 11.0 Hz, 1H), 6.69 (dd, J = 15.0, 11.0 Hz, 1H), 6.48 (dd, J = 15.0, 11.0 Hz, 1H), 6.45 (d, J = 11.0 Hz, 1H), 4.23 (d, J = 17.0 Hz, 2H), 4.06 (d, J = 17.0 Hz, 2H), 2.97 (s, 3H), 2.57 (s, 3H), 1.80 (s, 3H).

13C-NMR (125 MHz, d6-acetone)
δ 169.1, 142.1, 136.7, 130.3, 128.9, 97.7, 62.7, 47.1, 28.4, 15.4

11B-NMR (128 MHz, d6-acetone)
δ 11.8

HRMS (ESI+)
Calculated for C13H18BINO4 (M+H)+: 390.0374
Found: 390.0374
**MIDA boronate 4.61.** In a glovebox, to a 40 mL vial charged with a stir bar, 1-triethylgermanium-2-tributytin ethylene 4.50 (850 mg, 1.8 mmol) and vinyl iodide 4.6 (480 mg, 1.4 mmol) was added PdCl$_2$(MeCN)$_2$ (18 mg, 0.07 mmol), DMF (10.5 mL), and THF (3.5 mL). The vial was sealed with a PTFE-lined cap, removed from the glovebox, and placed in a 45 °C heating block and maintained at that temperature with stirring for 4 h 30 min. The reaction was cooled to 23 °C and concentrated *in vacuo*, azeotropically removing residual DMF with toluene (3 x 30 mL). The resulting residue was dry loaded onto celite and purified by column chromatography on florisil (Et$_2$O:MeCN 100:0 → 60:40) to afford MIDA boronate 4.61 as a pale yellow solid (280 mg, 50%).

**TLC (Et$_2$O:MeCN 6:1)**
R$_f$ = 0.33, stained by KMnO$_4$

**$^1$H-NMR (500 MHz, d$_6$-acetone)**
δ 6.98 (dd, $J = 17.0$, 11.0 Hz, 1H), 6.59 (d, $J = 18.5$ Hz, 1H), 6.18 (d, $J = 11.0$ Hz, 1H), 6.11 (d, $J = 18.5$ Hz, 1H), 5.78 (d, $J = 17.0$ Hz, 1H), 4.21 (d, $J = 17.0$ Hz, 2H), 4.02 (d, $J = 17.0$ Hz, 2H), 2.98 (s, 3H), 1.89 (s, 3H), 1.04 (t, $J = 8.0$ Hz, 9H), 0.83 (q, $J = 8.0$ Hz, 6H).

**$^{13}$C-NMR (125 MHz, d$_6$-acetone)**
δ 169.1, 148.9, 139.2, 137.1, 134.3, 127.2, 62.1, 47.3, 12.3, 9.1, 4.7

**$^{11}$B-NMR (128 MHz, d$_6$-acetone)**
δ 11.1

**HRMS (ESI+)**
Calculated for C$_{18}$H$_{31}$BGeNO$_4$ (M+H)$^+$: 410.1558
Found: 410.1560
MIDA boronate 4.12. To a 40 mL vial charged with a stir bar and MIDA boronate 4.61 (280 mg, 0.69 mmol) was added EtCN (7 mL). The solution was cooled to -78 °C. To a second 40 mL vial charged with a stir bar and N-iodosuccinimide (NIS, 310 mg, 1.4 mmol) was added EtCN (7 mL). The solution was cooled to -78 °C. The cooled NIS solution was dropwise transferred to the cooled reaction solution. The solution continued to stir at -78 °C for 3 h. After this time, saturated aq. Na₂S₂O₃ (8 mL) and EtOAc (8 mL) were added to the reaction solution. The reaction solution was warmed to 23 °C with vigorous stirring. The solution was poured into a separatory funnel and diluted with saturated aq. Na₂S₂O₃:H₂O (1:1, 30 mL) and EtOAc (30 mL). After shaking, the layers were separated and the aqueous layer was extracted with EtOAc (30 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated in vacuo. The resulting residue triturated with Et₂O (2 x 10 mL) to afford MIDA boronate 4.12 as a pale yellow solid (231.3 mg, 90%).

¹H-NMR (500 MHz, d₆-acetone)
δ 7.15 (d, J = 15.0 Hz, 1H), 6.94 (dd, J = 17.0, 11.0 Hz, 1H), 6.56 (d, J = 15.0 Hz, 1H), 6.20 (d, J = 11.0 Hz, 1H), 5.88 (d, J = 17.0 Hz, 1H), 4.23 (d, J = 17.0 Hz, 2H), 4.05 (d, J = 17.0 Hz, 2H), 3.01 (s, 3H), 1.90 (s, 3H).

¹³C-NMR (125 MHz, d₆-acetone)
δ 169.0, 138.3, 137.3, 136.5, 134.9, 77.0, 62.3, 47.4, 12.2

¹¹B-NMR (128 MHz, d₆-acetone)
δ 11.2

HRMS (ESI+)
Calculated for C₁₂H₁₆BINO₄ (M+H)⁺: 376.0217
Found: 376.0220
**General deprotection condition.** To a vial charged with a stir bar and MIDA boronate (1.0 eq.) was added solid NaHCO₃ (5.0 eq.), pinacol (1.5 eq.), and MeOH (0.2 M). The suspension was stirred at 45 °C for 3 h. The suspension was cooled to 23 °C and filtered through celite, eluting with acetone. The solution was concentrated *in vacuo* and residual MeOH was azeotropically removed with toluene. To the resulting residue was added solid NaHCO₃ (5.0 eq.), finely ground CaCl₂ (5.0 eq.), and toluene (0.2 M). The suspension was stirred at 23 °C for 1 h. The suspension was filtered through celite, eluting with acetone. The solution was concentrated *in vacuo* and residual toluene was azeotropically removed with MeCN to provide the pinacol ester, which was used immediately in the next reaction.

**General pinacol ester cross-coupling reaction condition.** In a glovebox, to a vial charged with a stir bar, pinacol ester (1.1-1.3 eq.), and MIDA boronate (1.0 eq.) was added 2nd generation XPhosPd cycle (10 mol %), anhydrous Cs₂CO₃ (4.0 eq.), and DMSO (0.05 M). The vial was capped, removed from the glovebox, and stirred at 35 °C for 12-16 h. After this time, the solution was cooled to 23 °C and poured into a separatory funnel. The solution was diluted with H₂O:brine (1:1, at least 3 times the volume of DMSO used in the reaction) and EtOAc (equal volume to H₂O:brine). After shaking, the layers were separated, and the aqueous layer was extracted with EtOAc (same volume as above). The combined organic layers were washed with H₂O:brine (1:1, same volume as above). The organic layer was dried over MgSO₄, filtered, and concentrated *in vacuo*. The resulting residue was dry loaded onto celite and purified by column chromatography on silica, florisil, or C18 silica to afford the MIDA boronate.

**General MIDA boronate cross-coupling reaction condition.** In a glovebox, to a vial charged with a stir bar, MIDA boronate (1.0 eq.) and halide (1.5 eq) was added 2nd generation XPhosPd cycle (10 mol %), finely ground NaOH (7.5 eq.), and THF (0.05 M total concentration, 5:1
THF:H₂O, see below for water). The vial was capped with a septum cap, removed from the glovebox, and degassed H₂O (5:1 THF:H₂O) was added in one portion. The solution was stirred at 23 °C for 1-4 h. The reaction solution was diluted with Et₂O and H₂O. After shaking, the aqueous layer was removed and extracted with Et₂O (2 times). The combined organic layers were dried over MgSO₄, filtered, and concentrated \textit{in vacuo}. The resulting residue was dry loaded onto celite and purified by column chromatography on florisil or C18 silica to afford the polyene product.

Pinacol ester 4.62. Following the general deprotection condition, MIDA boronate 4.37\(^{10}\) (1.5 g, 5.7 mmol), NaHCO₃ (2.4 g, 28.3 mmol), pinacol (1.0 g, 8.5 mmol), and MeOH (28 mL) were stirred at 45 °C for 3 h. After filtration and concentration, to the residue was added NaHCO₃ (2.4 g, 28.3 mmol), CaCl₂ (3.1 g, 28.3 mmol), and toluene (28 mL). After stirring at 23 °C for 1 h, filtering, and concentrating, pinacol ester 4.62 was obtained as a clear, colorless oil (1.3 g, 95%). Characterization was consistent with literature precedent.\(^{11}\)

MIDA boronate 4.63. In a glovebox, to a 20 mL vial charged with boronic acid 4.63 (103.9 mg, 0.67 mmol) was added MIDA boronate 4.1 (135.9 mg, 0.52 mmol), Pd(OAc)₂ (5.7 mg, 0.025 mmol), XPhos (26.3 mg, 0.055 mmol), anhydrous Cs₂CO₃ (543.8 mg, 1.7 mmol) and THF (10.4 mL). The vial was sealed with a cap and removed from the glovebox. The solution was stirred in a subdued light environment at 45 °C for 19 hr. The reaction mixture was filtered through a pad of Celite, concentrated \textit{in vacuo}, dry loaded onto Celite from an acetone solution, and purified via flash chromatography on silica (Et₂O:acetone 100:0 \(\rightarrow\) 80:20) to afford MIDA boronate 4.64 as a white solid (69.1 mg, 46%).
TLC (Et$_2$O:MeCN 4:1)  
R$_f$ = 0.51, stained by KMnO$_4$

$^1$H-NMR (400 MHz, d$_6$-acetone)  
$\delta$ 6.52 (dd, $J = 17.4$, 10.0 Hz, 1H), 6.09 (dd, $J = 15.0$, 10.0 Hz, 1H), 5.70 (dd, $J = 15.0$, 7.0 Hz, 1H), 5.53 (d, $J = 17.4$ Hz, 1H), 4.17 (d, $J = 17.0$ Hz, 2H), 3.99 (d, $J = 17.0$ Hz, 2H), 2.98 (s, 3H), 2.01 (m, 1H), 1.77-1.57 (m, 5H), 1.36-1.03 (m, 5H).

$^{13}$C-NMR (100 MHz, d$_6$-acetone)  
$\delta$ 169.1, 143.9, 142.0, 130.9, 62.1, 47.2, 41.4, 33.4, 26.7, 26.5

$^{11}$B-NMR (128 MHz, d$_6$-acetone)  
$\delta$ 11.4

HRMS (ESI+)
Calculated for C$_{15}$H$_{23}$BNO$_4$ (M+H)$^+$: 292.1720
Found: 292.1718

MIDA boronate #. In a glovebox, to a 20 mL vial charged with boronic acid 4.63 (97.8 mg, 0.64 mmol) was added MIDA boronate 4.2 (130.1 mg, 0.50 mmol), Pd(OAc)$_2$ (8.7 mg, 0.039 mmol), XPhos (28.8 mg, 0.060 mmol), anhydrous Cs$_2$CO$_3$ (493.2 mg, 1.5 mmol) and THF (6.7 mL). The vial was sealed with a cap and removed from the glovebox. The solution was stirred in a subdued light environment at 35 °C for 20.5 hr. The reaction mixture was filtered through a pad of Celite, concentrated in vacuo, dry loaded onto Celite from an acetone solution, and purified via flash chromatography on silica (Et$_2$O:acetone 100:0 → 80:20) to afford MIDA boronate 4.65 as a pale yellow solid (81.2 mg, 56%).
TLC (Et<sub>2</sub>O:MeCN 4:1)

R<sub>f</sub> = 0.57, stained by KMnO<sub>4</sub>

<sup>1</sup>H-NMR (500 MHz, d<sub>6</sub>-acetone)

δ 6.68-6.56 (m, 2H), 5.66 (dd, J = 14.5, 7.0 Hz, 1H), 5.25 (d, J = 13.0 Hz, 1H), 4.20 (d, J = 17.0 Hz, 2H), 4.00 (d, J = 17.0 Hz, 2H), 3.01 (s, 3H), 2.02 (m, 1H), 1.77-1.58 (m, 5H), 1.37-1.02 (m, 5H).

<sup>13</sup>C-NMR (125 MHz, d<sub>6</sub>-acetone)

δ 168.9, 145.1, 144.0, 127.9, 62.3, 47.2, 41.6, 33.4, 26.7, 26.6

<sup>11</sup>B-NMR (128 MHz, d<sub>6</sub>-acetone)

δ 11.2

HRMS (ESI+)

Calculated for C<sub>15</sub>H<sub>23</sub>BNO<sub>4</sub> (M+H): 292.1720

Found: 292.1720

**MIDA boronate #.** In a glovebox, to a 20 mL vial charged with boronic acid 4.63 (100.1 mg, 0.65 mmol) was added MIDA boronate 4.3 (143.0 mg, 0.52 mmol), Pd(OAc)<sub>2</sub> (5.7 mg, 0.025 mmol), XPhos (24.8 mg, 0.052 mmol), anhydrous Cs<sub>2</sub>CO<sub>3</sub> (509.2 mg, 1.6 mmol) and THF (6.7 mL). The vial was sealed with a cap and removed from the glovebox. The solution was stirred in a subdued light environment at 45 °C for 21 hr. The reaction mixture was filtered through a pad of Celite, concentrated in vacuo, dry loaded onto Celite from an acetone solution, and purified via flash chromatography on silica (Et<sub>2</sub>O:acetone 100:0 → 80:20) to afford MIDA boronate 4.66 as a white solid (108.2 mg, 68%).

TLC (Et<sub>2</sub>O:MeCN 4:1)

R<sub>f</sub> =0.46, stained by KMnO<sub>4</sub>
\(^1\)H-NMR (500 MHz, d\(_6\)-acetone)
\[
\delta 6.42 (ddd, J = 15.0, 11.0, 1.0 Hz, 1H), 6.32 (dd, J = 11.0, 1.5 Hz, 1H), 5.68 (dd, J = 15.0, 7.0 Hz, 1H), 4.19 (d, J = 17.0 Hz, 2H), 4.02 (d, J = 17.0 Hz, 2H), 2.96 (s, 3H), 2.07 (m, 1H), 1.76 (d, J = 1.5 Hz, 3H), 1.75-1.61 (m, 5H), 1.36-1.06 (m, 5H).
\]
\(^13\)C-NMR (125 MHz, d\(_6\)-acetone)
\[
\delta 169.2, 142.2, 137.6, 124.9, 62.6, 47.0, 41.8, 33.6, 26.7, 26.5, 15.0
\]
\(^11\)B-NMR (128 MHz, d\(_6\)-acetone)
\[
\delta 11.8
\]
HRMS (ESI+)
Calculated for C\(_{16}\)H\(_{24}\)BNO\(_4\)Na (M+Na): 328.1696
Found: 328.1704

**MIDA boronate #**. In a glovebox, to a 20 mL vial charged with boronic acid 4.63 (105.2 mg, 0.68 mmol) was added MIDA boronate 4.4 (135.1 mg, 0.49 mmol), Pd(OAc)\(_2\) (5.8 mg, 0.026 mmol), XPhos (23.8 mg, 0.050 mmol), anhydrous Cs\(_2\)CO\(_3\) (488.7 mg, 1.5 mmol) and THF (6.7 mL). The vial was sealed with a cap and removed from the glovebox. The solution was stirred in a subdued light environment at 45 °C for 21 hr. The reaction mixture was filtered through a pad of Celite, concentrated \textit{in vacuo}, dry loaded onto Celite from an acetone solution, and purified via flash chromatography on silica (Et\(_2\)O:acetone 100:0 → 80:20) to afford MIDA boronate 4.67 as a white solid (43.3 mg, 29%).

TLC (Et\(_2\)O:MeCN 4:1)
\[
R_f = 0.58, \text{ stained by KMnO}_4
\]
$^1$H-NMR (500 MHz, d$_6$-acetone)
\[ \delta \ 6.55-6.47 \ (m, 2H), \ 5.56 \ (dd, J = 14.0, 7.0 \ Hz, 1H), \ 4.24 \ (d, J = 17.0 \ Hz, 2H), \ 4.03 \ (d, J = 17.0 \ Hz, 2H), \ 2.96 \ (s, 3H), \ 1.98 \ (m, 1H), \ 1.76 \ (s, 3H), \ 1.73-1.59 \ (m, 5H), \ 1.34-1.01 \ (m, 5H). \]

$^{13}$C-NMR (125 MHz, d$_6$-acetone)
\[ \delta \ 169.0, \ 142.2, \ 142.1, \ 127.3, \ 63.0, \ 47.3, \ 41.6, \ 33.6, \ 26.8, \ 26.6, \ 24.7 \]

$^{11}$B-NMR (128 MHz, d$_6$-acetone)
\[ \delta \ 11.6 \]

HRMS (ESI+)
Calculated for C$_{16}$H$_{24}$BNO$_4$Na(M+Na)$^+$: 328.1696
Found: 328.1694

**MIDA boronate 4.68.** Following the general pinacol ester cross-coupling condition, pinacol ester 4.62 (135 mg, 0.57 mmol), MIDA boronate 4.5 (135 mg, 0.40 mmol), 2$^{\text{nd}}$ generation XPhosPd cycle (35 mg, 0.05 mmol), Cs$_2$CO$_3$ (580 mg, 1.8 mmol), and DMSO (9 mL) were combined and stirred at 35 °C for 15 h, the reaction was worked up using H$_2$O:brine (1:1, 30 mL) and EtOAc (30 mL). After drying, filtering, and concentrating, the residue was dry loaded onto celite and purified by column chromatography on florisil (Et$_2$O:MeCN 100:0 \rightarrow 60:40) to afford MIDA boronate 4.68 as a pale yellow solid (99.2 mg, 78%).

TLC (Et$_2$O:MeCN 6:1)
\[ R_f = 0.49, \text{stained by KMnO}_4 \]
$^1$H-NMR (500 MHz, d$_6$-acetone)  
$\delta$ 6.59 (dd, $J = 17.0, 10.0$ Hz, 1H), 6.27 (dd, $J = 15.0, 10.0$ Hz, 1H), 6.21 (dd, $J = 15.0, 10.0$ Hz, 1H), 6.09 (dd, $J = 15.0, 10.0$ Hz, 1H), 5.73 (dd, $J = 15.0, 7.0$ Hz, 1H), 5.65 (d, $J = 17.0$ Hz, 1H), 4.20 (d, $J = 17.0$ Hz, 2H), 4.01 (d, $J = 17.0$ Hz, 2H), 2.98 (s, 3H), 2.03 (m, 1H), 1.80-1.55 (m, 5H), 1.36-1.00 (m, 5H).

$^{13}$C-NMR (125 MHz, d$_6$-acetone)  
$\delta$ 169.1, 143.5, 142.4, 135.0, 133.6, 128.7, 62.1, 47.3, 41.6, 33.4, 26.6, 26.5

$^{11}$B-NMR (128 MHz, d$_6$-acetone)  
$\delta$ 11.3

HRMS (ESI+)
Calculated for C$_{17}$H$_{25}$BNO$_4$ (M+H)$^+$: 318.1877
Found: 318.1878

**MIDA boronate 4.69.** Following the general pinacol ester cross-coupling condition, pinacol ester 4.62 (220 mg, 0.93 mmol), MIDA boronate 4.6 (250 mg, 0.72 mmol), 2nd generation XPhosPd cycle (56 mg, 0.07 mmol), Cs$_2$CO$_3$ (934 mg, 2.9 mmol), and DMSO (14 mL) were combined and stirred at 35 °C for 14 h 30 min, the reaction was worked up using H$_2$O:brine (1:1, 30 mL) and EtOAc (30 mL). After drying, filtering, and concentrating, the residue was dry loaded onto celite and purified by column chromatography on florisil (Et$_2$O:MeCN 100:0 → 60:40) to afford MIDA boronate 4.69 as a pale yellow solid (176.5 mg, 74%).

TLC (Et$_2$O:MeCN 6:1)  
$R_f$ =0.49, stained by KMnO$_4$
$^1$H-NMR (400 MHz, $d_6$-acetone)
\[ \delta 6.95 \text{ (dd, } J = 17.0, 11.0 \text{ Hz, } 1\text{H}), 6.11 \text{ (d, } J = 16.0 \text{ Hz, } 1\text{H}), 6.08 \text{ (d, } J = 11.0 \text{ Hz, } 1\text{H}), \]
\[ 5.73 \text{ (dd, } J = 16.0, 7.0 \text{ Hz, } 1\text{H}), 5.68 \text{ (d, } J = 17.0 \text{ Hz, } 1\text{H}), 4.22 \text{ (d, } J = 17.0 \text{ Hz, } 2\text{H}), 4.03 \text{ (d, } J = 17.0 \text{ Hz, } 2\text{H}), 3.00 \text{ (s, } 3\text{H}), 1.86 \text{ (s, } 3\text{H}), 2.07 \text{ (m, } 1\text{H}), 1.78-1.58 \text{ (m, } 5\text{H}), 1.38-1.05 \text{ (m, } 5\text{H}). \]

$^{13}$C-NMR (100 MHz, $d_6$-acetone)
\[ \delta 169.1, 139.2, 137.1, 136.5, 133.1, 132.4, 62.2, 47.3, 41.9, 33.8, 26.7, 26.6, 12.9 \]

$^{11}$B-NMR (128 MHz, $d_6$-acetone)
\[ \delta 11.4 \]

HRMS (ESI+)
Calculated for C$_{18}$H$_{27}$BNO$_4$ (M+H)$^+$: 332.2033
Found: 332.2043

MIDA boronate 4.70. Following the general pinacol ester cross-coupling condition, pinacol ester 4.62 (88 mg, 0.37 mmol), MIDA boronate 4.7 (100 mg, 0.29 mmol), 2$^\text{nd}$ generation XPhosPd cycle (23 mg, 0.03 mmol), Cs$_2$CO$_3$ (374 mg, 1.1 mmol), and DMSO (6 mL) were combined and stirred at 35 $^\circ$C for 13 h, the reaction was worked up using H$_2$O:brine (1:1, 30 mL) and EtOAc (30 mL). After drying, filtering, and concentrating, the residue was dry loaded onto celite and purified by column chromatography on florisil (Et$_2$O:MeCN 100:0 $\rightarrow$ 60:40) to afford MIDA boronate 4.70 as a pale yellow solid (71 mg, 75%).

TLC (Et$_2$O:MeCN 6:1)
\[ R_f = 0.50, \text{ stained by KMnO}_4 \]
$^1$H-NMR (500 MHz, d$_6$-acetone)

$\delta$ 6.28-6.24 (m, 2H), 6.09 (dd, $J =$ 16.0, 8.0 Hz, 1H), 5.73 (dd, $J =$ 15.0, 7.0 Hz, 1H), 5.36 (s, 1H), 4.20 (d, $J =$ 17.0 Hz, 2H), 4.03 (d, $J =$ 17.0 Hz, 2H), 3.00 (s, 3H), 2.02 (m, 1H), 1.93 (s, 3H), 1.76-1.59 (m, 5H), 1.35-1.05 (m, 5H).

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

$\delta$ 169.0, 148.6, 141.8, 138.6, 129.8, 129.1, 62.3, 47.0, 41.6, 33.5, 26.7, 26.5, 15.5

$^{11}$B-NMR (128 MHz, d$_6$-acetone)

$\delta$ 11.3

HRMS (ESI+)

Calculated for C$_{18}$H$_{27}$BNO$_4$ (M+H)$^+$: 332.2033

Found: 332.2038

MIDA boronate 4.71. Following the general pinacol ester cross-coupling condition, pinacol ester 4.62 (26 mg, 0.11 mmol), MIDA boronate 4.8 (30 mg, 0.08 mmol), 2$^{nd}$ generation XPhosPd cycle (6.5 mg, 0.008 mmol), Cs$_2$CO$_3$ (108 mg, 0.33 mmol), and DMSO (2 mL) were combined and stirred at 35 °C for 14 h, the reaction was worked up using H$_2$O:brine (1:1, 15 mL) and EtOAc (15 mL). After drying, filtering, and concentrating, the residue was dry loaded onto celite and purified by column chromatography on florisil (Et$_2$O:MeCN 100:0 → 60:40) to afford MIDA boronate 4.71 as a pale yellow solid (23 mg, 81%).

TLC (Et$_2$O:MeCN 4:1)

$R_f =$0.67, stained by KMnO$_4$
**H-NMR (500 MHz, d$_6$-acetone)**
\[ \delta 6.61 \text{ (dd, } J = 17.0, 10.0 \text{ Hz, 1H}), 6.38-6.18 \text{ (m, 4H)}, 6.11 \text{ (dd, } J = 15.0, 10.0 \text{ Hz, 1H}), 5.72 \text{ (dd, } J = 15.0, 7.0 \text{ Hz, 1H}), 5.68 \text{ (d, } J = 17.0 \text{ Hz, 1H}), 4.21 \text{ (d, } J = 17.0 \text{ Hz, 2H}), 4.03 \text{ (d, } J = 17.0 \text{ Hz, 2H}), 2.99 \text{ (s, 3H)}, 2.02 \text{ (m, 1H)}, 1.77-1.59 \text{ (m, 5H)}, 1.35-1.05 \text{ (m, 5H)}.\]

**C-NMR (125 MHz, d$_6$-acetone)**
\[ \delta 169.0, 143.5, 142.1, 135.4, 134.9, 134.8, 131.6, 129.0, 62.3, 47.3, 41.7, 33.5, 26.7, 26.6 \]

**B-NMR (128 MHz, d$_6$-acetone)**
\[ \delta 11.4 \]

**HRMS (ESI+)**
Calculated for C$_{19}$H$_{27}$BNO$_4$ (M+H)$^+$: 344.2033
Found: 344.2030

**MIDA boronate 4.72.** Following a modified version of the general pinacol ester cross-coupling condition, boronic acid 4.63 (15.3 mg, 0.10 mmol), MIDA boronate 4.9 (27.1 mg, 0.08 mmol), 2$^{nd}$ generation XPhosPd cycle (6.5 mg, 0.008 mmol), Cs$_2$CO$_3$ (108 mg, 0.33 mmol), and THF (2 mL) were combined and stirred at 35 °C for 15 h, the reaction was worked up by filtering through celite and concentrating. The residue was dry loaded onto celite and purified by column chromatography on florisil (Et$_2$O:MeCN 100:0 → 60:40) to afford MIDA boronate 4.72 as a pale yellow solid (14.7 mg, 50%).

**TLC (Et$_2$O:MeCN 4:1)**
\[ R_f = 0.68, \text{ stained by KMnO}_4 \]
$^1$H-NMR (500 MHz, d$_6$-acetone)

$\delta$ 6.63 (d, $J = 17.5$ Hz, 1H), 6.55 (dd, $J = 14.0$, 11.0 Hz, 1H), 6.32 (dd, $J = 15.0$, 11.0 Hz, 1H), 6.22-6.15 (m, 2H), 5.72 (dd, $J = 15.0$, 7.0 Hz, 1H), 5.71 (d, $J = 17.5$ Hz, 1H), 4.21 (d, $J = 17.0$ Hz, 2H), 4.04 (d, $J = 17.0$ Hz, 2H), 3.00 (s, 3H), 2.07 (m, 1H), 1.89 (s, 3H), 1.77-1.60 (m, 5H), 1.36-1.06 (m, 5H).

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

$\delta$ 169.0, 147.4, 142.0, 136.3, 135.6, 133.4, 129.4, 128.2, 62.3, 47.3, 41.7, 33.6, 26.8, 26.6, 12.5

$^{11}$B-NMR (128 MHz, d$_6$-acetone)

$\delta$ 11.4

HRMS (ESI+)

Calculated for C$_{20}$H$_{29}$BNO$_4$ (M+H)$^+$: 358.2190

Found: 358.2188

[MIDA boronate 4.73. Following the general pinacol ester cross-coupling condition, pinacol ester 4.62 (205 mg, 0.87 mmol), MIDA boronate 4.12 (250 mg, 0.67 mmol), 2nd generation XPhosPd cycle (52.5 mg, 0.07 mmol), Cs$_2$CO$_3$ (869 mg, 2.7 mmol), and DMSO (13 mL) were combined and stirred at 35 °C for 14 h, the reaction was worked up using H$_2$O:brine (1:1, 40 mL) and EtOAc (40 mL). After drying, filtering, and concentrating, the residue was dry loaded onto celite and purified by reverse phase column chromatography on C18 silica gel (H$_2$O:MeCN 90:10 $\rightarrow$ 0:100) to afford MIDA boronate 4.73 as a pale yellow solid (76 mg, 32%).

TLC (Et$_2$O:MeCN 6:1)

$R_f$ =0.32, stained by KMnO$_4$
1H-NMR (500 MHz, d6-acetone)

δ 6.97 (dd, J = 17.0, 11.0 Hz, 1H), 6.34 (dd, J = 15.0, 10.0 Hz, 1H), 6.24 (d, J = 15.5 Hz, 1H), 6.15 (d, J = 11.0 Hz, 1H), 6.12 (dd, J = 15.0, 10.0 Hz, 1H), 5.74 (d, J = 15.5 Hz, 1H), 5.72 (d, J = 17.0 Hz, 1H), 4.21 (d, J = 17.0 Hz, 2H), 4.04 (d, J = 17.0 Hz, 2H), 2.99 (s, 3H), 2.05 (m, 1H), 1.90 (s, 3H), 1.76-1.60 (m, 5H), 1.35-1.05 (m, 5H).

13C-NMR (125 MHz, d6-acetone)

δ 169.1, 141.6, 139.2, 136.7, 136.0, 133.6, 130.5, 129.3, 62.2, 47.3, 41.7, 33.5, 26.7, 26.5, 12.8

11B-NMR (128 MHz, d6-acetone)

δ 11.4

HRMS (ESI+)

Calculated for C20H29BNO4 (M+H)+: 358.2190
Found: 358.2189

Pinacol ester 4.74. Following the general deprotection condition, MIDA boronate 4.68 (50 mg, 0.16 mmol), NaHCO3 (66 mg, 0.79 mmol), pinacol (28 mg, 0.24 mmol), and MeOH (1 mL) were stirred at 45 °C for 3 h. After filtration and concentration, to the residue was added NaHCO3 (66 mg, 0.79 mmol), CaCl2 (87 mg, 0.79 mmol), and toluene (1 mL). After stirring at 23 °C for 1 h, filtering, and concentrating, pinacol ester 4.74 was obtained as a clear, colorless oil (44 mg, 98%).

1H-NMR (500 MHz, d6-acetone)

δ 6.97 (dd, J = 17.5, 11.0 Hz, 1H), 6.41 (dd, J = 15.0, 10.0 Hz, 1H), 6.24 (dd, J = 15.0, 11.0 Hz, 1H), 6.12 (dd, J = 15.0, 11.0 Hz, 1H), 5.81 (dd, J = 15.0, 7.0 Hz, 1H), 5.46 (d, J
= 17.5 Hz, 1H), 2.07 (m, 1H), 2.05 (s, 3H), 1.77-1.60 (m, 5H), 1.34-1.03 (m, 5H), 1.23 (s, 12H).

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

δ 150.6, 144.2, 138.0, 133.2, 128.7, 83.6, 41.7, 33.4, 26.7, 26.6, 25.1

\(^{11}\)B-NMR (128 MHz, d\(_6\)-acetone)

δ 30.6

HRMS (ESI+)

Calculated for C\(_{18}\)H\(_{30}\)BO\(_2\) (M+H): 289.2339

Found: 289.2342

**Pinacol ester 4.75.** Following the general deprotection condition, MIDA boronate 4.69 (134 mg, 0.40 mmol), NaHCO\(_3\) (170 mg, 2.0 mmol), pinacol (72 mg, 0.60 mmol), and MeOH (4 mL) were stirred at 45 °C for 3 h. After filtration and concentration, to the residue was added NaHCO\(_3\) (170 mg, 2.0 mmol), CaCl\(_2\) (224 mg, 2.0 mmol), and toluene (4 mL). After stirring at 23 °C for 1 h, filtering, and concentrating, pinacol ester 4.75 was obtained as a clear, colorless oil (119 mg, 97%).

\(^1\)H-NMR (400 MHz, d\(_6\)-acetone)

δ 7.34 (dd, J = 17.0, 11.0 Hz, 1H), 6.13 (d, J = 15.5 Hz, 1H), 6.10 (d, J = 11.0 Hz, 1H), 5.82 (dd, J = 15.5, 7.0 Hz, 1H), 5.49 (d, J = 17.0 Hz, 1H), 2.07 (m, 1H), 1.91 (s, 3H), 1.79-1.59 (m, 5H), 1.37-1.05 (m, 5H), 1.24 (s, 12H).

\(^{13}\)C-NMR (100 MHz, d\(_6\)-acetone)

δ 146.1, 139.7, 138.6, 132.9, 131.9, 83.6, 41.9, 33.6, 26.7, 26.6, 25.2, 13.0
Pinacol ester 4.76. Following the general deprotection condition, MIDA boronate 4.70 (71 mg, 0.21 mmol), NaHCO₃ (90 mg, 1.1 mmol), pinacol (38 mg, 0.32 mmol), and MeOH (1.1 mL) were stirred at 45 °C for 3 h. After filtration and concentration, to the residue was added NaHCO₃ (90 mg, 1.1 mmol), CaCl₂ (119 mg, 1.1 mmol), and toluene (1.1 mL). After stirring at 23 °C for 1 h, filtering, and concentrating, pinacol ester 4.76 was obtained as a clear, colorless oil (59 mg, 91%).

\[
\begin{align*}
\delta & 6.40 \text{ (dd, } J = 15.0, 11.0 \text{ Hz, } 1H), 6.25 \text{ (d, } J = 15.0 \text{ Hz, } 1H), 6.12 \text{ (dd, } J = 15.0, 11.0 \text{ Hz, } 1H), 5.81 \text{ (dd, } J = 15.0, 7.0 \text{ Hz, } 1H), 5.25 \text{ (s, } 1H), 2.01 \text{ (s, } 3H), 2.06 \text{ (m, } 1H), 1.77-1.61 \text{ (m, } 5H), 1.36-1.05 \text{ (m, } 5H), 1.25 \text{ (s, } 12H). \\
\delta & 156.1, 143.3, 137.3, 132.8, 128.9, 83.3, 41.7, 33.4, 26.7, 26.6, 25.2, 16.6
\end{align*}
\]

HRMS (ESI+)
Calculated for C₁₉H₃₂BO₂ (M+H)⁺: 303.2495
Found: 303.2495
Pinacol ester 4.77. Following the general deprotection condition, MIDA boronate 4.73 (76 mg, 0.21 mmol), NaHCO₃ (88 mg, 1.1 mmol), pinacol (38 mg, 0.32 mmol), and MeOH (1.0 mL) were stirred at 45 °C for 3 h. After filtration and concentration, to the residue was added NaHCO₃ (89 mg, 1.1 mmol), CaCl₂ (117 mg, 1.1 mmol), and toluene (1.0 mL). After stirring at 23 °C for 1 h, filtering, and concentrating, pinacol ester 4.77 was obtained as a clear, colorless oil (67 mg, 96%).

\[ \delta 7.35 (\text{dd}, J = 17.0, 11.0 \text{ Hz}, 1\text{H}), 6.42 (\text{dd}, J = 15.0, 10.0 \text{ Hz}, 1\text{H}), 6.26 (\text{d}, J = 15.5 \text{ Hz}, 1\text{H}), 6.17 (\text{d}, J = 11.0 \text{ Hz}, 1\text{H}), 6.14 (\text{dd}, J = 15.0, 10.0 \text{ Hz}, 1\text{H}), 5.78 (\text{dd}, J = 15.0, 7.0 \text{ Hz}, 1\text{H}), 5.52 (\text{d}, J = 17.0 \text{ Hz}, 1\text{H}), 2.06 (\text{m}, 1\text{H}), 1.95 (\text{s}, 3\text{H}), 1.77-1.60 (\text{m}, 5\text{H}), 1.38-1.06 (\text{m}, 5\text{H}), 1.25 (\text{s}, 12\text{H}). \]

\[ \delta 146.0, 142.5, 139.9, 135.6, 133.1, 131.9, 129.3, 83.6, 41.7, 33.5, 26.7, 26.6, 25.2, 12.9 \]

\[ \delta 30.5 \]

HRMS (ESI+)

Calculated for C₂₁H₄₄BO₂ (M+H)⁺: 329.2652

Found: 329.2656

MIDA boronate 4.78. Following the general pinacol ester cross-coupling condition, pinacol ester 4.74 (44 mg, 0.15 mmol), MIDA boronate 4.8 (46 mg, 0.13 mmol), 2nd generation XPhosPd
cycle (10.0 mg, 0.01 mmol), Cs₂CO₃ (166 mg, 0.5 mmol), and DMSO (2.5 mL) were combined and stirred at 35 °C for 14 h, the reaction was worked up using H₂O:brine (1:1, 15 mL) and EtOAc (15 mL). After drying, filtering, and concentrating, the residue was dry loaded onto celite and purified by column chromatography on florisil (hexanes:EtOAc 80:20 → 0:100) to afford MIDA boronate 4.78 as a pale yellow solid (30 mg, 60%).

TLC (Et₂O:MeCN 6:1)

Rₛ =0.57, stained by KMnO₄

¹H-NMR (500 MHz, d₆-DMSO)

δ 6.51 (dd, J = 17.0, 10.0 Hz, 1H), 6.40-6.21 (m, 8H), 6.08 (dd, J = 16.0, 11.0 Hz, 1H), 5.72 (dd, J = 15.0, 7.0 Hz, 1H), 5.64 (d, J = 17.0 Hz, 1H), 4.21 (d, J = 17.0 Hz, 2H), 4.00 (d, J = 17.0 Hz, 2H), 2.74 (s, 3H), 2.02 (m, 1H), 1.76-1.56 (m, 5H), 1.30-1.00 (m, 5H).

¹³C-NMR (125 MHz, d₆-DMSO)

δ 169.3, 142.0, 141.6, 141.0, 134.9, 134.3, 134.2, 134.0, 132.8, 132.5, 131.3, 128.5, 61.5, 46.9, 40.5, 32.5, 35.8, 25.6

¹¹B-NMR (128 MHz, d₆-DMSO)

δ 10.4

HRMS (ESI+)

Calculated for C₂₃H₃₁BNO₄ (M+H): 396.2346

Found: 396.2343

MIDA boronate 4.79. Following the general pinacol ester cross-coupling condition, pinacol ester 4.75 (51 mg, 0.17 mmol), MIDA boronate 4.11 (50 mg, 0.13 mmol), 2nd generation XPhosPd cycle (10.1 mg, 0.01 mmol), Cs₂CO₃ (168 mg, 0.5 mmol), and DMSO (2.5 mL) were
combined and stirred at 35 °C for 14 h 30 min, the reaction was worked up using H₂O:brine (1:1, 15 mL) and EtOAc (15 mL). After drying, filtering, and concentrating, the residue was dry loaded onto celite and purified by column chromatography on florisil (hexanes:EtOAc 90:10 → 0:100) to afford MIDA boronate 4.79 as a pale yellow solid (29 mg, 51%).

TLC (Et₂O:MeCN 6:1)

R_f = 0.50, stained by KMnO₄

¹H-NMR (500 MHz, d₆-acetone)

δ 6.75-6.65 (m, 3H), 6.56-6.50 (m, 1H), 6.38 (d, J = 15.0 Hz, 1H), 6.32-6.26 (m, 1H), 6.15 (d, J = 16.0 Hz, 1H), 6.14 (d, J = 11.0 Hz, 1H), 5.71 (dd, J = 15.0, 7.0 Hz, 1H), 4.23 (d, J = 17.0 Hz, 2H), 4.06 (d, J = 17.0 Hz, 2H), 2.97 (s, 3H), 2.07 (m, 1H), 1.98 (s, 3H), 1.89 (s, 3H), 1.83 (s, 3H), 1.77-1.60 (m, 5H), 1.37-1.06 (m, 5H).

¹³C-NMR (125 MHz, d₆-acetone)

δ 169.1, 137.9, 137.7, 137.4, 136.4, 136.3, 133.4, 132.9, 131.2, 131.1, 130.3, 125.9, 62.7, 47.1, 42.0, 33.9, 26.8, 26.7, 15.4, 13.0, 12.8

¹¹B-NMR (128 MHz, d₆-acetone)

δ 11.7

HRMS (ESI+)

Calculated for C₂₆H₃₇BNO₄ (M+H)+: 438.2816

Found: 438.2808

MIDA boronate 4.80. Following the general pinacol ester cross-coupling condition, pinacol ester 4.76 (83 mg, 0.27 mmol), MIDA boronate 4.9 (69 mg, 0.21 mmol), 2nd generation XPhosPd cycle (16.5 mg, 0.02 mmol), Cs₂CO₃ (274 mg, 0.8 mmol), and DMSO (4 mL) were combined
and stirred at 35 °C for 15 h, the reaction was worked up using H2O:brine (1:1, 25 mL) and EtOAc (25 mL). After drying, filtering, and concentrating, the residue was dry loaded onto celite and purified by reverse phase column chromatography on C18 silica gel (H2O:MeCN 95:5 → 0:100) to afford MIDA boronate 4.80 as a yellow solid (16 mg, 18%).

TLC (Et2O:MeCN 6:1)
R_f =0.43, stained by KMnO4

1H-NMR (500 MHz, d6-acetone)
δ 6.76 (dd, J = 15.0, 11.0 Hz, 1H), 6.69 (d, J = 11.0 Hz, 1H), 6.67 (d, J = 17.0 Hz, 1H), 6.39-6.22 (m, 4H), 6.14 (dd, J = 15.0, 10.0 Hz, 1H), 5.75 (d, J = 17.5 Hz, 1H), 5.73 (dd, J = 15.0, 7.0 Hz, 1H), 4.22 (d, J = 17.0 Hz, 2H), 4.04 (d, J = 17.0 Hz, 2H), 3.01 (s, 3H), 2.02 (m, 1H), 1.92 (s, 3H), 1.85 (s, 3H), 1.77-1.60 (m, 5H), 1.36-1.06 (m, 5H).

13C-NMR (125 MHz, d6-acetone)
δ 169.0, 147.3, 141.6, 137.0, 136.9, 136.1, 133.9, 132.4, 131.6, 130.4, 130.3, 129.6, 62.3, 47.3, 41.8, 33.6, 26.8, 26.6, 12.8, 12.6

11B-NMR (128 MHz, d6-acetone)
δ 11.8

HRMS (ESI+)
Calculated for C25H35BNO4 (M+H)+: 424.2659
Found: 424.2663

MIDA boronate 4.81. Following the general pinacol ester cross-coupling condition, pinacol ester 4.77 (65 mg, 0.20 mmol), MIDA boronate 4.10 (92.4 mg, 0.24 mmol), 2nd generation XPhosPd cycle (15.6 mg, 0.02 mmol), Cs2CO3 (258 mg, 0.8 mmol), and DMSO (4 mL) were
combined and stirred at 35 °C for 15 h, the reaction was worked up using H₂O:brine (1:1, 20 mL) and EtOAc (20 mL). After drying, filtering, and concentrating, the residue was dry loaded onto celite and purified by reverse phase column chromatography on C18 silica gel (H₂O:MeCN 90:10 → 0:100) to afford MIDA boronate 4.81 as a yellow solid (28.4 mg, 31%).

TLC (Et₂O:MeCN 6:1)
R₇ =0.32, stained by KMnO₄

¹H-NMR (500 MHz, d₆-acetone)
δ 6.77-6.67 (m, 3H), 6.50 (d, J = 11.0 Hz, 1H), 6.41 (d, J = 15.0 Hz, 1H), 6.38-6.24 (m, 4H), 6.14 (dd, J = 15.0, 10.0 Hz, 1H), 5.73 (dd, J = 15.0, 7.0 Hz, 1H), 4.23 (d, J = 17.0 Hz, 2H), 4.06 (d, J = 17.0 Hz, 2H), 2.97 (s, 3H), 2.04 (m, 1H), 1.97 (s, 3H), 1.92 (s, 3H), 1.84 (s, 3H), 1.79-1.59 (m, 5H), 1.37-1.06 (m, 5H).

¹³C-NMR (125 MHz, d₆-acetone)
δ 169.2, 141.5, 139.1, 137.8, 136.9, 136.7, 136.1, 133.7, 132.5, 131.2, 130.5, 130.2, 129.6, 125.2, 62.7, 47.1, 41.8, 33.6, 26.7, 26.6, 15.4, 12.8, 12.7

¹¹B-NMR (128 MHz, d₆-acetone)
δ 11.8

HRMS (ESI+)
Calculated for C₂₈H₃₉BNO₄ (M+H)⁺: 464.2972
Found: 464.2970

MIDA boronate 4.82. Following the general pinacol ester cross-coupling condition, pinacol ester 4.75 (159 mg, 0.53 mmol), MIDA boronate 4.12 (153 mg, 0.44 mmol), 2nd generation XPhosPd cycle (34.5 mg, 0.04 mmol), Cs₂CO₃ (571 mg, 1.8 mmol), and DMSO (9 mL) were
combined and stirred at 35 °C for 15 h, the reaction was worked up using H$_2$O:brine (1:1, 25 mL) and EtOAc (25 mL). After drying, filtering, and concentrating, the residue was dry loaded onto celite and purified by column chromatography on florisil (Et$_2$O:MeCN 100:0 → 55:45) to afford MIDA boronate 4.82 as a yellow solid (128 mg, 74%).

TLC (Et$_2$O:MeCN 4:1)  
$R_f$ =0.64, stained by KMnO$_4$

$^1$H-NMR (400 MHz, d$_6$-acetone)  
$\delta$ 7.00 (dd, $J$ = 17.0, 11.0 Hz, 1H), 6.72 (dd, $J$ = 15.0, 11.0 Hz, 1H), 6.35 (d, $J$ = 15.0 Hz, 1H), 6.20 (d, $J$ = 11.0 Hz, 1H), 6.14 (d, $J$ = 15.0 Hz, 1H), 6.13 (d, $J$ = 11.0 Hz, 1H), 5.75 (d, $J$ = 17.0 Hz, 1H), 5.70 (dd, $J$ = 15.0, 7.0 Hz, 1H), 4.22 (d, $J$ = 17.0 Hz, 2H), 4.04 (d, $J$ = 17.0 Hz, 2H), 3.00 (s, 3H), 2.07 (m, 1H), 1.96 (s, 3H), 1.89 (s, 3H), 1.80-1.60 (m, 5H), 1.38-1.05 (m, 5H).

$^{13}$C-NMR (100 MHz, d$_6$-acetone)  
$\delta$ 169.1, 139.2, 137.7, 137.0, 136.5, 136.4, 134.2, 133.3, 130.9, 126.4, 62.2, 47.4, 41.9, 33.8, 26.7, 26.6, 12.9, 12.8

$^{11}$B-NMR (128 MHz, d$_6$-acetone)  
$\delta$ 11.2

HRMS (ESI+)  
Calculated for C$_{23}$H$_{33}$BNO$_4$ (M+H)$^+$: 398.2503  
Found: 398.2505

MIDA boronate 4.83. Following the general pinacol ester cross-coupling condition, pinacol ester 4.75 (180 mg, 0.60 mmol), MIDA boronate 4.10 (210 mg, 0.54 mmol), 2$^{nd}$ generation
XPhosPd cycle (43 mg, 0.05 mmol), Cs$_2$CO$_3$ (706 mg, 2.2 mmol), and DMSO (11 mL) were combined and stirred at 35 °C for 13 h 30 min, the reaction was worked up using H$_2$O:brine (1:1, 50 mL) and EtOAc (50 mL). After drying, filtering, and concentrating, the residue was dry loaded onto celite and purified by reverse phase column chromatography on C18 silica gel (H$_2$O:MeCN 90:10 → 0:100) to afford MIDA boronate **4.83** as a yellow solid (100 mg, 48%).

**TLC** (Et$_2$O:MeCN 4:1)

R$_f$ = 0.60, stained by KMnO$_4$

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

δ 6.75-6.65 (m, 3H), 6.50 (d, J = 11.0 Hz, 1H), 6.40 (d, J = 15.0 Hz, 1H), 6.33 (d, J = 10.0 Hz, 1H), 6.18 (d, J = 10.0 Hz, 1H), 6.14 (d, J = 15.0 Hz, 1H), 5.72 (dd, J = 15.0, 7.0 Hz, 1H), 4.23 (d, J = 17.0 Hz, 2H), 4.06 (d, J = 17.0 Hz, 2H), 2.97 (s, 3H), 2.07 (m, 1H), 1.96 (s, 3H), 1.88 (s, 3H), 1.84 (s, 3H), 1.77-1.61 (m, 5H), 1.37-1.06 (m, 5H).

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

δ 169.2, 139.1, 137.7, 136.8, 136.7, 136.3, 133.7, 133.3, 131.2, 131.1, 130.0, 125.0, 62.2, 47.1, 42.0, 33.8, 26.7, 26.6, 15.3, 12.9, 12.8

**$^{11}$B-NMR** (128 MHz, d$_6$-acetone)

δ 11.9

**HRMS** (ESI+)

Calculated for C$_{26}$H$_{37}$BNO$_4$ (M+H)$^+$: 438.2816

Found: 438.2818

**Pinacol ester 4.84.** Following the general deprotection condition, MIDA boronate **4.82** (49 mg, 0.12 mmol), NaHCO$_3$ (51 mg, 0.61 mmol), pinacol (22 mg, 0.18 mmol), and MeOH (1.2 mL)
were stirred at 45 °C for 3 h. After filtration and concentration, to the residue was added NaHCO₃ (51 mg, 0.61 mmol), CaCl₂ (68 mg, 0.61 mmol), and toluene (1.2 mL). After stirring at 23 °C for 1 h, filtering, and concentrating, pinacol ester 4.84 was obtained as a clear, colorless oil (44 mg, 97%).

**1H-NMR (500 MHz, d₆-acetone)**

δ 7.36 (dd, J = 17.0, 11.0 Hz, 1H), 6.81 (dd, J = 15.0, 11.0 Hz, 1H), 6.36 (d, J = 15.0 Hz, 1H), 6.21 (d, J = 11.0 Hz, 1H), 6.15 (d, J = 15.0 Hz, 1H), 6.14 (d, J = 11.0 Hz, 1H), 5.74 (d, J = 16.0, 7.0 Hz, 1H), 5.54 (d, J = 17.0 Hz, 1H), 2.07 (m, 1H), 2.01 (s, 3H), 1.91 (s, 3H), 1.78-1.59 (m, 5H), 1.35-1.09 (m, 5H), 1.25 (s, 12H).

**13C-NMR (125 MHz, d₆-acetone)**

δ 146.0, 140.3, 137.3, 137.0, 133.6, 133.3, 130.8, 129.0, 127.7, 83.7, 42.0, 33.8, 26.8, 26.7, 25.1, 13.0, 12.9

**11B-NMR (128 MHz, d₆-acetone)**

δ 30.4

HRMS (ESI+)

Calculated for C₂₄H₃₈BO₂ (M+H)+: 369.2965

Found: 369.2957

**Pinacol ester 4.85.** Following the general deprotection condition, MIDA boronate 4.83 (30 mg, 0.07 mmol), NaHCO₃ (29 mg, 0.35 mmol), pinacol (12 mg, 0.10 mmol), and MeOH (0.5 mL) were stirred at 45 °C for 3 h. After filtration and concentration, to the residue was added NaHCO₃ (29 mg, 0.35 mmol), CaCl₂ (39 mg, 0.35 mmol), and toluene (0.5 mL). After stirring at 23 °C for 1 h, filtering, and concentrating, pinacol ester 4.85 was obtained as a clear, colorless oil (28 mg, 99%).

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

$\delta$ 6.89 (d, $J = 11.0$ Hz, 1H), 6.87-6.63 (m, 3H), 6.38 (d, $J = 15.0$ Hz, 1H), 6.30 (d, $J = 11.0$ Hz, 1H), 6.15 (d, $J = 15.0$ Hz, 1H), 6.15 (d, $J = 11.0$ Hz, 1H), 5.72 (dd, $J = 15.0$, 7.0 Hz, 1H), 2.07 (m, 1H), 2.01 (s, 3H), 1.90 (s, 3H), 1.80 (s, 3H), 1.77-1.59 (m, 5H), 1.33-1.04 (m, 5H), 1.25 (s, 12H).

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

$\delta$ 143.5, 138.8, 137.7, 136.7, 136.6, 133.4, 133.3, 132.6, 131.1, 129.7, 126.5, 83.9, 42.0, 33.9, 26.8, 26.7, 25.2, 14.6, 13.0, 12.9

$^{11}$B-NMR (128 MHz, d$_6$-acetone)

$\delta$ 30.7

HRMS (ESI+)

Calculated for C$_{27}$H$_{41}$BO$_2$ (M+H)$^+$: 408.3200

Found: 408.3193

MIDA boronate 4.86. Following the general pinacol ester cross-coupling condition, pinacol ester 4.84 (76 mg, 0.21 mmol), MIDA boronate 4.10 (81 mg, 0.21 mmol), 2$^{nd}$ generation XPhosPd cycle (16 mg, 0.02 mmol), Cs$_2$CO$_3$ (270 mg, 0.83 mmol), and DMSO (4 mL) were combined and stirred at 35 °C for 13 h, the reaction was worked up using H$_2$O:brine (1:1, 20 mL) and EtOAc (20 mL). After drying, filtering, and concentrating, the residue was dry loaded onto celite and purified by column chromatography on florisil (Et$_2$O:MeCN 100:0 $\rightarrow$ 60:40) to afford MIDA boronate 4.86 as a yellow solid (54 mg, 52%).

TLC (Et$_2$O:MeCN 6:1)

$R_f$ =0.48 stained by KMnO$_4$
$^1$H-NMR (500 MHz, d$_6$-acetone)

$\delta$ 6.76-6.67 (m, 4H), 6.50 (d, $J = 11.0$ Hz, 1H), 6.41 (d, $J = 15.0$ Hz, 1H), 6.38 (d, $J = 15.0$ Hz, 1H), 6.36-6.28 (m, 2H), 6.15 (d, $J = 17.0$ Hz, 1H), 6.14 (d, $J = 11.0$ Hz, 1H), 5.71 (dd, $J = 15.0$, 7.0 Hz, 1H), 4.23 (d, $J = 17.0$ Hz, 2H), 4.06 (d, $J = 17.0$ Hz, 2H), 2.98 (s, 3H), 2.03 (m, 1H), 1.98 (s, 6H), 1.90 (s, 3H), 1.85 (s, 3H), 1.78-1.60 (m, 5H), 1.36-1.07 (m, 5H).

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

$\delta$ 169.2, 139.1, 137.9, 137.8, 137.3, 137.0, 136.5, 136.4, 133.8, 133.5, 133.2, 131.3, 131.2, 130.9, 126.1, 125.4, 62.7, 47.1, 42.0, 33.9, 26.8, 26.7, 15.4, 13.0, 12.8, 12.8

$^{11}$B-NMR (128 MHz, d$_6$-acetone)

$\delta$ 11.8

HRMS (ESI+)

Calculated for C$_{31}$H$_{43}$BNO$_4$ (M+H)$^+$: 504.3285

Found: 504.3287

**MIDA boronate 4.87.** Following the general pinacol ester cross-coupling condition, pinacol ester $4.85$ (26.0 mg, 0.06 mmol), MIDA boronate $4.9$ (17.4 mg, 0.05 mmol), 2$^{nd}$ generation XPhosPd cycle (4.2 mg, 0.005 mmol), Cs$_2$CO$_3$ (69.1 mg, 0.21 mmol), and DMSO (1.1 mL) were combined and stirred at 35 °C for 13 h, the reaction was worked up using H$_2$O:brine (1:1, 10 mL) and EtOAc (10 mL). After drying, filtering, and concentrating, the residue was dry loaded onto celite and purified by reverse phase column chromatography on C18 silica gel (H$_2$O:MeCN 95:5 → 0:100) to afford MIDA boronate $4.87$ as an orange solid (10.7 mg, 38%).
TLC (Et₂O:MeCN 6:1)  
R_f =0.40 stained by KMnO₄

¹H-NMR (500 MHz, d₆-acetone)  
δ 6.81-6.62 (m, 5H), 6.48 (d, J = 15.0 Hz, 1H), 6.38 (d, J = 15.0 Hz, 1H), 6.32 (dd, J = 18.0, 10.0 Hz, 1H), 6.29 (d, J = 11.0 Hz, 1H), 6.15 (d, J = 15.0 Hz, 1H), 6.14 (d, J = 11.0 Hz, 1H), 6.14 (m, 1H), 5.75 (d, J = 18.0 Hz, 1H), 5.71 (dd, J = 15.0, 7.0 Hz, 1H), 4.22 (d, J = 17.0 Hz, 2H), 4.04 (d, J = 17.0 Hz, 2H), 3.01 (s, 3H), 2.01 (m, 1H), 1.98 (s, 6H), 1.95 (s, 3H), 1.90 (s, 3H), 1.77-1.60 (m, 5H), 1.35-1.04 (m, 5H).

¹³C-NMR (125 MHz, d₆-acetone)  
δ 169.0, 139.4, 137.6, 137.0, 136.9, 134.4, 134.2, 133.4, 133.3, 133.0, 132.4, 132.3, 132.0, 131.3, 130.7, 130.6, 127.0, 126.9, 62.3, 47.3, 42.1, 33.9, 26.8, 26.6, 15.1, 13.0, 12.8, 12.7

¹¹B-NMR (128 MHz, d₆-acetone)  
δ 11.5

HRMS (ESI+)  
Calculated for C₃₃H₄₅BNO₄ (M+H)⁺: 530.3442  
Found: 530.3441

**Triene 4.22.** In a glovebox, to a 20 mL vial charged with MIDA boronate 4.64 (69.1 mg, 0.24 mmol) was added vinyl iodide 4.38 (38.7 mg, 0.18 mmol), Pd(OAc)$_2$ (3.8 mg, 0.017 mmol), XPhos (10.4 mg, 0.022 mmol), finely ground NaOH (55.7 mg, 1.4 mmol) and THF (3.0 mL). The vial was sealed with a septum cap and removed from the glovebox. To the reaction was added degassed DI H₂O (0.6 mL). The solution was stirred in a subdued light environment at 23 °C for 4.5 hr. The reaction mixture was filtered through a pad of MgSO₄/Celite, concentrated in
vacuo, dry loaded onto Celite from an acetone solution, and purified via flash chromatography on silica (Hexanes/EtOAc 100:0 → 70:30) to afford triene 4.22 as a yellow oil (20.3 mg, 51%).

TLC (Hexanes:EtOAc 4:1)

\[ R_f = 0.19, \text{ stained by KMnO}_4 \]

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

\[ \delta \ 6.12-5.97 \text{ (m, 4H), 5.65 \ (dd, } J = 15.0, 7.0 \text{ Hz, 1H), 5.63 \ (dd, } J = 15.0, 7.0 \text{ Hz, 1H), 3.65 \ (t, } J = 6.5 \text{ Hz, 2H), 2.18 \ (q, } J = 7.5 \text{ Hz, 2H), 2.00 \ (m, 1H), 1.77-1.60 \ (m, 6H), 1.38 \ (bs, 1H), 1.32-1.00 \ (m, 6H). \]

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

\[ \delta \ 140.6, 133.0, 131.6, 131.1, 130.6, 127.7, 62.4, 40.8, 32.8, 32.2, 29.1, 26.1, 26.0 \]

HRMS (ESI+)

Calculated for C$_{15}$H$_{25}$O (M+H)$^+$: 221.1905

Found: 221.1907

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**Triene 4.23.** In a glovebox, to a 20 mL vial charged with MIDA boronate 4.65 (58.2 mg, 0.20 mmol) was added vinyl iodide 4.38 (37.6 mg, 0.18 mmol), Pd(OAc)$_2$ (7.1 mg, 0.032 mmol), XPhos (21.7 mg, 0.046 mmol), finely ground NaOH (47.4 mg, 1.2 mmol) and THF (2.5 mL). The vial was sealed with a septum cap and removed from the glovebox. To the reaction was added degassed DI H$_2$O (0.5 mL). The solution was stirred in a subdued light environment at 23 °C for 4 hr. The reaction mixture was filtered through a pad of MgSO$_4$/Celite, concentrated in vacuo, dry loaded onto Celite from an acetone solution, and purified via flash chromatography on silica (Hexanes/EtOAc 100:0 → 70:30) to afford triene 4.23 as a yellow oil (19.7 mg, 51%).
TLC (Hexanes:EtOAc 4:1)
R_f = 0.21, stained by KMnO_4

^1^H-NMR (500 MHz, CDCl_3)
δ 6.52 (dd, J = 15.0, 9.0 Hz, 1H), 6.44 (dd, J = 15.0, 7.5 Hz, 1H), 5.90-5.80 (m, 2H), 5.69 (dd, J = 15.0, 7.5 Hz, 1H), 5.65 (dd, J = 15.0, 7.0 Hz, 1H), 3.67 (t, J = 6.5 Hz, 2H), 2.23 (q, J = 7.5 Hz, 2H), 2.04 (m, 1H), 1.78-1.60 (m, 6H), 1.35 (bs, 1H), 1.32-1.02 (m, 6H).

^1^3^C-NMR (125 MHz, CDCl_3)
δ 141.5, 134.1, 128.4, 127.4, 126.4, 123.1, 62.4, 41.1, 32.9, 32.3, 29.2, 26.1, 26.0

HRMS (ESI+)
Calculated for C_{15}H_{24}O_Na (M+Na)^+: 243.1725
Found: 243.1733

Triene 4.25. In a glovebox, to a 20 mL vial charged with MIDA boronate 4.66 (108.2 mg, 0.35 mmol) was added vinyl iodide 4.38 (60.0 mg, 0.28 mmol), Pd(OAc)_2 (3.3 mg, 0.015 mmol), XPhos (14.1 mg, 0.030 mmol), finely ground NaOH (84.6 mg, 2.1 mmol) and THF (5.0 mL). The vial was sealed with a septum cap and removed from the glovebox. To the reaction was added degassed DI H_2O (0.9 mL). The solution was stirred in a subdued light environment at 23 °C for 4 hr. The reaction mixture was filtered through a pad of MgSO_4/Celite, concentrated in vacuo, dry loaded onto Celite from an acetone solution, and purified via flash chromatography on silica (Hexanes/EtOAc 100:0 → 70:30) to afford triene 4.25 as a yellow oil (27.8 mg, 42%).

TLC (Hexanes:EtOAc 4:1)
R_f = 0.24, visualized by short wave UV
**1H-NMR (500 MHz, CDCl₃)**

δ 6.32 (ddd, J = 15.0, 11.0, 1.0 Hz, 1H), 6.09 (d, J = 15.5 Hz, 1H), 5.93 (d, J = 11.0 Hz, 1H), 5.65 (dd, J = 15.0, 7.0 Hz, 1H), 5.64 (dt, J = 15.0, 7.0 Hz, 1H), 3.66 (t, J = 6.5 Hz, 2H), 2.21 (q, J = 7.0 Hz, 2H), 2.04 (m, 1H), 1.83 (s, 3H), 1.77-1.60 (m, 6H), 1.42 (bs, 1H), 1.33-1.03 (m, 6H).

**13C-NMR (125 MHz, CDCl₃)**

δ 141.0, 135.4, 132.9, 129.8, 127.9, 124.1, 62.4, 41.2, 33.0, 32.5, 29.3, 26.1, 26.0, 12.7

**HRMS (ESI+)**

Calculated for C₁₆H₂₇O (M+H)^+: 235.2062

Found: 235.2052

**Triene 4.24.** In a glovebox, to a 20 mL vial charged with MIDA boronate 4.67 (43.3 mg, 0.14 mmol) was added vinyl iodide 4.38 (24.5 mg, 0.12 mmol), Pd(OAc)₂ (2.2 mg, 0.010 mmol), XPhos (6.2 mg, 0.013 mmol), finely ground NaOH (32.1 mg, 0.80 mmol) and THF (2.0 mL). The vial was sealed with a septum cap and removed from the glovebox. To the reaction was added degassed DI H₂O (0.4 mL). The solution was stirred in a subdued light environment at 23 °C for 4 hr. The reaction mixture was filtered through a pad of MgSO₄/Celite, concentrated *in vacuo*, dry loaded onto Celite from an acetone solution, and purified via flash chromatography on silica (Hexanes/EtOAc 100:0 → 70:30) to afford triene 4.24 as a yellow oil (15.4 mg, 57%).

**TLC (Hexanes:EtOAc 4:1)**

Rₜ = 0.23, visualized by short wave UV
**H-NMR (500 MHz, CDCl₃)**

δ 6.63 (d, J = 15.5 Hz, 1H), 6.46 (ddd, J = 15.0, 11.0, 1.0 Hz, 1H), 5.84 (d, J = 11.0 Hz, 1H), 5.69, (dt, J = 15.5, 7.0 Hz, 1H), 5.59 (dd, J = 15.0, 7.0 Hz, 1H), 3.68 (t, J = 6.5 Hz, 2H), 2.26 (q, J = 7.0 Hz, 2H), 2.03 (m, 1H), 1.84 (s, 3H), 1.77-1.60 (m, 6H), 1.34 (bs, 1H), 1.33-1.03 (m, 6H).

**C-NMR (125 MHz, CDCl₃)**

δ 140.2, 131.5, 130.0, 128.4, 127.7, 122.9, 62.5, 41.1, 33.0, 32.5, 29.6, 26.1, 26.0, 20.6

**HRMS (ESI+)**

Calculated for C_{16}H_{27}O (M+H)^+: 235.2062

Found: 235.2066

**Tetraene 4.26.** Following the general MIDA boronate cross-coupling reaction condition, MIDA boronate 4.68 (40.0 mg, 0.13 mmol), vinyl iodide 4.38 (34.8 mg, 0.16 mmol), 2nd generation XPhosPd cycle (9.9 mg, 0.013 mmol), NaOH (37.8 mg, 0.95 mmol), THF (2.1 mL), and degassed H₂O (0.4 mL) were combined and stirred at 23 °C for 4 h. The reaction was worked up using Et₂O (4.0 mL) and H₂O (4.0 mL) and the aqueous layer was extracted with Et₂O (2 x 4.0 mL). After drying, filtering, and concentrating, the residue was dry loaded onto celite and purified by column chromatography on florisil (hexanes:EtOAc 100:0 → 70:30) to afford tetraene 4.26 as a pale yellow solid (9.5 mg, 31%).

**TLC (hexanes:EtOAc 4:1)**

Rᵣ =0.29 stained by KMnO₄

**H-NMR (500 MHz, CDCl₃)**

δ 6.22-6.07 (m, 5H), 6.04 (ddd, J = 15.0, 10.0, 1.0 Hz, 1H), 5.68 (dt, J = 15.0, 7.0 Hz, 1H), 5.66 (dd, J = 15.0, 7.0 Hz, 1H), 3.66 (t, J = 6.5 Hz, 2H), 2.20 (q, J = 7.0 Hz, 2H), 2.01 (m, 1H), 1.80-1.60 (m, 6H), 1.30 (bs, 1H), 1.29-1.00 (m, 6H).
$^{13}$C-NMR (125 MHz, CDCl$_3$)

$\delta$ 141.1, 133.7, 133.1, 131.9, 131.3, 131.2, 130.8, 128.0, 62.4, 40.9, 32.8, 32.2, 29.1, 26.1, 26.0

HRMS (EI+)

Calculated for C$_{17}$H$_{26}$O: 246.1984

Found: 246.1975

**Tetraene 4.27.** Following the general MIDA boronate cross-coupling reaction condition, MIDA boronate 4.69 (22.5 mg, 0.07 mmol), vinyl iodide 4.38 (11.1 mg, 0.05 mmol), $2^{nd}$ generation XPhosPd cycle (2.1 mg, 0.003 mmol), NaOH (15.7 mg, 0.39 mmol), THF (0.9 mL), and degassed H$_2$O (0.2 mL) were combined and stirred at 23 °C for 4 h. The reaction was worked up using Et$_2$O (2.0 mL) and H$_2$O (2.0 mL) and the aqueous layer was extracted with Et$_2$O (2 x 2.0 mL). After drying, filtering, and concentrating, the residue was dry loaded onto celite and purified by column chromatography on florisil (hexanes:EtOAc 100:0 → 80:20) to afford tetraene 4.27 as a pale yellow solid (7.5 mg, 55%).

TLC (hexanes:EtOAc 4:1)

$R_f$ = 0.24 stained by KMnO$_4$

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

$\delta$ 6.50-6.40 (m, 1H), 6.24-6.18 (m, 2H), 6.08 (d, $J$ = 15.5 Hz, 1H), 6.00 (d, $J$ = 11.0 Hz, 1H), 5.69 (dt, $J$ = 15.0, 7.0 Hz, 1H), 5.64 (dd, $J$ = 15.0, 7.0 Hz, 1H), 3.67 (t, $J$ = 6.5 Hz, 2H), 2.21 (q, $J$ = 7.0 Hz, 2H), 2.03 (m, 1H), 1.85 (s, 3H), 1.78-1.61 (m, 6H), 1.57 (bs, 1H), 1.37-1.02 (m, 6H).
13C-NMR (125 MHz, CDCl3)
\[ \delta \] 135.9, 135.4, 133.5, 132.2, 131.6, 129.3, 127.7, 62.4, 41.2, 33.1, 32.2, 29.1, 26.2, 26.1, 12.7

HRMS (ESI+)
Calculated for C18H29O (M+H)^+: 261.2218
Found: 261.2211

Pentaene 4.28. Following the general MIDA boronate cross-coupling reaction condition, MIDA boronate 4.71 (20.0 mg, 0.058 mmol), vinyl iodide 4.38 (16.0 mg, 0.076 mmol), 2nd generation XPhosPd cycle (4.6 mg, 0.006 mmol), NaOH (17.5 mg, 0.43 mmol), THF (1.0 mL), and degassed H2O (0.2 mL) were combined and stirred at 23 °C for 1 h. The reaction was worked up using Et2O (2.0 mL) and H2O (2.0 mL) and the aqueous layer was extracted with Et2O (2 x 2.0 mL). After drying, filtering, and concentrating, the residue was dry loaded onto celite and purified by column chromatography on florisil (hexanes:EtOAc 100:0 → 70:30) to afford pentaene 4.28 as a pale yellow solid (7.0 mg, 44%).

TLC (hexanes:EtOAc 4:1)
\[ R_f \] =0.26 stained by KMnO4

1H-NMR (500 MHz, d_6-acetone)
\[ \delta \] 6.32-6.06 (m, 8H), 5.76 (dt, \( J = 15.0, 7.0 \) Hz, 1H), 5.68 (dd, \( J = 15.0, 7.0 \) Hz, 1H), 3.55 (q, \( J = 6.0 \) Hz, 2H), 3.29 (t, \( J = 6.0 \) Hz, 1H), 2.18 (q, \( J = 7.0 \) Hz, 2H), 2.03 (m, 1H), 1.79-1.51 (m, 6H), 1.37-1.03 (m, 6H).

13C-NMR (125 MHz, d_6-acetone)
\[ \delta \] 141.6, 135.7, 134.2, 133.9, 133.4, 133.3, 132.0, 131.9, 131.8, 129.2, 61.8, 41.7, 33.5, 33.3, 29.9, 26.7, 26.6
Pentaene 4.29. Following the general MIDA boronate cross-coupling reaction condition, MIDA boronate 4.72 (30.0 mg, 0.083 mmol), vinyl iodide 4.38 (36.0 mg, 0.17 mmol), 2nd generation XPhosPd cycle (6.6 mg, 0.008 mmol), NaOH (25.2 mg, 0.63 mmol), THF (1.4 mL), and degassed H₂O (0.3 mL) were combined and stirred at 23 °C for 1 h. The reaction was worked up by diluting with acetone, drying the organic layer over MgSO₄, filtering, and concentrating. The resulting residue was dry loaded onto celite and purified by column chromatography on florisil (hexanes:EtOAc 100:0 → 60:40) to afford pentaene 4.29 as a pale yellow solid (21.1 mg, 88%).

TLC (hexanes:EtOAc 4:1)

Rᵣ =0.18 stained by KMnO₄

¹H-NMR (500 MHz, CDCl₃)

δ 6.53 (dd, J = 15.0, 7.0 Hz, 1H), 6.46 (dd, J = 15.0, 11.0 Hz, 1H), 6.27-6.05 (m, 5H), 5.73 (dt, J = 15.0, 7.0 Hz, 1H), 5.69 (dd, J = 15.0, 7.0 Hz, 1H), 3.68 (t, J = 6.5 Hz, 2H), 2.21 (q, J = 7.0 Hz, 2H), 2.03 (m, 1H), 1.87 (s, 3H), 1.78-1.57 (m, 6H), 1.29 (bs, 1H), 1.28-1.00 (m, 6H).

¹³C-NMR (125 MHz, CDCl₃)

δ 141.3, 135.8, 134.8, 133.8, 133.5, 131.6, 131.4, 128.3, 127.8, 127.3, 62.4, 41.0, 32.8, 32.3, 29.2, 26.2, 26.0, 12.6

HRMS (EI+)

Calculated for C₂₀H₃₀O: 286.2297

Found: 286.2301
Hexaene 4.30. Following the general MIDA boronate cross-coupling reaction condition, MIDA boronate 4.82 (19.9 mg, 0.05 mmol), vinyl iodide 4.38 (8.8 mg, 0.04 mmol), 2nd generation XPhosPd cycle (1.6 mg, 0.002 mmol), NaOH (12.5 mg, 0.31 mmol), THF (0.9 mL), and degassed H$_2$O (0.2 mL) were combined and stirred at 23 °C for 4 h. The reaction was worked up using Et$_2$O (2.0 mL) and H$_2$O (2.0 mL) and the aqueous layer was extracted with Et$_2$O (2 x 2.0 mL). After drying, filtering, and concentrating, the residue was dry loaded onto celite and purified by column chromatography on florisil (hexanes:EtOAc 100:0 → 80:20) to afford hexaene 4.30 as a yellow solid (9.1 mg, 52%).

TLC (hexanes:EtOAc 4:1)

$R_f$ =0.24 stained by KMnO$_4$

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

δ 6.57 (dd, $J$ = 15.0, 11.0 Hz, 1H), 6.48 (dd, $J$ = 14.0, 11.0 Hz, 1H), 6.30 (d, $J$ = 15.0 Hz, 1H), 6.24 (dd, $J$ = 15.0, 11.0 Hz, 1H), 6.20 (dd, $J$ = 15.0, 11.0 Hz, 1H), 6.11 (d, $J$ = 11.0 Hz, 1H), 6.10 (d, $J$ = 15.5 Hz, 1H), 6.08 (d, $J$ = 11.0 Hz, 1H), 5.73 (dt, $J$ = 14.0, 7.0 Hz, 1H), 5.65 (dd, $J$ = 15.5, 7.0 Hz, 1H), 3.67 (t, $J$ = 6.5 Hz, 2H), 2.22 (q, $J$ = 7.0 Hz, 2H), 2.05 (m, 1H), 1.92 (s, 3H), 1.89 (s, 3H), 1.80-1.61 (m, 6H), 1.57 (bs, 1H), 1.34-1.05 (m, 6H).

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

δ 136.9, 136.0, 135.8, 135.5, 134.2, 133.1, 132.4, 131.6, 131.4, 130.1, 127.8, 124.7, 62.4, 41.2, 33.2, 32.2, 29.2, 26.2, 26.1, 12.9, 12.7

HRMS (ESI+)

Calculated for C$_{23}$H$_{35}$O (M+H)$^+$: 327.2688

Found: 327.2687
Heptaene 4.31. Following the general MIDA boronate cross-coupling reaction condition, MIDA boronate 4.78 (30.0 mg, 0.08 mmol), vinyl iodide 4.38 (24.1 mg, 0.11 mmol), 2nd generation XPhosPd cycle (6.0 mg, 0.008 mmol), NaOH (23.0 mg, 0.6 mmol), THF (1.3 mL), and degassed H₂O (0.3 mL) were combined and stirred at 23 °C for 1 h. The reaction was worked up using Et₂O (3.0 mL) and H₂O (3.0 mL) and the aqueous layer was extracted with Et₂O (2 x 3.0 mL). After drying, filtering, and concentrating, the residue was dry loaded onto celite and purified by column chromatography on florisil (hexanes:EtOAc 100:0 → 70:30) to afford heptaene 4.31 as an orange solid (7.8 mg, 32%).

TLC (hexanes:EtOAc 4:1)
\[ R_f = 0.23 \] stained by KMnO₄

¹H-NMR (500 MHz, d₆-acetone)
\[ \delta 6.40-6.21 (m, 8H), 6.19-6.07 (m, 2H), 6.05 (dd, J = 15.0, 11.0 Hz, 1H), 5.98 (dd, J = 8.0, 6.0 Hz, 1H), 5.79 (dt, J = 14.0, 7.0 Hz, 1H), 5.71 (dd, J = 15.0, 7.0 Hz, 1H), 3.55 (t, J = 6.5 Hz, 2H), 2.19 (q, J = 7.5 Hz, 2H), 2.09 (bs, 1H), 2.02 (m, 1H), 1.78-1.54 (m, 6H), 1.36-1.01 (m, 6H).

HRMS (EI+)
Calculated for C₂₃H₃₂O:
324.2453

Found:
324.2445

Heptaene 4.32. Following the general MIDA boronate cross-coupling reaction condition, MIDA boronate 4.83 (53.8 mg, 0.12 mmol), vinyl iodide 4.38 (39.1 mg, 0.18 mmol), 2nd generation XPhosPd cycle (9.7 mg, 0.012 mmol), NaOH (37.0 mg, 0.92 mmol), THF (2.0 mL), and degassed H₂O (0.5 mL) were combined and stirred at 23 °C for 4 h. The reaction was worked up
using Et₂O (4.0 mL) and H₂O (4.0 mL) and the aqueous layer was extracted with Et₂O (2 x 4.0 mL). After drying, filtering, and concentrating, the residue was dry loaded onto celite and purified by reverse phase column chromatography on C18 silica gel (H₂O:MeCN 85:15 → 0:100) to afford heptaene 4.32 as an orange solid (12.9 mg, 29%).

TLC (hexanes:EtOAc 4:1)
Rᶠ =0.26 stained by KMnO₄

¹H-NMR (500 MHz, d₆-acetone)
δ 6.72-6.62 (m, 3H), 6.37 (d, J = 15.0 Hz, 1H), 6.28 (d, J = 11.0 Hz, 1H), 6.22-6.09 (m, 4H), 5.78 (dt, J = 15.0, 7.0 Hz, 1H), 5.71 (dd, J = 15.5, 7.0 Hz, 1H), 3.56 (q, J = 6.0 Hz, 2H), 3.51 (t, J = 6.0 Hz, 1H), 2.22 (q, J = 7.5 Hz, 2H), 2.07 (m, 1H), 1.96 (s, 3H), 1.90 (s, 3H), 1.87 (s, 3H), 1.78-1.57 (m, 6H), 1.36-1.08 (m, 6H).

¹³C-NMR (125 MHz, d₆-acetone)
δ 146.6, 138.0, 136.7, 136.5, 136.0, 133.3, 133.2, 131.2, 131.1, 130.9, 130.4, 130.1, 125.6, 120.5, 61.8, 42.0, 33.8, 31.5, 30.2, 26.8, 26.7, 13.0, 12.9, 12.8

HRMS (EI+)
Calculated for C₂₆H₃₈O: 366.2923
Found: 366.2917

Heptaene 4.33. Following the general MIDA boronate cross-coupling reaction condition, MIDA boronate 4.80 (10.7 mg, 0.025 mmol), vinyl iodide 4.38 (8.0 mg, 0.038 mmol), 2nd generation XPhosPd cycle (2.0 mg, 0.003 mmol), NaOH (7.6 mg, 0.19 mmol), THF (0.5 mL), and degassed H₂O (0.1 mL) were combined and stirred at 23 °C for 2 h. The reaction was worked up using Et₂O (2.0 mL) and H₂O (2.0 mL) and the aqueous layer was extracted with Et₂O (2 x 2.0 mL). After drying, filtering, and concentrating, the residue was dry loaded onto celite and purified by
reverse phase column chromatography on C18 silica gel (H₂O:MeCN 95:5 → 0:100) to afford heptaene 4.33 as an orange solid (5.3 mg, 60%).

TLC (hexanes:EtOAc 4:1)

$R_f = 0.26$ stained by KMnO₄

$^1$H-NMR (500 MHz, d₆-acetone)

$\delta$ 6.74-6.64 (m, 2H), 6.38-6.09 (m, 8H), 5.80 (dt, $J = 15.0$, 7.0 Hz, 1H), 5.72 (dd, $J = 15.0$, 7.0 Hz, 1H), 3.55 (q, $J = 6.5$ Hz, 2H), 3.49 (t, $J = 6.5$ Hz, 1H), 2.19 (q, 7.0 Hz, 2H), 2.02 (m, 1H), 1.91 (s, 6H), 1.79-1.56 (m, 6H), 1.40-1.04 (m, 6H).

$^{13}$C-NMR (125 MHz, d₆-acetone)

$\delta$ 146.6, 141.4, 136.4, 136.2, 136.1, 135.5, 132.6, 132.6, 132.2, 130.6, 130.5, 130.0, 129.7, 129.6, 61.8, 41.8, 38.9, 33.6, 31.5, 26.8, 26.6, 13.9, 12.7

HRMS (EI+)

Calculated for C₂₆H₃₆O: 352.2766

Found: 352.2764

**Octaene 4.34.** Following the general MIDA boronate cross-coupling reaction condition, MIDA boronate 4.81 (28.4 mg, 0.061 mmol), vinyl iodide 4.38 (19.5 mg, 0.092 mmol), 2nd generation XPhosPd cycle (4.8 mg, 0.006 mmol), NaOH (18.4 mg, 0.46 mmol), THF (1.0 mL), and degassed H₂O (0.2 mL) were combined and stirred at 23 °C for 1 h 30 min. The reaction was worked up using Et₂O (2.0 mL) and H₂O (2.0 mL) and the aqueous layer was extracted with Et₂O (2 x 2.0 mL). After drying, filtering, and concentrating, the residue was dry loaded onto celite and purified by reverse phase column chromatography on C18 silica gel (H₂O:MeCN 90:10 → 0:100) to afford octaene 4.34 as an orange solid (6.9 mg, 29%).
TLC (hexanes:EtOAc 4:1)
\[ R_f = 0.27 \] stained by KMnO₄

¹H-NMR (500 MHz, d₆-acetone)
\[ \delta 6.91-6.59 \text{ (m, 3H)}, 6.41-6.06 \text{ (m, 9H)}, 5.79 \text{ (dt, } J = 15.0, 7.0 \text{ Hz, 1H)}, 5.73 \text{ (dd, } J = 15.0, 7.0 \text{ Hz, 1H)}, 3.55 \text{ (t, } J = 6.5 \text{ Hz, 2H)}, 2.21 \text{ (q, } J = 7.0 \text{ Hz, 2H)}, 2.01 \text{ (m, 1H)}, 1.97 \text{ (bs, 1H)}, 1.92 \text{ (s, 3H)}, 1.90 \text{ (s, 3H)}, 1.83 \text{ (s, 3H)}, 1.78-1.56 \text{ (m, 6H)}, 1.43-1.10 \text{ (m, 6H)}.\]

¹³C-NMR (125 MHz, d₆-acetone)
\[ \delta 146.6, 141.5, 137.6, 134.5, 134.4, 132.6, 132.4, 132.3, 132.0, 130.8, 130.7, 127.0, 126.9, 125.7, 120.6, 120.5, 61.8, 42.7, 39.0, 38.4, 31.5, 26.0, 24.5, 13.2, 13.0, 12.5 \]

HRMS (ESI+)
Calculated for C₂₆H₃₆O (M+H)⁺: 393.3157
Found: 393.3152

Nonaene 4.35. Following the general MIDA boronate cross-coupling reaction condition, MIDA boronate 4.86 (13.7 mg, 0.027 mmol), vinyl iodide 4.38 (4.8 mg, 0.023 mmol), 2nd generation XPhosPd cycle (0.9 mg, 0.001 mmol), NaOH (6.8 mg, 0.17 mmol), THF (0.5 mL), and degassed H₂O (0.1 mL) were combined and stirred at 23 °C for 4 h. The reaction was worked up using Et₂O (2.0 mL) and H₂O (2.0 mL) and the aqueous layer was extracted with Et₂O (2 x 2.0 mL). After drying, filtering, and concentrating, the residue was dry loaded onto celite and purified by column chromatography on florisil (hexanes:EtOAc 100:0 → 70:30) to afford nonaene 4.35 as an orange solid (4.3 mg, 36%).

TLC (hexanes:EtOAc 4:1)
\[ R_f = 0.28 \] stained by KMnO₄
\(^1\)H-NMR (500 MHz, CDCl\(_3\))
\[\delta \ 6.67-6.56 \ (m, 4H), \ 6.34 \ (d, \ J = 15.0 \ Hz, 1H), \ 6.32 \ (d, \ J = 15.0 \ Hz, 1H), \ 6.26-6.21 \ (m, 2H), \ 6.18 \ (d, \ J = 15.0 \ Hz, 1H), \ 6.14-6.07 \ (m, 3H), \ 5.72 \ (dt, \ J = 15.0, 7.0 \ Hz, 1H), \ 5.67 \ (dd, \ J = 15.0, 7.0 \ Hz, 1H), \ 3.68 \ (t, \ J = 6.0 \ Hz, 2H), \ 2.25 \ (q, \ J = 7.5 \ Hz, 2H), \ 2.05 \ (m, 1H), \ 1.96 \ (s, 6H), \ 1.91 \ (s, 3H), \ 1.90 \ (s, 3H), \ 1.75 \ (bs, 1H), \ 1.74-1.63 \ (m, 6H), \ 1.34-1.07 \ (m, 6H).\]

\(^{13}\)C-NMR (125 MHz, CDCl\(_3\))
\[\delta \ 137.4, \ 137.0, \ 136.5, \ 136.3, \ 136.1, \ 135.8, \ 135.6, \ 132.5, \ 132.4, \ 132.3, \ 132.2, \ 130.5, \ 130.2, \ 130.6, \ 129.8, \ 129.0, \ 125.0, \ 124.8, \ 62.5, \ 41.2, \ 33.2, \ 32.5, \ 29.4, \ 26.2, \ 26.1, \ 13.0, \ 12.9, \ 12.8, \ 11.4\]

HRMS (ESI+)
Calculated for C\(_{31}\)H\(_{45}\)O (M+H)
\[^+\]: 433.3470
Found: 433.3478

**Decaene 4.36.** Following the general MIDA boronate cross-coupling reaction condition, MIDA boronate 4.87 (30.0 mg, 0.057 mmol), vinyl iodide 4.38 (18.0 mg, 0.085 mmol), 2\(^{nd}\) generation XPhosPd cycle (4.5 mg, 0.006 mmol), NaOH (17.0 mg, 0.42 mmol), THF (1.0 mL), and degassed H\(_2\)O (0.2 mL) were combined and stirred at 23 °C for 1 h 30 min. The reaction was worked up using Et\(_2\)O (2.0 mL) and H\(_2\)O (2.0 mL) and the aqueous layer was extracted with Et\(_2\)O (2 x 2.0 mL). After drying, filtering, and concentrating, the residue was dry loaded onto celite and purified by reverse phase column chromatography on C18 silica (H\(_2\)O:MeCN 95:5 \(\rightarrow\) 0:100) to afford decaene 4.36 as an orange solid (mass ND).

TLC (hexanes:EtOAc 4:1)
\[R_f = 0.29\] stained by KMnO\(_4\)
$^1$H-NMR (500 MHz, d$_6$-acetone)

$\delta$ 6.80-6.67 (m, 4H), 6.41 (d, $J = 15.0$ Hz, 1H), 6.38 (d, $J = 15.0$ Hz, 1H), 6.37-6.27 (m, 4H), 6.26-6.11 (m, 4H), 5.81 (dd, $J = 15.0$, 7.5 Hz, 1H), 5.71 (dd, $J = 15.0$, 7.0 Hz, 1H), 3.80 (bs, 1H), 3.55 (t, $J = 6.0$ Hz, 2H), 2.20 (q, $J = 7.5$ Hz, 2H), 2.03 (m, 1H), 1.98 (s, 6H), 1.93 (s, 3H), 1.89 (s, 3H), 1.79-1.58 (m, 6H), 1.36-1.10 (m, 6H).

**MIDA boronate 4.20.** To a 200 mL round bottom flask charged with a stir bar and dicyclohexylborane (503 mg, 2.8 mmol), under an inert atmosphere, was added THF (28 mL). The solution was cooled to 0 °C and catecholborane (3.0 mL, 28.2 mmol) was added in one portion. The solution was stirred at 0 °C for an additional 5 min. A solution of alkyne 4.88 (4.18 g, 28.2 mmol) in THF (28 mL) was prepared and dropwise added to the cooled reaction solution over 15 min. The solution was warmed to 23 °C and stirred at this temperature for 15.5 h. After this time, to the solution was added N-methyliminodiacetic acid (MIDA, 6.31 g, 42.3 mmol) and DMSO (56 mL). The suspension was sealed under N$_2$ and placed in a 60 °C oil bath with stirring for 4.5 h. After this time, the solution was cooled to 23 °C and transferred to a separatory funnel and diluted with H$_2$O (300 mL) and EtOAc (300 mL). After shaking, the layers were separated and the aqueous layer was extracted with EtOAc (250 mL). The combined organic layers were washed with brine:H$_2$O (1:1, 250 mL). The organic layer were dried over MgSO$_4$, filtered and concentrated in vacuo. The resulting residue was dry loaded onto celite and purified by column chromatography on silica gel (Et$_2$O:MeCN 100:0 → 60:40) to afford MIDA boronate 4.20 as a white solid (5.43 g, 63%).

TLC (Et$_2$O:MeCN 6:1)

$R_f = 0.41$, stained by KMnO$_4$
\(^1\)H-NMR (500 MHz, d\(_6\)-acetone)

\[ \delta 6.53 \text{ (d, } J = 18.0 \text{ Hz, 1H)}, 5.48 \text{ (d, } J = 18.0 \text{ Hz, 1H)}, 4.23 \text{ (d, } J = 17.0 \text{ Hz, 2H)}, 4.05 \text{ (d, } J = 17.0 \text{ Hz, 2H)}, 3.06 \text{ (s, 3H)}, 1.99 \text{ (s, 2H)}, 1.69 \text{ (d, } J = 1.0 \text{ Hz, 3H)}, 1.61 \text{ (m, 2H)}, 1.45 \text{ (m, 2H)}, 1.01 \text{ (s, 6H)}. \]

HRMS (ESI+)

Calculated for C\(_{16}\)H\(_{25}\)BNO\(_4\) (M+H): 306.1877

Found: 306.1870

**Vinyl bromide 4.21.** To a 300 mL round bottom flask charged with a stir bar was added vinyl bromide 4.89\(^\text{12}\) (602 mg, 3.6 mmol), powdered mol sieves (3.0 g), silver carbonate (3.0 g, 10.9 mmol), sugar 4.90 (3.0 g, 7.3 mmol), hexanes (100 mL), and CH\(_2\)Cl\(_2\) (20 mL). The suspension was stirred at 23 °C for 48 h. After this time, the suspension was filtered through a pad of celite, rinsing the filter cake with hexanes. The filtrate was concentrated \textit{in vacuo} and the resulting residue was dry loaded onto celite and purified by reverse phase chromatography on C18 silica (H\(_2\)O:MeCN 90:10 → 0:100) to afford vinyl bromide 4.21 as a white solid (932 mg, 52%).

TLC (CH\(_2\)Cl\(_2\):EtOAc 2:1)

\[ R_f = 0.47 \text{ stained by KMnO}_4 \]

\(^1\)H-NMR (500 MHz, CDCl\(_3\))

\[ \delta 7.53 \text{ (q, } J = 1.5 \text{ Hz, 1H)}, 5.66 \text{ (d, } J = 8.0 \text{ Hz, 1H)}, 5.20 \text{ (t, } J = 9.5 \text{ Hz, 1H)}, 5.09 \text{ (dd, } J = 10.0, 8.0 \text{ Hz, 1H)}, 5.03 \text{ (t, } J = 9.5 \text{ Hz, 1H)}, 4.19 \text{ (dd, } J = 12.5, 4.5 \text{ Hz, 1H)}, 3.99 \text{ (dd, } J = 12.5, 1.5 \text{ Hz, 1H)}, 3.82 \text{ (m, 1H)}, 1.96 \text{ (s, 3H)}, 1.92 \text{ (s, 3H)}, 1.91 \text{ (s, 6H)}, 1.88 \text{ (s, 3H)}. \]
\[^{13}C\text{-NMR}\ (125 \text{ MHz, CDCl}_3)\]
\[
\begin{align*}
\delta &= 170.1, 169.6, 169.0, 168.9, 162.4, 132.4, 125.9, 92.1, 72.4, 72.1, 69.8, 67.5, 61.1, 20.4, 20.3, 20.2, 20.2, 15.3
\end{align*}
\]

HRMS (ESI+)

Calculated for C\(_{18}\)H\(_{23}\)BrNaO\(_{11}\) (M+H): 517.0321

Found: 517.0322

Pinacol ester 4.91. Following the general deprotection condition, MIDA boronate 4.20 (763 mg, 2.5 mmol), NaHCO\(_3\) (1.1 g, 12.5 mmol), pinacol (443 mg, 3.8 mmol), and MeOH (13 mL) were stirred at 45 °C for 3 h. After filtration and concentration, to the residue was added NaHCO\(_3\) (1.1 g, 12.5 mmol), CaCl\(_2\) (1.4 g, 12.5 mmol), and toluene (13 mL). After stirring at 23 °C for 1 h, filtering, and concentrating, pinacol ester 4.91 was obtained as a clear, colorless oil (686 mg, 99%). Characterization of this compound was consistent with previously reported data.\(^{13}\)

MIDA boronate 4.39. Following the general pinacol ester cross-coupling condition, pinacol ester 4.91 (545 mg, 2.0 mmol), MIDA boronate 4.6 (530 mg, 1.5 mmol), \(^2\)nd generation XPhosPd cycle (120 mg, 0.15 mmol), Cs\(_2\)CO\(_3\) (2.0 mg, 6.1 mmol), and DMSO (30 mL) were combined and stirred at 35 °C for 12 h 30 min, the reaction was worked up using H\(_2\)O:brine (1:1, 150 mL) and EtOAc (150 mL). After drying, filtering, and concentrating, the residue was dry loaded onto celite and purified by column chromatography on florisil (Et\(_2\)O:MeCN 100:0 → 60:40) to afford MIDA boronate 4.39 as a pale yellow solid (370 mg, 66%).
TLC (Et₂O:MeCN 6:1)
R_f =0.31 stained by KMnO₄

¹H-NMR (500 MHz, d₆-acetone)
δ 7.00 (dd, J = 17.0, 11.0 Hz, 1H), 6.24 (d, J = 16.5 Hz, 1H), 6.14 (d, J = 11.0 Hz, 1H), 6.11 (d, J = 16.5 Hz, 1H), 5.72 (d, J = 17.0 Hz, 1H), 4.21 (d, J = 17.0 Hz, 2H), 4.03 (d, J = 17.0 Hz, 2H), 3.00 (s, 3H), 2.02 (m, 2H), 1.95 (s, 3H), 1.70 (s, 3H), 1.61 (m, 2H), 1.48 (m, 2H), 1.02 (s, 6H).

¹³C-NMR (125 MHz, d₆-acetone)
δ 169.1, 139.2, 138.5, 137.3, 136.6, 133.0, 129.5, 127.8, 62.2, 47.3, 40.1, 34.5, 33.1, 29.1, 21.8, 19.8, 12.7

¹¹B-NMR (128 MHz, d₆-acetone)
δ 11.1

HRMS (ESI+)
Calculated for C₂₁H₃₁BNO₄ (M+H)^+: 372.2346
Found: 372.2346

Pinacol ester 4.92. Following the general deprotection condition, MIDA boronate 4.39 (370 mg, 1.0 mmol), NaHCO₃ (420 mg, 5.0 mmol), pinacol (177 mg, 1.5 mmol), and MeOH (5.0 mL) were stirred at 45 °C for 3 h. After filtration and concentration, to the residue was added NaHCO₃ (420 mg, 5.0 mmol), CaCl₂ (555 mg, 5.0 mmol), and toluene (5.0 mL). After stirring at 23 °C for 1 h, filtering, and concentrating, pinacol ester 4.92 was obtained as a clear, colorless oil (341 mg, 99%).
**1H-NMR (500 MHz, d$_6$-acetone)**

δ 7.38 (dd, $J = 17.0$, 11.0 Hz, 1H), 6.34 (d, $J = 16.0$ Hz, 1H), 6.17 (d, $J = 11.0$ Hz, 1H), 6.15 (d, $J = 16.0$ Hz, 1H), 5.53 (d, $J = 17.0$ Hz, 1H), 2.02 (m, 2H), 2.00 (s, 3H), 1.71 (s, 3H), 1.66-1.58 (m, 2H), 1.50-1.44 (m, 2H), 1.25 (s, 12H), 1.03 (s, 6H).

**13C-NMR (125 MHz, d$_6$-acetone)**

δ 146.0, 139.8, 138.4, 138.2, 132.6, 130.1, 129.3, 83.6, 40.2, 34.8, 33.5, 30.5, 29.2, 25.1, 21.9, 19.8, 12.8

**11B-NMR (128 MHz, d$_6$-acetone)**

δ 30.4

**HRMS (ESI+)**

Calculated for C$_{22}$H$_{36}$BO$_2$ (M+H)$^+$: 343.2808

Found: 343.2809

**MIDA boronate 4.40.** Following the general pinacol ester cross-coupling condition, pinacol ester 4.92 (341 mg, 1.0 mmol), MIDA boronate 4.11 (425 mg, 1.1 mmol), 2$^{nd}$ generation XPhosPd cycle (78 mg, 0.01 mmol), Cs$_2$CO$_3$ (1.3 mg, 4.0 mmol), and DMSO (20 mL) were combined and stirred at 35 °C for 16 h, the reaction was worked up using H$_2$O:brine (1:1, 100 mL) and EtOAc (100 mL). After drying, filtering, and concentrating, the residue was dry loaded onto celite and purified by reverse phase column chromatography on C18 silica (H$_2$O:MeCN 90:10 → 0:100) to afford MIDA boronate 4.40 as a pale yellow solid (174 mg, 37%).

**TLC (Et$_2$O:MeCN 6:1)**

R$_f$ =0.38 stained by KMnO$_4$
\(^1\)H-NMR (500 MHz, d\(_6\)-acetone)
\[\delta 6.76 (dd, J = 15.0, 11.0 \text{ Hz}, 1\text{H}), 6.75-6.70 (m, 2\text{H}), 6.57-6.52 (m, 1\text{H}), 6.42 (d, J = 15.0 \text{ Hz}, 1\text{H}), 6.33-6.29 (m, 1\text{H}), 6.26-6.15 (m, 3\text{H}), 4.24 (d, J = 17.0 \text{ Hz}, 2\text{H}), 4.07 (d, J = 17.0 \text{ Hz}, 2\text{H}), 2.99 (s, 3\text{H}), 2.04 (m, 2\text{H}), 2.01 (s, 3\text{H}), 2.00 (s, 3\text{H}), 1.84 (s, 3\text{H}), 1.72 (s, 3\text{H}), 1.66-1.58 (m, 2\text{H}), 1.52-1.45 (m, 2\text{H}), 1.04 (s, 6\text{H}).\]

\(^{13}\)C-NMR (125 MHz, d\(_6\)-acetone)
\[\delta 169.1, 138.8, 138.7, 138.3, 137.7, 137.4, 136.4, 133.1, 132.0, 131.2, 130.4, 129.7, 127.1, 125.9, 83.6, 62.6, 47.1, 40.4, 34.9, 33.6, 33.5, 29.3, 25.1, 19.9, 12.8, 12.7\]

\(^{11}\)B-NMR (128 MHz, d\(_6\)-acetone)
\[\delta 11.8\]

HRMS (ESI+)
Calculated for C\(_{29}\)H\(_{41}\)BNO\(_4\) (M+H): 478.3129
Found: 478.3127

**Pinacol ester 4.93.** Following the general deprotection condition, MIDA boronate 4.40 (174 mg, 0.4 mmol), NaHCO\(_3\) (150 mg, 1.8 mmol), pinacol (63 mg, 0.5 mmol), and MeOH (2.0 mL) were stirred at 45 °C for 3 h. After filtration and concentration, to the residue was added NaHCO\(_3\) (150 mg, 1.8 mmol), CaCl\(_2\) (200 mg, 1.8 mmol), and toluene (2.0 mL). After stirring at 23 °C for 1 h, filtering, and concentrating, pinacol ester 4.93 was obtained as a clear, colorless oil (160 mg, 99%).

\(^1\)H-NMR (500 MHz, d\(_6\)-acetone)
\[\delta 6.90 (d, J = 11.0 \text{ Hz}, 1\text{H}), 6.85 (d, J = 12.0 \text{ Hz}, 1\text{H}), 6.82 (d, J = 11.0 \text{ Hz}, 1\text{H}), 6.78 (dd, J = 15.0, 11.0 \text{ Hz}, 1\text{H}), 6.68 (dd, J = 12.0, 15.0 \text{ Hz}, 1\text{H}), 6.42 (d, J = 15.0 \text{ Hz}, 1\text{H}), 6.31 (d, J = 12.0 \text{ Hz}, 1\text{H}), 6.22 (dd, J = 17.0, 12.0 \text{ Hz}, 1\text{H}), 6.17 (d, J = 17.0 \text{ Hz}, 1\text{H}), 2.04 (m,
2H), 2.03 (s, 3H), 1.99 (s, 3H), 1.81 (s, 3H), 1.71 (s, 3H), 1.66-1.58 (m, 2H), 1.51-1.45 (m, 2H), 1.25 (s, 12H), 1.04 (s, 6H).

$^{13}$C-NMR (125 MHz, $d_6$-acetone)
δ 143.5, 138.7, 138.7, 138.6, 138.0, 136.8, 133.2, 132.7, 131.9, 129.7, 129.6, 127.3, 126.5, 83.8, 40.2, 34.8, 33.5, 29.2, 29.1, 25.1, 21.9, 19.8, 14.6, 12.8, 12.8

$^{11}$B-NMR (128 MHz, $d_6$-acetone)
δ 30.5

HRMS (ESI+)
Calculated for $C_{30}H_{46}BO_2$ (M+H)$^+$: 449.3591
Found: 449.3591

MIDA boronate 4.41. Following the general pinacol ester cross-coupling condition, pinacol ester 4.93 (160 mg, 0.4 mmol), MIDA boronate 4.9 (141 mg, 0.4 mmol), 2$^{nd}$ generation XPhosPd cycle (28 mg, 0.04 mmol), Cs$_2$CO$_3$ (469 mg, 1.4 mmol), and DMSO (7 mL) were combined and stirred at 35 °C for 13 h, the reaction was worked up using H$_2$O:brine (1:1, 50 mL) and EtOAc (50 mL). After drying, filtering, and concentrating, the residue was dry loaded onto celite and purified by reverse phase column chromatography on C18 silica (H$_2$O:MeCN 90:10 → 0:100) to afford MIDA boronate 4.41 as a pale yellow solid (61 mg, 30%).

TLC (Et$_2$O:MeCN 6:1)
$R_f$ =0.29 stained by KMnO$_4$

$^1$H-NMR (500 MHz, $d_6$-acetone)
δ 6.77-6.71 (m, 4H), 6.67 (d, $J$ = 18.0 Hz, 1H), 6.48 (d, $J$ = 15.0 Hz, 1H), 6.41 (d, $J$ = 16.0 Hz, 1H), 6.36 (d, $J$ = 11.0 Hz, 1H), 6.34 (d, $J$ = 11.0 Hz, 1H), 6.29 (d, $J$ = 11.0 Hz,
1H), 6.25-6.12 (m, 4H), 4.21 (d, J = 17.0 Hz, 2H), 4.04 (d, J = 17.0 Hz, 2H), 3.00 (s, 3H), 2.03 (m, 2H), 2.00 (s, 3H), 1.99 (s, 6H), 1.95 (s, 3H), 1.71 (s, 3H), 1.66-1.59 (m, 2H), 1.51-1.45 (m, 2H), 1.03 (s, 6H).

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

$\delta$ 169.1, 146.6, 144.1, 141.5, 138.8, 138.7, 137.7, 137.0, 136.6, 134.1, 132.0, 130.7, 127.3, 127.0, 126.6, 125.9, 125.0, 124.9, 124.5, 120.6, 62.3, 48.0, 40.3, 34.9, 33.6, 31.5, 29.3, 26.0, 19.9, 12.8, 12.7, 12.7, 12.6

$^{11}$B-NMR (128 MHz, d$_6$-acetone)

$\delta$ 11.5

HRMS (ESI+)

Calculated for C$_{36}$H$_{49}$BNO$_4$ (M+H)$^+$: 570.3755

Found: 570.3752

Neurosporaxanthin β-D-glucopyranoside tetraacetate 4.42. Following the general MIDA boronate cross-coupling reaction condition, MIDA boronate 4.41 (15.0 mg, 0.026 mmol), vinyl bromide 4.21 (19.6 mg, 0.040 mmol), 2nd generation XPhosPd cycle (2.1 mg, 0.003 mmol), NaOH (7.9 mg, 0.20 mmol), THF (0.5 mL), and degassed H$_2$O (0.1 mL) were combined and stirred at 23 °C for 1 h 15 min. The reaction was worked up using Et$_2$O (2.0 mL) and H$_2$O (2.0 mL) and the aqueous layer was extracted with Et$_2$O (2 x 2.0 mL). After drying, filtering, and concentrating, the residue was dry loaded onto celite and purified by column chromatography on silica (hexanes:EtOAc 100:0 → 90:10 → 60:40) to afford Neurosporaxanthin β-D-glucopyranoside tetraacetate 4.42 as an orange solid (12.8 mg, 59%).

TLC (hexanes:EtOAc 3:2)

$R_f$ =0.47 stained by KMnO$_4$
$^1$H-NMR (500 MHz, CDCl$_3$)

$\delta$ 7.33 (d, $J = 11.0$ Hz, 1H), 6.68 (dd, $J = 15.0$, 11.0 Hz, 1H), 6.68-6.65 (m, 3H), 6.62 (dd, $J = 15.0$, 11.0 Hz, 1H), 6.48 (dd, $J = 15.0$, 11.0 Hz, 1H), 6.48 (d, $J = 15.0$ Hz, 1H), 6.40 (d, $J = 11.0$ Hz, 1H), 6.35 (d, $J = 15.0$ Hz, 1H), 6.33 (d, $J = 11.0$ Hz, 1H), 6.26 (d, $J = 11.0$ Hz, 1H), 6.18 (d, $J = 16.0$ Hz, 1H), 6.16 (d, $J = 11.0$ Hz, 1H), 6.13 (d, $J = 16.0$ Hz, 1H), 5.78 (d, $J = 8.0$ Hz, 1H), 5.30 (t, $J = 9.0$ Hz, 1H), 5.27 (dd, $J = 9.5$, 8.0 Hz, 1H), 5.17 (t, $J = 9.5$ Hz, 1H), 4.32 (m, 1H), 4.13 (m, 1H), 3.89 (ddd, $J = 9.5$, 4.5, 2.5, 1H), 2.09 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 2.03 (s, 3H), 2.02 (m, 2H), 2.01 (s, 3H), 1.99 (s, 6H), 1.98 (s, 6H), 1.72 (s, 3H), 1.61 (m, 2H), 1.47 (m, 2H), 1.03 (s, 6H).

$^1$H-NMR for Neurosporaxanthin $\beta$-D-glucopyranoside tetraacetate \textbf{4.42}

<table>
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HRMS (ESI+)
Calculated for C\textsubscript{49}H\textsubscript{64}NaO\textsubscript{11} (M+H): 851.4346
Found: 851.4343

REFERENCES


6 The route to this building block was developed by Seiko Fujii.


10 Sigma Aldrich product number 703710.


