STEREOSELECTIVE SYNTHESIS AND ITERATIVE COUPLING OF C$_{sp}^3$ BORONATES FOR AUTOMATING SMALL MOLECULE SYNTHESIS

BY

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DISSEPTION

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ABSTRACT

Small molecules perform many important functions in nature, medicine, and technology. However, efforts to discover and optimize new small molecule function are often impeded by limitations in synthetic access to this class of compounds. In contrast to peptide and oligonucleotide syntheses, small molecule syntheses typically employ strategies and purification methods that are highly customized for each target. A broadly applicable automated process for the synthesis of different classes of small molecules has thus far remained elusive. To enable the more generalized automation of small molecule synthesis, a common building block-based strategy and a common purification process for the preparation of many different types of small molecules are needed.

Towards this goal, we focused on expanding the scope of a building block-based strategy involving the iterative coupling of boronate building blocks to include Csp$^3$-rich linear and polycyclic small molecules. The first approach undertaken was the discovery of a pinene-derived iminodiacetic acid (PIDA) ligand which enabled the stereoselective synthesis of a wide range of new types of Csp$^3$ boronates. The utility of these Csp$^3$ boronates was demonstrated in the synthesis of a pharmaceutically relevant target using a previously undescribed iterative Csp$^3$-Csp$^2$ coupling.

In order to access Csp$^3$-rich cyclic and polycyclic molecules via the same building block-based iterative coupling process, a linear-to-cyclized strategy inspired by the biosynthesis of polycyclic natural products was formulated. Iterative coupling of Csp$^3$ boronates generates linear precursors which can then be polycyclized to give the complex topology found in many polycyclic natural products. This strategy was utilized in the synthesis of four natural products and natural product-like cores from boronate building blocks.

This building block-based approach to synthesis was successfully automated with the discovery of a new type of catch-and-release purification protocol applicable to the boronate intermediates used in synthesis. 14 distinct classes of small molecules were constructed from boronate building blocks on a small molecule synthesizer using the same iterative coupling process. The synthesis-enabled advances in automating small molecule synthesis described in this dissertation now stands to better enable the scientific community to bring the substantial power of small molecule synthesis to bear upon many important unsolved problems in society.
To my parents and my brother
ACKNOWLEDGEMENTS

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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>2(^{nd}) gen. XPhos</td>
<td>chloro(2-dicyclohexylphosphino-2',4',6'-trisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)palladium(II)]</td>
</tr>
<tr>
<td>dba</td>
<td>dibenzylideneacetone</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DCE</td>
<td>1,2-dichloroethane</td>
</tr>
<tr>
<td>DCM</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>DMF</td>
<td>(N,N)-dimethylformamide</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-((N,N)-dimethylamino)-pyridine</td>
</tr>
<tr>
<td>DMPU</td>
<td>1,3-Dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
</tr>
<tr>
<td>dpff</td>
<td>1,1’-bis(diphenylphosphino)ferrocene</td>
</tr>
<tr>
<td>Fmoc</td>
<td>fluorenlymethoxycarbonyl</td>
</tr>
<tr>
<td>HFIPA</td>
<td>1,1,1,3,3,3-hexafluoro-2-propanol</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>HPLC</td>
<td>high-performance liquid chromatography</td>
</tr>
<tr>
<td>MIDA</td>
<td>$N$-methyliminodiacetic acid</td>
</tr>
<tr>
<td>MOM</td>
<td>methoxymethyl</td>
</tr>
<tr>
<td>NMP</td>
<td>$N$-methylpyrrolidine</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>o-tol</td>
<td>ortho-tolyl</td>
</tr>
<tr>
<td>PIDA</td>
<td>pinene-derived iminodiacetic acid</td>
</tr>
<tr>
<td>SPhos</td>
<td>2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetra-$N$-butylammonium fluoride</td>
</tr>
<tr>
<td>TBDPSE</td>
<td>2-(t-butyldiphenylsilyl)ethyl</td>
</tr>
<tr>
<td>TBS</td>
<td>$t$-butyldimethylsilyl</td>
</tr>
</tbody>
</table>
TIPS triisopropylsilyl

TMSE 2-(trimethylsilyl)ethyl

TLC thin layer chromatography

UV ultraviolet

XPhos 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl
1-1 DEVELOPING A PLATFORM FOR AUTOMATING SMALL MOLECULE SYNTHESIS

Small molecules perform many important functions in nature, medicine, and technology. However, efforts to discover and optimize new small molecule function are often impeded by limitations in synthetic access to this class of compounds. In contrast, general and automated synthesis platforms now exist for peptides\(^1\) and oligonucleotides.\(^2\) The resulting expanded access to these molecules has dramatically accelerated the discovery of their functional potential. Progress in the same direction has also been made for oligosaccharide synthesis\(^3\) and some organic polymers,\(^4\) but a similarly generalized synthesis platform does not yet exist for small molecules. Small molecule synthesis has thus far remained a time-intensive, complex process that lies solely in the domain of trained chemists.

However, despite their structural diversity, many small molecules possess inherent modularity that would enable systematic building block-based construction. Like peptides, oligonucleotides and oligosaccharides, most natural products are biosynthesized via the iterative assembly of a small set of building blocks, such as malonyl coenzyme A, isopentenyl pyrophosphate, and pyruvic acid.\(^5\) Many materials and pharmaceuticals comprise collections of aryl and/or heteroaryl components.\(^6\)

To harness this modularity, our group developed an iterative coupling platform for the synthesis of small molecules from boron-containing building blocks. The iterative assembly of these building blocks was enabled by the discovery of the N-methyliminodiacetic acid (MIDA) ligand, which can attenuate the reactivity of a boronic acid, similar to the way a fluorenylmethoxycarbonyl (Fmoc) group protects an amine (Figure 1-1).

![Figure 1-1](image)

**Figure 1-1.** The iterative coupling platform for small molecule synthesis from MIDA boronate building blocks is analogous to peptide synthesis from protected amino acids. D = deprotection, C = coupling
In the iterative coupling platform, making and coupling MIDA boronate building blocks are the two key components to synthesis. In this chapter, we summarize the efforts our group and others have made in the synthesis and iterative assembly of Csp$^2$ MIDA boronate building blocks, which have enabled access to a wide range of linear, Csp$^2$-rich small molecules, especially the polyene natural products.

1-2 SYNTHESIS OF Csp$^2$ MIDA BORONATE BUILDING BLOCKS

The benchtop stability of MIDA boronates has enabled more than 200 of these building blocks to be made commercially available. In addition, simple MIDA boronate building blocks can also be made from the corresponding commercial boronic acids by complexation with the MIDA ligand under various conditions.\(^7\)

Alkenyl boronic esters are commonly prepared by hydroboration of alkynes with catecholborane or pinacolborane. Because of the instability of many alkenyl boronic acids, it is desirable to convert the boronic ester directly into the corresponding MIDA boronates without hydrolyzing the boronic ester under acidic conditions, circumventing the sensitive boronic acid moiety. In the preparation of one MIDA boronate building blocks en route to the asymmetric total synthesis of (–)-peridinin\(^8\), we found that the pinacol boronic ester obtained by the dicyclohexylborane-catalyzed hydroboration of the corresponding alkyne can be converted into MIDA boronate 1.1 simply by treatment with MIDA and DMSO at 65 °C (Scheme 1-1). The unreacted pinacol boronic ester 1.1 was subjected to another 2 cycles of the reaction to give 1.2 in an overall yield of 73%. The Taylor group found that this hydroboration-transesterification sequence is general for the synthesis of alkenyl MIDA boronates from simple alkyne starting materials via hydroboration with catecholborane.\(^9\)

![Scheme 1-1](image)

Scheme 1-1. Synthesis of an alkenyl MIDA boronate from the alkyne via a hydroboration-transesterification reaction.

The MIDA boronate can also be installed directly onto a commercial starting material without the intermediacy of the boronic acid or ester. This is especially useful when the boronic acid or ester is too unstable to be isolated. The 2-heterocyclic borane is an archtypical unstable boronic acid containing an extremely labile carbon-boron bond. A “hot protocol” was developed for the synthesis of 2-pyridyl MIDA boronates. This procedure involved the direct treatment of the 2-pyridyl triisopropylborate salt with MIDA in DMSO at 115 °C.\(^10\) This procedure works well for a range of 2-heterocyclic, alkynyl, and
alkenyl MIDA boronates (Table 1-1). The use of elevated temperatures is necessary for high yields because at lower temperatures, the triisopropylborate salt undergoes decomposition faster than transesterification to the MIDA boronate, which is stable at 115 °C.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>M</th>
<th>B(OR)₃</th>
<th>% yield</th>
<th>Ref.</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Me &lt;br&gt; N=N-Li</td>
<td>B(OMe)₃</td>
<td>58</td>
<td>10</td>
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<tr>
<td>2</td>
<td>N=N-Li</td>
<td>B(OMe)₃</td>
<td>30</td>
<td>10</td>
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<tr>
<td>3</td>
<td>N=N-Li</td>
<td>B(OMe)₃</td>
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<td>B(OMe)₂</td>
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<td>5</td>
<td>Me &lt;br&gt; MgBr</td>
<td>B(OMe)₂</td>
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<td>6</td>
<td>MgBr &lt;br&gt; Br</td>
<td>B(OMe)₂</td>
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<td>7</td>
<td>MgBr &lt;br&gt; Br</td>
<td>B(OMe)₂</td>
<td>81</td>
<td>8</td>
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</tbody>
</table>

**Table 1-1.** Synthesis of MIDA boronates using the “hot protocol”.

Ingleson and co-workers developed a Friedel-Crafts type direct electrophilic borylation of arenes and heteroarenes using a borenium cation as the electrophile.¹¹ The same trends for site-selectivity is observed in this reaction as those for Friedel-Crafts reactions. This finding allows for the preparation of aryl and heteroaryl MIDA boronates without pre-functionalizing the arene with a halide.
In our early studies, we established that the MIDA boronate motif is compatible with a wide variety of reaction conditions involving acids, soft nucleophiles, reductants, oxidants, and electrophiles (Figure 1-2).\textsuperscript{12}
Figure 1-2. MIDA boronates are compatible with typical oxidation and reduction reactions, protecting group manipulations, as well as reactions that involve soft nucleophiles. They are generally incompatible with hard nucleophiles.

This general compatibility with a wide variety of common reaction and aqueous work-up conditions has allowed simple MIDA boronates that can be made on scale to be elaborated into complex MIDA boronates that are not readily accessed by other methods. For example, simple bifunctional building blocks (E)- and (Z)-1.5 can be engaged in a host of Pd-catalyzed cross-coupling reactions to generate a range of dienyl and enyne MIDA boronates (Figure 1-3).13,14 Importantly, in each of these reactions, the stereochemistry of the double bond in 1.5 is faithfully translated into the corresponding product.

Figure 1-3. Cross-coupling reactions explored with both stereoisomers of simple MIDA boronate building block 1.1 to yield diene and enyne MIDA boronates.

Ethynyl MIDA boronate 1.215 can also undergo a range of reactions to generate aryl and heteroaryl MIDA boronates. The Toste group was able to engage the alkyne moiety in Sonogashira
couplings to generate arylethynyl MIDA boronates which were then subjected to a gold-catalyzed cycloisomerization resulting in 2-benzofuranyl 1.7a or 2-indolyl MIDA boronates 1.7b (Scheme 1-2). This methodology obviates the need to handle these notoriously unstable boranes obtained in a typical lithiation and trapping sequence from the parent heterocycles. The Glorius group disclosed a Rh(III)-catalyzed C-H activation and annulation sequence with ethynyl MIDA boronate, further expanding the scope of boron-functionalized heterocycles (1.11 and 1.12) that can be accessed. In addition, the alkyne handle can undergo cycloaddition reactions to yield various types of heterocycles (1.8, 1.9 and 1.10) from 1,3 dipolarophiles and a highly-substituted arene (1.13).

Scheme 1-2. Cycloaddition reactions, and Sonogashira couplings followed by cycloisomerization reactions involving ethynyl MIDA boronate 1.6.

1-3 SYNTHESIS VIA SLOW-RELEASE CROSS-COUPLING

A challenge that arises from using unstable boronic acids as coupling partners arises from the problem of rapid decomposition under the reaction conditions. In both Suzuki-Miyaura cross-coupling and Rh-catalyzed additions of boronic acids to electrophiles, heat, base and/or the metal catalyst can cause the decomposition of boronic acids to become competitive with productive cross-coupling. This limits the synthetic utility of boronic acids. We reasoned that the scope of practical reactions involving boronic acids can be expanded with the rate-controlled hydrolysis of bench-stable MIDA boronates under the cross-coupling conditions, which would allow the 'slow release' of unstable boronic acids into the reaction mixture. This process, which we term slow-release cross-coupling, has been particularly useful for coupling unstable and even un-isolable boronic acids.

Using the slow-release protocol, higher isolated yields of the cross-coupled product are achieved with the MIDA boronate than with the corresponding freshly prepared boronic acid (Table 1-3). This
difference is especially remarkable for the indole MIDA boronate derivative (entry 6), with almost an 80% increase in the isolated yield. Importantly, only 1 equivalent of the MIDA boronate is required to achieve high yields. Furthermore, the isolated yields obtained with the MIDA boronates were comparable to those obtained using syringe-pump additions of the boronic acid. This method has been further demonstrated with a number of other unstable aryl, heteroaryl, alkyl, and vinyl MIDA boronates with a host of aryl chloride coupling partners.

![](image)

<table>
<thead>
<tr>
<th>entry</th>
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<th>1.16</th>
<th>% yield (1.14) (1.15)</th>
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<td>7</td>
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<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Table 1-3.** Cross-coupling efficiency of boronic acids and the corresponding MIDA boronate. 

- Reaction conditions:
  - 1.0 equiv. of 1.14 or 1.15 relative to p-t-butoxy chlorobenzene, 5 mol% of Pd(OAc)$_2$, 10 mol% SPhos, 7.5 equiv. of K$_3$PO$_4$, 0.07 M in 5:1 Dioxane:H$_2$O, 60 °C, 6 hr.
  - Cross-couplings were run at 100 °C.

Miller and coworkers utilized a highly regioselective double slow-release cross-coupling strategy of a tribromide while making atropisomerically enriched biaryl compounds. As shown in one of Miller’s several examples below (Scheme 1-3), the double Suzuki-Miyaura coupling was achieved.
through the use of functionalized MIDA boronates under slow-release conditions. The low concentration of free boronic acid made the system more amenable to distinguish the most reactive of the three bromides in the first coupling (often >10:1:1 regioselectivity), and further distinguished between the more reactive of the two remaining bromides in the second coupling (often >5:1 regioselectivity) with no racemization observed. Interestingly, it was found that the corresponding boronic acids exhibited very poor regioselectivity.

Scheme 1-3. Synthesis of atropoisomerically enriched polyaryls through Suzuki-Miyaura couplings

The slow-release strategy has been extended beyond Suzuki-Miyaura cross-coupling reactions. In diastereoselective Rh-catalyzed additions of organoboranes to chiral sulfinyl imines, Ellman and co-workers found that the rate-controlled hydrolysis of MIDA boronates \textit{in situ} led to dramatically increased yields to make a host of chiral \(\alpha\)-branched amines.\textsuperscript{22} These conditions were found in most cases to be more efficient than with the corresponding trifluoroborate salt and substantially more than the boronic acid under conditions optimized for each borane class. Brak and Ellman then applied this method in an efficient asymmetric synthesis of \((-\)\-) auantioclavine (Scheme 1-4), a natural alkaloid intermediate in the biosynthesis of the communesin family.\textsuperscript{23}

Scheme 1-4. Ellman’s synthesis of \((-\)\-) auantioclavine via a Rh-catalyzed asymmetric addition of a MIDA boronate into an \(N\)-\(t\)-butylsulfinyl imine.

1-4 SYNTHESIS VIA ITERATIVE COUPLING

The various methods available to synthesize MIDA boronate building blocks with pre-installed stereochemistry has enabled us to pursue the building block-based construction of small molecules using
the same process. We first demonstrated this with the synthesis of ratahine, a polyaryl natural product from a neo lignan family. The building blocks 1.18 – 1.21 are brought together by recursive cycles of deprotection and coupling to afford the natural product after a final global deprotection of the MOM groups (Scheme 1-5).

Scheme 1-5. Total synthesis of ratahine via iterative coupling

The polyene macrolide amphotericin B is a potent, ion-channel forming antifungal agent which has been refractory to microbial resistance despite widespread clinical utilization since the 1960s. One half of its complex structure consists of 7 contiguous E-alkenyl units. Another potent ion-channel forming polyene macrolide, vacidin A, contains an unusual Z,Z motif within the heptaene core (Figure 10). We have achieved both the synthesis of the polyene cores of both amphotericin B and vacidin A via a common reaction sequence using the iterative assembly of different stereochemically-defined building blocks (Scheme 1-6). Remarkably, all MIDA boronate intermediates were stable despite the extended conjugated polyene motifs, which are typically extremely sensitive to light, Lewis, and Bronsted acids. These 2 syntheses highlight the utility of pre-installing stereochemistry in the building blocks – the targets can be changed without changing the strategy for synthesis.
Scheme 1-6. Syntheses of the polyene core of Amphotericin B and vacidin A via iterative cycles of deprotection and coupling.

The ability to execute late-stage Suzuki-Miyaura coupling reactions to complete total syntheses of natural products is often impeded by the incompatibility of complex boranes with common reaction conditions. In addition, the borane reagents used to introduce boron are typically Lewis acidic and can lead to decomposition in complex molecule settings. These limitations can preclude the Suzuki-Miyaura transform in retrosynthetic analyses of complex molecules. The MIDA boronate platform provides solutions to this by enabling the preparation of complex boronate building blocks by allowing the masked boronic acid to be carried through multi-step synthesis and facilitates purification of the intermediates. The utility of these highly functionalized building blocks is demonstrated with the first stereocontrolled synthesis of (‒)-peridinin (Scheme 1-7). Three iterations of the deprotect-couple sequence followed by a global deprotection complete the total synthesis of the atypical carotenoid natural product. Notably, the four constituent MIDA boronate building blocks can be synthesized on decagram scale and stored for months without decomposition.

Scheme 1-7. First stereocontrolled synthesis of (‒)-peridinin via ICC.

Building on the progress made in polyene synthesis, our group undertook the challenge of developing a general synthesis to polyene motifs found in all polyene natural products. A general
retrosynthetic algorithm for systematically deconstructing the polyene motifs into a minimum number of MIDA boronate building blocks was devised. This analysis led our group to hypothesize that the polyene motifs in >75% of all polyene natural products can be constructed with 12 MIDA boronate building blocks and one coupling reaction. This hypothesis was tested and confirmed with the identification of the 15 polyene motifs found in >75% of the polyene natural products and their preparation using only the Suzuki-Miyaura cross-coupling to unite the MIDA boronate building blocks (Figure 1-4). This strategy also enabled the total synthesis of 3 polyene natural products using the same conditions used to assemble the polyene motifs.

![Diagram of polyene motifs](image)

**Figure 1-4.** Synthesis of the polyene motifs found in >75% of polyene natural products from MIDA boronate building blocks.

1-5 SUMMARY

The capacity of MIDA boronates to serve as stable boronic acid surrogates under multiple reaction conditions has allowed the synthesis of more complex MIDA boronate building blocks from simple MIDA boronates for small molecule synthesis with the iterative coupling platform. Many advances have been made in the synthesis and coupling of aryl, heteroaryl, and alkenyl MIDA boronate building blocks, which has allowed the platform to access linear, Csp²-rich molecules. The following thesis describes the expansion of the iterative coupling platform to include Csp³-rich and polycyclic small molecules via the stereoselective synthesis and coupling of Csp³ boronate building blocks. Together with the discovery of a generalized purification strategy for purifying MIDA boronates, the strategic advances
made enabled us to automate the synthesis of 14 distinct classes of small molecules. These studies illuminate a roadmap towards the more general and automated synthesis of small molecules.

1-6 REFERENCES

CHAPTER 2

A CHIRAL LIGAND FOR THE STEREOSELECTIVE SYNTHESIS OF C$_{sp}^3$ BORONATES

Junqi Li and Martin D. Burke

Efficient access to chiral, non-racemic C$_{sp}^3$ boronic acids and their derivatives is critical to realizing their potential as valuable building blocks in complex small molecule synthesis. This chapter details the discovery of a chiral ligand, “pinene-derived iminodiacetic acid” (PIDA), for the highly diastereoselective synthesis of oxiranyl C$_{sp}^3$ boronates. The oxiranyl boronates can be readily transformed into α-boryl aldehydes via a novel 1,2-migration of the boronate group that proceeds with complete maintenance of stereochemical purity. These α-boryl aldehydes can be manipulated into a variety of C$_{sp}^3$ boronates that were previously inaccessible. A new type of bifunctional PIDA boronate in which both the iodide and boron termini are attached to C$_{sp}^3$ carbons was also synthesized from the α-boryl aldehyde. We demonstrated the synthetic utility of this building block in the concise and modular synthesis of an inhibitor of a glucagon receptor via iterative C$_{sp}^3$ cross-coupling. Portions of this chapter were adapted from Li, J.; Burke, M. D. *J. Am. Chem. Soc.* 2011, *133*, 13774.
2-1 INTRODUCTION

The importance of efficient methods for accessing chiral, non-racemic Csp\textsuperscript{3} boronic acids and their derivatives has grown in parallel with recent advances in Csp\textsuperscript{3} cross-coupling of alkyl boronic acids and esters.\textsuperscript{1} The toolbox of asymmetric methods for constructing these building blocks is rapidly expanding,\textsuperscript{2} but the synthesis of highly functionalized Csp\textsuperscript{3} boronates remains a challenge. This is in large part due to the instability of the boronic acid or ester functionality and their incompatibility with different reaction conditions, thus precluding functionalization of the building blocks after installation of the carbon-boron bond. In view of these limitations, the goal was to develop an approach to the stereoselective synthesis of shelf-stable functionalized Csp\textsuperscript{3} boronates.

\textit{N}-methyliminodiacetic acid (MIDA) boronates are shelf-stable, crystalline solids that are compatible with common reaction conditions,\textsuperscript{3} enabling simple boron-containing starting materials to be transformed into more complex boronate building blocks.\textsuperscript{4} The crystal structures of many MIDA boronates have revealed that the N-methyl substituent is always closely positioned to the organic group appended to boron.\textsuperscript{3} Variable temperature NMR studies have demonstrated that the iminodiacetic acid framework is conformationally rigid in solution. It is also interesting to note that a chiral diol ligand on an sp\textsuperscript{2}-hybridized boron were not very effective in promoting a diastereoselective epoxidation reaction with the corresponding alkenyl boronic ester in Pietruszka’s studies.\textsuperscript{5} Presumably, this is due to weak asymmetric induction from the chiral ligand that is held in a distal position from the alkene.

Collectively, these observations suggested that the enforced proximity between the N-alkyl substituent of MIDA and the organic group bound to boron could be leveraged for effective transfer of stereochemical information during functionalizations of the corresponding boronates if the N-alkyl group were made chiral (Figure 2-1). In view of the versatility of epoxides in the preparation of other chiral building blocks, we questioned whether the epoxidation of alkenylboronates can be rendered asymmetric via such modifications of the MIDA ligand.

\textbf{Figure 2-1.} Leveraging the enforced proximity between the chiral R* group and the organic group bound to boron to achieve highly diastereoselective reactions.
2-2 IDENTIFYING A CHIRAL LIGAND FOR DIASTEREOSELECTIVE EPOXIDATION

To test this hypothesis, we first examined the epoxidation of alkenyl boronates under the influence of iminodiacetic acid ligands with chiral N-alkyl substituents (Table 2-1). We found that pinene-derived iminodiacetic acid ligand (2.1a, PIDA) gave >20:1 d.r. as determined by $^1$H-NMR of the crude reaction mixture in the epoxidation reaction under standard mCPBA conditions. Separating the chiral ligand from the nitrogen atom by a methylene spacer resulting in a large decrease in the d.r. (Table 2-1, entry 2), suggesting that the chiral group must be held in a rigid position proximal to the organic group appended to boron for effective transfer of stereochemical information from the chiral group. The use of less sterically bulky ligands such as 2.1c and 2.1d did not give satisfactory diastereomeric ratios.

<table>
<thead>
<tr>
<th>entry</th>
<th>2.1</th>
<th>2.3</th>
<th>d.r.</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>&gt;20:1</td>
</tr>
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<td>2</td>
<td></td>
<td></td>
<td>2:1:1</td>
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<td>3</td>
<td></td>
<td></td>
<td>2:7:1</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td>1:6:1</td>
</tr>
</tbody>
</table>

Table 2-1. Diastereoselective epoxidations of various iminodiacetic acid-based alkenylboronates

Both enantiomers of α-pinene are cheap and readily available on a very large scale, so PIDA has the potential to serve as a very practical chiral auxiliary. The PIDA ligand was initially synthesized by dialkylation of the chiral amine with chloroacetic acid under basic aqueous conditions, followed by treating the diacetate salt with a hot aqueous solution of BaCl$_2$·H$_2$O to form an insoluble barium chelate of PIDA. Protonation of this chelate with H$_2$SO$_4$ gives the PIDA ligand as an aqueous solution which is then concentrated to give the PIDA ligand as a white solid (Scheme 2-1a). The product generated using
this method can be used directly without purification. The procedure requires careful control of the pH during the protonation step is critical as lowering the pH below 3 results in formation of the ammonium salt of the ligand, which is highly hygroscopic and cannot be isolated. Although this method generated sufficient quantities of the ligand for subsequent studies, an improved procedure was needed for the practical synthesis of larger quantities of the ligand. This procedure starts with the dialkylation of the chiral with benzyl bromoacetate, followed by hydrogenolysis of the benzyl esters to generate the PIDA ligand (Scheme 2-1b). Although a silica gel column is required to purify the intermediate benzyl ester, this procedure proved to be more reproducible and more than 9 g of the ligand can be obtained in one run. This alkylation-hydrogenolysis sequence was later adapted by Dr. Ian Crouch for the large-scale synthesis of 2.3d.

We next explored the capacity of this ligand to enable the diastereoselective epoxidation of a variety of alkenylboronates. Trans 1,2-disubstituted alkenes with both alkyl and electronically different aryl substituents work well, giving rise to >20:1 d.r. (Table 2-2, entries 1-6). Cis 1,2-disubstituted (entry 7) and trisubstituted alkenes (entry 8) were also effective substrates. Somewhat diminished but still synthetically useful diastereoselectivities were observed with 1,1-disubstituted alkenes (entries 9-10), which are often challenging substrates for asymmetric functionalization due to the steric similarities between the two diastereotopic faces of the alkene. Even the simplest alkenyl boronate 2.2n was epoxidized with excellent diastereoselectivity and yield. The stereochemical configuration of the epoxides 2.3a, 2.3g and 2.3n were unambiguously confirmed by X-ray crystallography. The remaining product configurations were assigned by analogy. These oxiranyl PIDA boronates shared many of the characteristics of MIDA boronates – they are shelf-stable, crystalline solids that can be purified by silica gel chromatography, making them highly desirable chiral building blocks for complex molecule synthesis.
Table 2-2. Highly diastereoselective epoxidations of alkenyl PIDA boronates. \(^a\) Isolated yields after silica gel chromatography. \(^b\) Diastereomeric ratios determined via \(^1\)H-NMR analysis of the unpurified reaction mixtures. \(^c\) Conducted on a 15 mmol scale and isolated by crystallization.

2-3 PROPOSED MODEL FOR DIASTEREOSELECTIVITY

A model to explain the diastereoselectivity of the reaction was developed by first examining the crystal structures of 2.2g and 2.3g. Ignoring crystal packing effects, both the crystal structures show that the chiral pinane group is positioned in close proximity to the alkene. It is thus reasonable to assume that the transition state structure would also have a similar relative spatial position of the two groups. Notably, the distance between the methine hydrogen on the carbon attached to nitrogen and the hydrogen on the carbon attached to boron decreases by 0.3Å after epoxidation due to rehybridization of the carbon bound to boron (Figure 2-2). This implies that the space occupied by the hydrogen is subject to steric interactions with the bulky ligand.

Figure 2-2. X-ray structures of 2.2g (left) and 2.3g (right).
In this model, the alkenyl PIDA boronate can adopt two different conformations that can interconvert by rotation about the carbon-boron bond (Figure 2-3), which leads to two energetically different transition states. In both cases, mCPBA can only approach the alkene from the bottom face as the top face is blocked by the bulky chiral group. In the transition state, as the sp² carbon pyramidalizes, the carbon-hydrogen bond rotates upwards, resulting in some steric interaction between the hydrogen and the ligand (TS1). This steric interaction is however, much larger in the transition state involving the alternate conformer (TS2). This results in a large difference in the transition state energies, which in turn leads to high diastereoselectivities in the epoxidation of 1,2-substituted alkenes. For 1,1-disubstituted alkenes, the steric difference between a methyl group and methylene group in the transition states is smaller, thus leading to lower diastereoselectivities observed in the epoxidation reaction.

![Proposed transition states for the epoxidation of 2.2g.](image)

**Figure 2-3.** Proposed transition states for the epoxidation of 2.2g.

2-4 REARRANGEMENT OF OXIRANYL PIDA BORONATES

With the oxiranyl PIDA boronates in hand, we turned to exploring the synthetic utility of these chiral building blocks. We first attempted the Lewis acid-catalyzed epoxide ring-opening with TMSN₃. After screening different types of Lewis acids, we found that Mg(ClO₄)₂ promoted clean conversion of the epoxide to a new product as a single diastereomer, but the ¹H-NMR of this product was not consistent with the target azido-alcohol 2.7. After further characterization, the structure of the product was assigned to be an α-boryl aldehyde 2.8, which would be the product of a Meinwald rearrangement⁸ of the epoxide.
**Scheme 2-2.** Observed product of an attempted Lewis acid-catalyzed epoxide ring-opening reaction.

Carbon-bound boron enolates have been observed spectroscopically\(^9\) and are implicated in reactions,\(^{10}\) but are usually not stable enough to be isolated because of rapid 1,3-shift of the boryl group from carbon to oxygen to form the more stable oxygen-bound enolate.\(^{11}\) However, \(\alpha\)-boryl aldehydes with the PIDA ligand are stable solids that can be handled in air. We reasoned that the kinetic stability of the \(\alpha\)-boryl aldehyde arises from an \(sp^3\)-hybridized boron, which lacks the \(p\)-orbital required for interaction with the lone pair on the carbonyl oxygen during the 1,3-shift.

Four possible pathways arising from aryl, hydrogen, or boryl migration (Figure 2-4) exist for the Meinwald rearrangement. No ketone or acylboronate products were observed from \(^1\)H-NMR analysis of the crude reaction mixture, indicating that hydrogen migration was not operative. In addition, the \(\alpha\)-boryl aldehyde was formed as a single diastereomer. To determine whether aryl- or boryl-migration occurred during the rearrangement, the stereochemistry of the resulting products was used as a probe since the two pathways would lead to different diastereomers.

![Figure 2-4. Four possible pathways of the Meinwald rearrangement of oxiranyl PIDA boronates.](image)

The rearrangement of the epoxide was repeated using \(\text{Mg(ClO}_4\text{)}_2\) without \(\text{TMSN}_3\), giving the same \(\alpha\)-boryl aldehyde 2.8 in 84% yield. The aldehyde was then treated with a diol to form a ketal 2.9 from which X-ray quality crystals can be grown (Scheme 2-3). The crystal structure of the ketal showed that the \(\alpha\)-center of the precursor aldehyde is of the R configuration, which is consistent with the migration of the boron group. Independent contemporaneous studies by the Yudin group identified the same rearrangement using racemic epoxides and the MIDA ligand, and using a deuterium-labeled epoxide and \(\text{BF}_3\cdot\text{Et}_2\text{O}\) as the Lewis acid arrived at the same conclusion regarding selective migration of the MIDA boronate group (Scheme 2-3).\(^{12}\)
To our knowledge, this type of 1,2-migration of the boryl group has not been previously reported in the literature. It is interesting to note that in this case, the boryl group migrates preferentially over the phenyl group. Trans 1,2-disubstituted alkenyl PIDA boronates with an alkyl substituent can also undergo the rearrangement using BF$_3$·Et$_2$O with complete maintenance of stereochemical purity, although the migrating group has not been unambiguously confirmed in this case.

Gevorgyan and co-workers later utilized this 1,2 boryl migration in their synthesis of borylated furans.

2-5 NEW C$_{sp}^3$ BORONATES FROM α-BORYL ALDEHYDES

The stability of the α-boryl aldehyde allowed us to synthetically manipulate this versatile functional group via reduction to an alcohol followed by a Mitsunobu-type displacement of the alcohol by iodide. This reaction sequence thus generated a new type of bifunctional building block in which both the halide and the boron termini are attached to C$_{sp}^3$ carbons (Scheme 2-4).

Contemporaneous studies by Yudin and co-workers revealed that α-boryl aldehydes can undergo oxidation, carbon-carbon bond formation and nucleophilic addition reactions to give a variety of C$_{sp}^3$ boronates that are previously inaccessible or difficult to make by other methods (Figure 2-5). The group
also demonstrated that α-boryl carboxylic acids derived from the corresponding aldehydes can undergo Curtius rearrangement with retention of configuration at the migrating carbon.\textsuperscript{15a}

**Figure 2-5.** Examples of new types of Csp\textsuperscript{3} boronates that can be derived from α-boryl aldehydes.

2-6 CROSS-COUPLING OF Csp\textsuperscript{3} BORONATES

The diarylmethine motif is present in more than 2000 natural products and in several marketed pharmaceuticals (Figure 2-6). Employing a stereospecific cross-coupling reaction between benzylic Csp\textsuperscript{3} boronates and an aryl halide represents an opportunity to gain modular access to the chiral diarylmethine motif. Importantly, the stereochemistry is pre-installed in the Csp\textsuperscript{3} boronate building block which can then be coupled using a stereospecific reaction, thus translating the stereochemistry into the final product. The Crudden group first demonstrated that secondary benzylic pinacol boronic esters can undergo cross-coupling efficiently under palladium catalysis with high levels of stereoretention. Interfacing with this powerful chemistry provided an opportunity to employ the building blocks generated with the aforementioned methodology in a variety of ways.
Figure 2-6. Examples of natural products and pharmaceuticals containing the chiral diarylmethine motif.

PIDA boronate 2.13 represents a new type of bifunctional building block that has the potential to access important chiral targets such as the glucagon receptor antagonist 2.17 under evaluation via a previously undescribed iterative Csp$^3$ cross-coupling approach (Figure 2-7). 2.17 can be retrosynthesized into three building blocks with 2.13 as the key building block bearing the stereogenic center that would be translated into the final product. 2.13 would first be coupled to an arylzinc reagent in a Csp$^3$-Csp$^2$ Negishi reaction, followed by transesterification of the product to a pinacol boronic ester. Applying Crudden’s conditions to couple the resulting boronic ester with the aryl halide 2.18 would give the t-butyl ester of the final target 2.17.

Figure 2-7. Initial retrosynthesis of the glucagon receptor antagonist 2.14.

A model study employing 2.13 and phenylzinc bromide as the coupling partner was used to test the feasibility of the proposed Negishi coupling. The conditions optimized for the similar cross-couplings of arylzinc halides with alkyl iodides reported by Fu$^{16}$ or Knochel$^{17}$ did not give the desired product in this system. The major side product observed was the styrene formed by β-hydride elimination after oxidative addition, a common problem with the cross-coupling reactions of alkyl iodides.

In view of the difficulties in getting productive coupling, an alternative route to 2.14 involving the polarity reversal of the first two coupling partners was pursued. We reasoned that the problem of β-hydride elimination may be alleviated by first transforming 2.13 into an organozinc reagent via zinc
insertion and then coupling with an aryl iodide. Using a bulky phosphate ligand on Pd can promote reductive elimination after transmetalation,\textsuperscript{18} thus preventing $\beta$-hydride elimination.

We found that the organozinc reagent 2.17 generated from PIDA boronate 2.13 was stable in solution at room temperature.\textsuperscript{19} Treating 2.17 with $p$-bromobenzonitrile and diethyl zinc using a Pd catalyst and a Buchwald ligand gave the desired products without optimization. This new type of linchpin reagent containing a PIDA (or MIDA) boronate and a reactive organozinc moiety was later found to be useful for the synthesis of new Csp$^3$ boronates, as will be discussed later in Chapter 3. Having validated the feasibility of this approach, we turned to the synthesis of 2.14 via this new type of Csp$^3$-Csp$^2$ iterative cross-coupling strategy.

The presence of the free amide moiety in the aryl iodide 2.18 posed a potential problem of competitive proto-demetallation of the organozinc coupling partner. The Knochel group reported the use of the Buchwald ligand SPhos and slow addition of the organozinc reagent to enable Negishi couplings with unprotected amide functionalities.\textsuperscript{20} Using this report as the starting point, optimization studies were carried out (Figure 2-7) by varying the temperature, Pd, and ligand, and comparing the ratios of the desired product 2.19 to the proto-demetallated side product 2.20 in the crude reaction mixture. Pd$_3$dba$_3$ was a better Pd source than Pd(OAc)$_2$, and a higher temperature promoted productive coupling. The trialkylphosphine ligand PCy$_3$ was less effective than the RuPhos ligand. With the best conditions and using a slower rate of addition (0.1 mmol in 1 h) of 2.17, an isolated yield of 73% was obtained on a 0.2 mmol scale.

![Figure 2-8. Summary of the optimization studies for the Negishi coupling of 2.17 and 2.18.](image)

Transesterification of the PIDA boronate motif in 2.19 to the corresponding pinacol boronic ester 2.25 proceeded in 84% yield with complete maintenance of stereochemical purity. Importantly, the PIDA ligand was easily recovered from this reaction in 97% yield. Finally, cross-coupling of this chiral secondary boronic ester 2.21 with aryl iodide 2.15 employing the conditions developed by Crudden
provided the t-butyl ester of **2.14** with good maintenance of stereochemical purity (94:6 e.r.). Deprotection of the t-butyl ester completed a very efficient, modular, and highly stereocontrolled synthesis of **2.14** (Scheme 2-5). With the synthesis of **2.14** as the first example of an iterative Csp$^3$-Csp$^2$ cross-coupling cycle, the scope of the iterative coupling platform has now been expanded to potentially include Csp$^3$-rich targets.

![Scheme 2-5. Iterative Csp$^3$-Csp$^2$ cross-coupling for the modular synthesis of **2.14**.](image)

Attempts were also made to couple other the pinacol boronic ester **2.12** which was synthesized from alcohol protection and transesterification to the pinacol boronic ester. NaHCO$_3$ from the original protocol for the transesterification reaction was omitted in this reaction to prevent β-elimination of the siloxy group. The PIDA ligand was again recovered in good yield in the transesterification reaction (Scheme 2-6).

![Scheme 2-6. Synthesis of pinacol boronic ester **2.23** from **2.12**.](image)

The cross-coupling of **2.23** with iodosotoluene was examined using Pd(OAc)$_2$ or Pd$_3$dba$_3$ and several ligands (PPh$_3$, PrBu$_3$, PCy$_3$ or SPhos) combinations with Ag$_2$O as the base, including the
conditions developed by Crudden and co-workers. Under the conditions screened, no productive coupling occurred. The two major side products observed in the reaction mixtures were styrene and protodeboronated starting material, as well as unreacted iodotoluene (Scheme 2-7).

![Scheme 2-7](image)

Scheme 2-7. Attempted cross-coupling of 2.23 with iodotoluene under various conditions.

Styrene can be generated under the reaction conditions by two pathways: i) rapid β-elimination after complexation of the palladium-hydroxo to the pinacol boronic ester; or ii) “-ate” complexation with hydroxide in the presence of adventitious amounts of water followed by β-elimination (Scheme 2-8). The cross-coupling of 2.23 was not pursued further after these initial studies, and remains an unsolved problem.21,22

![Scheme 2-8](image)

Scheme 2-8. Proposed pathways for formation of the styrene side product from 2.23.

2-7 DIASTEREOSELECTIVE AZIRIDINATION OF ALKENYL PIDA BORONATES

Together with Johanna Moratz, we explored the potential of the PIDA ligand to gain stereocontrolled access to other types of strained 3-membered cyclic boronates. We first tested the aziridination of alkenyl PIDA boronate using an Atkinson-type aziridination23 reaction conditions. Using 3-amino-2-ethylquinazolin-4(3H)-one (Q-NH₂) with PhI(OAc)₂,24 we found that the aziridination reaction goes with a high d.r.25 of >20:1 as analyzed by 1H-NMR of the crude reaction mixture and an isolated yield of 86% (Scheme 2-9). Similar to the oxiranyl PIDA boronates, 2.24 is a stable solid that can be purified by silica gel chromatography.26 Notably, the use of N-aminophthalimide in place of Q-NH₂ gave a lower d.r. of 7:1, suggesting that the steric bulk on the aziridination reagent is important in
differentiating between the two enantiotopic faces of the alkene. Thus far, efforts to convert aziridine 2.24 into other types of Csp\textsuperscript{3} boronates via ring-opening reactions and removal of the quinazolinone protecting group have not been successful due to poor conversion and/or decomposition of the starting material.

The cyclopropanation of alkenyl PDA boronate 2.2a and 2.2h were also attempted. Using both Simmons-Smith and Pd-catalyzed cyclopropanation conditions, low or no diastereoselectivities were obtained (Scheme 2-10). This lack of stereoselectivity may be due to the highly reactive zinc or palladium carbenoids involved, leading to early transition states where interactions between the chiral substrate and reagent are weak. In non-selective reactions like the cyclopropanation reaction, a practical way of getting to the desired stereo-enriched products may be to use the chiral ligand to resolve the diastereomeric mixture by chromatography or crystallization, as described below in Section 2-8.

Our group and others have found that the PDA ligand and 2.1d can serve as chiral reagents for resolving racemic boronic acids. Ian Crouch and Pulin Wang used ligand 2.1d (now termed BIDA) to
resolve the commercially available $s$-butyl boronic acid. After complexation of the boronic acid with BIDA, the resulting two diastereomers can be separated by a silica gel column. This method for obtaining diastereomically pure BIDA boronates is effective for a variety of chiral boronic acids. Lee and Cheon used PIDA to resolve racemic 1,1\textsuperscript{'}-bi-2-napthol boronic acids by silica gel chromatography, allowing them to gain access to a range of enantiomerically pure 3,3\textsuperscript{'}-disubstituted 1,1\textsuperscript{'}-bi-2-napthol derivatives (Scheme 2-11). These examples and the PIDA-promoted diastereoselective epoxidation provide practical access to stereochemically pure boronic acids which can otherwise be difficult to access.

\begin{center}
\begin{tikzpicture}
  \node (a) at (0,0) {
    \begin{align*}
      \text{A) } & \begin{array}{c}
        \text{R} & \text{Me} \\
        \text{B(OH)}_2 \\
      \end{array} \\
      & \xrightarrow{2.1d} \begin{array}{c}
        \text{R} & \text{Me} \\
        \text{OBn} \\
        \text{N} & \text{B(O)}_2 \\
      \end{array} + \begin{array}{c}
        \text{R} & \text{Me} \\
        \text{OBn} \\
        \text{N} & \text{B(O)}_2 \\
      \end{array} \\
      & \text{separated by silica gel chromatography}
    \end{align*}
  
  \node (b) at (3,0) {
    \begin{align*}
      \text{B) } & \begin{array}{c}
        \text{racemic} \\
        \text{B(OH)}_2 \\
        \text{O} & \text{Me} \\
        \text{O} & \text{Me} \\
      \end{array} \\
      & \xrightarrow{2.1d} \begin{array}{c}
        \text{Me} \\
        \text{Ipch} \\
        \text{B(O)}_2 \\
        \text{O} & \text{Me} \\
        \text{O} & \text{Me} \\
      \end{array} + \begin{array}{c}
        \text{Me} \\
        \text{Ipch} \\
        \text{B(O)}_2 \\
        \text{O} & \text{Me} \\
        \text{O} & \text{Me} \\
      \end{array} \\
      & \text{separated by silica gel chromatography}
    \end{align*}
  
  \end{tikzpicture}
\end{center}

\textbf{Scheme 2-11.} Diastereomeric resolution of racemic boronic acids using the PIDA and BIDA ligands.

\section*{2.9 SUMMARY AND CONCLUSIONS}

Towards the goal of enabling a more general, building block-based approach to small molecule synthesis, we have developed the efficient stereoselective synthesis of new types of Csp\textsuperscript{3} boronate building blocks using a pinene-derived chiral ligand PIDA. A serendipitous discovery of a novel type of Meinwald rearrangement of oxiranyl PIDA boronates involving migration of the boryl group with complete maintenance of stereochemical purity allowed us to gain access to a synthetically versatile $\alpha$-boryl aldehyde building block. We also demonstrated the capacity to transform stereochemically pure dual Csp\textsuperscript{3}-hybridized halo PIDA boronates into a medicinally important chiral small molecule target via highly efficient and flexible iterative Csp\textsuperscript{3} cross-coupling. The stereoselective functionalization of alkenyl boronates bearing a chiral ligand and the diastereomeric resolution of chiral boronates described in this chapter now provide rapid access to stereochemically pure boron-containing building blocks for realizing their synthetic potential in complex molecule synthesis.
2-10 REFERENCES


6 Crouch, I. T.; Wang, P.; Burke, M. D., manuscript in preparation.


MIDA boronates are known to be stable to Negishi cross-coupling conditions, but Negishi reagents containing the MIDA or PIDA boronate motif were not known at the time of the work. Lee, S. J.; Gray, K. C.; Paek, J. S.; Burke, M. D. *J. Am. Chem. Soc.* **1998**, *120*, 11186-11187.


Only one invertomer of the aziridine was detected.


CHAPTER 2
EXPERIMENTAL SECTION

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

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

Structural analysis. $^1$H NMR and $^{13}$C NMR spectra were recorded at 20 °C on Varian Unity 500, Varian Unity Inova 500NB or Varian Unity 500 instruments. Chemical shifts (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; acetone, δ = 2.05, center line; 1,1,2,2-tetrachloroethane, 5.95) or to added tetramethylsilane (δ = 0.00). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sept = septet, m = multiplet, b = broad, app = apparent), coupling constant ($J$) in Hertz (Hz), and integration. Chemical shifts (δ) for $^{13}$C NMR are reported in ppm downfield from tetramethylsilane and referenced to carbon resonances in the NMR solvent (CDCl$_3$, δ = 77.0, center line; acetone, δ = 39.5, center line). Carbons bearing boron substituents were not observed (quadrupolar relaxation). $^{11}$B NMR were recorded using a 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 and Dr. Haijun Yao at the University of Illinois School of Chemical Sciences Mass Spectrometry Laboratory.

II. Experimental procedures
a. Synthesis of 2.1a – 2.1d

**General procedure for the synthesis of ligands 2.1a-d:**
To a stirred solution of chloroacetic acid (69 mmol, 2.3 equiv) in H$_2$O (60 ml) at 0 °C was added dropwise 5N NaOH solution (13.8 ml, 69 mmol, 2.3 equiv), keeping the temperature below 15 °C. The amine (30 mmol, 1 equiv) in IPA (30 ml) was then added in one portion. The ice bath was then removed and the reaction heated at 70 °C (oil bath temperature). After stirring for 2.5 h, the reaction turned clear from an initial biphasic mixture. Another 8.1 ml (40.5 mmol, 1.35 equiv) of the 5 N NaOH solution was added, and the reaction stirred for a further 14 h at the same temperature. The third portion of the NaOH solution (8.1 ml, 40.5 mmol, 1.35 equiv) was then added and stirred for an additional 2 h at 70 °C. The reaction was then heated up to 100 °C. BaCl$_2$.H$_2$O (7.69 g, 31.5 mmol, 1.05 equiv) in H$_2$O (30 ml) was heated until the solid dissolved completely. This heated solution was then added dropwise via pipette into the reaction mixture. After the addition, the reaction was stirred for an additional 15 min, during which the reaction became a thick white suspension. After cooling to room temperature, the white solid was collected by filtration and dried in a vacuum oven set at 100 °C. The mass of the Ba chelate was determined. The Ba chelate was then suspended in H$_2$O (60 ml) and heated in a 110 °C oil bath until boiling. 5M H$_2$SO$_4$ (1.95 equiv relative to the Ba chelate) was added dropwise, followed by rinsing with 5 ml H$_2$O. The resulting suspension was stirred for another 15 min in the oil bath, then cooled for 5 min and filtered through celite, rinsing with 10 ml H$_2$O. The filtrate was concentrated to dryness. The solid obtained was then redissolved in Et$_2$O/CH$_2$Cl$_2$ (1:10, 100 ml) and filtered to remove insoluble solids. The CH$_2$Cl$_2$ solution was then concentrated *in vacuo* and the solid obtained was used without further purification.

The general procedure was followed using (1R,2R,3R,5S)-(−)-Isopinocampheylamine (Sigma Aldrich, 4.59 g, 30 mmol), chloroacetic acid (6.52 g, 69 mmol) and NaOH (30 ml, 150 mmol). 11.33 g of the Ba chelate (93%) was obtained. 5.4 ml of 5M H$_2$SO$_4$ was used for the hydrolysis, and the ligand 2.1a was obtained as an off-white solid (6.63 g, 82%).

$^1$H-NMR (500 MHz, DMSO-d$_6$)
\[ \delta 3.45 \text{ (s, 4H)}, 3.23-3.18 \text{ (m, 1H)}, 2.32-2.23 \text{ (m, 1H)}, 2.19-2.12 \text{ (m, 1H)}, 1.91-1.86 \text{ (m, 1H)}, 1.75-1.69 \text{ (m, 2H)}, 1.64-1.60 \text{ (m, 1H)}, 1.15 \text{ (s, 3H)}, 1.03 \text{ (d, } J = 6.5 \text{, 3H)}, 0.92 \text{ (s, 3H)}, 0.79 \text{ (d, } J = 10 \text{ Hz, 1H}). \]

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

\[ \delta 173.5, 62.0, 53.8, 47.3, 40.9, 40.3, 38.7, 33.4, 29.6, 27.9, 23.0, 20.9. \]

HRMS (ESI+)

Calculated for C$_{14}$H$_{24}$NO$_4$: 270.1705

Found: 270.1703

Improved two-step procedure for the synthesis of 2.2a:

An oven-dried 500-mL three-necked round-bottom flask equipped with a 3cm egg-shaped PTFE-coated magnetic stir bar is cooled under an N$_2$ atmosphere. The vessel is charged with anhydrous K$_2$CO$_3$ (39.80 g, 288 mmol, 4.86 equiv) and flushed with N$_2$ for another 5 min. MeCN (200 ml) is added to the vessel, followed by (1S, 2S, 3S, 5R)-(+)-isopinocampheylamine (10 ml, 59.31 mmol, 1 equiv). With vigorous stirring, benzyl bromoacetate (22 ml, 138.9 mmol, 2.3 equiv) is added. The center neck of the vessel is sealed with a rubber septum. The reaction is lowered into a pre-heated oil bath and stirred vigorously at an internal temperature of 45 °C for 14 h. The reaction is cooled to 23 °C and filtered through Celite into a 1-L round-bottomed flask, rinsing the reaction vessel and filter cake with EtOAc (4 × 50 ml). The yellow filtrate is concentrated by rotary evaporation (40 °C, 30 mmHg) to give a viscous yellow liquid. CH$_2$Cl$_2$ (60 ml) is added, followed by Celite (25 g). The CH$_2$Cl$_2$ is removed via rotary evaporation. The celite pad is loaded onto a silica gel column and purified by flash chromatography to afford the product 2.6 as a clear, colorless oil (23.47 g, 52.20 mmol, 87% yield).

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

\[ \delta 7.35-7.31 \text{ (m, 10H)}, 5.13 \text{ (s, 4H)}, 3.67 \text{ (app s, 4H)}, 3.27-3.22 \text{ (m, 1H)}, 2.31-2.26 \text{ (m, 1H)}, 2.17-2.12 \text{ (m, 1H)}, 1.91-1.85 \text{ (m, 2H)}, 1.76-1.69 \text{ (m, 2H)}, 1.18 \text{ (s, 3H)}, 1.06 \text{ (d, } J = 7.0 \text{ Hz, 3H)}, 0.93 \text{ (s, 3H)}. \]

$^{13}$C-NMR (125 MHz, CDCl$_3$)
δ 172.1, 135.8, 128.5, 128.3, 128.2, 66.3, 62.7, 53.2, 47.9, 41.6 (2C), 39.0, 34.0, 30.8, 28.0, 23.2, 21.2.

To a 500-mL single-necked roundbottomed flask containing dibenzyl ester 2.6 (21.00 g, 46.71 mmol, 1 equiv) is added ethanol (300 ml), 10 wt% palladium on carbon (1.74 g, 1.635 mmol, 0.035 equiv) and a 3 cm PTFE-coated egg-shaped stir bar. The reaction vessel is sealed with a rubber septum and the resulting suspension stirred and degassed by bubbling N₂ through the suspension for 10 min. Hydrogen gas is then bubbled through the solution for 20 min. The vent needle is removed and the reaction stirred under a H₂ atmosphere for 14 h. The H₂-filled balloon is removed, and the reaction is purged of H₂ by bubbling N₂ through the suspension for 30 min. MeOH (100 ml) is added to the suspension. The suspension is filtered through Celite into a 1-L filtration flask. The round-bottomed flask and the filter cake were washed with MeOH (4 × 50 mL). The slightly yellow filtrate is transferred to a 1-L round-bottomed flask and concentrated to a solid via rotary evaporation. Diethyl ether (250 mL) and a 3 cm egg-shaped stir bar were added. The suspension is stirred for 4 h. The suspension is filtered, washing with the white solid with diethyl ether (4 × 50 mL) to afford 2.1a as a white powder (10.88 g, 40.14 mmol, 85.9%).

The general procedure was followed using (−)-cis-myrtanylamine (Sigma Aldrich, 4.59 g, 30 mmol), chloroacetic acid (6.52 g, 69 mmol) and NaOH (30 ml, 150 mmol). 11.33 g of the Ba chelate (93%) was obtained. 5.4 ml of 5M H₂SO₄ was used for the hydrolysis, and the ligand 2.1b was obtained as an off-white solid in about 70-80% purity (1.62 g, 20%).

¹H-NMR (500 MHz, DMSO-d₆)
δ 3.36 (s, 4H), 2.56 (d, J = 7.5 Hz, 2H), 2.30-2.26 (m, 1H), 2.12-2.09 (m, 1H), 1.93-1.91 (m, 1H), 1.87 – 1.72 (m, 4H), 1.53-1.45 (m, 1H), 1.12 (s, 3H), 0.91 (s, 3H), 0.84 (d, J = 9.5 Hz, 1H).

¹³C-NMR (125 MHz, DMSO-d₆)
δ 172.4, 59.6, 55.1, 43.5, 40.9, 38.6, 38.2, 32.9, 27.8, 25.8, 22.9, 19.5.
HRMS (ESI+)
Calculated for C\textsubscript{14}H\textsubscript{24}NO\textsubscript{4}: 270.1705
Found: 270.1700

The general procedure was followed using (S)-(+)\textsuperscript{-}1\textsuperscript{-}cyclohexylethylamine (Alfa Aesar, 12.72 g, 100 mmol), chloroacetic acid (21.74 g, 230 mmol) and NaOH (100 ml, 500 mmol). 27.84 g of the Ba chelate (74\%) was obtained. 14.4 ml of 5M H\textsubscript{2}SO\textsubscript{4} was used for the hydrolysis, and the ligand I\textsubscript{c} was obtained as an off-white solid (12.47 g, 51 \%).

\textsuperscript{1}H-NMR (500 MHz, DMSO-d\textsubscript{6})
\[ \delta \text{ 3.37 (d, } J = 17.5 \text{ Hz, 2H), 3.29 (d, } J = 17.5 \text{ Hz, 2H), 2.39 (m, 1H), 1.91 (app d, } J = 7.5 \text{ Hz, 1H), 1.65-1.51 (m, 4H), 1.24-1.03 (m, 5H), 0.92 (d, } J = 6.5 \text{ Hz, 3H), 0.89-0.78 (m, 1H}. \]

\textsuperscript{13}C-NMR (125 MHz, DMSO-d\textsubscript{6})
\[ \delta \text{ 173.4, 62.6, 53.2, 40.8, 30.0, 29.4, 26.1, 25.8, 25.8, 12.6} \]

HRMS (ESI+)
Calculated for C\textsubscript{12}H\textsubscript{22}NO\textsubscript{4}: 244.1550
Found: 244.1549

The general procedure was followed using (1S, 2S)-(+)\textsuperscript{-}2\textsuperscript{-}benzyloxyxyclopentylamine (Alfa Aesar, 5 g, 26.1 mmol), chloroacetic acid (5.68 g, 60.1 mmol) and NaOH (26.1 ml, 130.5 mmol). 5.87 g of the Ba chelate (67\%) was obtained. 3.40 ml of 5M H\textsubscript{2}SO\textsubscript{4} was used for the hydrolysis, and the ligand 2.1d was obtained as an off-white solid (3.36 g, 42 \%).

\textsuperscript{1}H-NMR (500 MHz, DMSO-d\textsubscript{6})
δ 12.2 (br s, 2H), 7.32-7.24 (m, 5H), 4.42 (d, J = 12 Hz, 1H), 4.36 (d, J = 11.5 Hz, 1H), 3.76-3.74 (m, 1H), 3.48 (d, J = 17.5 Hz, 2H), 3.43 (d, J = 18 Hz, 2H), 3.24-3.20 (m, 1H), 1.88-1.82 (m, 1H), 1.82-1.76 (m, 1H), 1.59-1.48 (m, 3H), 1.38-1.30 (m, 1H).

$^{13}$C-NMR (125 MHz, DMSO-d$_6$)
δ 173.0, 138.6, 128.1, 127.6, 127.3, 83.0, 70.4, 68.1, 53.6, 29.8, 28.4, 20.9.

HRMS (ESI+)
Calculated for C$_{16}$H$_{22}$NO$_5$: 308.1498
Found: 308.149

b. Synthesis of 2.2a – 2.2n

General procedure for the complexation of chiral ligands 2.1a-d to trans-2-phenylvinylboronic acid:
To a solution of trans-2-phenylvinylboronic acid (1.5 equiv) in toluene (30 ml) and DMSO (1.5 ml) was added the ligand 2.1 (typically 1-5 mmol, 1 equiv). The flask was fitted with a Dean-Stark trap. The Dean-Stark trap was fitted with an air-cooled condenser vented to ambient atmosphere. The stirred solution was refluxed with azeotropic removal of water for 2 h. The toluene was removed in vacuo, and the residue was taken up in 2:1 EtOAc/acetone (60 ml) and washed twice with 1:1 brine/H$_2$O (30 ml). The aqueous layer was extracted with 2:1 EtOAc/acetone (30 ml) and the combined organic phase washed with brine, dried over MgSO$_4$, filtered and concentrated in vacuo. The crude product was then purified by silica gel chromatography, eluting first with Et$_2$O to remove impurities, then with 1:4 (acetone/Et$_2$O).

The reaction was carried out on a 20 mmol scale with some modifications from the general procedure and purified without the use of silica gel chromatography: To a suspension of trans-2-phenylvinylboronic acid (2.96g, 20 mmol) in toluene (200 ml) was added the ligand 2.1a (9.68g, 36 mmol). The flask was fitted with a 50 ml Dean-Stark trap and an air-cooled condenser vented to ambient atmosphere. The stirred solution was refluxed with azeotropic removal of water for 2 h. After cooling to room temperature, the
crude solid product was collected via vacuum filtration. The filtrate was then concentrated to dryness and Et₂O (50 ml) was added. The resulting white precipitate was collected via vacuum filtration and the combined solids were then washed with additional Et₂O (50 ml). This solid was then taken up in acetone (150 ml) and passed slowly through a pad of silica gel in a 100 ml sintered funnel, eluting with additional acetone (50 ml). The filtrate thus obtained was concentrated and dried in vacuo, giving the product 2.2a (6.74 g, 88%).

TLC (Hexanes:acetone 3:2)

Rf = 0.27, visualized by short wave UV.

^1H-NMR (500 MHz, CDCl₃)

δ 7.47 (d, J = 7 Hz, 1H), 7.35 (t, J = 7 Hz, 1H), 7.29 (t, J = 7.5 Hz, 1H), 7.07 (d, J = 18 Hz, 1H), 6.31 (d, J = 18 Hz, 1H), 4.19 (d, J = 17 Hz, 1H), 3.84 (s, 2H), 3.70 (dt, J = 10, 6.5 Hz, 1H), 3.62 (d, J = 17.5 Hz, 1H), 2.57 – 2.52 (m, 1H), 2.46 – 2.42 (m, 1H), 2.17 (dquint, J = 6.5, 1.5 Hz, 1H), 2.02 (sept, J = 2.5 Hz, 1H), 1.89 (dt, J = 6, 2 Hz, 1H), 1.74 (dd, J = 15, 6.5, 2.5 Hz, 1H), 1.27 (d, J = 6.5 Hz, 3H), 1.22 (s, 3H), 0.92 (d, J = 11 Hz, 1H), 0.88 (s, 3H).

^13C-NMR (125 MHz, CDCl₃)

δ 169.5, 166.9, 144.6, 137.6, 128.7, 128.4, 126.7, 68.6, 60.6, 54.4, 49.0, 40.6, 39.1, 38.8, 32.1, 30.3, 27.0, 23.6, 23.4.

^11B-NMR (100 MHz, acetone-d₆)

δ 11.9

HRMS (ESI+)

Calculated for C₂₂H₂₉BNO₄: 382.2190
Found: 382.2187

The general procedure was followed using trans-2-phenylvinylboronic acid (0.22 g, 1.5 mmol), ligand 2.1b (0.606g, 2.25 mmol) in 20 ml toluene and 1 ml DMSO. A white solid was obtained (0.387 g, 68%).
TLC (Hexanes:EtOAc:Et₂O 2:2:1)

R<sub>f</sub> = 0.20, visualized by short wave UV.

<sup>1</sup>H-NMR (500 MHz, acetone-d<sub>6</sub>)

δ 7.50 (app d, J = 7 Hz, 2H), 7.34 (app t, J = 7.5 Hz, 2H), 7.28-7.25 (m, 1H), 6.93, (d, J = 18 Hz, 1H), 6.33 (d, J = 18 Hz, 1H), 4.17-4.08 (m, 4H), 3.45 (dd, J = 13.5, 6.5 Hz, 1H), 3.34 (dd, J = 13.5, 3 Hz, 1H), 2.74-2.68 (m, 1H), 2.38-2.26 (m, 2H), 2.16-2.11 (m, 1H), 2.01-1.94 (m, 1H), 1.92-1.76 (m, 3H), 1.15 (s, 3H), 1.08 (d, J = 10 Hz, 1H), 0.92 (s, 3H).

<sup>1</sup>C-NMR (125 MHz, CDCl<sub>3</sub>)

δ 167.8, 167.4, 144.2, 137.6, 128.6, 128.4, 126.7, 66.8, 58.5, 58.4, 47.3, 40.4, 38.1, 37.4, 31.9, 27.3, 25.6, 23.3 (2C).

<sup>1</sup>B-NMR (100 MHz, acetone-d<sub>6</sub>)

δ 11.9

HRMS (ESI+)

Calculated for C<sub>22</sub>H<sub>29</sub>BNO<sub>4</sub>: 382.2190

Found: 382.2187

The general procedure was followed using <i>trans</i>-2-phenylvinylboronic acid (0.74 g, 5 mmol), ligand 2.1c (1.82 g, 7.5 mmol) in 50 ml toluene and 2.5 ml DMSO. A white solid was obtained (0.311 g, 74%).

TLC (Hexanes:acetone 3:2)

R<sub>f</sub> = 0.38

<sup>1</sup>H-NMR (500 MHz, acetone-d<sub>6</sub>)

δ 7.52 (d, J = 8 Hz, 2H), 7.35 (t, J = 7.5 Hz, 2H), 7.27 (t, J = 7.5 Hz, 1H), 6.96, (d, J = 18 Hz, 1H), 6.46 (d, J = 18 Hz, 1H), 4.27 (d, J = 17 Hz, 1H), 4.19 (d, J = 17 Hz, 1H), 4.05 (d, J = 14.5 Hz, 1H), 4.02 (d, J = 17 Hz, 1H), 3.42-3.38 (m, 1H), 2.05 (m, 1H), 1.86-1.83 (m, 1H), 1.78-1.74 (m, 1H), 1.69-1.62 (m, 2H), 1.50-1.44 (m, 1H), 1.36-1.27 (m, 6H), 1.18-1.08 (m, 2H).
**13C-NMR (125 MHz, CDCl₃)**
\[ \delta 168.5, 167.7, 144.3, 128.6, 128.4, 126.7, 67.6, 56.8, 39.2, 32.1, 27.7, 26.4, 25.7, 25.7, 10.5. \]

**11B-NMR (100 MHz, acetone-d₆)**
\[ \delta 11.9 \]

HRMS (ESI+)
- Calculated for C₂₀H₂₇BNO₅: 356.2033
- Found: 356.2029

**Boronate ester 2.2d.** The general procedure was followed using *trans*-2-phenylvinylboronic acid (0.148 g, 1 mmol), ligand 2.1d (0.461 g, 1.5 mmol) in 15 ml toluene and 0.5 ml DMSO. An off-white solid was obtained (0.311 g, 74%).

**TLC (Hexanes:acetone 3:2)**
\[ R_f = 0.38 \]

**1H-NMR (500 MHz, acetone-d₆)**
\[ \delta 7.50 \text{ (d, } J = 8 \text{ Hz, 2H}), 7.38-7.29 \text{ (m, 6H), 7.26-7.22 \text{ (m, 1H), 7.18-7.13 \text{ (m, 1H), 6.96 \text{ (d, } J = 18 \text{ Hz, 1H), 6.46 \text{ (d, } J = 18.5 \text{ Hz, 1H), 4.62 \text{ (d, } J = 11.5 \text{ Hz, 1H), 4.55 \text{ (d, } J = 11 \text{ Hz, 1H), 4.41-4.38 \text{ (m, 1H), 4.29 \text{ (d, } J = 16.5 \text{ Hz, 1H), 4.19 \text{ (d, } J = 17.5 \text{ Hz, 1H), 4.14 \text{ (d, } J = 16.5 \text{ Hz, 1H), 4.05 \text{ (d, } J = 17 \text{ Hz, 1H), 3.70 \text{ (q, } J = 9 \text{ Hz, 1H), 2.30-2.25 \text{ (m, 1H), 2.20-2.15 \text{ (m, 1H), 1.82-1.6 \text{ (m, 4H).} \]

**13C-NMR (125 MHz, CDCl₃)**
\[ \delta 168.8, 167.5, 144.3, 137.5, 136.4, 128.8, 128.6, 128.5, 128.4, 128.3, 126.8, 79.3, 73.4, 72.0, 60.0, 55.4, 29.6, 26.2, 21.1. \]

**11B-NMR (100 MHz, acetone-d₆)**
\[ \delta 11.8 \]
**General procedure for the synthesis of boronates 2.2e-1 and 2.2f-1:**

**Preparation of boronic acid solution.** A 7 ml vial equipped with a stir bar was charged with the boronic acid (2.4 mmol). The vial was taken into the glovebox and THF (6 ml) was added. The mixture was stirred rapidly to give 0.4 M solution of the boronic acid.

**Preparation of catalyst stock solution.** In a glovebox, to a 7 ml vial equipped with a stir bar was added P(o-tolyl)$_3$ (170 mg, 0.55 mmol) and Pd$_2$dba$_3$ (128 mg, 0.14 mmol). THF (14 ml) was added to make a 0.01 M catalyst solution which was stirred at 23 °C for 10 min.

The freshly prepared catalyst stock solution was immediately for the preparation of 2.2e-1 and 2.2f-1:

This reaction was carried out in triplicate. A 7 ml vial (“reaction vial”) equipped with a stir bar was charged with (E)-(2-Iodoethenyl)boronate ester$^2$ (0.4 mmol), and Ag$_2$O (1.2 mmol). The vials were taken into the glovebox. To each reaction vial was added 0.5 ml THF. 1.5 ml (0.6 mmol) of the boronic acid solution was added to the reaction vial, followed by 2 ml of the catalyst stock solution (0.02 mmol Pd$_2$dba$_3$, 0.08 mmol P(o-tolyl)$_3$). The reaction was then sealed with a cap, removed from the glovebox and placed in a heating block pre-equilibrated at 45 °C. The reaction was stirred for 24 h at 45 °C, then cooled to 23 °C. The reaction mixture was filtered through celite, combining the filtrates from the triplicate reactions. The celite pad was rinsed with THF (2 ×10 ml). The combined filtrate was concentrated in vacuo. The crude product was taken up in CH$_2$Cl$_2$ and loaded onto a silica gel column. The non-polar impurities were eluted with Et$_3$O, and the product was eluted with 10-33% Et$_3$O/acetone.
The general procedure was followed using a stock solution of 3-methoxycarbonyl-phenylboronic acid (432 mg, 2.4 mmol) and (E)-(2-Iodoethenyl)boronate ester (124 mg, 0.4 mmol) and Ag₂O (278 mg, 1.2 mmol) in each of 3 reaction vials. MIDA boronate 2.2e-1 (340 mg, 89%) was obtained as a white solid after silica gel chromatography.

TLC (Hexanes:EtOAc 1:1)

Rᵣ = 0.22, visualized by UV, stained by KMnO₄.

¹H-NMR (500 MHz, acetone-d₆)

δ 8.14 (t, J = 1.5 Hz, 1H), 7.90 (dt, J = 7.5, 1.5 Hz, 1H), 7.76 (d, J = 7.5 Hz, 1H), 7.49 (t, J = 8.0 Hz, 1H), 7.02 (d, J = 18.5 Hz, 1H), 6.47 (d, J = 18.5 Hz, 1H), 4.29 (d, J = 17 Hz, 2H), 4.13 (d, J = 17 Hz, 2H), 3.89 (s, 3H), 3.09 (s, 3H).

¹³C-NMR (125 MHz, acetone-d₆)

δ 168.5, 166.5, 141.1, 139.0, 131.4, 130.9, 129.1, 128.8, 127.3, 61.8, 51.8, 46.8.

HRMS (ESI+)

Calculated for C₁₅H₁₇BNO₆: 318.1149

Found: 318.1154

The general procedure was followed using a stock solution of 4-fluoro-phenylboronic acid (84 mg, 2.4 mmol) and (E)-(2-Iodoethenyl)boronate ester (124 mg, 0.4 mmol) and Ag₂O (278 mg, 1.2 mmol) in each of 3 reaction vials. MIDA boronate 2.2f-1 (162 mg, 49%) was obtained as a white solid after silica gel chromatography.

TLC (Hexanes:acetone 1:1)

Rᵣ = 0.24, visualized by short wave UV.

¹H-NMR (500 MHz, acetone-d₆)

δ 7.58-7.54 (m, 2H), 7.13-7.09 (m, 2H), 6.93 (d, J = 18.5 Hz, 1H), 6.30 (d, J = 18 Hz, 1H), 4.27 (d, J = 17 Hz, 1H), 4.09 (d, J = 16.5 Hz, 1H), 3.06 (s, 3H).
$^1$C-NMR (125 MHz, acetone-d$_6$)
\[ \delta 169.1, 163.3 \text{ (d, } J = 244 \text{ Hz)}, \; 141.5, 135.7, 129.2 \text{ (d, } J = 8.8 \text{ Hz)}, \; 116.0 \text{ (d, } J = 21.4 \text{ Hz)}, \; 62.3, 47.4. \]

HRMS (ESI+)

Calculated for C$_{13}$H$_{24}$BNO$_4$F: 278.1000

Found: 278.0998

In an unoptimized procedure, to a suspension of 2.2e-1 (322 mg, 1.02 mmol) in MeOH (10 ml) in a 20 ml vial was added K$_2$CO$_3$ (421 mg, 3.05 mmol) under ambient atmosphere. The vial was capped and placed in a heating block pre-heated to 45 °C. The reaction was stirred at 45 °C for 30 min and then allowed to cool to 23 °C. The yellow solution of the boronic ester was poured into 20 ml 6N HCl. The solution was transferred to a separatory funnel and extracted with Et$_2$O (2 × 25 ml). To the aqueous layer was added brine (10 ml) and the aqueous layer was extracted with 1:1 THF/Et$_2$O (25 ml). The organic phase was then dried over MgSO$_4$, filtered and concentrated in vacuo to afford boronic acid 2.2e-2. The boronic acid was then suspended in toluene (30 ml) and 2.1a was added. The mixture was refluxed with a Dean-Stark trap for 2 h. The reaction was cooled to 23 °C and concentrated in vacuo. CH$_2$Cl$_2$ (30 ml) was added and stirred briefly. The excess ligand 2.1a was removed by filtration. To the filtrate was added celite, and the suspension was concentrated in vacuo. The celite pad was loaded onto a silica gel column and the product 2.2e purified by flash chromatography (100% Et$_2$O – 20% acetone/Et$_2$O) to afford a white solid (298 mg, 67% over 2 steps).

TLC (Hexanes:EtOAc 1:1)

\[ R_f = 0.27, \text{ visualized by short wave UV.} \]

$^1$H-NMR (500 MHz, CDCl$_3$)
\[ \delta 8.14 \text{ (s, 1H)}, \; 7.95 \text{ (d, } J = 8 \text{ Hz, 1H)}, \; 7.63 \text{ (d, } J = 8 \text{ Hz, 1H)}, \; 7.43 \text{ (t, } J = 7.5 \text{ Hz, 1H)}, \; 7.11 \text{ (d, } J = 18.5 \text{ Hz, 1H)}, \; 6.38 \text{ (d, } J = 18 \text{ Hz, 1H)}, \; 4.21 \text{ (d, } J = 17.5 \text{ Hz, 1H)}, \; 3.93 \text{ (s, 3H)}, \; 3.88 \text{ (d, } J = 15.5 \text{ Hz, 1H)}, \; 3.82 \text{ (d, } J = 15.5 \text{ Hz, 1H)}, \; 3.71 \text{ (dt, } J = 10, 6.5 \text{ Hz, 1H)}, \; 3.56 \text{ (d, } J = 17 \text{ Hz, 1H)}, \; 2.47-2.52 \text{ (m, 1H)}, \]
2.48-2.43 (m, 1H), 2.18-2.16 (m, 1H), 2.03-2.02 (m, 1H), 1.92-1.90 (m, 1H), 1.74 (ddd, J = 13, 6, 2 Hz, 1H), 1.29 (d, J = 7 Hz, 3H), 1.23 (s, 3H), 0.92 (d, J = 11 Hz, 1H), 0.88 (s, 3H).

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

$\delta$ 169.5, 166.9 (2H), 143.4, 137.9, 131.2, 130.6, 129.3, 128.7, 127.6, 68.6, 60.6, 54.4, 52.2, 49.0, 40.5, 39.1, 38.8, 32.0, 30.3, 27.0, 23.6, 23.4

HRMS (ESI+)

Calculated for C$_{24}$H$_{31}$BNO$_6$: 440.2244

Found: 440.2250

To a solution of 2.2f-1 (139 mg, 0.50 mmol) in THF (5 ml) was added 1N NaOH (1.5 ml, 1.5 mmol) under ambient atmosphere and temperature and stirred vigorously for 15 min. The reaction was quenched with the addition of sat. NH$_4$Cl solution (5 ml). The mixture was stirred for 3 min, then transferred to a separatory funnel, rinsing with Et$_2$O (5 ml). After phase separation, the aqueous phase extracted with 1:2 THF/Et$_2$O (2 × 7.5 ml). The organic phase was dried over MgSO$_4$, filtered and concentrated in vacuo to give the boronic acid 2.2f-2. The solid was suspended up in toluene (20 ml) and 2.1a (20 mg, 0.75 mmol) was added. The reaction was heated to reflux with a Dean-Stark trap for 2 h. After cooling to room temperature, toluene was removed in vacuo. CH$_2$Cl$_2$ (30 ml) was added and stirred briefly. The excess ligand 2.1a was removed by filtration. To the filtrate was added celite, and the suspension was concentrated in vacuo. The celite pad was loaded onto a silica gel column and the product purified by flash chromatography (100% Et$_2$O – 20% acetone/Et$_2$O) to afford a white solid 2.2f (136 mg, 68% over 2 steps).

TLC (Hexanes:EtOAc 1:1)

$R_f = 0.30$, visualized by short wave UV.

$^1$H-NMR (500 MHz, CDCl$_3$)
δ 7.44-7.41, (m, 2H), 7.05-7.01 (m, 3H), 6.20 (d, J = 18 Hz, 1H), 4.19 (d, J = 17.5 Hz, 1H), 3.85 (s, 2H), 3.69 (dt, J = 10, 6.5 Hz, 1H), 3.63 (d, J = 17.5 Hz, 1H), 2.52 (tt, J = 12, 2.5 Hz, 1H), 2.44 (ddt, J = 11, 6, 2 Hz, 1H), 2.19-2.16 (m, 1H), 2.03-2.00 (m, 1H), 1.90 (dt, J = 6, 2 Hz, 1H), 1.73 (ddd, J = 15, 6, 2.5 Hz, 1H), 1.28 (d, J = 7 Hz, 3H), 1.22 (s, 3H), 0.92 (d, J = 11 Hz, 1H), 0.88 (s, 3H).

13C-NMR (125 MHz, CDCl3)
δ 169.5, 166.9, 162.8 (d, J = 247 Hz), 143.3, 133.8, 128.3 (d, J = 7.8 Hz), 115.6 (d, J = 21.4 Hz), 66.6, 60.6, 54.4, 49.0, 40.5, 39.1, 38.8, 32.1, 30.3, 27.0, 23.6, 23.4.

HRMS (ESI+)
Calculated for C22H28BFNO4: 400.2095
Found: 400.2101

To a solution of 2.2g-1 (197 mg, 1 mmol) in THF (10 ml) was added 1N NaOH (3 ml, 3 mmol) under ambient atmosphere and temperature and stirred vigorously for 15 min. The reaction was quenched with the addition of sat. NH4Cl solution (10 ml). The mixture was stirred for 3 min, then transferred to a separatory funnel, rinsing with Et2O (10 ml). After phase separation, the organic phase was washed with another portion of sat. NH4Cl solution (10 ml) and the combined aqueous phase extracted with 1:1 THF/Et2O (15 ml). The organic phase was dried over MgSO4, filtered and concentrated in vacuo to give the boronic acid 2.2g-2 as a white solid. The solid was taken up in toluene (15 ml) and DMSO (0.75 ml) and 2.1a (404 mg, 1.5 mmol) was added. The reaction was heated to reflux with a Dean-Stark trap for 1.5 h. After cooling to room temperature, toluene was removed in vacuo. The residue was taken up in 2:1 EtOAc/acetone (15 ml) and washed twice with 1:1 H2O/brine (10 ml). The aqueous layers were extracted with 2:1 EtOAc/acetone (15 ml). The combined organic phase was dried over MgSO4, filtered and concentrated. The crude product was purified by silica gel chromatography, eluting first with Et2O then with 1:4 acetone/Et2O to give 2.2g as a white solid (166 mg, 52% over 2 steps).

TLC (Hexanes:acetone 3:2)
Rf = 0.41, stained by KMnO4
$^1$H-NMR (500 MHz, acetone-$d_6$)

$\delta$ 6.13 (dq, $J = 8.5$ Hz, 1H), 5.66 (dd, $J = 17.5$, 1.5 Hz, 1H), 4.19 (d, $J = 18$ Hz, 1H), 4.18 (d, $J = 16$ Hz, 1H), 4.09 (d, $J = 15.5$ Hz, 1H), 3.94 (d, $J = 18$ Hz, 1H), 3.87 (dt, $J = 10$, 3 Hz, 1H), 2.57-2.51 (m, 1H), 2.49-2.42 (m, 2H), 2.00 (sept, $J = 3$ Hz, 1H), 1.91 (dt, $J = 6$, 2 Hz, 1H), 1.79 (dd, $J = 6.5$, 1.5 Hz, 3H), 1.61 (ddd, $J = 15$, 6.5, 1.5 Hz, 1H), 1.33 (d, $J = 7$ Hz, 3H), 1.25 (s, 3H), 1.04 (d, $J = 10.5$ Hz, 1H), 0.98 (s, 3H).

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

$\delta$ 170.2, 167.2, 140.8, 67.9, 60.3, 54.5, 49.6, 41.0, 39.0, 38.5, 31.8, 30.3, 26.9, 23.0, 22.9, 20.8.

$^{11}$B-NMR (100 MHz, acetone-$d_6$)

$\delta$ 11.5

HRMS (ESI+)

Calculated for C$_{17}$H$_{27}$BNO$_4$: 320.2033

Found: 320.2035

In an unoptimized procedure, TBS-protected propargyl alcohol (5.17 g, 30.4 mmol) was weighed into a dry 20 ml Ichem vial and the vial was sealed with a septum cap. The vial was flushed with N$_2$ for 20 min, then catecholborane (3.4 ml, 31.9 mmol) was added neat in one portion. The reaction was stirred at 60 °C
in a heating block for 15 h. After cooling to room temperature, 4.36 g (approx. 15 mmol) of this crude product was diluted in THF (150 ml) and 1N NaOH (45 ml, 45 mmol) was added. After vigorous stirring for 10 min, the mixture was transferred to a separatory funnel and the phases separated. The organic layer was washed with 1N NaOH (60 ml), then H2O (60 ml) and 1:1 H2O/brine (60 ml). The organic phase was then dried over MgSO4, filtered and concentrated to give a yellow oil as the boronic acid 2.2i-1 (1.48 g, 6.85 mmol). The boronic acid 2.2i-1 was then dissolved in toluene (60 ml) and DMSO (3 ml). 2.1a was then added, and the mixture was heated to reflux with a Dean-Stark trap for 2h. The reaction was then cooled to room temperature. Toluene was then removed in vacuo. Et2O was added to the residue and the precipitate, which is the crude product, was obtained by vacuum filtration. Purification by silica gel chromatography (30-100% EtOAc/hexane) gave a white solid 2.2i (405 mg, ~30% from boronic acid).

TLC (Hexanes:acetone 3:2)  
Rf = 0.51 visualized by KMnO4

1H-NMR (500 MHz, CDCl3)  
δ 6.22 (dt, J = 17.5, 4Hz, 1H), 5.94 (dt, J = 17.5, 2 Hz, 1H), 4.26-4.25 (m, 2H), 4.23 (d, J = 18 Hz, 1H), 4.18 (d, J = 15.5 Hz, 1H), 4.12 (d, J = 15 Hz, 1H), 3.98 (d, J = 18 Hz, 1H), 3.86 (dt, J = 10.5, 6 Hz, 1H), 2.59-2.53 (m, 1H), 2.49-2.41 (m, 2H), 1.99 (sept, J = 3 Hz, 1H), 1.92 (dt, J = 6, 2 Hz, 1H), 1.66 (ddd, J = 15, 6.5, Hz, 1H), 1.34 (d, J = 7 Hz, 3H), 1.25 (s, 3H), 1.07 (d, J = 10.5 Hz, 1H), 0.99 (s, 3H), 0.9 (s, 9H), 0.1 (s, 6H).

13C-NMR (125 MHz, CDCl3)  
δ 169.7, 167.0, 146.2, 68.4, 64.3, 60.3, 54.2, 49.0, 40.6, 38.9, 38.8, 32.0, 30.8, 30.2, 27.0, 25.9, 23.5 (2C), 15.2, -5.4.

11B-NMR (100 MHz, acetone-d6)  
δ 11.8

HRMS (ESI+)  
Calculated for C23H41BNO5Si: 450.2847  
Found: 450.2845
The boronate ester 2.2i (1.52 g, 3.38 mmol) was dissolved in CH₂Cl₂ (68 ml) and cooled to 0 °C. H₂O (0.34 ml) followed by TFA (6.80 ml) was then added. The reaction was stirred at 0 °C for 30 min. The reaction was washed briefly with H₂O (30 ml), then twice with sat. aqueous NaHCO₃ (30 ml). The combined aqueous layer was washed with CH₂Cl₂ (30 ml). The organic phase was then dried over MgSO₄, filtered and concentrated. Following purification by silica gel chromatography (40 → 80% EtOAc/hexane), a white solid 2.2h was obtained. (737 mg, 65%).

TLC (Hexanes:acetone 3:2)

Rᶠ = 0.20, visualized by KMnO₄

¹H-NMR (500 MHz, acetone-d₆)

δ 6.26 (dt, J = 18, 4 Hz, 1H), 5.89 (app d, J = 17.5 Hz, 1H), 4.12 (d, J = 15 Hz, 1H), 4.12 (m, 2H), 3.89 (dt, J = 10, 6.5 Hz, 1H), 2.56 (m, 1H), 2.48-2.2 (m, 2H), 1.99 (sept, J = 3 Hz, 1H), 1.91 (dt, J = 6, 2.5 Hz, 1H), 1.63 (ddd, J = 15, 6.5, 5 Hz, 1H), 1.35 (d, J = 7 Hz, 3H), 1.25 (s, 3H), 1.06 (d, J = 10.5 Hz, 1H), 0.97 (s, 3H).

¹³C-NMR (125 MHz, acetone-d₆)

δ 170.8, 167.9, 146.5, 68.5, 64.5, 60.9, 55.2, 50.2, 41.6, 39.6, 39.1, 32.3, 30.9, 27.5, 23.6, 23.6.

¹¹B-NMR (100 MHz, acetone-d₆)

δ 11.8

HRMS (ESI+)

Calculated for C₁₇H₂₇BNO₅: 336.1982
Found: 336.1979

To a solution of 2.2j-¹⁴ (117 mg, 0.45 mmol) in THF (5 ml) was added 1N NaOH (1.4 ml, 1.4 mmol) under ambient atmosphere and temperature and stirred vigorously for 15 min. The reaction was diluted with Et₂O and quenched with the addition of sat. NH₄Cl solution (10 ml). The mixture was stirred for 3
min, then transferred to a separatory funnel. After phase separation, the organic phase was washed with another portion of sat. NH₄Cl solution (10 ml) and the combined aqueous phase extracted with 3:2 THF/Et₂O (10 ml then 5 ml). The combined organic phase was dried over MgSO₄, filtered and concentrated in vacuo to give the boronic acid 2.2j-2 as a white solid. The solid was taken up in benzene (30 ml) and 2.1a (182 mg, 0.675 mmol) was added. The reaction was heated to reflux with a Dean-Stark trap for 2 h. After cooling to room temperature, benzene was removed in vacuo. CH₂Cl₂ (30 ml) was added and stirred briefly. The excess ligand 2.1a was removed by filtration. To the filtrate was added celite, and the suspension was concentrated in vacuo. The celite pad was loaded onto a silica gel column and the product purified by flash chromatography (100% Et₂O – 20% acetone/Et₂O) to afford a white solid (100 mg, 58% over 2 steps) as the pure cis-isomer.

TLC (Hexanes:EtOAc 1:1)

Rf = 0.52, visualized by short wave UV.

¹H-NMR (500 MHz, acetone-d₆)

δ 7.37 – 7.27 (m, 5H), 5.92 (d, J = 15 Hz, 1H), 4.04 (d, J = 17.5 Hz, 1H), 3.69 (dt, J = 10.5, 6.5 Hz, 1H), 3.29 (d, J = 14.5 Hz, 1H), 3.27 (d, J = 18 Hz, 1H), 2.54 (d, J = 15 Hz, 1H), 2.53-2.48 (m, 1H), 2.43 – 2.39 (m, 1H), 2.00 – 1.98 (m, 1H), 1.97 – 1.94 (m, 1H), 1.85 (dt, J = 6, 2.5 Hz, 1H), 1.50 (ddd, J = 15, 6.5, 2.5 Hz, 1H), 1.25 (s, 3H), 1.02 (s, 3H), 0.99 (d, J = 7 Hz, 3H), 0.82 (d, J = 11 Hz, 1H).

¹³C-NMR (125 MHz, CDCl₃)

δ 169.4, 166.7, 144.8, 139.6, 128.6, 128.0, 127.6, 67.8, 61.5, 55.0, 49.0, 40.7, 38.8, 38.7, 32.1, 30.4, 27.1, 23.3, 23.0.

HRMS (ESI+)

Calculated for C₂₂H₂₉BNO₄: 382.2190

Found: 382.2198

To an oven-dried 300-mL 3-neck round-bottomed flask equipped with a magnetic stir bar, two rubber septa (side and center arm) and a thermometer with an adapter (side arm) was added THF (75 mL) and
trimethyl borate (6 mL, 53.6 mmol, 1.1 equiv) under an atmosphere of N₂. The solution was cooled to -70 °C (internal temperature) in a dry ice/acetone bath. The Grignard reagent (97.5 mL, 48.75 mmol, 0.50 M in THF) was cannulated directly into the reaction vessel over 30 min. The reaction vessel was removed from the bath after 5 min and allowed to warm to ambient temperature over the course of 3 h resulting in a white slurry. While the slurry of the “ate” complex was warming to ambient temperature, an oven-dried 200-mL 3-neck round-bottomed flask equipped with a magnetic stir bar, a thermometer, a rubber septum and a distillation train (center arm) was charged with MIDA (15.78 g, 107.3 mmol, 2.2 equiv) and DMSO (75 mL). Using a heating mantle and variac, the suspension was brought to an internal temp of 150 °C. The suspension of the “ate” complex was added directly into the DMSO solution of MIDA over the course of 1 h via cannula transfer (Teflon cannula) under a positive pressure of N₂ at a rate such that the internal temperature remained between 120–150 °C. After the addition was completed the reaction vessel was washed with THF (20 mL) and the washes added via cannula transfer to the reaction vessel containing the MIDA solution. The remaining THF and MeOH were allowed to distill off (~15 min). The reaction vessel was allowed to cool to ambient temperature. The reaction mixture was then transferred to a 1 L separatory funnel. To this was added 100 ml of de-ionized water, 100 ml of brine, 150 ml of ethyl acetate, and 100 ml of acetone. After mixing, the organic layer was separated, and the aqueous layer was extracted thrice with 50 mL of 3:2 ethyl acetate: acetone solution. TLC showed no product in the aqueous layer. The combined organic fractions were then washed with 100 mL of brine (3×), and dried by stirring with MgSO₄ and Darco. The organic fractions were then concentrated to form a orange-brown oil, which was taken up in 50 ml acetone. Et₂O (400 ml) was slowly added to the acetone solution. 2 phases formed. After vacuum filtration to trap the oil, crystals formed which were recovered by another filtration. The filtrate was concentrated, and the residue taken up in 20 ml of acetone. 100 ml of Et₂O and 100 ml of hexane was added sequentially, and the mixture allowed to crystallize overnight. After filtration, the filtrate was concentrated, the residue taken up in ~ 10 ml acetone, and Et₂O (100 ml) was layered on top and the solution was allowed to stand and crystallize. The crystals were collected by vacuum filtration and the filtrate discarded. An off-white solid was obtained as an inseparable mixture of 2 MIDA boronates (4.43 g, 43%). This mixture was used without further purification for the synthesis of 2.2k.

In an unoptimized procedure, to a solution of the crude product containing 2.2k-1 (1.69 g, 8.01 mmol) in THF (80 ml) was added 1N NaOH (24 ml, 24 mmol) under ambient atmosphere and temperature and
stirred vigorously for 15 min. The reaction was diluted with Et₂O (40 ml) and quenched with the addition of sat. NH₄Cl solution (50 ml). The mixture was stirred for 3 min, then transferred to a separatory funnel. After phase separation, the aqueous phase extracted with 2:1 THF/Et₂O (2 × 30 ml). The combined organic phase was dried over MgSO₄, filtered and concentrated \textit{in vacuo} to give the boronic acid 2.2k-2. The solid was taken up in toluene (60 ml) and 2.1a (3.23 g, 12.0 mmol) was added. The reaction was heated to reflux with a Dean-Stark trap for 2 h. After cooling to room temperature, toluene was removed \textit{in vacuo}. CH₂Cl₂ (50 ml) was added and stirred briefly. The excess ligand 2.1a was removed by filtration. To the filtrate was added celite, and the suspension was concentrated \textit{in vacuo}. The celite pad was loaded onto a silica gel column and the product purified by flash chromatography (Et₂O – 20% acetone/Et₂O) to afford a white solid (710 mg, 27% over 2 steps) as the pure product 2.2k.

TLC (Hexanes:EtOAc 1:1)

$R_f = 0.30$, visualized by KMnO₄

$^1$H-NMR (500 MHz, CDCl₃)

$\delta$ 5.12 (s, 1H), 4.10 (d, $J = 17$ Hz, 1H), 3.76 (d, $J = 15.5$ Hz, 1H), 3.76 (d, $J = 15.5$ Hz, 1H), 3.72 (dt, $J = 10.5$, 6 Hz, 1H), 3.46 (d, $J = 17.5$ Hz, 1H), 2.47-2.41 (m, 2H), 2.15-2.12 (m, 1H), 1.99-1.98 (m, 1H), 1.91 (dt, $J = 6$, 2 Hz, 1H), 1.87 (s, 3H), 1.85 (s, 3H), 1.58 (ddd, $J = 15$, 6, 2 Hz, 1H), 1.30 (d, $J = 6.5$ Hz, 3H), 1.25 (s, 3H), 0.95 (s, 3H), 0.89 (d, $J = 10.5$ Hz, 1H).

$^{13}$C-NMR (125 MHz, CDCl₃)

$\delta$ 169.6, 166.8, 151.2, 68.5, 61.0, 54.1, 49.1, 40.6, 39.1, 38.9, 32.1, 30.2, 29.7, 27.1, 23.6, 23.3, 21.4.

HRMS (ESI+)

Calculated for C₁₈H₂₉BNO₄: 334.2190

Found: 334.2191

To a solution of 1-phenylvinylboronic acid (296 mg, 2 mmol) was added 1a (808 mg, 3 mmol). The mixture was refluxed with a Dean-Stark trap for 2 h. The reaction was then cooled to 23 °C and
concentrated in vacuo. The residue was taken up in CH₂Cl₂ and absorbed onto celite. The celite pad was loaded onto a silica gel column and the product purified by flash chromatography (Et₂O – 20% acetone/Et₂O) to give a slightly yellow solid. The solid was triturated with acetone (2 ml) and filtered to obtain a white solid 2.21 (374 mg, 49%).

TLC (Hexanes:EtOAc 1:1)

Rᵣ = 0.34, visualized by short wave UV

¹H-NMR (500 MHz, CDCl₃)

δ 7.37-7.32 (m, 4H), 7.29-7.26 (m, 1H), 5.96 (d, J = 3 Hz, 1H), 5.75 (d, J = 3 Hz, 1H), 4.18 (d, J = 17 Hz, 1H), 3.59 (d, J = 15.5 Hz, 1H), 3.48 (d, J = 17.5 Hz, 1H), 3.48 (m, 1H), 3.25 (d, J = 15.5 Hz, 1H), 2.50-2.45 (m, 1H), 2.39 (ddt, J = 11, 6, 2 Hz, 1H), 1.98-1.94 (m, 1H), 1.81 (dt, J = 6, 2 Hz, 1H), 1.56 (ddd, J = 15.5, 6.5, 2.5 Hz, 1H), 1.21 (s, 3H), 0.94 (d, J = 6.5 Hz, 3H), 0.85 (d, J = 10.5 Hz, 1H), 0.84 (s, 3H).

¹³C-NMR (125 MHz, CDCl₃)

δ 169.1, 166.9, 144.1, 129.3, 128.9, 127.2, 126.8, 67.7, 61.7, 55.3, 48.9, 40.5, 39.0, 38.8, 31.9, 30.0, 27.1, 23.3, 23.1

HRMS (ESI+)

Calculated for C₂₂H₂₉BNO₄: 382.2190

Found: 382.2192

To a solution of 2.2m-1⁵ (197 mg, 1 mmol) in THF (10 ml) was added 1N NaOH (3 ml, 3 mmol) under ambient atmosphere and temperature and stirred vigorously for 15 min. The reaction was quenched with the addition of sat. NH₄Cl solution (10 ml). The mixture was stirred for 3 min, then transferred to a separatory funnel, rinsing with Et₂O (10 ml). After phase separation, the organic phase was washed with another portion of sat. NH₄Cl solution (10 ml) and the combined aqueous phase extracted with 1:1 THF/Et₂O (15 ml). The organic phase was dried over MgSO₄, filtered and concentrated in vacuo to give the boronic acid 2.2m-2 as a white solid. (Note: the boronic acid is unstable, should not be dried
completely and must be used immediately.) The boronic acid 2.2m-2 was taken up in toluene (15 ml) and DMSO (0.75 ml) and 2.1a (404 mg, 1.5 mmol) was added. The reaction was heated to reflux with a Dean-Stark trap for 1.5 h. After cooling to room temperature, toluene was removed in vacuo. The residue was taken up in 2:1 EtOAc/acetone (15 ml) and washed twice with 1:1 H2O/brine (10 ml). The aqueous layers were extracted with 2:1 EtOAc/acetone (15 ml). The combined organic phase was dried over MgSO4, filtered and concentrated. The crude product was purified by silica gel chromatography, eluting first with Et2O then with 1:4 acetone/Et2O to give a white solid as the pure product 2.2m (153 mg, 48% over 2 steps).

TLC (Hexanes:acetone 3:2)

\[ R_f = 0.44, \text{stained by KMnO}_4 \]

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

\[ \delta 5.57 \text{ (br s, 1H)}, 5.47 \text{ (br s, 1H)}, 4.20, (d, J = 17.5 \text{ Hz, 1H}), 3.89 (d, J = 16 \text{ Hz, 1H}), 3.86 (d, J = 16 \text{ Hz, 1H}), 3.72 (dt, J = 10.5, 6.5 \text{ Hz, 1H}), 3.62 (d, J = 17.5 \text{ Hz, 1H}), 2.53 - 2.48 (m, 1H), 2.43 - 2.39 (m, 1H), 2.18 - 2.15 (m, 1H), 1.97 - 1.96 (m, 1H), 1.89 (dt, J = 6, 2 \text{ Hz, 1H}), 1.86 (s, 3H), 1.56 (ddd, J = 15, 6, 2.5 \text{ Hz, 1H}), 1.30 (d, J = 7 \text{ Hz, 3H}), 1.23 (s, 3H), 0.92 (s, 3H), 0.89 (d, 1H). \]

$^1$C-NMR (125 MHz, CDCl$_3$)

\[ \delta 169.6, 166.9, 126.0, 68.8, 61.4, 55.2, 49.0, 40.5, 39.1, 38.8, 31.9, 30.3, 27.0, 23.8, 23.4, 22.0. \]

$^{11}$B-NMR (100 MHz, acetone-d$_6$)

\[ \delta 11.6 \]

HRMS (ESI+)  1

Calculated for C$_{17}$H$_{27}$BNO$_4$:  320.2033

Found:  320.2034

To a solution of 2.2n-1$^6$ (183 mg, 1 mmol) in THF (10 ml) was added 1N NaOH (3 ml, 3 mmol) under ambient atmosphere and temperature and stirred vigorously for 15 min. The reaction was quenched with the addition of sat. NH$_4$Cl solution (10 ml). The mixture was stirred for 3 min, then transferred to a
separatory funnel, rinsing with Et₂O (10 ml). After phase separation, the organic phase was washed with another portion of sat. NH₄Cl solution (10 ml) and the combined aqueous phase extracted with 1:1 THF/Et₂O (15 ml). The organic phase was dried over MgSO₄, filtered and concentrated in vacuo to give the boronic acid as a white solid. The solid was taken up in toluene (15 ml) and DMSO (0.75 ml) and 2.1a (404 mg, 1.5 mmol) was added. The reaction was heated to reflux with a Dean-Stark trap for 1.5 h. After cooling to room temperature, toluene was removed in vacuo. The residue was taken up in 2:1 EtOAc/acetone (15 ml) and washed twice with 1:1 H₂O/brine (10 ml). The aqueous layers were extracted with 2:1 EtOAc/acetone (15 ml). The combined organic phase was dried over MgSO₄, filtered and concentrated. The crude product was purified by silica gel chromatography, eluting first with Et₂O then with 1:4 acetone/Et₂O to give a white solid as the pure product 2.2n (153 mg, 55% over 2 steps).

TLC (Hexanes:acetone 3:2)
Rᵣ = 0.39, visualized by KMnO₄

¹H-NMR (500 MHz, CDCl₃)
δ 6.04 (dd, J = 19.5, 14 Hz, 1H), 5.11 (dd, J = 13.5, 3.5 Hz, 1H), 5.84 (dd, J = 19, 3.5 Hz, 1H), 4.15 (d, J = 17.5 Hz, 1H), 3.78 (d, J = 15.5 Hz, 1H), 3.73 (d, J = 15.5 Hz, 1H), 3.67 (dt, J = 13, 6.5 Hz, 1H), 3.46 (d, J = 17.5 Hz, 1H), 2.52 – 2.43 (m, 2H), 2.14 (dquint, J = 7, 2 Hz, 1H), 2.02 (sept, J = 3 Hz, 1H), 1.92 (dt, J = 6, 2 Hz, 1H), 1.67 (dd, J = 15, 6, 2.5 Hz, 1H), 1.30 (d, J = 7 Hz, 3H), 1.26 (s, 3H), 0.95 (s, 3H), 0.90 (d, J = 11 Hz, 1H).

¹³C-NMR (125 MHz, acetone-d₆)
δ 170.2, 167.8, 130.1, 68.6, 61.0, 55.2, 50.2, 41.6, 39.6, 39.2, 32.3, 31.0, 27.4, 23.6.

¹¹B-NMR (100 MHz, acetone-d₆)
δ 11.3

HRMS (ESI+)
Calculated for C₁₆H₂₅BNO₄: 306.1877
Found: 306.1872

c. Synthesis of 2.3a – 2.3n
General procedure for the epoxidation of boronate esters 2.2a-d (Table 1):
To a solution of the boronate ester 2.2 (0.1 mmol) in CH$_2$Cl$_2$ at 0 °C was added mCPBA (max 77%, 43 mg, 0.19 mmol) portionwise over 3 min under ambient atmosphere. The reaction was stirred for 12 h, gradually raising the temperature to rt. The reaction was then concentrated in vacuo at 20 °C, and $^1$H-NMR analysis was carried out. Conversions for all 4 substrates (2.2a-d) are >95%. The peaks from the protons on the epoxide were used to determine the d.r. Note that except for 2.3a for which all stereogenic centers have been assigned, the stereochemistry of the epoxide shows only the relative i.e. trans configuration of the epoxide substituents.

The general procedure was followed using boronate ester 2.2a (38 mg, 0.1 mmol) and mCPBA (43 mg, 0.19 mmol). d.r. >20:1

TLC (Hexanes:acetone 3:2)
$R_f$ = 0.46, visualized by KMnO$_4$
\(^1\)H-NMR (500 MHz, CDCl\(_3\))
\[\delta 7.40-7.35 (m, 4H), 7.33-7.30 (m, 1H), 4.40 (dt, J = 10.5, 3.5 Hz, 1H), 4.36 (d, J = 18 Hz, 1H), 4.22 (d, J = 15 Hz, 1H), 4.14 (d, J = 17.5 Hz, 1H), 4.12 (d, J = 17.5 Hz, 1H), 3.83 (d, J = 2.5 Hz, 1H), 2.92-2.86 (m, 1H), 2.62-2.57 (m, 1H), 2.57 (d, J = 2.5 Hz, 1H), 2.53-2.47 (m, 1H), 2.11-2.08 (m, 1H), 2.00 (dt, J = 5.5, 2 Hz, 1H), 1.85 (ddd, J = 14.5, 4, 2.5 Hz, 1H), 1.45 (d, J = 6.5 Hz, 3H), 1.31 (s, 3H), 1.14 (d, J = 11 Hz, 1H), 1.10 (s, 3H).\]

\(^1^3\)C-NMR (125 MHz, CDCl\(_3\))
\[\delta 169.1, 166.4, 137.9, 128.5, 128.1, 125.5, 68.1, 61.8, 56.7, 54.7, 49.0, 40.6, 39.2, 39.0, 32.1, 30.6, 27.1, 23.5, 23.5\]

\(^1^1\)B-NMR (128 MHz, CDCl\(_3\))
\[\delta 10.5\]

HRMS (ESI+):
Calculated for C\(_{22}\)H\(_{29}\)BNO\(_5\): 398.2139
Found: 398.2135

The general procedure was followed using boronate ester 2.2b (38 mg, 0.1 mmol) and mCPBA (43 mg, 0.19 mmol). d.r. = 1.86:1
The general procedure was followed using boronate ester 2.2c (36 mg, 0.1 mmol) and mCPBA (43 mg, 0.19 mmol). d.r. = 2.7:1
The general procedure was followed using boronate ester \(2.2d\) (42 mg, 0.1 mmol) and mCPBA (43 mg, 0.19 mmol). d.r. = 1.56:1

**General procedure for the epoxidation of boronate esters 3a, 3e-n (Table 2):**

To a solution of the PIDA boronate \(2.2\) (0.25 mmol) in \(\text{CH}_2\text{Cl}_2\) at 0 °C was added mCPBA (max 77%, 106 mg, 0.475 mmol) portionwise over 3 min under ambient atmosphere. The reaction was stirred for 2.5-12 h, gradually raising the temperature to rt in the ice/water bath. The reaction was then concentrated \textit{in vacuo} at 20 °C, and \(^1\text{H}-\text{NMR}\) analysis of the crude reaction mixture was performed to determine the d.r. The crude product was then purified by chromatography on a silica gel or florisil column.
The epoxidation of 2.2a was carried out on a 15 mmol scale as follows: A solution of boronate ester 2.2a (5.72 g, 15 mmol) in CH₂Cl₂ (300 ml) was cooled to 0 °C. mCPBA (max 77%, 4.47 g, 20 mmol) was added portionwise under ambient atmosphere over 10 min. The reaction was stirred for 8 h, maintaining the bath temperature at 0-10 °C. The reaction was then concentrated to approximately 50 ml of CH₂Cl₂, and Et₂O was added (150 ml). The solution was stirred vigorously for 5 min, and the white solid (crude product) formed was obtained by vacuum filtration. The filtrate was concentrated to approximately 20 ml of CH₂Cl₂ and Et₂O (100 ml) and hexane (50 ml) was added. The white solid formed was collected by vacuum filtration. The filtrate, containing mostly mCPBA, m-chlorobenzoic acid and other non-polar impurities, was discarded. The combined white solid was dissolved in a minimum amount of CH₂Cl₂ in a 250 ml Erlenmeyer flask and layered with hexane (CH₂Cl₂:hexane 1:2). The flask was then cooled to -20 °C in a freezer. This recrystallized product was then collected by vacuum filtration and washed with CH₂Cl₂/hexane 1:10. The white solid was then dried in vacuo (3.87 g, 65%). Spectral data are identical to that obtained in the reaction in Table 1.

X-ray quality crystals were obtained by making a saturated solution of 2.3a in 1 ml of 1,2-dichloroethane and layering it with about 2 ml of hexane. The layers were allowed to slowly mix at room temperature, giving the desired crystals.

The general procedure was followed using boronate ester 2.3e (88 mg, 0.2 mmol) and mCPBA (69 mg, 0.4 mmol). The crude product was then taken up in a minimum amount of CH₂Cl₂, absorbed onto celite and loaded onto a silica gel column equilibrated with 50% Et₂O/hexane. The non-polar impurities were eluted with 50% Et₂O/hexane. The product was then eluted with 30% EtOAc/hexanes. After concentration at room temperature, the solid was washed with Et₂O:hexanes 1:1 (5 ml) to remove residual
mCPBA and vacuum filtered. The epoxide was then dried \textit{in vacuo}, giving the product as a white solid (65 mg, 71%). d.r. >20:1.

TLC (Hexanes:EtOAc 1:1)

\[ R_f = 0.33, \text{ visualized by UV/vis or KMnO}_4 \]

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

\[ \delta 7.98-7.97 (m, 2H), 7.50-7.49 (m, 1H), 7.44-7.41 (m, 1H), 4.39 (dt, J = 10, 6.5 Hz, 1H), 4.25 (d, J = 17.5 Hz, 1H), 4.06 (d, J = 15 Hz, 1H), 4.01 (d, J = 2.5 Hz, 1H), 3.92 (s, 3H), 3.74 (d, J = 15.5 Hz, 1H), 3.49 (d, J = 17 Hz, 1H), 2.76-2.71 (m, 1H), 2.53-2.45 (m, 1H), 2.49 (d, J = 2.5 Hz, 1H), 2.22-2.20 (m, 1H), 2.08-2.07 (m, 1H), 1.99-1.97 (m, 1H), 1.84 (ddd, J = 15, 5.5, 2.5 Hz, 1H), 1.39 (d, J = 6.5 Hz, 3H), 1.30 (s, 3H), 1.11 (s, 3H), 0.95 (d, J = 11 Hz, 1H). \]

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

\[ \delta 169.2, 166.8, 166.5, 138.6, 130.5, 130.1, 129.9, 128.6, 126.6, 68.3, 61.7, 56.3, 54.7, 52.2, 49.1, 40.6, 39.2, 38.9, 32.1, 30.6, 27.0, 23.6, 23.5. \]

HRMS (ESI+)

Calculated for C$_{24}$H$_{31}$BNO$_7$: 456.2194

Found: 456.2196

The general procedure was followed using boronate ester 2.2f (80 mg, 0.2 mmol) and mCPBA (69 mg, 0.4 mmol). The crude product was then taken up in a minimum amount of CH$_2$Cl$_2$, absorbed onto celite and loaded onto a silica gel column equilibrated with 50% Et$_2$O/hexane. The non-polar impurities were eluted with 50% Et$_2$O/hexane, then with 80% Et$_2$O/hexanes. The product was then eluted with 30% EtOAc/hexanes. The epoxide was then dried \textit{in vacuo}, giving the product 2.3f as a white solid (43 mg, 52%). d.r. >17:1.

TLC (Hexanes:EtOAc 1:1)

\[ R_f = 0.39, \text{ visualized by UV/vis or KMnO}_4 \]
\[^1\text{H-NMR}\ (500\ \text{MHz, CDCl}_3)\]

\[\delta 7.27 - 7.25\ (m, 2H), 7.05 - 7.01\ (m, 2H), 4.38\ (dt, J = 10, 6.5\ Hz, 1H), 4.24\ (d, J = 17.5\ Hz, 1H), 4.05\ (d, J = 15\ Hz, 1H), 3.94\ (d, J = 3\ Hz, 1H), 3.72\ (d, J = 15\ Hz, 1H), 3.48\ (d, J = 17.5\ Hz, 1H), 2.74 - 2.69\ (m, 1H), 2.50\ (ddt, J = 11, 6, 2\ Hz, 1H), 2.45\ (d, J = 3\ Hz, 1H), 2.22 - 2.17\ (m, 1H), 2.09 - 2.05\ (m, 1H), 1.98\ (dt, J = 6.5, 2.5\ Hz, 1H), 1.84\ (ddd, J = 15, 6, 2.5\ Hz, 1H), 1.38\ (d, J = 6.5\ Hz, 3H), 1.30\ (s, 3H), 1.09\ (s, 3H), 0.94\ (d, J = 11\ Hz, 1H).
\\
\[^1\text{C-NMR}\ (125\ \text{MHz, CDCl}_3)\]

\[\delta 169.2, 166.5, 163.9, 133.9, 127.4\ (d, J = 7.8\ Hz), 115.7\ (d, J = 21.4\ Hz), 68.4, 62.0, 56.5, 55.0, 49.3, 40.9, 39.5, 39.2, 32.4, 30.9, 27.3, 23.8, 23.7.\]

\[\text{HRMS (ESI+)}\]

Calculated for C\textsubscript{22}H\textsubscript{28}BNO\textsubscript{5}F: 416.2045

Found: 416.2052

The general procedure was followed using boronate ester 2.2g (80 mg, 0.25 mmol) and mCPBA (106 mg, 0.475 mmol). The crude product was then taken up in a minimum amount of CH\textsubscript{2}Cl\textsubscript{2} and loaded onto a silica gel column equilibrated with 30% Et\textsubscript{2}O/hexane. The non-polar impurities were eluted with 30% Et\textsubscript{2}O/hexane. The product was then eluted with 2:2:6 (acetone/Et\textsubscript{2}O/hexane). After concentration at room temperature, the solid was washed with Et\textsubscript{2}O (5-10 ml) to remove residual mCPBA and vacuum filtered. The epoxide was then dried in vacuo, giving the product as a white solid 2.3g (51 mg, 64%). d.r. >20:1.

\[\text{TLC (Hexanes:acetone 3:2)}\]

R\textsubscript{f} = 0.46, visualized by KMnO\textsubscript{4}

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

\[\delta 4.29\ (dt, J = 10.5, 6.5\ Hz, 1H), 4.20\ (d, J = 17\ Hz, 1H), 3.98\ (d, J = 15\ Hz, 1H), 3.65\ (d, J = 15\ Hz, 1H), 3.42\ (d, J = 17\ Hz, 1H), 3.07\ (m, 1H), 2.72-2.66\ (m, 1H), 2.51-2.45\ (m, 1H), 2.17-2.14\ (m, 1H), 2.12\ (d, J = 3\ Hz, 1H), 2.05\ (sept, J = 3\ Hz, 1H), 1.94\ (dt, J = 6, 2.5\ Hz, 1H), 1.81\ (ddd, J = 15, 6, 2.5\ Hz, 1H), 1.37\ (d, J = 5\ Hz, 3H), 1.33\ (d, J = 7\ Hz, 3H), 1.27\ (s, 3H), 1.04\ (s, 3H), 0.92\ (d, J = 10\ Hz, 1H).
\\
\[^1\text{C-NMR}\ (125\ \text{MHz, CDCl}_3)\]

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δ 169.2, 166.3, 109.7, 67.9, 61.7, 54.6, 53.2, 49.0, 40.6, 39.2, 38.9, 32.1, 30.5, 27.0, 23.6, 23.5.

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

δ 10.7

HRMS (ESI+)

Calculated for C$_{17}$H$_{27}$BNO$_5$: 336.1982
Found: 336.1977

X-ray quality crystals were obtained by making a saturated solution of 2.3g in 1 ml of 1,2-dichloroethane and layering it with about 2 ml of hexane. The layers were allowed to slowly mix at room temperature, giving the desired crystals.

The general procedure was followed using boronate ester 2.2h (84 mg, 0.25 mmol) and mCPBA (106 mg, 0.475 mmol). The crude product was then taken up in a minimum amount of CH$_2$Cl$_2$ and loaded onto a silica gel column equilibrated with 30% Et$_2$O/hexane. The non-polar impurities were eluted with 30% Et$_2$O/hexane. The product was then eluted with 2:2:6 (acetone/Et$_2$O/hexane). After concentration at room temperature, the solid was washed with Et$_2$O (5-10 ml) to remove residual mCPBA and vacuum filtered. The epoxide was then dried in vacuo, giving the product as a white solid 2.3h (68 mg, 77%). d.r. >20:1.

TLC (Hexanes:acetone 3:2)

$R_f$ = 0.22, visualized by KMnO$_4$
$^1$H-NMR (500 MHz, acetone-$d_6$)
$\delta$ 4.29 (d, $J = 18$ Hz, 1H), 4.30-4.26 (m, 1H), 4.13 (d, $J = 15.5$ Hz, 1H), 4.06 (d, $J = 18.5$ Hz, 1H), 3.98 (d, $J = 15.5$ Hz, 1H), 3.02 (dt, $J = 6$, 3 Hz, 1H), 2.80-2.74 (m, 1H), 2.57-2.51 (m, 1H), 2.50-2.44 (m, 1H), 1.97 (dt, $J = 6$, 2.5 Hz, 1H), 1.79 (ddd, $J = 15$, 6, 2.5 Hz, 1H), 1.39 (d, $J = 7.5$ Hz, 3H), 1.28 (s, 3H), 1.10 (d, $J = 10.5$ Hz, 1H), 1.05 (s, 3H).

$^{13}$C-NMR (125 MHz, CDCl$_3$)
$\delta$ 170.7, 167.2, 68.8, 64.1, 61.9, 57.8, 55.4, 50.2, 41.6, 39.7, 39.1, 32.3, 31.2, 27.4, 23.9, 23.7.

$^{11}$B-NMR (128 MHz, acetone-$d_6$)
$\delta$ 10.8

HRMS (ESI+)
Calculated for C$_{17}$H$_{27}$BNO$_6$: 352.1931
Found: 352.1925

The general procedure was followed using boronate ester 2.3i (45 mg, 0.1 mmol) and mCPBA (106 mg, 0.475 mmol). The crude product was then taken up in a minimum amount of CH$_2$Cl$_2$ and loaded onto a silica gel column equilibrated with 30% Et$_2$O/hexane. The non-polar impurities were eluted with 30% Et$_2$O/hexane. The product was then eluted with 2:2:6 (acetone/Et$_2$O/hexane). After concentration at room temperature, the solid was washed with Et$_2$O (5-10 ml) to remove residual mCPBA and vacuum filtered. The epoxide was then dried *in vacuo*, giving the product as a white solid (35 mg, 75%). d.r. >20:1.

TLC (Hexanes:acetone 3:2)
$R_f$ = 0.51, visualized by KMnO$_4$

$^1$H-NMR (500 MHz, CDCl$_3$)
$\delta$ 4.31 (dt, $J = 10.5$, 6 Hz, 1H), 4.21 (d, $J = 18$ Hz, 1H), 4.01 (dd, $J = 12.5$, 2.5 Hz, 1H), 3.99 (d, $J = 15.5$ Hz, 1H), 3.64 (d, $J = 15$ Hz, 1H), 3.63 (dd, $J = 12.5$, 4.5 Hz, 1H), 3.42 (d, $J = 17$ Hz, 1H), 3.17 (quint, $J = 3$ Hz, 1H), 2.70-2.65 (m, 1H), 2.50-2.46 (m, 1H), 2.39 (d, $J = 3$ Hz, 1H), 2.16-2.15 (m, 1H),
2.05 (sept, J = 3 Hz, 1H), 1.95 (dt, J = 6.5, 2.5 Hz, 1H), 1.81 (ddd, J = 15, 6, 3 Hz, 1H), 1.33 (d, J = 6.5 Hz, 3H), 1.27 (s, 3H), 1.02 (s, 3H), 0.89 (s, 9H), 0.07 (s, 3H), 0.07 (s, 3H).

$^1$C-NMR (125 MHz, CDCl$_3$)

$\delta$ 169.2, 166.3, 67.9, 63.2, 61.7, 57.2, 54.6, 49.0, 40.6, 39.2, 38.9, 32.0, 30.5, 27.0, 25.9, 23.5, 23.5, 18.3, -5.3, -5.4.

$^1$B-NMR (128 MHz, CDCl$_3$)

$\delta$ 11.3

HRMS (ESI+)

Calculated for C$_{23}$H$_{41}$BNO$_6$Si: 466.2796

Found: 466.2798

The general procedure was followed using PIDA boronate 2.2j (38 mg, 0.1 mmol) and mCPBA (35 mg, 0.2 mmol) with a reaction time of 11 h. The crude product was purified with a florisil column (80% Et$_2$O/hexane, then 20% - 40% EtOAc/hexane), giving the product as a white solid (38 mg, 96%). d.r. = 17:1.

TLC (Hexanes:EtOAc 1:1)

R$_f$ = 0.4, stained by KMnO$_4$

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

$\delta$ 7.36-7.28 (m, 5H), 4.42 (dt, J = 10, 7 Hz, 1H), 4.33 (d, J = 5 Hz, 1H), 4.10 (d, J = 17.5 Hz, 1H), 3.66 (d, J = 15 Hz, 1H), 3.54 (d, J = 15 Hz, 1H), 3.30 (d, J = 17 Hz, 1H), 2.77 – 2.71 (m, 1H), 2.72 (d, J = 5.5 Hz, 1H), 2.47 (ddt, J = 11, 6, 2 Hz, 1H), 2.13 – 2.10 (m, 1H), 2.08 – 2.05 (m, 1H), 1.95 (dt, J = 6, 2 Hz, 1H), 1.80 (ddd, J = 14.5, 6, 2.5 Hz, 1H), 1.34 (d, J = 7 Hz, 3H), 1.29 (s, 3H), 1.10 (s, 3H), 0.89 (d, J = 7 Hz, 1H).

$^1$C-NMR (125 MHz, CDCl$_3$)
δ 169.1, 165.2, 136.6, 128.2, 127.5, 125.7, 67.8, 61.3, 57.9, 54.5, 49.0, 40.6, 39.1, 39.0, 32.1, 30.5, 27.1, 23.5, 23.4.

HRMS (ESI+)

Calculated for C$_{22}$H$_{29}$BNO$_5$: 398.2139
Found: 398.2141

The general procedure was followed using boronate ester 2.2k (83 mg, 0.25 mmol) and mCPBA (86 mg, 0.5 mmol). The reaction was stopped after 2.5 h. The crude product was then taken up in 15 ml of CH$_2$Cl$_2$, absorbed onto celite, concentrated in vacuo and loaded onto a silica gel column. The product was purified by silica gel chromatography (50% Et$_2$O/hexanes to 80% Et$_2$O/hexanes to 30% EtOAc/hexanes). The product 2.3k was obtained as a white solid (43 mg, 49%). d.r. >20:1.

TLC (Hexanes:EtOAc 1:1)

$R_f = 0.42$, visualized by KMnO$_4$

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

δ 4.28 (dt, $J = 10.5, 6$ Hz, 1H), 4.18 (d, $J = 17.5$ Hz, 1H), 3.90 (d, $J = 15$ Hz, 1H), 3.72 (d, $J = 15$ Hz, 1H), 3.48 (d, $J = 17.5$ Hz, 1H), 2.65 – 2.60 (m, 1H), 2.48 – 2.44 (m, 1H), 2.18 (s, 1H), 2.18-2.15 (m, 1H), 2.06 – 2.03 (m, 1H), 1.93 (dt, $J = 5.5$, 1.5 Hz, 1H), 1.78 (ddd, $J = 15$, 6.5, 3 Hz, 1H), 1.41 (s, 3H), 1.39 (s, 3H), 1.32 (d, $J = 6.5$ Hz, 3H), 1.26 (s, 3H), 1.02 (s, 3H), 0.94 (d, $J = 11$ Hz, 1H).

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

δ 169.4, 166.2, 67.7, 61.4, 60.1, 54.4, 49.0, 40.7, 39.2, 38.9, 31.9, 30.5, 27.2, 27.0, 23.5 (2C), 20.4

HRMS (ESI+)

Calculated for C$_{18}$H$_{29}$BNO$_5$: 350.2139
Found: 350.2138
The general procedure was followed using boronate ester 2.2l (95 mg, 0.25 mmol) and mCPBA (86 mg, 0.5 mmol). The crude product was then taken up in 10 ml of CH₂Cl₂, absorbed onto celite, concentrated in vacuo and loaded onto a silica gel column. The product was purified by silica gel chromatography (50% Et₂O/hexanes to 30% EtOAc/hexanes to 35% EtOAc/hexanes). The product 2.3l was obtained as a white solid (74 mg, 75%). d.r. (isolated product) 14:1, d.r. (crude product) = 11:1. Note: d.r. was increased slightly after column purification.

TLC (Hexanes:EtOAc 1:1)

Rₚ = 0.47, stained by KMnO₄

¹H-NMR (500 MHz, CDCl₃)

δ 7.54 (d, J = 7 Hz, 2H), 7.31 – 7.27 (m, 2H), 7.22 (dt, J = 7.5, 2 Hz, 1H), 4.24 (d, J = 14.5 Hz, 1H), 4.09 (d, J = 17 Hz, 1H), 4.02 (dt, J = 10.5, 6 Hz, 1H), 3.68 (d, J = 14.5 Hz, 1H), 3.49 (d, J = 17 Hz, 1H), 3.27 (d, J = 7 Hz, 1H), 2.51 (d, J = 6.5 Hz, 1H), 2.29 (ddt, J = 11, 6, 2 Hz, 1H), 2.09 – 2.03 (m, 1H), 1.82 (dt, J = 5.5, 2 Hz, 1H), 1.56 (sept, J = 3.5 Hz, 1H), 1.33 (d, J = 6.5 Hz, 3H), 1.11 (s, 3H), 1.08 (dd, J = 6, 2.5 Hz, 1H), 1.00 – 0.95 (m, 1H), 0.77 (d, J = 11 Hz, 1H), 0.72 (s, 3H).

¹³C-NMR (125 MHz, CDCl₃)

δ 169.7, 166.9, 141.4, 128.8, 127.2, 125.2, 67.6, 61.3, 57.7, 55.3, 49.1, 41.0, 39.7, 39.0, 32.0, 29.4, 27.1, 24.0, 23.9.

HRMS (ESI+)

Calculated for C₂₂H₂₉BNO₅: 398.2139

Found: 398.2141

Epoxide 3h. The general procedure was followed using boronate ester 2.2h (80 mg, 0.25 mmol) and mCPBA (106 mg, 0.475 mmol). The crude product was then taken up in a minimum amount of CH₂Cl₂ and loaded onto a silica gel column equilibrated with 30% Et₂O/hexane. The non-polar impurities were eluted with 30% Et₂O/hexane. The product was then eluted with 2:2:6 (acetone/Et₂O/hexane). After
concentration at room temperature, the solid was washed with Et₂O (5-10 ml) to remove residual mCPBA and vacuum filtered. The epoxide was then dried in vacuo, giving the product as a white solid (49 mg, 49%). d.r. 10:1.

TLC (Hexanes:acetone 3:2)

Rᵥ = 0.40, stained by KMnO₄

¹H-NMR (500 MHz, CDCl₃)

δ 4.54 (dt, J = 10.5, 6.5 Hz, 1H), 4.22 (d, J = 17.5 Hz, 1H), 3.89 (d, J = 15 Hz, 1H), 3.64 (d, J = 15 Hz, 1H), 3.40 (d, J = 17 Hz, 1H), 2.85 (d, J = 5.5 Hz, 1H), 2.71 (m, 1H), 2.58 (d, J = 5 Hz, 1H), 2.49-2.45 (m, 1H), 2.13 (m, 1H), 2.07 (sept, J = 3 Hz, 1H), 1.94 (dt, J = 6, 2 Hz, 1H), 1.74 (ddd, J = 15, 6, 2.5 Hz, 1H), 1.39 (s, 3H), 1.32 (d, J = 7 Hz, 3H), 1.27 (s, 3H), 1.04 (s, 3H), 0.93 (d, J = 11 Hz, 1H).

¹³C-NMR (125 MHz, CDCl₃)

δ 169.3, 166.3, 67.3, 61.4, 55.3, 54.9, 49.0, 40.7, 39.3, 39.0, 32.0, 30.6, 27.0, 23.5, 23.4, 21.2

¹¹B-NMR (96 MHz, CDCl₃)

δ 10.8

HRMS (ESI+)

Calculated for C₁₇H₂₇BNO₅: 336.1982
Found: 336.1976

Epoxide 3n. The general procedure was followed using boronate ester 2.2h (76 mg, 0.25 mmol) and mCPBA (106 mg, 0.475 mmol). The crude product was then taken up in a minimum amount of CH₂Cl₂ and loaded onto a silica gel column equilibrated with 30% Et₂O/hexane. The non-polar impurities were eluted with 30% Et₂O/hexane. The product was then eluted with 2:2:6 (acetone/Et₂O/hexane). After concentration at room temperature, the solid was washed with Et₂O (5-10 ml) to remove residual mCPBA and vacuum filtered. The epoxide was then dried in vacuo, giving the product as a white solid (66 mg, 82%). d.r. >20:1.
TLC (Hexanes:acetone 3:2)

$R_f = 0.43$, visualized by KMnO$_4$

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

$\delta$ 4.29 (dt, $J = 10.5, 6.5$ Hz, 1H), 4.22 (d, $J = 17.5$ Hz, 1H), 3.98 (d, $J = 15$ Hz, 1H), 3.68 (d, $J = 15$ Hz, 1H), 3.48 (d, $J = 17$ Hz, 1H), 2.87 (dd, $J = 6, 5$ Hz, 1H), 2.78 (dd, $J = 6, 3.5$ Hz, 1H), 2.72-2.66 (m, 1H), 2.51-2.45 (m, 1H), 2.39 (dd, $J = 5, 3.5$ Hz, 1H), 2.18-2.17 (m, 1H), 2.06 (sept, $J = 3$ Hz, 1H), 1.95 (dt, $J = 6, 2$ Hz, 1H), 1.83 (ddd, $J = 15, 6, 2.5$ Hz, 1H), 1.34 (d, $J = 7$ Hz, 3H), 1.27 (s, 3H), 1.03 (s, 3H), 0.92 (d, $J = 11$ Hz, 1H).

$^1$C-NMR (125 MHz, CDCl$_3$)

$\delta$ 169.5, 166.6, 68.1, 61.6, 54.7, 49.0, 45.5, 40.6, 39.2, 38.9, 32.0, 30.5, 27.0, 23.5, 23.5.

$^1$B-NMR (128 MHz, CDCl$_3$)

$\delta$ 11.0

HRMS (ESI+)

Calculated for $\text{C}_{16}\text{H}_{25}\text{BNO}_5$: 322.1826

Found: 322.1824

X-ray quality crystals were obtained by making a saturated solution of 2.3h in 1 ml of 1,2-dichloroethane and layering it with about 2 ml of hexane. The layers were allowed to slowly mix at room temperature, giving the desired crystals.
A dry Schlenk flask was charged with 2.3a (795 mg, 2 mmol) and dry CH₂Cl₂ (40 ml) under a nitrogen atmosphere. The flask was flushed with nitrogen and cooled to 0 °C. Mg(ClO₄)₂ (2 mmol) was then added in one portion, and the reaction was stirred in the ice/water bath for 2 h. The reaction was then warmed up to room temperature and filtered through celite, washing with additional CH₂Cl₂ (20 ml). The filtrate was then concentrated in vacuo at room temperature to afford an off-white solid 2.8. No purification of this product was necessary for subsequent reactions. Note: the stereogenic α-carbon of the aldehyde epimerizes on silica gel.

¹H-NMR (500 MHz, acetone-d₆)
δ 9.88 (d, J = 2.5 Hz, 1H), 7.45 (dd, J = 7, 1.5 Hz, 2H), 7.39 (t, J = 7.5 Hz, 2H), 7.32 (tt, J = 7.5, 1.5 Hz, 1H), 4.29 (d, J = 18 Hz, 1H), 4.07 (d, J = 18 Hz, 1H), 4.04 (d, J = 15.5 Hz, 1H), 3.93 (br s, 1H), 3.66 (d, J = 10.5, 6 Hz, 1H), 2.98-2.92 (m, 1H), 2.86 (d, J = 15.5 Hz, 1H), 2.45 (ddt, J = 11, 6, 2 Hz, 1H), 2.38 (ddt, J = 13, 6.5, 2 Hz, 1H), 2.11 (sept, J = 3 Hz, 1H), 1.88-1.86 (m, 1H), 1.85-1.83 (m, 1H), 1.26 (s, 3H), 1.08 (d, J = 11 Hz, 1H), 0.99 (s, 3H), 0.93 (d, J = 7 Hz, 3H).

¹³C-NMR (125 MHz, CDCl₃)
δ 199.9, 168.5, 166.1, 134.4, 129.4, 128.7, 127.4, 67.0, 61.6, 55.3, 48.8, 40.6, 38.8, 38.6, 31.6, 30.3, 27.0, 23.1, 23.0.

HRMS (ESI+)
Calculated for C₂₂H₂₉BNO₅: 398.2139
Found: 398.2140
**Acetal 6.** A 40ml vial equipped with a stir bar was charged with aldehyde 2.8 (397 mg, 1 mmol), (S,S)-hydrobenzoin (643 mg, 3 mmol) and MgSO₄ (1 g). CH₂Cl₂ (20 ml) was added, followed by pTsOH•H₂O (3.8 mg, 0.02 mmol). The vial was flushed briefly with nitrogen and placed in a heat block. The reaction was stirred at 35 °C for 3 h. After cooling to room temperature, the suspension was filtered through celite and the filtrate was concentrated *in vacuo*. The crude product was purified by silica gel chromatography (acetone/Et₂O/hexane 1:4:15 →1:2:7 →1:1:3) to afford 6 (394 mg, 66%) as a white solid.

TLC (Hexanes:EtOAc:Et₂O 2:2:1)

R_f = 0.69, visualized by short wave UV.

**¹H-NMR (500 MHz, CDCl₃)**

δ 7.61, (app d, J = 6.5 Hz, 2H), 7.38 (app t, J = 7.5 Hz, 2H), 7.32-7.25 (m, 7H), 7.19-7.17 (m, 2H), 7.15-7.13 (m, 2H), 6.04 (d, J = 2.5 Hz, 1H), 4.75 (d, J = 8 Hz, 1H), 4.31 (d, J = 8 Hz, 1H), 4.17 (d, J = 17.5 Hz, 1H), 3.79 (dt, J = 10, 6 Hz, 1H), 3.44 (d, J = 15 Hz, 1H), 3.42 (d, J = 17 Hz, 1H), 3.00 (d J = 2.5 Hz, 1H), 2.92 (d, J = 15 Hz, 1H), 2.77-2.72 (m, 1H), 2.44-2.42 (m, 1H), 2.07 (m, 1H), 1.96 (m, 1H), 1.85-1.81 (m, 2H), 1.26 (s, 3H), 0.96 (s, 3H), 0.91-0.89 (m, 4H).

**¹³C-NMR (125 MHz, CDCl₃)**

δ 168.9, 166.5, 138.7, 137.7, 136.5, 130.8, 128.6, 128.4, 128.3, 128.2, 127.9, 127.2, 126.9, 126.4, 106.1, 87.4, 84.9, 66.4, 61.6, 55.3, 48.8, 40.6, 38.9, 38.8, 31.7, 30.9, 30.3, 27.0, 23.2, 23.1.

**HRMS (ESI+)***

Calculated for C₃₆H₄₁BNO₆: 594.3027

Found: 594.3028

X-ray quality crystals were obtained by layering a solution of 2.9 in 1 ml of 1,2-dichloroethane and layering it with about 2 ml of hexane. The layers were allowed to slowly mix at room temperature, giving the desired crystals.
A dry 100 ml Schlenk flask was charged with aldehyde 2.8 (2.19 mg, 5.51 mmol) under an atmosphere of nitrogen. CH₂Cl₂ (60 ml) was added and the solution was cooled to -5 °C in an ice/salt bath. AcOH (15 ml) was added slowly. NaBH(OAc)₃ (1.75 g, 8.27 mmol) was then added portionwise to the solution over 3 min. The reaction was stirred at 0 °C for 2 h, then a second portion of NaBH(OAc)₃ (584 mg, 2.76 mmol) was added over 3 min. A third portion of NaBH(OAc)₃ (584 mg, 2.76 mmol) was added over 3 min after another 2 h. The reaction was stirred for another 4 h, then quenched with H₂O (20 ml). The mixture was stirred for 5 min until the organic layer became clear and effervescence ceased. The mixture was then transferred to a separatory funnel. After phase separation, the organic layer was washed H₂O (30 ml), then with phosphate buffer (pH = 7, 0.5 M, 25 ml × 2). The combined aqueous layer was extracted with DCM (30 ml). The organic phase was dried over MgSO₄, filtered and concentrated. The crude product was purified by silica gel chromatography (30-45% EtOAc/hexane). A white solid 2.12 was obtained (1.56 g, 71%).

TLC (Hexanes:acetone)

Rₜ = 0.32, visualized by KMnO₄
H-NMR (500 MHz, acetone-d$_6$)

$\delta$ 7.39 (app d, $J = 7.5$ Hz, 2H), 7.33 (app t, $J = 7.5$ Hz, 2H), 7.24 (app t, $J = 7$ Hz, 1H), 4.29 (d, $J = 18$ Hz, 1H), 4.07 (d, $J = 18$ Hz, 1H), 4.04 (d, $J = 15.5$ Hz, 1H), 3.66 (d, $J = 10.5$, 6 Hz, 1H), 2.82 (d, $J = 15$ Hz, 1H), 2.82-2.77 (m, 1H), 2.61 (dd, $J = 6$, 4 Hz, 1H), 2.44 (ddt, $J = 11$, 6, 2 Hz, 1H), 2.33 (ddt, $J = 13$, 6.5, 2 Hz, 1H), 2.08 (m, 2H), 1.86 (dt, $J = 5.5$, 2 Hz, 1H), 1.76 (ddd, $J = 14.5$, 6, 2.5 Hz, 1H), 1.27 (s, 3H), 1.05 (d, $J = 11$ Hz, 1H), 1.01 (s, 3H), 0.93 (d, $J = 7$ Hz, 3H).

C-NMR (125 MHz, CDCl$_3$)

$\delta$ 168.9, 166.5, 140.8, 129.4, 128.4, 126.9, 66.6, 65.5, 61.8, 55.2, 48.8, 40.6, 38.8, 38.7, 31.7, 30.2, 27.0, 23.1, 23.0.

HRMS (ESI+)

Calculated for C$_{22}$H$_{31}$BNO$_5$: 400.2295

Found: 400.2297

To a dry 25 ml Schlenk flask was added PPh$_3$ (346 mg, 1.32 mmol), imidazole (112 mg, 1.65 mmol) and a solution of the alcohol 2.12 (438 mg, 1.10 mmol) in DCM (15 ml) under a positive pressure of N$_2$. I$_2$ (335 mg, 1.32 mmol) was then added in one portion. The reaction was stirred for 2 h, then transferred to a separatory funnel and washed with 10 ml H$_2$O. The aqueous layer was extracted with 10 ml DCM. The combined organic layer was dried over MgSO$_4$, filtered and concentrated. The crude product was purified by silica gel chromatography (40 to 60% EtOAc/hexanes). The off-white solid was then dissolved in DCM (approx. 25 ml) and passed through a pad of activated charcoal. The colorless filtrate was then concentrated in vacuo to give a white solid (235 mg, 42%).

TLC (Hexanes:EtOAc 1:1)

$R_f = 0.42$, visualized by short wave UV.

H-NMR (500 MHz, CDCl$_3$)

$\delta 7.38 - 7.26$ (m, 5H), 4.15 (d, $J = 17$ Hz, 1H), 4.01 (dd, $J = 10$, 3.5 Hz, 1H), 3.69 (dt, $J = 10.5$, 6 Hz, 1H), 3.55 (dd, $J = 12.5$, 10 Hz, 1H), 3.40 (d, $J = 17.5$ Hz, 1H), 3.39 (d, $J = 15$ Hz, 1H), 2.73 (d, $J =
15 Hz, 1H), 2.69 – 2.63 (m, 2H), 2.45 (ddt, J = 11.5, 6, 1 Hz, 1H), 2.08 (sept, J = 3 Hz, 1H), 1.96 – 1.91 (m, 1H), 1.85 (dt, J = 6, 2 Hz, 1H), 1.76 (ddd, J = 15, 6, 2.5 Hz, 1H), 1.26 (s, 3H), 0.97 (s, 3H), 0.88 (d, 1H), 0.85 (d, J = 7 Hz, 1H).

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

$\delta$ 168.3, 166.1, 142.1 (2C), 129.3, 127.4 (3C), 66.6, 61.7, 55.5, 48.8, 40.6, 38.8 (2C), 31.7, 30.3, 27.0, 23.1, 22.9.

HRMS (ESI+)

Calculated for C$_{22}$H$_{30}$BNO$_4$I: 510.1313

Found: 510.1309

In a glovebox, Zn dust (172 mg, 2.63 mmol) was weighed into a flame-dried 7 ml vial equipped with a stir bar. Another 7 ml vial was charged with a THF solution (1.2 ml) of the iodide 2.13 (446 mg, 0.876 mmol). Both vials, together with another empty 7 ml vial, were sealed with septum cap and removed from the glovebox. The vial containing Zn dust was placed under argon, and 3 drops of TMSCl followed by 3 drops of 1,2-dibromoethane were added. The THF solution of iodide 7 was then added to the Zn dust in one portion via syringe under argon. The reaction vial was then placed in a heating block and stirred at 45°C for 1.5 h. The vial was then removed from the block and 3.2 ml of THF was added to form a 0.2 M solution of the organozinc 2.17.

Preparation of catalyst stock solution. A dry 7 ml vial equipped with a star bar was charged with RuPhos$^{7}$ (9.5 mg, 0.02 mmol). The vial was brought into the glovebox, and Pd$_2$dba$_3$ (4.6 mg, 0.005 mmol) was added. THF (1.5 ml) was added, and the mixture stirred at rt for 3 min.

The freshly prepared catalyst stock solution was immediately for the preparation of 2.19:
A dry 7 ml vial equipped with a stir bar was charged with iodide 2.18 (75 mg, 0.2 mmol) and brought into the glovebox. To this was added NMP (1.2 ml) followed by 1.2 ml (0.004 mmol Pd\(_2\)dba\(_3\), 0.016 mmol RuPhos) of the catalyst solution. The vial was sealed with a septum cap, stirred briefly and then brought out of the glovebox. The vial was placed in a heating block pre-equilibrated to 60 °C, and the solution of the organozinc reagent 2.17 (1.5 ml, approx. 0.3 mmol) was added over 3 h with the aid of a syringe pump. After the addition was complete, the reaction was stirred for another 2 h at 60 °C, then cooled to rt. The reaction was diluted with Et\(_2\)O (10 ml) and washed with sat. NH\(_4\)Cl (2 × 5 ml) and H\(_2\)O (2 × 5 ml). The combined aqueous layers were extracted with Et\(_2\)O (10 ml). The organic phase was then dried over MgSO\(_4\), filtered and concentrated. The residue was taken up in DCM (5 ml), absorbed onto celite and loaded onto a silica gel column. The product 2.19 was obtained as a white solid after column chromatography (92 mg, 73%).

**TLC (Hexanes:EtOAc 3:2)**

R\(_f\) = 0.36, visualized by short wave UV.

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

\(\delta\) 7.49 (d, \(J = 8.5\) Hz, 2H), 7.30-7.13 (m, 4H), 7.14 (app t, \(J = 7.5\) Hz, 1H), 6.96 (d, \(J = 8\) Hz, 2H), 6.72 (t, \(J = 6\) Hz, 1H), 4.16 (d, \(J = 17.5\) Hz, 1H), 3.64 – 3.57 (m, 3H), 3.45 (d, \(J = 15.5\) Hz, 2H), 3.39 (dd, \(J = 14\), 3 Hz, 1H), 3.04 (app t, \(J = 14\) Hz, 1H), 2.66 – 2.61 (m, 1H), 2.51 (t, \(J = 5.5\) Hz, 1H), 2.44 – 2.41 (m, 2H), 2.06 – 2.05 (m, 1H), 1.95 – 1.92 (m, 1H), 1.83 -1.78 (m, 2H), 1.44 (s, 9H), 1.23 (s, 3H), 0.89 (d, \(J = 7.5\) Hz, 1H), 0.87 (s, 3H), 0.81 (d, \(J = 7\) Hz, 3H).

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

\(\delta\) 172.2, 168.9, 167.3, 166.7, 145.9, 142.1, 131.7, 128.9, 126.5, 126.4, 81.1, 66.4, 62.0, 55.7, 48.8, 40.6, 38.8 (2C), 38.7, 35.3, 35.1, 31.7, 30.3, 28.1, 27.0, 23.0, 22.9.

**HRMS (ESI+)**

Calculated for C\(_{36}\)H\(_{48}\)BN\(_2\)O\(_7\): 631.3555

Found: 631.3560
PIDA boronate 2.19 (91.3 mg, 0.145 mmol) was dissolved in DCM (1.5 ml) in a 7 ml vial under ambient atmosphere. Pinacol (18 mg, 0.152 mmol) was added, followed by MeOH (1.5 ml). The vial was capped and placed in a heating block and stirred at 40 °C for 3.5 h. The reaction was concentrated in vacuo. The residue was azeotroped 5 times with benzene until a white solid was obtained. Benzene (5 ml) was then added and the suspension filtered, rinsing with additional benzene. The filtrate was concentrated in vacuo to give a white solid tainted with a light brown color. The crude product was then purified on a florisil column (20 – 30% EtOAc/hexanes), giving 2.21 as a colorless oil that slowly crystallized over time (58.5 mg, 84%). The white solid obtained by filtration (PIDA) was dissolved in MeOH, and concentrated in vacuo, azeotroping with benzene to remove residual MeOH. PIDA was recovered in 96% yield (37.6 mg).

TLC (EtOAc:hexanes 3:2)
$R_f = 0.59$, visualized by short wave UV

$^1$H-NMR (500 MHz, CDCl$_3$)
\[
\begin{align*}
\delta & 7.61 (d, J = 8 \text{ Hz}, 2\text{H}), 7.26 – 7.19 (m, 4\text{H}), 7.21 (d, J = 8 \text{ Hz}, 2\text{H}), 7.15 – 7.12 (m, 1\text{H}), 6.81 (t, J = 6 \text{ Hz}, 1\text{H}), 3.66 (q, J = 6 \text{ Hz}, 1\text{H}), 3.19 (dd, J = 13.5, 9 \text{ Hz}, 1\text{H}), 2.98 (dd, J = 13.5, 7.5 \text{ Hz}, 1\text{H}), 2.65 (dd, J = 9.5, 7.5 \text{ Hz}, 1\text{H}), 2.54 (t, J = 6.5 \text{ Hz}, 2\text{H}), 1.45 (s, 9\text{H}), 1.12 (s, 6\text{H}), 1.11 (s, 6\text{H}).
\end{align*}
\]

$^{13}$C-NMR (125 MHz, CDCl$_3$)
\[
\begin{align*}
\delta & 172.2, 167.2, 145.6, 142.0, 131.9, 129.0, 128.3, 126.6 (2\text{C}), 125.5, 83.5, 81.1, 38.6, 35.4, 35.1, 28.1, 24.5.
\end{align*}
\]

HRMS (ESI+)

Calculated for C$_{28}$H$_{39}$BNO$_5$: 480.2921

Found: 480.2924

$[\alpha]^{23}_{D} +47.0^\circ$ (c = 1.0, CHCl$_3$)

The e.r. was determined by chiral HPLC using a ChiraCel OD-H (4.6 × 250 mm) column:

Conditions: 5% IPA/hexane, flow rate = 0.8 ml/min, temperature = 23 °C, detection wavelength = 214 nm

$t_r$(major) 14.92 min, $t_r$(minor) 13.42 min; e.r. > 95:5
A flame-dried 7 ml vial equipped with a stir bar was charged with Ag₂O (5.7 mg, 0.249 mmol) and brought into the glove box. PPh₃ (2.8 mg, 0.0106 mmol) was then added into the vial, followed by a solution of the pinacol boronic ester 2.21 (9.9 mg, 0.21 mmol) and iodide 2.15 (6.1 mg, 0.0166 mmol) in DME (0.23 ml). To this mixture was added a solution of Pd₂dba₃ (0.609 mg, 0.00066 mmol) in DME (0.1 ml). The vial was sealed with a cap, brought out of the glove box and stirred at 60 °C for 22.5 h. The reaction was then cooled to room temperature, diluted with THF (1.5 ml) and filtered through celite, eluting with THF. The filtrate was then concentrated in vacuo. The crude product was purified by silica gel chromatography (15 – 20% EtOAc/hexanes) to afford a yellow oil as the product (3.9 mg, 40%).

TLC (Hexanes:EtOAc 3:2)

Rᵣ = 0.5, visualized by short wave UV.

¹H-NMR (500 MHz, CDCl₃)

δ 7.58 (d, J = 8 Hz, 2H), 7.48 (dt, J = 6.5, 2 Hz, 2H), 7.34 – 7.37 (m, 1H), 7.26 – 7.18 (m, 3H), 7.08 (d, J = 8.5 Hz, 1H), 6.78 (t, J = 5.5 Hz, 1H), 4.29 (t, J = 7.5 Hz, H), 3.65 (q, J = 6 Hz, 2H), 3.44 (d, J = 8 Hz, 1H), 2.53 (t, J = 6 Hz, 2H), 1.45 (s, 9H).

¹³C-NMR (125 MHz, CDCl₃)
δ 172.3, 167.1, 148.6, 144.7, 143.9, 143.7, 139.9, 132.3, 129.0, 128.5, 128.0, 127.2, 126.9, 126.8, 126.5, 125.2, 121.2, 81.2, 52.9, 42.0, 35.4, 35.1, 28.1.

HRMS (ESI+)

Calculated for C$_{35}$H$_{35}$NO$_4$F$_3$: 590.2518
Found: 590.2512

$[\alpha]_{D}^{23}$ -13.2° (c = 1.0, CHCl$_3$)

The e.r. was determined by chiral HPLC using a ChiraCel OD-H (4.6 × 250 mm) column:

Conditions: 20% IPA/hexane, flow rate = 0.7 ml/min, temperature = 23 °C, detection wavelength = 214 nm.

t$_r$(major) 9.92 min, t$_r$(minor) 8.48 min; e.r. 94: 6

To a solution of the $t$-butyl ester **tBu-2.14** in DCM (0.6 ml) in a 2 ml vial was added TFA (0.1 ml) under ambient atmosphere. The vial was sealed and the reaction was stirred at room temperature for 2 h. The solvent was then removed in vacuo, and TFA removed by co-evaporation with DCM. The crude product was then purified by silica gel chromatography (EtOAc – EtOAc + 0.1% AcOH) to afford the product as a white solid (3.0 mg, 85%).

TLC (Hexanes:EtOAc 3:7)

R$_f$ = 0.28, visualized by shortwave UV.

$^1$H-NMR (500 MHz, CDCl$_3$)
δ 7.55 (d, J = 8 Hz, 1H), 7.49 (d, J = 8.5 Hz, 1H), 7.35-7.33 (m, 3H), 7.26 – 7.20 (m, 9 H, 1H), 7.11 (d, J = 8 Hz, 2H), 6.82 (t, J = 6 Hz, 1H), 4.29 (t, J = 8 Hz, 1H), 3.73 (q, J = 6 Hz, 2H), 3.45 (d, J = 7.5 Hz, 2H), 2.74 (t, J = 5.5 Hz, 2H).

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

δ 176.4, 167.6, 148.6, 144.7, 144.3, 143.6, 140.0, 139.9, 131.8, 129.3, 129.0, 128.5 (2C), 127.9, 127.2, 126.9, 126.5, 125.2, 121.2, 52.9, 41.9, 35.2, 33.7.

HRMS (ESI+)

Calculated for C$_{31}$H$_{27}$NO$_4$F$_3$: 534.1892
Found: 534.1887

The e.r. was determined by chiral HPLC using a ChiraCel OD-H (4.6 x 250 mm) column:

Conditions: 20% IPA/hexane, flow rate = 0.6 ml/min, temperature = 23 °C, detection wavelength = 214 nm.

t$_r$(major) 13.11 min, t$_r$(minor) 10.65 min; e.r. 94:6.

*Preparation of catalyst stock solution.* A dry 20 ml vial was charged with Pd(OAc)$_2$ (11.2 mg, 0.05 mmol) and SPhos$^8$ (41 mg, 0.1 mmol) under ambient atmosphere. The vial was taken into the glovebox. THF (12.5 ml) was added and the mixture stirred for 20 min, forming a clear brown solution.
The freshly prepared catalyst stock solution was immediately for the preparation of **2.15-1**: A 20 ml vial equipped with a stir bar was charged with 3-bromophenyl MIDA boronate\(^9\) (312 mg, 1 mmol) and 4-(trifluoromethoxy)phenylboronic acid (309 mg, 1.5 mmol). This was repeated for another 20 ml vial. Finely ground \(\text{K}_3\text{PO}_4\) (637 mg, 3 mmol) was weighed into each of the 2 reaction vials. THF (5 ml) was added to each of the reaction vials, followed by 5 ml (0.05 mmol Pd(OAc)\(_2\), 0.1 mmol SPhos) of the catalyst solution. The reaction vials were sealed with Teflon-lined caps, brought out of the glovebox and stirred at 65 °C in a heating block for 14 h. The reaction was then cooled to rt, then filtered through celite, combining the filtrates from the 2 reactions. The celite pad was washed with additional THF (20 ml). Celite was added to the filtrate and the mixture concentrated *in vacuo*. The celite (containing the absorbed crude product) was loaded onto a silica gel column. The column was eluted with Et\(_2\)O to remove non-polar impurities, then with 20% acetone/hexanes followed by 30% acetone/hexanes to elute the product. The fractions containing the product were concentrated *in vacuo*, affording the pure product as a white solid (586 mg, 75%).

TLC (Hexanes:acetone 1:1)

\(R_f = 0.32\), visualized by short wave UV.

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

\(\delta 7.84\) (app s, 1H), \(7.80\) (d, \(J = 9\) Hz, 2H), \(7.69\) (dt, \(J = 8, 1.5\) Hz, 1H), \(7.58\) (d, \(J = 7.5\) Hz, 1H), \(7.49\) (t, \(J = 15\) Hz, 1H), \(7.42\) (d, \(J = 8.5\) Hz, 2H), \(4.38\) (d, \(J = 17\) Hz, 2H), \(4.21\) (d, \(J = 17\) Hz, 2H), \(2.82\) (s, 3H).

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

\(\delta 169.3, 141.5, 139.8, 132.9, 132.0, 129.6, 129.3, 128.6, 122.2, 62.9, 48.4\).

HRMS (ESI+)

Calculated for \(\text{C}_{18}\text{H}_{16}\text{BNO}_5\text{F}_3\): 394.1074

Found: 394.1078
To a solution of MIDA boronate 2.15-1 (763 mg, 1.94 mmol) in THF (20 ml) was added 1N NaOH (6 ml) in one portion under ambient atmosphere. The mixture was stirred vigorously for 20 min at rt, then diluted with Et₂O (20 ml) quenched with sat. NH₄Cl (20 ml). The mixture was stirred briefly and transferred to a separatory funnel. After shaking and phase separation, the aqueous layer was washed with THF/Et₂O 1:1 (20 ml). The combined organic phase was dried over MgSO₄, filtered and concentrated. The residue was dried *in vacuo* to give the boronic acid 2.15-2 as an off-white solid (540 mg, 98%). The solid was transferred to a 40 ml and N-iodosuccinimide (646 mg, 2.87 mmol) was added. The vial was sealed with a septum cap and evacuated under high vacuum and back-filled with N₂. This cycle was repeated twice. MeCN was then added, the vial placed in a heating block and the reaction stirred at 81 °C for 36 h. The reaction was cooled to rt and concentrated *in vacuo* to approximately 5 ml of MeCN. After dilution with Et₂O (30 ml), the organic phase was washed with 1M NaHSO₃ (30 ml × 2), then with H₂O (30 ml). The combined aqueous phase was extracted with Et₂O (30 ml). The organic layer was dried over MgSO₄, filtered and concentrated, giving a brown liquid and a white crystalline solid. This residue was taken up in a minimum amount of Et₂O and loaded onto a silica gel column. The column was flushed with hexanes. The fractions containing product were concentrated *in vacuo*, giving a yellow oil. This yellow oil was further purified by dissolving it in pentane and passing through a short silica gel pad, eluting with pentane. A colorless oil was obtained (679 mg, 89%).

**TLC (Hexanes)**

Rₚ = 0.45, visualized by short wave UV

**¹H-NMR (500 MHz, CDCl₃)**

δ 7.91 (t, J = 2 Hz, 1H), 7.70 (ddd, J = 7.5, 1.5, 1 Hz, 1H), 7.55 (dt, J = 8.5, 2 Hz, 2H), 7.51 (ddd, J = 8, 1.5, 1 Hz), 7.29 (dd, J = 9, 1 Hz, 1H), 7.18 (t, J = 8 Hz, 1H).

**¹³C-NMR (125 MHz, CDCl₃)**

δ 149.0, 142.0, 138.3, 136.6, 136.1, 130.5, 128.5, 126.3, 121.5, 121.3, 94.8.

**HRMS (EI+)**

Calculated for C₁₃H₄IOF₃: 363.95723

Found: 363.95628
To a suspension of the MIDA boronate 2.27\(^{10}\) (6.37 g, 24.86 g) in DCM (125 ml) at 0 °C was added mCPBA (7.29 g, 42.26 mmol) portionwise over 10 min under ambient atmosphere. The reaction was stirred for 12 h, gradually rising to RT in the ice/water bath. A white suspension was obtained, which was filtered to remove the white solids. The filtrate was concentrated (at 23 °C) to about 5 ml DCM, and the white solids were added back into the rbf. With vigorous stirring, 160 ml of Et\(_2\)O was added and the mixture was stirred for 5 min. The white solid (product) was obtained by filtration, rinsing with 40 ml of Et\(_2\)O. The filtrate containing impurities and trace amounts of the product, was discarded. The product was then returned to the rbf and stirred with another 100 ml of Et\(_2\)O. The white solid was obtained after filtration, rinsing with 50 ml of Et\(_2\)O. The solid was then dried in vacuo. White solid (6.28 g, 92%).

TLC (Hexanes:acetone 1:1)

R\(_f\) = 0.38, stained by KMnO\(_4\)

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

δ 7.37 – 7.27 (m, 5H), 4.36 (d, \(J = 17.2\) Hz, 1H), 4.29 (d, \(J = 16.8\) Hz, 1H), 4.18 (d, \(J = 17.2\) Hz, 1H), 4.04 (d, \(J = 16.8\) Hz, 1H), 3.80 (d, \(J = 3.2\) Hz, 1H), 3.35 (s, 3H), 2.45 (d, \(J = 2.8\) Hz, 1H).

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

δ 169.3, 168.3, 140.1, 129.2, 128.6, 126.4, 63.0, 62.8, 56.5, 47.0.

HRMS (ESI+)

Calculated for C\(_{13}\)H\(_{15}\)NO\(_5\): 276.1043

Found: 276.1057

A flame-dried 300 ml rbf equipped with a stir bar was charged with the MIDA boronate 2.28 (2.59 g, 10 mmol) and DCM (100 ml) under ambient atmosphere. The mixture was stirred to form slightly cloudy solution. Mg(ClO\(_4\))\(_2\) (2.23 g, 10 mmol) was then added portionwise over 3 min. The rbf was capped with

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a cap plug and stirred at rt for 2 h 15 min. The reaction was then filtered through celite, rinsing with 50 ml DCM. The filtrate (slightly cloudy) was concentrated in vacuo to give a fluffy white solid. 50 ml Et₂O was added to the solid, and the suspension stirred for 5 min, then vacuum-filtered. The solid was returned to the rbf and stirred with another 40 ml Et₂O for 5 min. The suspension was filtered, and the white solid was dried in vacuo. This crude product 2.29 (2.26 g, 87%) was used without further purification.

TLC (Hexanes:acetone 1:1)
Rf = 0.34, stained by KMnO₄.

¹H-NMR (500 MHz, acetone-d₆)
δ 9.82 (d, J = 2.5 Hz, 1H), 7.37 – 7.25 (m, 4H), 7.26 – 7.23 (m, 1H), 4.28 (d, J = 17 Hz, 1H), 4.26 (d, J = 17 Hz, 1H), 3.74 (d, J = 17 Hz, 1H), 3.72 (br s, 1H), 3.20 (s, 3H).

¹³C-NMR (125 MHz, acetone-d₆)
δ 168.2, 137.3, 130.6, 129.3, 127.0, 63.6, 63.3, 47.1.

HRMS (ESI+)
Calculated for C₁₃H₁₅BNO₅: 276.1043
Found: 276.1044

To a flame-dried 200 ml 3-neck rbf was added MIDA boronate 2.29 (2.26 g, 8.72 mmol) under positive N₂ atm. DCM (100 ml) was added, and the mixture stirred at rt until a homogeneous solution was formed. The solution was cooled to 0 °C in an ice/water bath and AcOH (25 ml) was then added slowly. After stirring for another 5 min, NaBH(OAc)₃ (2.77 g, 13.1 mmol, 1.5 eq) was added. The reaction was stirred at 0 °C for 2 h, then another portion of NaBH(OAc)₃ (0.92 g, 4.34 mmol, 0.5 eq) was added. After stirring at 0 °C for another 2.5 h, the third portion of NaBH(OAc)₃ (0.92 g, 4.34 mmol, 0.5 eq) was added. The reaction was gradually raised to RT, stirring for 11.5 h. 50 ml of H₂O was added slowly to quench the reaction. The mixture was transferred to a 500 ml sep funnel, rinsing with 50 ml DCM. After phase separation, the organic layer was washed with pH 7 phosphate buffer (1 M, 2 × 50 ml). The combined aqueous phase was extracted with 50 ml DCM. The organic phase was dried over MgSO₄, filtered and concentrated in vacuo. The aqueous layer was thus extracted with EtOAc/acetone 2:1 (150 ml). This
organic phase was then washed with brine (50 ml), dried over MgSO$_4$, filtered, combined with the rest of the product and concentrated. AcOH was present, forming a thick oil with the product. 100 ml Et$_2$O was then added to this oil with vigorous stirring. The white suspension was filtered, washing the white solid with additional Et$_2$O (50 ml). The solid was dissolved in acetone and transferred into a rbf. The filtrate was concentrated, and additional white solid precipitated with 50 ml Et$_2$O. The solid was dissolved in acetone, and transferred to the rbf containing the rest of the product dissolved in acetone. An equal volume of hexane was added, and the mixture concentrated in vacuo to give a white fluffy solid. Residual water was azeotroped with PhMe, followed by hexane. The white solid was then dried in vacuo (1.54 g, 64%, ~ 80-90% purity). This crude product 2.30 was used without further purification.

TLC (Hexanes:acetone 1:1)
\[ R_f = 0.14, \text{ stained by KMnO}_4. \]

$^1$H-NMR (500 MHz, acetone-$d_6$)
\[
\delta 7.28 - 7.27 (m, 2H), 7.23 - 7.20 (m, 2H), 7.11 (tt, J = 7.5, 1Hz, 1H), 4.19 (d, J = 16 Hz, 1H), 4.14 (d, J = 15 Hz, 1H), 4.11 (d, J = 14.5 Hz, 1H), 3.94 (t, J = 9 Hz, 1H), 3.79 (d, J = 8.5 Hz, 1H), 3.66 (d, J = 17 Hz, 1H), 3.15 (s, 3H), 2.56 (t, J = 7.5 Hz, 1H).
\]

$^{13}$C-NMR (125 MHz, acetone-$d_6$)
\[
\delta 169.0, 168.8, 144.0, 130.0, 128.8, 125.9, 66.1, 63.6, 63.0, 46.7.
\]

HRMS (ESI+)

Calculated for C$_{13}$H$_{15}$NO$_5$Na: 300.1019

Found: 300.1018

A flame-dried 100 ml Schlenk flask was charged with PPh$_3$ (1.87 g, 7.12 mmol), imidazole (0.808 g, 11.86 g) and I$_2$ (1.81 g, 7.12 mmol). DCM (50 ml) was added and the mixture stirred, forming a slightly yellow solution with white solid. After stirring for 5 min, the alcohol 2.30 (1.315 g, 4.75 mmol) was added as a solid under positive N$_2$ atmosphere. The reaction was then stirred for 2.5 h. Another 0.1 g of I$_2$ was added. The reaction was stirred for an additional 1 h. 40 ml H$_2$O was then added, and the mixture transferred to a separatory funnel. After phase separation, the organic layer was washed with another 30
ml H₂O. The combined aqueous phase was extracted with 50 ml DCM. The organic extracts were then dried over MgSO₄, filtered and concentrated to give a white solid. To this solid was added 50 ml Et₂O. The suspension was stirred for 30 min and filtered, washing with additional Et₂O. The white solid was taken up in acetone, absorbed onto celite and loaded onto a silica gel column. The product was purified by chromatography (100% Et₂O to 30% EtOAc/Et₂O to 50% acetone/hexane). The fractions containing the product were concentrated to give a white solid. To remove residual triphenylphosphine oxide, the solid was triturated with acetone (~5ml) and Et₂O (20 ml). The suspension was filtered, and the white solid washed again with 50 ml Et₂O. After filtration, the white solid 2.31 was dried in vacuo (736 mg, 40%).

TLC (Hexanes:acetone 3:2)

Rf = 0.28, stained by KMnO₄.

¹H-NMR (500 MHz, acetone-d₆)

δ 7.32 – 7.21 (m, 5H), 4.27 (d, J = 17 Hz, 1H), 4.10 (d, J = 17 Hz, 1H), 4.08 (d, J = 17 Hz, 1H), 4.00 (dd, J = 10, 3.5 Hz, 1H), 3.53 (dd, J = 13, 10 Hz, 1H), 3.16 (d, J = 16.5 Hz, 1H), 3.02 (s, 3H), 2.66 (dd, J = 13, 2.5 Hz, 1H).

¹³C-NMR (125 MHz, acetone-d₆)

δ 168.4, 167.9, 143.8, 129.7, 129.3, 127.0, 63.3, 63.0, 46.5, 15.5.

HRMS (ESI+)

Calculated for C₁₃H₁₆NO₄I: 388.0217

Found: 388.0226

In a glovebox, Zn dust (78.5 mg, 1.2 mmol) was weighed into a flame-dried 7 ml vial equipped with a stir bar. Another 7 ml vial was charged with a THF:NMP 3:1 solution (0.8 ml) of the iodide 2.31 (155 mg, 0.4 mmol). Both vials were sealed with septum caps and removed from the glovebox. The vial containing Zn dust was placed under argon, and 3 drops of TMSCl followed by 3 drops of 1,2-dibromoethane were added. The solution of iodide 2.31 was then added to the Zn dust in one portion via syringe under argon.
The reaction vial was then placed in a heating block and stirred at 45 °C for 1.5 h. The vial was then removed from the block and 1.2 ml of THF was added to form a 0.2 M solution of the organozinc 2.32.

Preparation of catalyst stock solution. A dry 7 ml vial equipped with a star bar was charged with RuPhos\(^\text{11}\) (9.5 mg, 0.02 mmol). The vial was brought into the glovebox, and Pd\(_2\text{dba}_3\) (4.6 mg, 0.005 mmol) was added. THF (1.5 ml) was added, and the mixture stirred at rt for 3 min.

The freshly prepared catalyst stock solution was immediately for the preparation of 2.33:
A dry 7 ml vial equipped with a stir bar was charged with iodide 2.21 (75 mg, 0.2 mmol) and brought into the glovebox. To this was added NMP (0.75 ml) and THF (0.45 ml) followed by 1.2 ml (0.004 mmol Pd\(_2\text{dba}_3\), 0.016 mmol RuPhos) of the catalyst solution. The vial was sealed with a septum cap, stirred briefly and then brought out of the glovebox. The vial was placed in a heating block pre-equilibrated to 60 °C, and the solution of the organozinc reagent 2.32 (1.5 ml, approx. 0.3 mmol) was added over 3 h with the aid of a syringe pump. After the addition was complete, the reaction was stirred for another 2 h at 60 °C, then cooled to rt. The reaction was diluted with Et\(_2\text{O}\) (7 ml) and washed with sat. NH\(_4\)Cl (2 × 5 ml) and H\(_2\text{O}\) (2 × 5 ml). The combined aqueous layers were extracted with THF:Et\(_2\text{O}\) 1:1 (10 ml). The organic phase was then dried over MgSO\(_4\), filtered and concentrated. The residue was taken up in acetone (5 ml), absorbed onto celite and loaded onto a silica gel column. The product 2.33 was obtained as a white solid after column chromatography (86 mg, 85%).

TLC (Hexanes:acetone 1:1)

\[ R_f = 0.28, \text{visualized by short wave UV} \]

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

\[
\begin{align*}
\delta & \quad 7.60 – 7.57 \text{ (m, 1H), 7.58 (d, J = 8 Hz, 1H), 7.17 – 7.11 \text{ (m, 4H), 7.05 – 7.01 \text{ (m, 1H), 7.02 (d, J = 8 Hz, 1H), 4.26 (d, J = 17.5 Hz, 1H), 4.11 (d, J = 14 Hz, 1H), 4.07 (d, J = 13.5 Hz, 1H), 3.54 (q, J = 7, 2H), 3.31 (dd, J = 14, 3 Hz, 1H), 3.15 (d, J = 17 Hz, 1H), 3.02 (s, 3H), 2.93 (dd, J = 13.5, 12.5 Hz, 1H), 2.59 (dd, J = 12, 3 Hz, 1H), 2.51 (t, J = 7 Hz, 1H), 1.41 (s, 9H).}
\end{align*}
\]

\(^1\)C-NMR (100 MHz, acetone-d\(_6\))

83
δ 171.7, 168.9, 168.3, 167.2, 146.7, 143.9, 132.8, 130.2, 129.4, 128.9, 127.4, 126.0, 80.6, 63.5, 63.1, 46.3, 39.3, 36.5, 36.0, 28.2.

To a 7 ml vial charged with MIDA boronate 2.21 (58 mg, 0.114 mmol), pinacol (20 mg, 0.171 mmol) and NaHCO₃ (48 mg, 0.57 mmol) was added MeOH (3 ml) under ambient atmosphere. The vial was capped and placed in a heating block and stirred at 45 °C for 5 h. The reaction was concentrated in vacuo. The residue was azeotroped 5 times with benzene until a white solid was obtained. Benzene (5 ml) was then added and the suspension filtered, rinsing with additional benzene. The filtrate was concentrated in vacuo to give a colorless oil residue. To this was added hexanes (10 ml), mixed thoroughly. The supernatant hexanes solution was then concentrated in vacuo to give the racemic pinacol ester rac-2.21. ¹H-NMR data matches that of enantioenriched 2.21.

A flame-dried 7 ml vial equipped with a stir bar was charged with Ag₂O (30.6 mg, 0.132 mmol) and brought into the glove box. PPh₃ (23.1 mg, 0.088 mmol) was then added into the vial, followed by a solution of the racemic pinacol boronic ester rac-2.21 (52 mg, 0.132 mmol) and iodide 2.15 (32 mg, 0.088 mmol) in DME (1.6 ml). To this mixture was added a solution of Pd₂dba₃ (4.83 mg, 0.0158 mmol) in DME (1 ml). The vial was sealed with a cap, brought out of the glove box and stirred at 85 °C for 24 h. The reaction was then cooled to room temperature and filtered through celite, eluting with Et₂O. The filtrate was then concentrated in vacuo. The crude product was purified by silica gel chromatography (15 – 20% EtOAc/hexanes) to afford a yellow oil as the product (48.5 mg, 93%). ¹H-NMR data matches that of enantioenriched tBu-2.14.
To a 7 ml vial containing racemic **rac-tBu-2.14** (24 mg, 0.041 mmol) was added TFA:DCM 1:4 (1 ml). The vial was sealed with a septum cap and vented to the atmosphere via a 22-gauge needle. The reaction was stirred at room temperature for 2 h. The solvent was then removed **in vacuo**. Residual TFA was removed by azeotroping with DCM (3 × 5 ml) to give a brown/orange oil. The crude product was purified by silica gel chromatography (EtOAc:hexanes:AcOH 7:3:0.4). The product was obtained as a white solid (16.2 mg, 74%). ^1^H-NMR data matches that of enantioenriched **2.14**.

**REFERENCES**

   This compound is also available from Sigma-Aldrich (product no. 707252).
6. Uno, B. E.; Gillis, E. P., Burke, M. D. *Tetrahedron*. **2009**, *65*, 3130-3138. This compound is also available from Sigma-Aldrich (product no. 704415).
CHAPTER 3
A LINEAR-TO-CYCLIZED STRATEGY FOR THE BUILDING BLOCK-BASED SYNTHESIS OF (POLY)CYCLIC MOLECULES

Junqi Li, Seiko Fujii, Michael J. Schmidt, Andrea M. E. Palazzolo, Jonathan W. Lehmann, and Martin D. Burke

Topologically complex polycyclic natural products containing multiple bridged and/or fused rings are challenging targets for building block-based construction. However, Nature often makes these molecules from simpler linear precursors which are biosynthesized via the iterative assembly of a small set of building blocks. This suggests that an analogous linear-to-cyclized process can be used for the construction of these molecules from building blocks. This chapter details the expansion of scope of the iterative coupling strategy from Csp²-rich linear molecules to include the total synthesis of five Csp³-rich (poly)cyclic natural products and natural product-like cores. Using the same iterative coupling process described in chapters 1 and 2, linear precursors to the cyclic targets were prepared from Csp³ and Csp² boronate building blocks and then cyclized to generate 5 structurally distinct (poly)cyclic skeletons.

Dr. Seiko Fujii and Andrea Palazzolo conducted the synthesis of the steroid-like core. The synthesis of building block 3.18 was carried out in collaboration with Michael Schmidt, and Jonathan Lehmann executed the synthesis of the building block 3.52. Portions of this chapter were adapted from Li, J.; Ballmer, S. G.; Gillis, E. P.; Fujii, S.; Schmidt, M. J.; Palazzolo, A. M. E.; Lehmann, J. W.; Morehouse, G. F.; Burke, M. D. Science 2015, 347, 1221-1226
3-1 INTRODUCTION

Natural products are diverse in structure (Figure 3-1), which necessitates the continuing development of methods to overcome challenges in total synthesis. The traditional approach to total synthesis have been to develop a customized synthesis for each target. As a result of this customized approach, automating synthesis has been carried out on *ad hoc* basis. This substantially limits synthetic access to small molecules for the study and application of their functional potential. In recent years, efforts have been made on developing unified strategies that can be applied to the synthesis of a collection of structurally related targets. However, a generalized strategy for the synthesis of many different structurally distinct natural products remains a formidable challenge.

The biosynthetic origin of natural products allows us to think about a hierarchy of structural complexity of natural products. Like peptides, oligonucleotides and oligosaccharides, many natural products are biosynthesized via the iterative assembly of a small set of building blocks, such as malonyl coenzyme A, isopentenyl pyrophosphate, and pyruvic acid. The iterative assembly of building blocks thus results in linear molecules (Figure 3-1A). The next level of complexity is installed when linear precursors from building block assembly undergo a macrocyclization event, often enzyme-mediated, to form macrocyclic natural products (Figure 3-1B). A higher level of complexity is built when multiple bonds are formed during the cyclization. Nature uses a repertoire of these cyclizations, such as Diels-Alder cycloadditions, cation-π cyclizations, iminium ion-triggered cascades, and epoxide opening cascades (Figure 3-1C). In some cases, individual cyclized fragments can further dimerize to generate dimeric or pseudo-dimeric natural products (Figure 3-1D).

**Figure 3-1.** A collection of natural products with progressive levels of structural complexity.
This general approach to the biosynthesis of many of these complex natural products led us to hypothesize that an analogous linear-to-cyclized strategy might enable the iterative coupling platform described in Chapters 1 and 2 to access many such structures. In this strategy, the same building block assembly process is used to generate a linear precursor, which is then (poly)cyclized into the topologically complex products. The stereochemical information in the building blocks is first translated into linear precursors via stereospecific couplings and then into the targeted products via stereospecific and/or stereoselective (poly)cyclization reactions. To enable such cyclizations, the linear precursors must be suitably flexible and therefore rich in sp³ hybridized carbons. Building block-based assembly of these precursors thus requires Csp³ couplings, which can be challenging. To test this strategy, we elected to target the synthesis of 5 structurally distinct cyclic molecules 3.1 – 3.5 (Figure 3-2) that represent natural products from different biosynthetic pathways. The main challenge is the stereoselective synthesis and coupling of the boronate building blocks.

![Figure 3-2. Cyclic targets for testing the linear-to-cyclized approach. The targets can be accessed via different cyclization reactions.](image)

**3-2 FORMAL TOTAL SYNTHESIS OF CITEROFURAN 3.1**

We first developed a few guiding principles in planning the synthesis of 3.1 to 3.5. We aimed to minimize the number of Csp³ couplings in our disconnections, and only Csp³-Csp² (vs Csp³-Csp³) couplings will be used. In addition, because alkyl iodides are prone to β-hydride elimination after oxidative addition, especially if transmetallation is the turnover-limiting step, we opted to make the Csp³ coupling partner be the boronic acid.

Citreofuran is a macrocyclic polyketide-derived lactone that is known to have DNA-cleaving properties. It contains both Csp³ and atropisomerism stereochemical elements. The macrolactone can be derived from the linear precursor seco-acid 3.6, which in turn can in theory be assembled from the building blocks 3.7, 3.8 and 3.9 (Figure 3-3).

![Figure 3-3. Retrosynthesis of citreofuran 3.1.](image)
The synthesis of the building block 3.7 started from the chiral pool material \((R)-(+)\)-3-butyn-2-ol, which is subjected to hydroboration with catecholborane after protection of the silyl group. The resulting boronic ester is converted into the alkenyl MIDA boronate 3.11. The final Csp\(^3\) boronate 3.7 is then obtained from the hydrogenation of C=C bond. 3.8 is synthesized from an electrophilic bromination of commercially available 2-furanyl MIDA boronate. The capping aryl halide building block is synthesized from published procedures. A TMSE group was chosen as a protecting group for the ester so that only one step is needed for the deprotection of the linear precursor 3.6.

![Scheme 3-1](image)


The first coupling was a Csp\(^3\)-Csp\(^2\) coupling between the the aryl halide 3.8 and Csp\(^3\) boronic acid resulting from the basic hydrolysis of boronate 3.7. Our group had discovered anhydrous conditions for coupling secondary alkyl boronic acids\(^4\), but those conditions have not been investigated with heteroaryl halides containing a MIDA boronate functionality. Using conditions modified from that study (Pd[P(o-tol)]\(_2\) and Ag\(_2\)O/K\(_2\)CO\(_3\) as the base mixture), we obtained an isolated yield of 46%. In this coupling reaction, 4 equivalents of the boronic acid and 25 mol\% was necessary to reach complete conversion due to competitive \(\beta\)-hydride elimination leading to decomposition of the boronic acid. The Pd-hydride intermediate from \(\beta\)-hydride elimination also resulted in the formation of protodehalogenation product arising from reductive elimination (Scheme 3-2). Under the best optimized conditions, a ratio of 15:1 of desired product: protodehalogenated product was obtained.
Scheme 3-2. Proposed mechanism for the formation of the protodehalogenated side product.

Deprotection of the MIDA boronate 3.15 gives a 2-furanyl boronic acid for the next coupling reaction. A slow addition protocol\(^5\) was used for the coupling of the boronic acid to the aryl bromide 3.9 as 2-heterocyclic boronic acids are prone to decomposition under the reaction conditions. With the 2\(^{nd}\) generation Buchwald XPhos palladacycle and K\(_3\)PO\(_4\), an isolated yield of 87% of the fully protected linear precursor 3.6 was obtained. Removal of the silyl groups would reveal the seco-acid which is known to undergo an atropdiastereoselective Mitsunobu lactonization to form the macrocycle.\(^6\)

Scheme 3-3. Building block assembly via iterative cycles of coupling and deprotection to generate 3.6. D = deprotection; C = coupling.

3-3 FORMAL TOTAL SYNTHESIS OF OBLONGOLIDE 3.2

Oblongoline is a norsesquiterpene \(\gamma\)-lactone natural product containing a 6,6,5-tricyclic core with five \(\text{Csp}^3\) stereogenic centers, one of which is quaternary.\(^7\) A lactonization and Diels-Alder disconnection reduces the target to a relatively simple linear precursor, which can be further retrosynthesized into three building blocks (Figure 3-4).

Figure 3-4. Retrosynthesis of oblongoline 3.2.
Since the Diels-Alder reaction is a stereospecific reaction in which the configuration of the C=C bonds translates to the relative configuration of the stereogenic centers in the cycloaddition product, it is important that the C=C configurations is installed in the building blocks with high selectivity and maintained in the building block assembly process. The most difficult part of the synthesis was making the chiral non-racemic bifunctional MIDA boronate building block 3.18, which involved 2 critical elements – setting the stereocenter and stereoselectively forming the E-alkenyl iodide.

In planning the synthesis of 3.18 we realized that the methodology described in Chapter 2 involving the Negishi coupling with an organozinc reagent containing a MIDA (or PIDA) boronate and an aryl halide would allow us to install the Z-alkenyl iodide with excellent stereoselectivity. The vinyl iodide coupling partner would come from a highly regioselective hydrozirconation-iodinolysis sequence developed by Negishi and co-workers (Figure 3-5).

![Figure 3-5. Retrosynthesis of building block 3.18.](image)

The synthesis of 3.18 commenced with the acylation of Evans’ (S)-4-Benzyl-2-oxazolidinone with crotonic acid, followed by methylation at the α-position with a diastereoselectivity of 3.6:1 with the desired diastereomer as the major product. After separation of the diastereomers, the imide was reduced to the alcohol 3.23. The corresponding tosylate 3.24 was subjected to a hydroboration-hydrolysis-MIDA complexation sequence to give the MIDA boronate 3.25 as a single regioisomer. A Finkelstein reaction with the tosylate installs the iodide. The MIDA boronate 3.26 is then converted into the organozinc reagent 3.19 which underwent a Negishi coupling with the vinyl iodide 3.20. Iododesilylation with the conditions developed by the Zakarian group generated the desired E-alkenyl iodide 3.18 as a single stereoisomer.
Assembly of the building blocks started from the hydrolysis of the commercially available MIDA boronate 3.17 to give the boronic acid which would then undergo coupling with the bifunctional building block 3.18. Initial attempts at coupling were made using the 2nd generation XPhos Buchwald Palladacycle, and K$_3$PO$_4$ as the base, but this resulted in the formation of 3 isomeric products (Scheme 3-5).

We reasoned that 3.30 might be formed from β-hydride elimination followed by re-insertion into the β-position before reductive elimination.$^{10}$ Re-insertion into the position proximal to the protected alcohol may have been promoted by coordination of the oxygen to the Pd center (Scheme 3-6).
After a ligand screen, the 1,1'-bis(diphenylphosphino)ferrocene (dpff) ligand in combination with a Ag₂O/K₂CO₃ base mixture was found to be effective in eliminating the cis isomer 3.31. It was found that the Pd source influenced both the conversion and the ratio of the isomers (Table 3-1). Pd(OAc)₂ was the optimal Pd source, with only one isomer detected in the ¹H-NMR of the crude reaction mixture. A 47% isolated yield of MIDA boronate 3.29 was obtained with slow addition of the boronic acid into the reaction mixture.

Table 3-1. A screen of palladium sources for optimizing the coupling of rac-3.18 and 3.28. Ratios were determined by ¹H-NMR analysis of the crude reaction mixture.

After deprotection of 3.29, the boronic acid was engaged in a Csp³-Csp² coupling with the vinyl bromide 3.19 using the same conditions used for the Csp³-Csp² coupling in the synthesis of citreofuran (Scheme 3-3), giving an isolated yield of 46% of the protected linear precursor 3.31 (Scheme 3-7). Removal of the TIPS group and a substrate-controlled endo-equatorial Diels-Alder reaction followed by an intramolecular lactonization would generate oblongolide.¹¹
Scheme 3-7. Building block assembly via iterative cycles of coupling and deprotection to generate 3.31.

3.4 FORMAL SYNTHESIS OF THE HEXAHYDROINDENE CORE 3.3

The hexahydroindene core 3.3 can be derived from the linear precursor 3.33 by an intramolecular Diels-Alder reaction. Unlike the synthesis of oblongolide, no Csp\(^3\) stereocenters are present in the linear precursor. In this case, the enantioselectivity can be controlled using a rapidly expanding toolbox of chiral catalysts.\(^{12}\) We thus aimed to use the organocatalytic intramolecular Diels-Alder reaction developed by MacMillan and co-workers to transform the linear precursor into the desired trans-bicyclic compound.\(^{13}\) The linear precursor 3.33 can again be retrosynthesized into 3 building blocks. 3.34 is a commercially available building block, so the focus of building block synthesis was on the bifunctional building block 3.35.

Figure 3-6. Retrosynthesis of hexahydroindene core 3.13.

We reasoned that the most straightforward synthesis of 3.35 was hydrostannylation followed by iodinolysis of the bromoalkyne 3.37\(^{14}\), which can be synthesized from a TMS-protected Grignard reagent and trimethyl borate. However, hydrostannylation with tributyltin hydride gave an inseparable mixture of the vinyl iodies 3.35, 3.36 and 3.37 in the ratio 88:9:3 after iododestannylation.

Scheme 3-8. Initial attempt at the stereoselective synthesis of 3.35.

We thus turned to the approach we took for the synthesis of the building block 3.18 for oblongolide. The bifunctional iodo MIDA boronate 3.39 was first synthesized from the commercial 3-bromopropylboronic acid pinacol ester. Zinc insertion into the carbon-iodine bond generates the
organozinc reagent which then undergoes a Negishi coupling with the vinyl iodide. Iodo-desilylation of the vinyl silane 3.40 then generated the desired E-vinyl iodide as a single stereoisomer.

![Scheme 3-9](image)

**Scheme 3-9.** Synthesis of building block 3.35 via the Negishi coupling of 3.40.

The capping building block was synthesized starting from allyl alcohol which underwent a hydrozirconation-iodinolysis sequence to give the vinyl iodide 3.42. This compound was volatile and unstable when concentrated, leading to a low yield. Oxidation to the aldehyde by MnO₂ gives the aldehyde which was used immediately in the ketalization reaction. The resulting ketal was a stable and can be purified by silica gel chromatography.

![Scheme 3-10](image)

**Scheme 3-10.** Synthesis of building block 3.36.

With the building blocks in hand, we began the synthesis of the linear precursor to the hexahydroindenone core (Scheme 3-11). Hydrolysis of the MIDA boronate 3.34 gives the boronic acid which undergoes cross-coupling with the bifunctional vinyl iodide 3.35 without isomerization with Pd(OAc)₂ and P(ο-tol)₃.¹⁵ It should be noted that the use of the Wittig reaction for diene synthesis resulted in a mixture containing 83.3% of the desired E,E-diene due to the stereoselective nature of the Wittig reaction.¹² Deprotection of the resulting MIDA boronate and coupling with the vinyl iodide 3.36 using the same Csp³-Csp³ coupling conditions for the synthesis of citreofuran and oblongolide generates the desired protected linear precursor 3.44.
3-5 FORMAL SYNTHESIS OF THE STEROID-LIKE CORE 3.4

The steroid-like core 3.4 contains a 6,6-trans-fused bicycle that can be retrosynthesized into a terpene-like linear precursor containing an aryl capping group 3.45 (Figure 3-7). 3.45 can be further broken down into 3 building blocks 3.46, 3.47 and 3.48 which can be assembled via iterative Csp\(^3\)-Csp\(^2\) couplings.

![Figure 3-7. Retrosynthesis of the steroid-like core 3.4.](image)

The synthesis of 3.45 was carried out by Dr. Seiko Fujii and Andrea Palazzolo using the same iterative coupling process that was used for the synthesis of targets 3.1 – 3.3. The first Csp\(^3\)-Csp\(^2\) coupling with the vinyl iodide proved to be challenging because of decomposition of the iodide 3.47 under typical anhydrous Suzuki-Miyaura cross-coupling conditions, but good yields were obtained using a Negishi coupling between 3.45 and 3.46. Deprotection of the intermediate followed by a second Csp\(^3\)-Csp\(^2\) coupling with the aryl iodide proceeded in good yields, giving the desired linear precursor that could undergo a Lewis acid-catalyzed cation-\(\pi\) cyclization to generate the tricyclic core (see Chapter 4).\(^{16}\)

![Scheme 3-12. Synthesis of the linear precursor 3.45.](image)
3-6 TOTAL SYNTHESIS OF THE SECODAPHNANE CORE 3.5

The daphniphyllum alkaloids are a family of structurally diverse alkaloids consisting of more than 200 members characterized to date with at least 16 core structures. Heathcock proposed the secodaphnane core to be the primordial alkaloid from which the other daphniphyllum cores are derived. Heathcock and co-workers also proposed the biosynthesis of the secodaphnane core from squalene, and executed the biomimetic synthesis of the pentacyclic core from a squalene-like linear precursor, thus supporting the notion that both the secodaphnane core and cholesterol are biosynthesized from the same prenyl building blocks.

Figure 3-8. Common biosynthetic origins of steroids (e.g. cholesterol) and the daphniphyllum alkaloids.

The common biosynthetic origins of the daphniphyllum alkaloids and the steroids guided us in designing the synthesis to the target 3.5, which contains the secodaphnane core present in the proto-daphniphylline. We realized that the monoterpene tail of the linear precursor can be constructed with the same building blocks 3.46 and 3.47 as that used in the synthesis of the steroid-like core. To avoid a challenging Csp3-Csp3 coupling, we installed a C=C bond in the capping halide building block which could be selectively reduced in the presence of the other C=C bond. Installing the appropriate protecting groups provided the capping building block 3.52 for the iterative assembly of the linear precursor.

Figure 3-9. Retrosynthesis of the secodaphnane core 3.5.

The synthesis of the capping building block 3.52 can be simplified by introducing the vinyl halide as the last step in the synthesis via a halide-selective Negishi coupling. This would also give us an option
of installing either an E- or Z-vinyl halide without the need to start the building block synthesis from the first step.


We questioned whether the E-vinyl bromide E-3.52 might be prone to β-hydride elimination to generate the undesired alkyne after oxidative addition during the Csp3-Csp2 coupling in the assembly of the precursor. We thus opted to first test the coupling of boronic acid 3.54 with the Z-3.52. Using the conditions for optimized for the Csp3-Csp2 couplings, we were only able to obtain an isolated yield of 34% for the desired product Z-3.51 (Scheme 3.14).


Separation and NMR analysis of each of the side products revealed that there were a number of reaction pathways that led to the decomposition of the vinyl halide Z-3.52 during the reaction. After transmetallation, β-hydride elimination followed by reductive elimination on the Pd-hydride species leads to formation of proto-dehalogenated product 3.55. Unexpectedly, we also observed the formation of side products 3.56a and 3.56b resulting from a competing intramolecular Heck reaction. Oxidative addition into the carbon-bromine bond, followed by intramolecular migratory insertion into the terminal C=C bond forms a cyclopentene which then undergoes β-hydride elimination to form 3.56a as a mixture of E and Z isomers and 3.56b. We were unable to increase the selectivity of the Suzuki-Miyaura coupling over the Heck reaction after several attempts at optimizing the reaction.22
Scheme 3-15. Competitive pathways in the coupling of 3.54 and Z-3.52 leading to formation of multiple side products.

We thus synthesized the E-vinyl halide E-3.52 by changing the dibromide component to test the Suzuki-Miyaura coupling. Gratifyingly, we obtained a 53% isolated yield of the desired product 3.51 (Scheme 3-16), thus allowing us to complete the synthesis of the linear precursor via iterative assembly of the building blocks 3.46, 3.47, E-3.52.


With the fully assembled linear target 3.51 in hand, we were in a position to test the synthesis of the secdaphnane core 3.5. A conjugate reduction with magnesium turnings in methanol, followed by reduction of the ester and removal of the TIPS protecting group furnishes the diol 3.59. Using the one-pot reaction sequence optimized by Heathcock and co-workers for the synthesis of proto-daphniphylline19, the diol was oxidized to the bis-aldehyde, which was treated with methylamine gas to form the bis-imine. Addition of dry acetic acid to the bis-imine at 80 °C initiates two sequential hetero-Diels-Alder reactions followed by an aza-Prins cyclization to generate the pentacyclic core 3.5. The structure was unambiguously confirmed by X-ray structure analysis of the N-bromoacyl derivative of 3.5.
Scheme 3-17. Synthesis of 3.5 from the linear precursor 3.51.

3.7 SUMMARY AND CONCLUSIONS

With accelerating advances in method development, the total synthesis of even very complex polycyclic natural products can be accomplished. However, a major challenge in synthesis is creating a generalized process that can be applied for the synthesis of structurally distinct classes of small molecules. Towards this overarching goal, our group developed a building block-based, iterative coupling approach that is analogous to peptide synthesis. This approach has been successfully demonstrated on Csp²-rich linear targets, especially polyene natural products, but applying the same iterative coupling approach to Csp³-rich cyclic molecules now requires an advance in synthetic strategy. In this chapter, we present a biosynthesis-inspired linear-to-cyclized approach which enabled us to successfully expand the scope of the iterative coupling platform to include 5 (poly)cyclic targets representing natural products from different biosynthetic pathways. Building block assembly using both Csp³-Csp³ and Csp²-Csp² couplings generates the linear precursors, which can undergo various cyclization conditions (Mitsunobu lactonization, Diels-Alder reactions, cation-π cyclization, and iminium ion-triggered cascade cyclization) to give the desired (poly)cyclic structures. The goals achieved in this chapter lay the groundwork for the more general synthesis of complex small molecules using the iterative coupling platform in combination with the linear-to-cyclized approach. In the next chapter, we demonstrate how the synthesis of the linear precursors can be automated to provide expedient access to the synthesis of the corresponding polycyclic structures.

The continued progress towards the more general synthesis of small molecules first requires a complete structural analysis of all natural products outlined in the Introduction of this chapter, which will certainly require the aid of intelligent computer programs that can recognize structural patterns in small molecules. However, analysis of a small section of the entire set of natural products can already define the important problems that need to be solved for the synthesis of natural products to become more general – i) the identification and construction of building blocks, ii) the development of new methods for the iterative assembly of building blocks, iii) the expansion of the catalyst toolbox for cyclization of linear molecules, and iv) the development of mild and selective methods for dimerizing natural product-like fragments.
REFERENCES


21 Preliminary studies carried out by Dr. Seiko Fujii utilized a benzoate group in place of the TIPS group for the protection of the terminal alcohol. It was later found that competitive oxidative addition occurred on the benzoate group to form the Pd π-allyl complex during the synthesis of the linear precursor.
We reasoned that increasing the concentration of the reaction might increase the selectivity for the desired product. However, the boronic acid is prone to form boroxine upon concentration, and thus had to be used directly in the coupling reaction as a solution in THF after work-up. Concentrating the THF solution of the boronic acid beyond 0.1M led to formation of the boroxine, which is detrimental to the reaction. See reference 4.
CHAPTER 3
EXPERIMENTAL SECTION

Materials. Commercial reagents were purchased from Sigma-Aldrich, Fisher Scientific, Alfa Aesar, TCI America, or Frontier Scientific, and were used without further purification unless otherwise noted. Most of the building blocks used in these studies are available from commercial sources. The following MIDA boronates were purchased from Sigma-Aldrich: 2-furanyl MIDA boronate (701017). XPhos 2nd generation palladacycle refers to chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (741825, Sigma-Aldrich). 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.

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. Organic solutions were concentrated via rotary evaporation under reduced pressure with a bath temperature of 23 °C unless otherwise noted. Reactions were monitored by analytical thin layer chromatography (TLC) performed using the indicated solvent on E. Merck silica gel 60 F254 plates (0.25mm). Compounds were visualized by exposure to a UV lamp (λ = 254 nm), and/or a solution of KMnO₄, followed by brief heating using a Varitemp heat gun. Column chromatography was performed using Merck silica gel grade 9385 60Å (230-400 mesh).

Structural analysis. ¹H NMR and ¹³C NMR spectra were recorded at 20 °C on Varian Unity 500, Varian Unity Inova 500NB or Varian Unity 500 instruments. Chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane and referenced to residual protium in the NMR solvent (CHCl₃, δ = 7.26; acetone, δ = 2.05, center line) or to added tetramethylsilane (δ = 0.00). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sept = septet, m = multiplet, b = broad, app = apparent), coupling constant (J) in Hertz (Hz), and integration. Chemical shifts (δ) for ¹³C NMR are reported in ppm downfield from tetramethylsilane and referenced to carbon resonances in the NMR solvent (CDCl₃, δ = 77.0, center line; acetone, δ = 39.5, center line). Carbons bearing boron substituents were not observed (quadrupolar relaxation). High resolution mass spectra (HRMS) were performed by Furong Sun and Dr. Haijun Yao at the University of Illinois School of Chemical Sciences Mass Spectrometry Laboratory.
A flame-dried 250 mL Schlenk flask equipped with a stir bar was charged with imidazole (7.28 g, 107.0 mmol, 1.5 equiv). The flask was sealed with a rubber septum, evacuated and back-filled with N₂ (×3). DMF (50 mL) was added via syringe, followed by neat (R)-(+)-3-butyne-2-ol (5g, 71.34 mmol, 1.0 equiv). The flask was placed in a water bath at RT. Triisopropylsilyl chloride (23 mL, 107.3 mmol, 1.5 equiv) was then added neat dropwise over 5 min. The reaction was stirred at rt for 14.5 h, then partitioned between H₂O (250 mL) and Et₂O (200 mL), rinsing with Et₂O (50 mL). The aqueous phase was extracted with Et₂O (150 mL). The combined organics were washed with H₂O (150 mL), brine, dried over MgSO₄, filtered and concentrated in vacuo. The crude product was purified by SiO₂ column chromatography (100% pentane-5% Et₂O/pentane) to give the pure product 3.10 as a colorless liquid (12.58 g, 78% yield).

TLC (100% hexanes)

Rf = 0.27, visualized by KMnO₄

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

δ 4.59 (dq, J = 6.5, 2.0 Hz, 1H), 2.37 (d, J = 2.0 Hz, 1H), 1.46 (d, J = 6.0 Hz, 3H), 1.15-1.07 (m, 21H).

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

δ 86.6, 71.0, 58.8, 25.6, 17.9 (2C), 12.1.

HRMS (ESI⁺)

Calculated for C₁₃H₂₆OSi: 226.1753

Found: 226.1751

\[ [\alpha]^{23}_D +40.3^\circ \ (c = 0.9, \text{ CHCl}_3). \]

The following procedure was carried out in quadruplicate. A flame-dried 40 mL vial was charged with alkyne 3.10 (2.63 g, 11.62 mmol, 1.0 equiv) and a stir bar. The vial was flushed with Ar., then sealed with a PTFE septum cap. Catecholborane (1.3 mL, 12.2 mmol, 1.05 equiv) was added via syringe and the
reaction stirred for 7 h at 70 °C. The reaction mixtures from the 4 vials were combined into an Erlenmeyer flask, rinsing with THF (140 mL total). The flask was placed in an ice-water bath and cooled to 0 °C. 1N NaOH (100 mL) was added slowly. The mixture was stirred for 15 min at 0 °C, then the ice-water bath was removed and the reaction stirred for another 15 min. The dark brown mixture was then transferred to a separatory funnel and diluted with Et2O (280 mL). After mixing and phase separation, the aqueous phase was extracted with Et2O (70 mL). The combined organics were washed with sat. aq. Na2CO3 (70 mL × 5), brine (140 mL), dried over MgSO4, filtered and concentrated. The crude boronic acid was diluted with benzene (100 mL) and stored at – 20 °C overnight. After warming the frozen mixture to rt, benzene was removed in vacuo. The residue was transferred to a 500 mL single neck rbf, rinsing with PhMe (250 mL). DMSO (25 mL) was added, followed by MIDA (7.18 g, 48.8 mmol, 1.05 equiv). The mixture was stirred and heated to reflux with a Dean-Stark trap for 4.5 h, then cooled briefly. PhMe was removed in vacuo and the residue was partitioned between EtOAc (250 mL) and H2O (150 mL). The aqueous layer was extracted with EtOAc (100 mL). The combined organics were washed with 1:1 H2O/brine (120 mL × 2), brine, dried over MgSO4, filtered and concentrated. The crude product was purified by SiO2 column chromatography (100% Et2O-10% acetone/Et2O). The colorless fractions containing the product were concentrated to give 3.11 as a white solid (5.79 g, 32% yield).

TLC (40% acetone/hexanes)

Rf = 0.50, visualized by KMnO4 stain

1H-NMR (500 MHz, CDCl3)

δ 6.15 (dd, J = 18.0, 5.5 Hz, 1H), 5.68 (dd, J = 18.0, 1.5 Hz, 1H), 4.52-4.47 (m, 1H), 4.21 (d, J = 17.0 Hz, 1H), 4.21 (d, J = 16.5 Hz, 1H), 4.01 (d, J = 17.0 Hz, 1H), 3.97 (d, J = 17.0 Hz, 1H), 3.00 (s, 3H), 1.24 (d, J = 6.5 Hz, 3H), 1.12-1.07 (m, 21H).

13C-NMR (125 MHz, CDCl3)

δ 169.0 (2C), 150.1, 71.5, 62.2 (2C), 47.3, 25.1, 18.5, 18.4, 13.0.

HRMS (ESI+)

Calculated for C18H35BNO5Si: 384.2378
Found: 384.2383
A 200 mL single neck rbf was charged with MIDA boronate 3.11 (4.59 g, 11.97 mmol, 1.0 equiv), a stir bar and 10 wt% Pd/C (255 mg, 0.24 mmol, 0.02 equiv). The rbf was sealed with a rubber septum, evacuated and back-filled with N₂ (×3). EtOAc (60 mL) was added via syringe and H₂ was bubbled through the mixture from a balloon for 5 min. The mixture was then stirred under a H₂ atmosphere for 15 min at rt, then at 45 °C for 45 min. The reaction was cooled to rt and purged with N₂, then filtered through celite, rinsing with CH₂Cl₂ (100 mL). The filtrate was concentrated in vacuo and the crude product purified on a SiO₂ column (30%-35%-40% acetone/hexanes) to give a white solid as the pure product 3.7 (3.81 g, 83% yield).

TLC (40% acetone/hexanes)
\[ R_f = 0.47, \text{ visualized by KMnO}_4 \text{ stain.} \]

\(^1\)H-NMR (500 MHz, CDCl₃)
\[ \delta 4.18 (d, J = 17.0 \text{ Hz, 1H}), 4.18 (d, J = 17.0 \text{ Hz, 1H}), 4.02 (d, J = 16.5 \text{ Hz, 1H}), 4.01 (d, J = 16.5 \text{ Hz, 1H}), 3.96 (dq, J = 12.5, 6.5 \text{ Hz, 1H}), 3.10 (s, 3H), 1.65-1.58 (m, 1H), 1.52-1.45 (m, 1H), 1.17 (d, J = 6.0 \text{ Hz, 3H}), 1.08 (m, 21H), 0.71-0.62 (m, 2H). \]

\(^13\)C-NMR (125 MHz, CDCl₃)
\[ \delta 168.8, 168.7, 71.3, 62.6 (2C), 46.2, 35.2, 23.4, 18.5 (2C), 13.2. \]

HRMS (ESI+)
\[ \text{Calculated for C}_{18}\text{H}_{37}\text{BNO}_5\text{Si: 386.2534} \]
\[ \text{Found: 386.2528} \]

A flame-dried 250 mL Schlenk flask was charged with 2-furanyl MIDA boronate (Aldrich catalog # 701017, 2.00 g, 8.97 mmol, 1.0 equiv) and THF (90 mL). The solution was cooled to 0 °C in an ice-water bath. N-bromosuccinimide was added as a solid under a positive pressure of N₂. The reaction was stirred in the cold bath, gradually warming to rt. After 3 h 15 min, the reaction was cooled to 0 °C and another
portion of N-bromosuccinimide (239 mg, 1.35 mmol, 0.15 equiv) was added. The reaction was stirred for another 4 h, gradually warming to rt. The reaction mixture was then transferred to a separatory funnel and diluted with EtOAc (100 mL). The organics were washed with sat. aq. Na$_2$SO$_3$ (100 mL ×2). The aqueous phase was extracted with EtOAc (100 mL). The combined organics were washed with brine, dried over MgSO$_4$, filtered and concentrated in vacuo. The crude product was purified by silica gel column (20%-40%-60% EtOAc/Et$_2$O). The fractions containing product were concentrated and taken up in 10 mL acetone. 1:1 Et$_2$O/hexanes (100 mL) was layered on top of the acetone solution and the mixture was left to stand at RT. The white solid obtained were filtered and dried in vacuo to give the pure product 3.8 (871 mg, 32% yield).

TLC (50% acetone/hexanes)

R$_f$ = 0.47, visualized by KMnO$_4$ stain.

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

δ 6.72 (d, $J = 3.0$ Hz, 1H), 6.44 (d, $J = 3.5$ Hz, 1H), 4.38 (d, $J = 17.0$ Hz, 2H), 4.18 (d, $J = 17.0$ Hz, 2H), 2.92 (s, 3H).

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

δ 168.7, 125.3, 121.6, 112.4, 62.5, 47.9.

HRMS (ESI+)

Calculated for C$_9$H$_{10}$BNO$_5$Br: 301.9835

Found: 301.9826

A 300 mL single neck rbf equipped with a stir bar was charged with methyl ester 3.12$^2$ (6.43 g, 17.75 mmol, 1.0 equiv) and THF (160 mL) under ambient atmosphere. The solution was cooled to 0 °C in an ice-water bath. N-bromosuccinimide (3.22 g, 18.11 mmol, 1.02 equiv) was added as a solid slowly over 2 min. The reaction was stirred at 0 °C for 15 min, then the ice-water bath was removed and the reaction warmed to rt. The reaction was stirred for a total of 2.5 h. The reaction mixture was concentrated in vacuo. The residue was taken up in CH$_2$Cl$_2$ and the crude product was adsorbed onto celite in vacuo. The celite
pad was loaded onto a SiO\(_2\) column for purification (50-70\% DCM/hexanes). The fractions containing product were concentrated in vacuo to give a white solid, which was dissolved in hot Et\(_2\)O/hexanes (approx. 1:9, 500 mL) and left to cool at RT to allow crystallization overnight. The white solid formed was obtained by vacuum filtration, rinsing with hexanes (60 mL) and dried \textit{in vacuo}, giving the pure product \textbf{3.13} (4.75 g, 68\% yield).

\textbf{TLC} (60\% DCM/hexanes) \\
\texttt{R}_f = 0.35, \text{visualized by shortwave UV.}\\

\(^1\text{H}-\text{NMR}\) (500 MHz, CDCl\(_3\)) \\
\(\delta\) 7.47-7.45 (m, 2H), 7.40-7.32 (m, 8H), 6.58 (d, \(J = 3.0\) Hz, 1H), 6.55 (d, \(J = 2.5\) Hz, 1H), 5.10 (s, 2H), 5.01 (s, 2H), 3.81 (s, 2H), 3.72 (s, 3H).

\(^{13}\text{C}-\text{NMR}\) (125 MHz, CDCl\(_3\)) \\
\(\delta\) 170.9, 158.5, 155.9, 136.4, 136.3, 135.9, 128.6, 128.5, 128.1, 127.9, 127.5, 126.9, 109.1, 106.5, 100.9, 70.8, 70.3, 52.2, 42.0.

\textbf{HRMS} (ESI+) \\
Calculated for C\(_{23}\)H\(_{22}\)O\(_4\)Br: 441.0701 \\
Found: 441.0705

A 40 mL Ichem vial equipped with a stir bar was charged with methyl ester \textbf{3.13} (932 mg, 2.11 mmol, 1.0 equiv), followed by EtOH (10 mL), H\(_2\)O (10 mL) and KOH (2.37 g, 42.24 mmol, 20 equiv), forming a thick suspension. THF (10 mL) was then added. The vial was sealed and stirred vigorously at 60 °C. The solids gradually dissolved to form a clear biphasic mixture. After 2 h 15 min, the reaction was cooled to RT and transferred to a 125 mL Erlenmeyer flask, rinsing with H\(_2\)O. With vigorous stirring, the reaction was neutralized to pH 3 with 2N HCl at rt. The mixture was transferred to a separatory funnel, rinsing with Et\(_2\)O and H\(_2\)O. The organic layer was diluted with EtOAc (50 mL). After mixing and phase separation, the aqueous layer was extracted with EtOAc (50 mL). The combined organics were washed with brine (50 mL \(\times\) 2), dried over MgSO\(_4\), filtered and concentrated \textit{in vacuo} to give \textbf{3.14} as a white
solid that was used directly for the next step without purification. $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 7.47-7.44 (m, 2H), 7.42-7.30 (m, 8H), 6.59 (d, $J = 2.5$ Hz, 1H), 6.56 (d, $J = 2.5$ Hz, 1H), 5.10 (s, 2H), 5.00 (s, 2H), 3.85 (s, 2H).

A flame-dried 25 mL Schlenk flask equipped with a stir bar was charged with acid 74-3 obtained above, and DMAP (28.2 mg, 0.23 mmol, 0.11 equiv). CH$_2$Cl$_2$ (18 mL) was added, followed by trimethylsilylethanol (0.61 mL, 4.26 mmol, 2.0 equiv). EDC.HCl (445 mg, 2.32 mmol, 1.1 equiv) was added as a solid. The reaction was stirred for 18 h at RT, then transferred to a separatory funnel. The organic layer was washed sequentially with H$_2$O, 1N HCl and sat. NaHCO$_3$, then with brine, dried over MgSO$_4$, filtered and concentrated in vacuo. The crude product was purified by SiO$_2$ column chromatography (10-20% EtOAc/hexanes) to give a white cloudy liquid 3.9 (1.27 g, 71% yield over 2 steps) that turned into a white solid after storage in the freezer.

TLC (20% EtOAc/hexanes)

$R_f = 0.59$, visualized by UV.

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

$\delta$ 7.54-7.34 (m, 10 H), 6.80 (d, $J = 2.5$ Hz, 1H), 6.75 (d, $J = 2.5$ Hz, 1H), 5.22 (s, 3H), 5.11 (s, 3H), 4.21-4.17 (m, 2H), 3.79 (s, 2H), 1.02-0.98 (m, 2H), 0.04 (s, 9H).

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

$\delta$ 170.6, 158.5, 155.9, 136.4 (2C), 136.2, 128.6, 128.5, 128.1, 127.9, 127.6, 127.0, 109.2, 106.6, 101.0, 70.9, 70.3, 63.3, 42.4, 17.2, -1.5.

HRMS (ESI+)

Calculated for C$_{27}$H$_{32}$O$_4$SiBr: 527.1253

Found: 527.1261
A mixture of the MIDA boronate 3.7 (963 mg, 2.5 mmol) in THF (23 mL) and 1N NaOH (7.5 mmol, 7.5 mL) was stirred under ambient atmosphere and temperature for 20 min. The reaction was quenched with the addition of saturated aqueous NH₄Cl (20 mL). The mixture was transferred to a separatory funnel, diluting with Et₂O (20 mL). After mixing and phase separation, the aqueous phase was extracted with Et₂O (10 mL). The combined organics were washed with brine, dried over MgSO₄, filtered and concentrated in vacuo. The residue was transferred into an oven-dried 40 mL vial as a solution in DCM. The solution was concentrated and dried on high vac to give a white semi-solid which was used directly in the next reaction.

To the vial containing the boronic acid was added a stir bar, bromide 3.8 (302 mg, 1 mmol), Ag₂O (603 mg, 2.6 mmol), and K₂CO₃ (719 mg, 5.2 mmol). The vial was taken into the glovebox and Pd[P(o-tol)_3]₂ (179 mg, 0.25 mmol) was added into the vial. The vial was then sealed with a septum cap and removed from the glovebox. THF (15 mL) was added and the reaction was stirred at 60 °C in a heating block for 11.5 h. The reaction was cooled to RT, then diluted with EtOAc and filtered through celite. To the solution containing the crude product was added celite, and the mixture concentrated in vacuo. The celite pad was loaded onto a silica gel column for purification (15 to 20 to 25% acetone/hexanes). The fractions were concentrated to give a yellow solid, which was taken p in 40% EtOAc/hexanes and loaded onto a second silica gel column (5 cm length). The yellow impurity was removed by eluting with 40% EtOAc/hexanes. The product was eluted with 60 to 80% EtOAc/hexanes. A white solid was obtained as the pure product 3.15 (208 mg, 46%) after concentrating the fractions.

**¹H-NMR (500 MHz, acetone-d₆)**

δ 6.55 (d, J = 4.0 Hz, 1H), 6.04 (d, J = 3.5 Hz, 1H), 4.33 (d, J = 21 Hz, 2H), 4.11-4.07 (m, 3H), 2.85 (s, 3H), 2.74 (t, J = 9.5 Hz, 2H), 1.86-1.79 (m, 2H), 1.22 (d, J = 7.5 Hz, 3H), 1.07 (m, 21H).

**¹³C-NMR (125 MHz, acetone-d₆)**

δ 168.9, 160.3, 119.5, 105.8, 68.7, 62.2, 47.6, 38.8, 24.4, 23.7, 23.7, 18.5 (2C), 13.2.
A mixture of the MIDA boronate 3.15 (43 mg, 0.095 mmol) in THF (1 mL) and 1N NaOH (0.3 mmol, 0.3 mL) was stirred under ambient atmosphere and temperature for 30 min. The reaction was quenched with the addition of saturated aqueous NH₄Cl (1 mL). The mixture was transferred to a separatory funnel, diluting with Et₂O (2 mL). After mixing and phase separation, the aqueous phase was extracted with Et₂O (2 mL). The combined organics were washed with brine, dried over MgSO₄, filtered and transferred into 20 mL vial as a solution in Et₂O/THF (8mL). The solution was concentrated to a final volume of 3 mL under Ar. A 7 mL vial was charged with a stir bar, bromide 3.9 (23.7 mg, 0.045 mmol), G2-XPhos palladacycle (3.5 mg, 0.0045 mmol), and K₃PO₄ (57.3 mg, 0.27 mmol). The vial was evacuated and filled with Ar (×4). 1mL of the boronic acid was transferred into the reaction via syringe under Ar. The remaining 2 mL of the solution was added slowly into the reaction mixture with a syringe pump at a rate of 1.4 mL/h, with the reaction stirring at 55 °C in a heat block. After the addition, the reaction was stirred for another 12 h at the same temperature. The reaction was then cooled to RT, then filtered through celite, eluting with Et₂O. The filtrate was concentrated in vacuo to a black residue, which was purified by silica gel chromatography (35 to 45 to 50% DCM/hexanes). The pure product was obtained as a colorless oil (29.2 mg, 87%).

¹H-NMR (500 MHz, CDCl₃)
δ 7.50-7.48 (m, 2H), 7.43-7.39 (m, 4H), 7.37-7.32 (m, 3H), 7.31-7.28 (m, 1H), 6.77 (d, J = 2.5 Hz, 1H), 6.68 (d, J = 2.5 Hz, 1H), 6.37 (d, J = 3.0 Hz, 1H), 6.10 (d, J = 3.0 Hz, 1H), 5.14 (s, 2H), 5.13 (s, 2H), 4.14-4.08 (m, 3H), 3.64 (d, J = 1.5 Hz, 2H), 2.75 (t, J = 8.0 Hz, 2H), 1.92-1.80 (m, 2H), 1.24 (d, J = 6.5 Hz, 3H), 1.09-1.08 (m, 21H), 0.98-0.95 (m, 2H), 0.03 (s, 9H).

¹³C-NMR (125 MHz, CDCl₃)
δ 171.6, 160.2, 158.8, 155.8, 148.1, 138.2, 138.1, 137.1, 129.3, 129.1, 128.7, 128.5, 128.4, 128.0, 115.4, 112.0, 110.2, 106.6, 100.3, 70.9, 70.6, 68.7, 63.0, 40.9, 38.8, 24.5, 23.8, 18.6, 18.5, 17.9, 13.2, -1.5.

HRMS (ESI+)
Calculated for C₄₄H₆₃O₆Si₂: 743.4163
Found: 743.4166
In an oven-dried 3-neck 1000 mL RBF, a solution of (S)-4-benzyl-oxazolidin-2-one (25.35 g, 143.08 mmol), crotonic acid (24.81 g, 288.2 mmol), and DMAP (2.28 g, 18.67 mmol) in anhydrous CH₂Cl₂ (500 mL) was cooled to 4 °C (internal temp) under N₂ using an ice-water bath. To this was added DCC (59.12 g, 286.55 mmol), causing an exotherm (internal temperature rose to ~10 °C). After approximately 10 min, a precipitate began to form. After 18 h, TLC showed full consumption of the acid while oxazolidinone remained. Another portion of crotonic acid (6.15 g, 71.42 mmol) and DCC (14.52 g, 70.37 mmol) were added at 0 °C and the reaction was stirred and warmed to RT for a further 3 h. The reaction was filtered through a Buchner funnel, rinsing with CH₂Cl₂ (150 mL). The filtrate was then washed with sat. NaHCO₃ (200 mL), 1:1 sat. NaHCO₃/water (200 mL), and water (200 mL). The aqueous layer was then extracted with CH₂Cl₂ (200 mL). The combined organics were then dried over Na₂SO₄, filtered, and concentrated in vacuo to give a thick orange slurry. After storage overnight under nitrogen at 0 °C, the slurry was taken up in a minimum of CH₂Cl₂, loaded onto Celite, and purified by column chromatography (9 cm × 13 cm height, equilibrated with CH₂Cl₂, gradient: 100% DCM to 2.5% EtOAc/DCM to 5% EtOAc/DCM). The resulting product was still impure, so was passed through another silica gel column (9 cm x 8 cm, CH₂Cl₂) before recrystallizing from a minimum of hot EtOAc to yield 3.21 (21.37 g , 61% yield) as a waxy solid. ¹H-NMR matches literature data.³ (46) The solid was further dried by azeotroping with toluene (2 × 100mL) and drying under high vacuum (~3 h).

An oven-dried 1000 mL RBF was fitted with a stir-bar, a cryogenic thermometer, an addition funnel, and an N₂/vacuum inlet. The warm flask was then vac/N₂-filled (3 ×) before adding THF (340 mL) and iPr₂NH (13.5 mL, 96.3 mmol) and cooling to -70 °C. nBuLi (1.6 M in hexanes, 60.0 mL, 96 mmol) was then added to the addition funnel via syringe before adding to the reaction over ~25 min. After stirring at -70 °C for a further 25 min, HMPA (16.7 mL, 96.0 mmol) was added in a dropwise fashion (via the addition funnel, over ~10 min). The solution was allowed to stir at -70 °C for approximately 1 h. A separate 500 mL single neck rbf containing imide 3.21 was vac/N₂-filled (3 ×). The white solid was then taken up in THF (120 mL) with stirring. This solution was then added to the addition funnel via syringe and added to LDA solution in a slow, dropwise manner (+68 to -70 °C, over ~50 min) giving a translucent
orange solution which was stirred for a further 30 minutes at this temperature before adding neat MeI (16.5 mL, 265 mmol) in a dropwise manner (over ~35 min) at -70 °C. The yellow solution was stirred at -70 °C for 1 h and then the iPrOH/dry ice bath was replaced with an ice/brine bath, allowing it to stir for 45 min before warming to room temperature and stirring for another 30 min. The reaction was then again placed in an ice/brine bath and quenched with sat. NH₄Cl (300 mL). The mixture was then transferred to a separatory funnel, rinsing with Et₂O. After mixing and phase separation, the aqueous layer was extracted with Et₂O (3 × 250 mL). The combined organic layers were washed with brine (200 mL), dried over MgSO₄, filtered and concentrated in vacuo to give a fluorescent yellow oil. Crude ¹H NMR showed with a d.r. of 3.6:1 (desired:undesired diastereomer). The desired diastereomer was purified by splitting the crude material into two batches and running two columns on each batch (for four total columns). Gradient: 100% hexanes to 7.5% EtOAc/hexanes, in 2.5% increments. The columns gave 3.22 (9.67 g, 43% yield) as a colorless oil with a d.r. of >20:1 by ¹H NMR.

¹H-NMR (500 MHz, CDCl₃)
δ 7.36 – 7.27 (m, 3H), 7.24 – 7.19 (m, 2H), 5.98 (ddd, J = 17.2, 10.3, 7.7 Hz, 1H), 5.20 (dt, J = 17.3, 1.1 Hz, 1H), 5.14 (dt, J = 10.3, 1.0 Hz, 1H), 4.66 (ddd, J = 10.5, 7.2, 3.7 Hz, 1H), 4.46 (ddt, J = 7.8, 6.9, 5.9 Hz, 2H), 4.23 – 4.15 (m, 1H), 3.29 (dd, J = 13.4, 3.3 Hz, 1H), 2.78 (dd, J = 13.4, 9.6 Hz, 1H), 1.35 (d, J = 6.9 Hz, 3H).

A solution of imide 3.22 (9.67 g, 37.3 mmol) in Et₂O (300 mL) was cooled to ~0 °C in an ice/brine bath, stirring for ~15 minutes before adding H₂O (1.68 mL, 93.3 mmol) via syringe. With vigorous stirring, LiBH₄ (2.04 g, 93.7 mmol) was added in four portions in a slow, cautious manner (a vigorous exotherm was noted, with effervescence). After the addition was complete, the flask was fitted with a rubber septum which had already been pierced with a N₂ inlet needle and vent needle. The mixture was stirred in the ice/brine bath for 1.5 h before being warmed to room temperature and stirring for 40 min. TLC analysis (20% EtOAc/hexanes) showed no remaining starting material. The reaction mixture was cooled in an ice/water bath for ~5 min before being quenched with sat. Rochelle’s salt (70 mL, added slowly via addition funnel). The biphasic reaction mixture was vigorously stirred for 10 min before being transferred to a separatory funnel. After mixing and phase separation, the organic layer was drained into a RBF containing sat. Rochelle’s salt (150 mL) and stirred for 1 hour. The combined aqueous layers were extracted (2 × 100 mL Et₂O). The combined organic layers were then washed with brine (100 mL), dried over Na₂SO₄, filtered, and concentrated to ~35 mL (house vacuum, room temperature), at which point,
oxazolidinone side product had begun crystallizing out. To this solution was added 150 mL pentane, which caused the precipitation of more oxazolidinone. This mixture was filtered, washing the solids with ~50 mL of 30% Et₂O/pentane. The resulting cloudy filtrate was loaded directly atop a silica gel column (5 cm x 7 cm height) and eluted (gradient: 30% Et₂O/pentane to 40% Et₂O/pentane to 50% Et₂O/pentane). The product came off in ~1000 mL of eluent, which was concentrated to give a solution of the product alcohol 3.23 (1H NMR calculation: 2.36 g, 74% yield) in Et₂O/pentane, which was used directly in the next step. A small sample had the solvents fully removed to give enough pure alcohol to obtain an optical rotation which is in agreement with the known literature value. 1H-NMR matches literature data.4 [α]D24: -29.8 (c=1.42, CHCl₃).

A flask containing a concentrated solution of alcohol 3.23 (2.36 g, 27.4 mmol) in Et₂O/pentane was charged with a stir bar and CH₂Cl₂ (70 mL). The solution was then stirred in an ice/water bath and cooled for 15 min, during which DMAP (402.8 mg, 3.3 mmol) and Et₃N (11.5 mL, 82.5 mmol) were added. After cooling, pTsCl (6.28 g, 32.9 mmol) was added under ambient atmosphere, rinsing the funnel with another portion of CH₂Cl₂ (20 mL). The flask was then fitted with a rubber septum, purged with N₂ for ~5 minutes, and then allowed to stir under N₂ for 15 h, gradually warming to room temperature. TLC showed no remaining starting material (20% EtOAc/hexanes). The reaction was then quenched with water (50 mL). The biphasic mixture was stirred rapidly for 10 min before transferring to a separatory funnel. After mixing and phase separation, the aqueous layer was extracted with CH₂Cl₂ (2 x 75 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated in vacuo to ~20 mL. To this solution was added several scoops of Celite, and the solvent was removed in vacuo to give the crude product loaded on Celite. This was loaded atop a silica gel column equilibrated with 5% Et₂O/hexanes. Gradient: 5% Et₂O/hexanes to 7.5% Et₂O/hexanes to 10% Et₂O/hexanes. The fractions containing product were concentrated to give 3.24 (5.06 g, 77% yield) as a colorless oil.

TLC (10% EtOAc/hexanes)
Rf = 0.34, visualized by UV, stained by KMnO₄.

1H-NMR (500 MHz, CDCl₃)
δ 7.76 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 7.9 Hz, 2H), 5.60 (ddd, J = 17.3, 10.4, 7.0 Hz, 1H), 5.05 – 4.98 (m, 2H), 3.89 (dd, J = 9.4 and 6.4 Hz, 1H), 3.82 (dd, J = 9.4 and 6.8 Hz, 1H), 2.53 – 2.45 (m, 1H), 2.42 (s, 3H), 0.98 (d, J = 6.8 Hz, 3H).
\(^{13}\)C-NMR (125 MHz, CDCl\(_3\))
\[ \delta 144.8, 138.4, 133.0, 129.9, 127.9, 116.0, 74.0, 37.0, 21.7, 16.0. \]

HRMS (ESI+)
- Calculated for NaC\(_{12}\)H\(_{16}\)O\(_3\)S: 263.0718
- Found: 263.0716

Note: this reaction was done in duplicate, and the two vials were combined for workup. An oven-dried 40 mL vial was charged with tosylate 3.24 (1.01 g, 4.19 mmol), sealed with a septum cap, and then vac/filled with N\(_2\) (\(\times3\)). CH\(_2\)Cl\(_2\) (10.0 mL) was then added via syringe, followed by a solution of HBBr\(_2\)SMe\(_2\) (1.0 M in CH\(_2\)Cl\(_2\), 5.0 mL, 5.0 mmol) at room temperature. The vial was then placed in a 40 °C heating block and allowed to stir for 10 h. \(^1\)H NMR of an aliquot of the reaction revealed nearly complete conversion. Separately, a rbf flask containing 100 mL Et\(_2\)O and 50 mL water was cooled to 0 °C in an ice bath. The two vials containing the reaction mixtures were cannulated into this rbf in a dropwise fashion with vigorous stirring. After stirring for \(~10\) min, the biphasic mixture was transferred to a separatory funnel. After mixing and phase separation, the aqueous layer was extracted with Et\(_2\)O (2 \(\times\) 100 mL). The combined organics were washed with brine (100 mL), dried over Na\(_2\)SO\(_4\), and vacuum filtered. The solution was then concentrated to \(~15\) mL of a cloudy mixture and used directly in the next step.
To the solution of the boronic acid in a rbf was added MIDA (1.53 g, 10.4 mmol), and a PhH:DMSO mixture (10:1, 88 mL). The rbf was then fitted with a Dean-Stark trap and a water-cooled condenser. The mixture was stirred and refluxed for 1 h, after which TLC showed complete conversion. The reaction mixture was cooled to room temperature and transferred to a separatory funnel containing 1:1 brine/water (100 mL) and EtOAc (100 mL), rinsing with EtOAc. After mixing and phase separation, the aqueous layer was extracted with EtOAc (100 mL). The combined organics were then washed with 1:1 brine/water (100 mL), brine (100 mL), and then dried over Na\(_2\)SO\(_4\). After filtration, the solution was concentrated, giving a viscous oil. This oil was diluted with acetone (\(~5\) mL) before adding hexanes (100 mL) in a slow, dropwise fashion via addition funnel, causing a white powdery solid to precipitate. The white solid was collected by vacuum filtration and then dried under high vacuum to give 3.25 (2.14 g, 64% yield).
TLC (50% acetone/hexanes)

\[ R_f = 0.31, \text{ visualized by UV, stained by KMnO}_4. \]

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

\[
\begin{align*}
\delta & \quad 7.81 \,(d, J = 8.3 \text{ Hz}, 2\text{H}), \,
7.48 \,(d, J = 7.9 \text{ Hz}, 2\text{H}), \,
4.17 \,(d, J = 16.9 \text{ Hz}, 2\text{H}), \,
4.00 \,(d, J = 16.9 \text{ Hz}, 2\text{H}), \,
3.96 \,(dd, J = 9.6, 5.5 \text{ Hz}, 1\text{H}), \,
3.86 \,(dd, J = 9.5, 6.5 \text{ Hz}, 1\text{H}), \,
3.06 \,(s, 3\text{H}), \,
2.46 \,(s, 3\text{H}), \,
1.74 \,(dq, J = 12.9, 6.5 \text{ Hz}, 1\text{H}), \,
1.45 - 1.36 \,(m, 1\text{H}), \,
1.19 \,(dddd, J = 13.8, 12.3, 7.5, 4.8 \text{ Hz}, 1\text{H}), \,
0.88 \,(d, J = 6.7 \text{ Hz}, 3\text{H}), \,
0.61 \,(dt, J = 13.2, 4.8 \text{ Hz}, 1\text{H}), \,
0.51 \,(dt, J = 13.2, 4.9 \text{ Hz}, 1\text{H}).
\end{align*}
\]

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

\[
\begin{align*}
\delta & \quad 168.7, 145.7, 134.5, 130.8, 128.7, 75.8, 62.7, 46.3, 35.9, 28.0, 21.5, 16.6.
\end{align*}
\]

HRMS (ESI+)

Calculated for C$_{17}$H$_{25}$BNO$_7$S: 398.1445

Found: 398.1451

A flame-dried 40 mL vial was charged with MIDA boronate 3.25 (761.8 mg, 1.92 mmol) and NaI (444.6 mg, 2.97 mmol). Acetone (6.0 mL, HPLC grade) was added via syringe under a positive pressure of N$_2$. The reaction was then stirred for 13 h in a 60 °C heating block before TLC showed complete conversion. The reaction mixture was then poured into a separatory funnel containing EtOAc (100 mL) and water (100 mL), rinsing once with EtOAc. Upon shaking, a persistent emulsion formed. After adding brine (30 mL) and re-shaking, the aqueous layer was extracted with EtOAc (100 mL). The combined organic layers were then washed with sat. Na$_2$S$_2$O$_3$ (2 × 50 mL) and brine (100 mL), dried over Na$_2$SO$_4$, filtered and concentrated. The crude product was then taken up in a minimum of acetone and hexanes (100 mL) was added in a slow, dropwise fashion via addition funnel causing the product to precipitate out as a fine white powder. This powder was isolated via vacuum filtration and dried overnight under high vacuum to give 3.26 (550 mg, 81% yield).

TLC (50% acetone/hexanes)

\[ R_f = 0.41, \text{ visualized by UV, stained by KMnO}_4. \]

$^1$H-NMR (500 MHz, acetone-$d_6$)
δ 4.20 (d, J = 16.9 Hz, 2H), 4.04 (dd, J = 16.9 and 1.4 Hz, 2H), 3.39 (dd, J = 9.6 and 4.0 Hz, 1H), 3.29 (dd, J = 9.6 and 5.7 Hz, 1H), 3.13 (s, 3H), 1.49 - 1.39 (m, 2H), 1.38 - 1.29 (m, 1H), 1.00 (d, J = 6.2 Hz, 3H), 0.69 - 0.62 (m, 2H).

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

δ 168.8, 62.6, 46.3, 37.8, 31.6, 20.7, 18.7.

HRMS (ESI+)

Calculated for \( \text{C}_{10}\text{H}_{18}\text{BNO}_4\text{I} \): 354.0374

Found: 354.0372.

The following procedure was modified from a known literature procedure.\(^5\) An oven-dried 1L 3-neck rbf equipped with a thermometer and stir bar was added \( \text{Cp}_2\text{ZrCl}_2 \) (30.56 g, 104.5 mmol, 1.15 equiv). The flask was sealed with rubber septa and evacuated and back-filled with Ar (×3). THF (225 mL) was added via cannula. The solution was cooled to an internal temperature of 4 °C in an ice-water bath. DiBAIH solution (1 M in THF, 100 mL, 100 mmol, 1.1 equiv) was cannulated into the rbf, keeping the internal temperature at 3-4 °C. The addition took 23 min. The reaction was then stirred at 3 °C for 30 min. Phenyltrimethylsilylethylene (16.1 mL, 91.1 mmol, 1.0 equiv) was added neat via syringe at the same temperature over 10 min. The reaction was then allowed to warm to 18 °C over 3 h. The reaction was then cooled to -69 °C (internal temperature) in a dry ice/IPA bath. Under air, solid \( \text{I}_2 \) (30.0 g, 118.18 mmol, 1.3 equiv) was added to a graduated conical flask containing THF (150 mL). The flask was sealed with a rubber septum and stirred to dissolve the \( \text{I}_2 \). The solution was then cannulated into the reaction flask under Ar, maintain the internal temperature at ≤ -65 °C. The addition took 1 h 15 min. After the addition was complete, the reaction was stirred at −70 °C for 1.5 h. The dry ice bath was removed and the reaction quenched with 1N HCl (200 mL). The mixture was stirred vigorously, then transferred to a 2L separatory funnel and extracted with Et\(_2\)O (100 mL). The aqueous layer was extracted with Et\(_2\)O (100 mL). The combined organics were washed with sat. aq. \( \text{Na}_2\text{S}_2\text{O}_3 \) (200 mL), brine, dried over MgSO\(_4\), filtered and concentrated \textit{in vacuo}. During solvent removal, a large amount of solids precipitated. To the concentrated residue was added hexanes (150 mL). The suspension was filtered to remove the orange solids, rinsing with hexanes (100 mL). The filtrate was concentrated to a yellow oil. The product was
purified by a total of 3 SiO<sub>2</sub> columns (hexanes) to the pure product as a colorless oil 3.20 (15.66 g, 60% yield).

TLC (hexanes)

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

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

\[ \delta 7.52-7.51 \text{ (m, 2H), 7.41-7.38 (m, 3H), 7.20 (d, J = 16.5 Hz, 1H), 6.75 (d, J = 16.0 Hz, 1H), 0.38 (s, 3H)}. \]

\(^{13}\)C-NMR (125 MHz, CDCl<sub>3</sub>)

\[ \delta 148.3, 136.5, 133.7, 129.5, 128.0, 91.5, -2.9. \]

Formation of the organozinc reagent: Iodide 3.26 (1.36 g, 3.85 mmol) was weighed into an oven-dried 40 mL vial. This and another empty vial were taken into the glove box. THF (4.5 mL) and DMF (1.5 mL) were added to dissolve the iodide. The other vial was charged with Zn dust (754.6 mg, 11.54 mmol) and a magnetic stir bar before sealing both vials and removing from the glove box. Under a positive pressure of N<sub>2</sub>, TMSCl and 1,2-dibromoethane were added to the vial containing the Zn dust (three drops each from a 25 gauge needle). This was stirred briefly before transferring the iodide 3.26 solution to this vial via syringe. The vial was then rinsed with another portion of THF (1.4 mL). The vial was placed into a 45 °C heating block for 2 h. At this point, a small aliquot was removed, quenched with sat. NH₄Cl, and extracted with EtOAc. \(^1\)H NMR of the extract showed full conversion. The reaction vial was then taken into the glove box and filtered through an HPLC iso-disc syringe-tip filter into a dry 40 mL vial. This colorless solution was stored in the glove box for approximately 36 h before use in the next step.

In the glovebox, (E)-(2-iodovinyl)dimethyl(phenyl)silane 3.20 (1.12 g, 3.90 mmol) was weighed into the 40 mL vial, followed by the addition of THF (8.6 mL) and DMF (2.1 mL). RuPhos (182 mg, 0.390 mmol) and Pd<sub>2</sub>(dba)<sub>3</sub> (90.1 mg, 0.0984 mmol) were then added to the solution in that order. The vial was then sealed and removed from the glove box, along with the vial containing the solution of alkylzinc prepared above. The vial containing the catalyst was placed into a 60 °C heating block and had a N<sub>2</sub> inlet needle inserted into the septum. The alkylzinc solution was then slowly added to this vial with the assistance of a syringe pump (~75 min). The reaction stirred for a total of 8 h (from the beginning of the addition). The
reaction was then cooled to room temperature and transferred to a separatory funnel containing sat. NH₄Cl (80 mL) and EtOAc (60 mL). The vial was rinsed with a further 20 mL EtOAc. After shaking, a persistent emulsion formed which was resolved by adding a small amount (~5 mL) of brine and remixing. After phase separation, the aqueous layer was extracted with EtOAc (80 mL). The combined organic layers were then washed with 1:1 water:brine (100 mL) and brine (100 mL). The organic layers were then stirred over MgSO₄ and Darco before filtering through Celite. ¹H NMR of the crude mixture showed product to be the primary component. The crude mixture was dry loaded onto Celite and then purified by column chromatography (silica gel, equilibrated with 20% acetone/hexanes, gradient: 20% to 25% to 30% acetone/hexanes) to give 3.27 (1.003 g, 67% yield) as a slightly off-white foam.

TLC (50% acetone/hexanes)

\[ R_f = 0.53, \text{ visualized by UV, stained by KMnO}_4. \]

¹H-NMR (500 MHz, acetone-d₆)

\[ \delta 7.56 - 7.52 (m, 2H), 7.38 - 7.33 (m, 3H), 6.15 (dt, J = 18.5, 6.8 Hz, 1H), 5.79 (dt, J = 18.5, 1.4 Hz, 1H), 4.17 (d, J = 16.9 Hz, 2H), 4.00 (dd, J = 16.8, 3.7 Hz, 2H), 3.07 (s, 3H), 2.25 (dddd, J = 13.5, 6.6, 5.3, and 1.6 Hz, 1H), 2.03 - 1.95 (m, 1H), 1.56 - 1.48 (m, 1H), 1.46 - 1.37 (m, 1H), 1.23 (dddd, J = 13.6, 12.2, 7.3, 4.8 Hz, 1H), 0.89 (d, J = 6.7 Hz, 3H), 0.72 - 0.56 (m, 1H), 0.31 (s, 6H). \]

¹³C-NMR (125 MHz, acetone-d₆)

\[ \delta 168.8, 149.2, 139.9, 134.6, 129.7, 129.6, 128.6, 62.7, 46.3, 45.0, 36.0, 31.8, 19.7, -2.2. \]

HRMS (ESI+)

Calculated for C₂₀H₃₁NO₄SiB: 388.2115
Found: 388.2112

A vial containing vinyl silane 3.27 (176.9 mg, 0.46 mmol) was charged with a stir bar and HFIPA (2.0 mL). The mixture was then sonicated briefly to give a homogenous solution. The vial was then cooled to 0 °C in an ice-water bath before adding 2,6-lutidine (40 μL, 0.34 mmol) under ambient atmosphere. NIS (156.4 mg, 0.70 mmol) was then added in three portions over about 2 min, yielding a purple/red mixture. The mixture was then stirred in the ice-water bath for 70 min before TLC showed complete conversion.
Sat. Na$_2$S$_2$O$_3$ (5 mL) was added at 0 °C and the mixture was stirred for 10 min, after which a faint yellow color remained. The reaction mixture was transferred to a separatory funnel containing EtOAc (10 mL) and sat. Na$_2$S$_2$O$_3$ (10 mL). After shaking and phase separation, the aqueous layer was extracted with EtOAc (15 mL). The combined organic layers were washed with brine (20 mL), dried over Na$_2$SO$_4$, and treated with Darco before filtering. This solution was concentrated to give a colorless sticky residue. This residue was taken up into a minimum of acetone (~1 mL) and 50 mL of hexanes was dripped into this solution with vigorous stirring in a slow, dropwise manner via addition funnel, precipitating an off-white powder. This off-white powder was isolated via vacuum filtration and dried under high vacuum to give 3.18 (104.1 mg, 60% yield).

TLC (50% acetone/hexanes)

R$_f$ = 0.50, visualized by UV, stained by KMnO$_4$.

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

δ 6.54 (dt, $J$ = 14.9 and 7.6 Hz, 1H), 6.14 (d, $J$ = 14.3 Hz, 1H), 4.17 (d, $J$ = 16.9 Hz, 2H), 4.01 (dd, $J$ = 16.9 and 1.7 Hz, 2H), 3.10 (s, 3H), 2.80 (d, $J$ = 16.9 Hz, 3H), 2.18 – 2.11 (m, 1H), 1.96 – 1.89 (m, 1H), 1.56 – 1.46 (m, 1H), 1.44 – 1.34 (m, 1H), 1.26 – 1.17 (m, 1H), 0.88 (d, $J$ = 6.7 Hz, 3H), 0.71 – 0.55 (m, 2H).

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

δ 168.8, 146.7, 75.7, 62.6, 46.2, 43.5, 35.7, 31.5, 19.4.

HRMS (ESI+)

Calculated for C$_{12}$H$_{20}$BNO$_4$I: 380.0530

Found: 380.0527

In an unoptimized procedure, to a solution of tert-butylmethacrylate (5 mL, 30.77 mmol, 1.0 equiv) in CCl$_4$ (100 mL) was added neat bromine (1.6 mL, 31.38 mmol, 1.02 equiv) slowly over 1 min under ambient atm. The rbf was sealed with a rubber septum and the reaction stirred under an N$_2$ atm, warming to RT overnight. The reaction was stirred for 17.5 h, then 1M Na$_2$S$_2$O$_3$ (50 mL) was added to quench the reaction. The mixture was stirred vigorously until the organic layer turns from red-orange to colorless.
The layers were separated and the aqueous phase extracted with CH$_2$Cl$_2$ (50 mL × 2). The combined organics were washed with brine, dried over MgSO$_4$, filtered and concentrated to give a colorless liquid, which was a mixture of the dibromide and the starting material in a ratio of 8.5:1. This material was dissolved in THF and cooled to 0 °C. DBU was added neat via syringe under ambient atm over 3 min. The reaction was stirred for 17 h. H$_2$O (100 mL) and Et$_2$O (100 mL) was added and the mixture stirred vigorously. The layers were separated and the aqueous layer extracted with Et$_2$O (50 mL). The combined organics were washed with brine, dried over MgSO$_4$, filtered and concentrated in vacuo to give an orange liquid which was a mixture of the desired vinyl bromide and the dibromide in the ratio 12:1. This material was resubjected to the reaction using DBU (0.9 mL, 6 mmol) and THF (100 mL) to consume the remaining dibromide. The reaction was subjected to the same work-up procedure described above and purified by SiO$_2$ column chromatography, giving the pure product 3.19 as a colorless liquid (4.09 g, 60% yield over 2 steps). $^1$H-NMR matches literature data.

A mixture of the MIDA boronate 3.28 (1.00 g, 2.71 mmol) in THF (27 mL) and 1N NaOH (8.2 mmol, 8.2 mL) was stirred under ambient atmosphere and temperature for 20 min. The reaction was quenched with the addition of saturated aqueous NH$_4$Cl (25 mL). After briefly stirring, the mixture was transferred to a separatory funnel, rinsing with Et$_2$O (10 mL). After mixing and phase separation, the aqueous phase was extracted with Et$_2$O (2 × 25 mL). The combined organics were washed with brine, dried over MgSO$_4$, filtered and concentrated in vacuo. The residue was taken up in Et$_2$O (5 mL), causing some white solid to precipitate. The some suspension was filtered through celite, eluting with Et$_2$O (10 mL). The filtrate was collected in a 40 mL vial. The solution was concentrated in vacuo to give a white foamy solid which was used in the coupling reaction.

A flame-dried 40 mL vial was charged with iodide rac-3.18 (303 mg, 0.8 mmol), Pd(OAc)$_2$ (9.0 mg, 0.04 mmol), and Ag$_2$O (556 mg, 2.4 mmol). The vial was taken into the glovebox. K$_2$CO$_3$ (663 mg, 4.8 mmol) and dppf (42 mg, 0.076 mmol) were added. The boronic acid in the 40 mL was dissolved in THF (16.9 mL). 5 mL of this soltion was added to the reaction vial. The vials were sealed with septum caps and removed from the glovebox, then placed under N$_2$. The reaction vial was stirred at 45 °C in a heating block. A 10 mL syringe was charged with 10mL of the boronic acid solution. The solution was then slowly added to the reaction vial with the aid of a syringe pump over 2.5 h. The reaction was stirred for a total of 12.5 h. The reaction was cooled to RT, then filtered through celite, rinsing with EtOAc. The crude product was purified by SiO$_2$ column chromatography.
product was adsorbed onto celite in vacuo. The celite pad was loaded onto a silica gel column equilibrated with 20% acetone/hexanes. A white solid 3.29 (176 mg, 47%) was obtained after column purification (20 to 30 to 40% acetone/hexanes).

$^1$H-NMR (500 MHz, acetone-d$_6$)  
$\delta$ 6.31-6.26 (m, 1H), 6.11-6.06 (m, 1H), 5.71-5.62 (m, 2H), 4.31 (app d, $J = 5$ Hz, 2H), 4.17 (d, $J = 16.5$ Hz, 2H), 4.01 (d, $J = 16.5$ Hz, 1H), 4.01 (d, $J = 16.5$ Hz, 1H), 3.09 (s, 3H), 2.18-2.13 (m, 1H), 1.91 (quint, $J = 7.5$ Hz, 1H), 1.51-1.38 (m, 2H), 1.10-1.07 (m, 21H), 0.86 (d, $J = 6.5$ Hz, 3H), 0.71-0.57 (m, 2H).

$^{13}$C-NMR (125 MHz, acetone-d$_6$)  
$\delta$ 168.7, 133.5, 131.9, 131.2, 130.6, 128.4, 64.3, 62.6, 46.2, 40.5, 36.5, 31.8, 19.6, 18.3, 12.7

HRMS (ESI+):  
Calculated for C$_{24}$H$_{43}$NO$_5$SiB:  464.3004  
Found:  464.3007

A mixture of the MIDA boronate 3.29 (33.1 mg, 0.071 mmol) in THF (0.71 mL) and 1N NaOH (0.22 mmol, 0.22 mL) was stirred under ambient atmosphere and temperature for 20 min. The reaction was quenched with the addition of saturated aqueous NH$_4$Cl (1 mL). After briefly stirring, the mixture was transferred to a separatory funnel, rinsing with Et$_2$O (2 mL). After mixing and phase separation, the aqueous phase was extracted with Et$_2$O (2 × 2 mL). The combined organics were washed with brine, dried over MgSO$_4$, filtered and concentrated in vacuo to give the boronic acid which was used directly for the coupling.

TLC (40% CH$_2$Cl$_2$/hexanes)  
$R_f$ = 0.25, visualized by UV, stained by KMnO$_4$.

$^1$H-NMR (500 MHz, CDCl$_3$)
δ 6.64 (dt, J = 7.5, 1.5 Hz, 1H), 6.32-6.27 (m, 1H), 6.13-6.08 (m, 1H), 5.72-5.64 (m, 2H), 4.31 (app d, J = 4.5 Hz, 2H), 2.25-2.10 (m, 3H), 2.01-1.95 (m, 1H), 1.76 (d, J = 1.5 Hz, 3H), 1.57 (sextet, J = 6.5 Hz, 1H), 1.50-1.43 (m, 10 H), 1.30-1.24 (m, 1H), 1.14-1.06 (m, 21H), 0.92 (d, J = 7.0 Hz, 3H).

13C-NMR (125 MHz, CDCl3)
δ 167.6, 141.2, 132.3, 131.2, 130.5, 129.7, 129.0, 79.9, 63.7, 40.0, 35.2, 33.0, 28.1, 26.3, 19.4, 18.0, 12.3, 12.0.

HRMS (ESI+)
Calculated for C27H50O3SiNa: 473.3427
Found: 473.3430

To a solution of 3-bromopropylboronic acid pinacol ester (1.00 g, 4.02 mmol, 1.0 equiv) in a solution of THF (4 mL) and H2O (3 mL) was added solid NaIO4 (4.30 g, 20.08 mmol, 5.0 equiv) at 0 °C under ambient atm. 1N HCl (8.1 mL, 8.1 mmol, 2.01 equiv) was then added slowly over 3 min. The reaction was stirred in the ice-water bath for 3 h, then transferred to a separatory funnel and diluted with H2O (25 mL) and EtOAc (25 mL). After mixing and phase separation, the aqueous layer was extracted with EtOAc (25 mL × 2). The combined organics were washed with sat. aq. Na2S2O3 (25 mL), brine, dried over MgSO4, filtered and concentrated to 5 mL. Benzene (25 mL) was added and the solution was concentrated to 20 mL. Another portion of benzene (25 mL) was added, followed by DMSO and MIDA (591 mg, 4.02 mmol, 1.0 equiv). The mixture was heated to reflux with a Dean-Stark trap and a water-cooled condenser for 1 h. The reaction was then transferred to a separatory funnel containing H2O (50 mL) and EtOAc (50 mL). After mixing and phase separation, the aq. layer was extracted with EtOAc (25 mL × 2). The combined organics were washed with H2O, brine, dried over MgSO4, filtered and concentrated to give a white solid. The solid was washed with EtOAc, filtered and dried in vacuo to give the pure product 3.38 (781 mg, 67% yield).

1H-NMR (500 MHz, acetone-d6)
δ 4.21 (d, J = 17.0 Hz, 2H), 4.06 (d, J = 17.0 Hz, 2H), 3.51 (t, J = 7.0 Hz, 2H), 3.12 (s, 3H), 1.95 – 1.87 (m, 2H), 0.80 – 0.73 (m, 2H).

13C-NMR (125 MHz, acetone-d6)
δ 168.7, 62.7; 46.3, 37.7, 29.1.

HRMS (ESI+)

- Calculated for C₈H₁₄NO₄BrB: 278.0199
- Found: 278.0195

MIDA boronate 3.38 (825 mg, 2.97 mmol, 1.0 equiv) and NaI (1.56 g, 10.39 mmol, 3.5 equiv) were added into a 40 mL Ichem vial equipped with a stir bar. Under ambient atm, acetone (20 mL) was added. The vial was sealed with a PTFE-lined cap and stirred at 60 °C for 4 h. This reaction was carried out in quadruplicate. The reactions were cooled to RT, then combined and filtered through celite, rinsing with EtOAc. The filtrate was concentrated in vacuo to give a yellow viscous liquid. EtOAc (100 mL) was added and the solution transferred to a separatory funnel containing H₂O (100 mL), rinsing with EtOAc (100 mL). After mixing and phase separation, the aqueous layer was extracted with EtOAc (60 mL × 2). The combined organics were washed with sat. aq. Na₂S₂O₃ (50 mL × 2). The organic phase was washed with brine, dried over MgSO₄, filtered and concentrated to give a white solid. To the white solid was added acetone (approx. 3 mL), Et₂O (25 mL) and hexanes (50 mL) sequentially. The mixture was stirred for 5 min, then vacuum filtered. The product 3.39 (3.68 g, 95% yield) was obtained as a white solid after drying in vacuo.

¹H-NMR (500 MHz, acetone-d₆)

δ 4.21 (d, J = 17.0 Hz, 2H), 4.05 (d, J = 17.0 Hz, 2H), 3.31 (t, J = 7.0 Hz, 2H), 3.12 (s, 3H), 1.94 – 1.85 (m, 2H), 0.79 – 0.71 (m, 2H).

¹³C-NMR (125 MHz, acetone-d₆)

δ 168.7, 62.6, 46.3, 30.0, 11.6.

HRMS (ESI+)

- Calculated for C₈H₁₄NO₄IB: 326.0061
- Found: 326.0061
A flame-dried 20 mL vial equipped with a stir bar was charged with Zn dust (588 mg, 9 mmol, 3.0 equiv). A separate flame-dried 7 mL vial equipped with a stir bar was charged with MIDA boronate 3.39 (975 mg, 3.0 mmol, 1.0 equiv). DMF (2 mL) and THF (3.5 mL) were added to dissolve 3.39. Under Ar, 3 drops of TMSCl followed by 3 drops of 1,2-dibromoethane were added sequentially to the vial containing Zn dust from a syringe with a 25 gauge needle. With stirring, the solution containing 3.39 was transferred to this vial via syringe, rinsing with THF (0.5 mL). The reaction was stirred at 45 °C for 1.5 h. The vial was taken into the glovebox and stored at RT overnight. In the glovebox, a flame-dried 40 mL vial was charged with vinyl iodide 3.20 (1.32 g, 4.13 mmol, 1.5 equiv), RuPhos (128 mg, 0.275 mmol, 0.1 equiv) and Pd$_2$dba$_3$ (63 mg, 0.069 mmol, 0.025 equiv), followed by DMF (7 mL). The organozinc solution (5.5 mL) was added, followed by THF (14 mL). The vial was sealed with a PTFE-lined cap, removed from the glovebox and stirred at 60 °C for 7 h. The reaction was cooled to rt and quenched with sat. aq. NH$_4$Cl (25 mL). The aqueous layer was extracted with EtOAc (25 mL × 2). The combined organics were washed with H$_2$O, brine, dried over MgSO$_4$, filtered and concentrated in vacuo. The crude product was purified by SiO$_2$ column chromatography (20-30-35% acetone/hexanes). The pure fractions containing product were concentrated in vacuo and the resulting solid triturated with acetone/hexanes to give a white solid. The supernatant was combined with mixed fractions from the column and re-subjected to SiO$_2$ column purification. The solids obtained were combined to give the pure product 3.41 (588 mg, 60% yield).

TLC (50% acetone/hexanes)

$R_f = 0.58$, visualized by shortwave UV.

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

$\delta$ 7.56 – 7.51 (m, 2H), 7.37 – 7.30 (m, 3H), 6.18 (dt, $J = 18.5$, 6.5 Hz, 1H), 5.79 (dt, $J = 18.5$, 1.5 Hz, 1H), 4.17 (dt, $J = 17.0$ Hz, 2H), 4.00 (d, $J = 16.9$ Hz, 2H), 3.07 (s, 3H), 2.25 – 2.16 (m, 2H), 1.53 – 1.45 (m, 2H), 0.68 – 0.63 (m, 2H), 0.30 (s, 6H).

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

$\delta$ 168.8, 150.3, 139.9, 134.5, 129.6, 128.5, 128.0, 62.6, 46.2, 40.7, 24.2, -2.3.

HRMS (ESI+)

Calculated for C$_{18}$H$_{27}$BNO$_4$Si: 360.1802

125
A flame-dried 10 mL Schlenk flask equipped with a stir bar was charged with vinyl silane 3.41 (500 mg, 1.39 mmol, 1.0 equiv). HFIPA (5.6 mL) was added via syringe. The solution was cooled in an ice-brine bath. 2,6-lutidine (0.115 mL, 0.97 mmol, 0.7 equiv) was added. After 10 min, N-iodosuccinimide (470 mg, 2.09 mmol, 1.5 equiv) was added as a solid in one portion. The reaction was stirred at the same temperature for 1 h, then quenched with sat. aq. Na$_2$S$_2$O$_3$ (5 mL). The mixture was stirred vigorously for 5 min, then partitioned between EtOAc (20 mL) and H$_2$O (10 mL). The aqueous layer was extracted with EtOAc (20 mL). The combined organics were washed with sat. aq. Na$_2$S$_2$O$_3$ (20 mL), brine (× 2), dried over MgSO$_4$, filtered and concentrated in vacuo. The residue was azeotroped once with CH$_2$Cl$_2$. Et$_2$O (30 mL) was added to the crude product and the mixture stirred for 5 min. The suspension was filtered and the solid rinsed with Et$_2$O (10 mL × 2), giving the pure product 3.35 as a white solid (372 mg, 76% yield).

TLC (50% acetone/hexanes)
\[ R_f = 0.44, \text{ visualized by KMnO}_4 \text{ stain.} \]

$^1$H-NMR (500 MHz, acetone-$d_6$)
\[ \delta 6.57 \text{ (dt, } J = 14.5, 7.0 \text{ Hz, 1H}), 6.13 \text{ (dt, } J = 14.5, 1.5 \text{ Hz, 1H}), 4.18 \text{ (d, } J = 17.0 \text{ Hz, 2H}), 4.02 \text{ (d, } J = 17.0 \text{ Hz, 2H}), 3.09 \text{ (s, 3H)}, 2.12 \text{ (dq, } J = 7.3, 1.5 \text{ Hz, 2H}), 1.53 - 1.43 \text{ (m, 2H)}, 0.68 - 0.61 \text{ (m, 2H).} \]

$^{13}$C-NMR (125 MHz, acetone-$d_6$)
\[ \delta 168.8, 147.9, 75.1, 62.6, 46.2, 39.5, 24.0 \]

HRMS (ESI+)
\[ \text{Calculated for C}_{10}H_{18}BNO}_4I: \quad 352.0217 \]
\[ \text{Found:} \quad 352.0229 \]

A dry 500 mL Schlenk flask equipped with a stir bar was charged with Cp$_2$Zr$_2$Cl$_2$ (14.86 g, 50.83 mmol, 1.0 equiv) under Ar. The flask was sealed with a rubber septum. THF (120 mL) was cannulated into the flask. The cloudy suspension was cooled to 0 °C. DiBAI-H solution (1M in THF, 50 mL, 50 mmol, 1.1
equiv) was added into the reaction over 25 min with the aid of a syringe pump. The reaction mixture was stirred at 0 °C for 45 min. Propargyl alcohol (2.7 mL, 46.21 mmol, 1.0 equiv) was added neat dropwise into the reaction flask over 15 min. After the addition, the cold bath was removed and the reaction stirred at RT for 1.5 h, then cooled to -78 °C. Iodine (15.25 g, 60.07 g, 1.3 equiv) was added to a 100 mL single neck rbf. THF (24 mL) was added via syringe under Ar. The mixture was stirred to dissolve the solids. The solution was then cannulated into the reaction flask over 30 min, rinsing with THF (5 mL). The reaction was then stirred for 45 min at -78 °C. The cold bath was removed and the reaction quenched with the addition of 1N HCl (100 mL). The mixture was transferred to a separatory funnel, rinsing with H₂O (50 mL) and Et₂O (50 mL). After mixing, brine (50 mL) was added to aid separation. The aqueous phase was extracted with Et₂O (100 mL × 2). The combined organics were washed with sat. aq. Na₂S₂O₃ (100 mL, then 50 mL). The organics were washed with sat. aq. NaHCO₃, brine, dried over MgSO₄, filtered through celite and concentrated to 50 mL. Celite was added and the crude product adsorbed onto celite in vacuo for SiO₂ column purification. The fractions containing 3.42 were concentrated to a small volume (~5 mL) and transferred into a 40 mL vial, rinsing with CH₂Cl₂. The solution (0.95 g, 11% yield based on NMR) was used for the next reaction. ¹H-NMR matches literature data.

To the allylic alcohol 3.42 (0.95g, 5.14 mmol, 1.0 equiv) in CH₂Cl₂ (20 mL) was added MnO₂ (activated, 8.94 g, 102.8 mmol, 20 equiv) in one portion under ambient atmosphere and temperature. The reaction was stirred for 1.5 h, then another portion of MnO₂ (2.23 g, 25.6 mmol, 5 equiv) was added and the reaction stirred for another 15 min. The reaction was filtered through celite, rinsing with additional CH₂Cl₂ (10 mL). To the filtrate was added neopentyl glycol (1.62 g, 15.6 mmol, 3.0 equiv ), followed by MgSO₄ (3.02 g) and pTsOH.H₂O (25.6 mg, 0.135 mmol, 0.026 equiv). The reaction was stirred at 35 °C for 1.5 h, then cooled to rt. After filtering to remove MgSO₄, the filtrate was concentrated in vacuo. The crude product was purified by SiO₂ column chromatography to give 3.36 (505 mg, 37% yield over 2 steps) as a colorless liquid. TLC (20% EtOAc in Hexanes): Rf = 0.71, visualized with UV, stained with KMnO₄; ¹H-NMR (500 MHz, CDCl₃): δ 6.69 (dd, J = 14.5, 1.0 Hz, 1H), 6.60 (dd, J = 15.0, 4.0 Hz, 1H), 4.80 (dd, J = 4.0, 1.0 Hz, 1H), 3.64 (dd, J = 10.0, 1.5 Hz, 1H), 3.48 (d, J = 10.5 Hz, 1H), 1.19 (s, 3H), 0.74 (s, 3H); ¹³C-NMR (125 MHz, CDCl₃): δ 142.0, 100.6, 82.5, 77.2, 30.2, 22.9, 21.8; HRMS (EI+) calculated for C₈H₁₃O₂I [M]+ m/z 267.9960, found 267.9972.
A mixture of the MIDA boronate 3.34 (2.09 g, 8.07 mmol) in THF (70 mL) and 1N NaOH (24.2 mmol, 24.2 mL) was stirred under ambient atmosphere and temperature for 20 min. The reaction was quenched with the addition of saturated aqueous NH₄Cl (70 mL). After briefly stirring, the mixture was transferred to a separatory funnel, rinsing with Et₂O (20 mL). After mixing and phase separation, the aqueous phase was extracted with Et₂O (2 × 50 mL). The combined organics were washed with brine, dried over MgSO₄, filtered and concentrated in vacuo to give a white solid that was used in the coupling reaction.

A flame-dried 40 mL vial was charged with iodide 3.35 (198 mg, 0.566 mmol), boronic acid (167 mg, 1.13 mmol), Pd(OAc)₂ (6.4 mg, 0.0283 mmol), and Ag₂O (262 mg, 1.13 mmol). Inside the glovebox, P(o-tol)₃ (34.5 mg, 0.113 mmol), K₂CO₃ (469 mg, 3.40 mmol) and THF (10 mL). The vial was sealed, brought out of glovebox, and stirred at 55 °C in a heating block for 12 h. The reaction was cooled to RT, then filtered through celite, rinsing with EtOAc. The filtrate was concentrated in vacuo to give a yellow residue, which was taken up in DCM/acetone and adsorbed onto celite in vacuo. The celite pad was loaded onto a silica gel column equilibrated at 30% acetone/hexanes. The non-polar impurities were eluted with 30% acetone/hexanes. The product was then eluted with 50% acetone/hexanes. The product 3.43 was obtained as a white solid (121 mg, 65%).

**1H-NMR (500 MHz, acetone-d₆)**

δ 7.43 (app d, J = 7.5 Hz, 2H), 7.32-7.29 (m, 2H), 7.21-7.18 (m, 1H), 6.86 (dd, J = 15.5, 10.5 Hz, 1H), 6.48 (d, J = 15.5 Hz, 1H), 6.24 (dd, J = 15.0, 10.5 Hz, 1H), 5.89 (dt, J = 15.0 Hz, 7.5 Hz, 1H), 4.18 (d, J = 17 Hz, 2H), 4.02 (d, J = 17 Hz, 2H), 3.09 (s, 3H), 2.19 (app q, J = 7 Hz, 2H), 1.54-1.48 (m, 2H), 0.69-0.66 (m, 2H).

**13C-NMR (125 MHz, acetone-d₆)**

δ 168.8, 138.6, 136.8, 131.6, 130.6, 130.4, 129.4, 127.9, 126.9, 62.6, 46.2, 36.6, 24.9.

**HRMS (ESI+)**

Calculated for C₁₈H₂₃O₄BN: 328.1720

Found: 328.1719

A mixture of the MIDA boronate 3.43 (73 mg, 0.22 mmol) in THF (2.2 mL) and 1N NaOH (0.67 mmol, 0.67 mL) was stirred under ambient atmosphere and temperature for 20 min. The reaction was quenched with the addition of saturated aqueous NH₄Cl (2.2 mL). After briefly stirring, the mixture was transferred
to a separatory funnel, rinsing with Et$_2$O (10 mL). After mixing and phase separation, the aqueous phase was extracted with 1:2 THF:Et$_2$O (2 × 5 mL). The combined organics were washed with brine, dried over MgSO$_4$, filtered and concentrated in vacuo in a 7 mL vial. The boronic acid was used directly in the coupling reaction.

To the vial containing boronic acid was added Ag$_2$O (51.7 mg, 0.223 mmol) and a stir bar. Inside the glovebox, K$_2$CO$_3$ (93.9 mg, 0.68 mmol) and Pd[P(o-tol)$_3$]$_2$ (20.0 mg, 0.028 mmol) into the vial. A solution of the iodide 3.36 (31 mg, 0.117 mmol) in THF (2.0 mL) and THF (0.2 mL) was then added. The vial was sealed with a Teflon-lined cap, brought out of the glovebox, stirred at 55 °C in a heating block for 14.5 h. The reaction was cooled to RT, and filtered through celite, rinsing with Et$_2$O. The filtrate was concentrated in vacuo at RT. The crude product was purified on a silica gel column (2 to 5 to 10% Et$_2$O/pentane) and then re-purified with a silica gel column (5% Et$_2$O/pentane). A colorless oil was obtained as the pure product 3.44.

TLC (80% CH$_2$Cl$_2$/hexanes)

$R_f = 0.35$, visualized by UV, stained by KMnO$_4$.

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

\[
\delta 7.37 \text{ (app d, } J = 8 \text{ Hz, } 2H), 7.30 \text{ (app t, } J = 7.5 \text{ Hz, } 2H), 7.19 \text{ (t, } J = 7.0 \text{ Hz, } 1H), 6.74 \text{ (dd, } J = 15.5, 10.5 \text{ Hz, } 1H), 6.44 \text{ (d, } J = 16 \text{ Hz, } 1H), 6.21 \text{ (dd, } J = 15, 10.5 \text{ Hz, } 1H), 5.93 \text{ (dt, } J = 15.5, 7.0 \text{ Hz, } 1H), 5.80 \text{ (dt, } J = 15.5, 7.0 \text{ Hz, } 1H), 5.59 \text{ (ddt, } J = 16.0, 5.5, 1.0 \text{ Hz, } 1H), 4.85 \text{ (d, } J = 5.0 \text{ Hz, } 1H), 3.65 \text{ (d, } J = 11.5 \text{ Hz, } 2H), 3.50 \text{ (d, } J = 10.5 \text{ Hz, } 2H), 2.17 \text{ (q, } J = 7.0 \text{ Hz, } 2H), 2.12 \text{ (q, } J = 7.0 \text{ Hz, } 2H), 1.55 \text{ (quint, } J = 7.5 \text{ Hz, } 2H), 1.22 \text{ (s, } 3H), 0.74 \text{ (s, } 3H).
\]

$^1$C-NMR (125 MHz, CDCl$_3$)

\[
\]

HRMS (ESI+)

Calculated for C$_{21}$H$_{29}$O$_2^-$: 313.2168

Found: 313.2156
A 100 mL flask was charged with potassium tert-butoxide (5.30 g, 47.2 mmol, 1.2 eq.), fitted with a septum, and vac-filled with nitrogen before adding THF (55 mL). The mixture was cooled to 0 °C and methyl P,P-bis(2,2,2-trifluoroethyl)phosphonoacetate (8.3 mL, 39.3 mmol, 1.0 eq.) was added dropwise over 10 min, giving a clear orange mixture. After 40 min of stirring at 0°C, methyl iodide (12.2 mL, 197 mmol, 5.0 eq.) was added dropwise over 15 min at 0 °C, giving a cloudy orange/white mixture. The reaction was gradually warmed to room temperature and allowed to stir overnight. After 22 h, the reaction mixture was cooled to 0 °C, quenched with saturated NH₄Cl (25 mL), and transferred to a separatory funnel with water (25 mL) and ethyl acetate (25 mL). After mixing and phase separation, the aqueous layer was extracted with ethyl acetate (3 x 50 mL EtOAc). Combined organic layers were dried over Na₂SO₄, filtered, and concentrated to yield a red oil that contained a mixture of starting material, product, and bismethylated byproduct. The crude material was purified by column chromatography (9 cm diameter column, 1L of SiO₂, 4:1 hexanes/EtOAc) to afford 3.52-2 as a pure colorless oil (5.32 g, 41% yield). ¹H-NMR identical to literature.⁷

A dry 1 L two neck round bottom flask was charged with 18-crown-6 (30.34 g, 115 mmol, 5.0 equiv.), fitted with a thermometer, sealed with a septum, and vac-filled with N₂. THF (450 mL) was added, and the resulting clear, colorless solution was cooled to -78 °C. Phosphonoacetate 3.52-2 (7.31 g, 22.0 mmol, 1.0 equiv.) was added, using THF (25 mL) for quantitative transfer. KHMDS (1 M in THF, 22 mL, 1.0 equiv.) was added dropwise to the reaction flask over 10 min, accompanied by a color change to light orange / pink. The resulting solution was stirred at -78 °C for 30 min before adding aldehyde 3.52-1 (4.28 g, 22.0 mmol, 1.0 equiv.), using 25 mL THF for quantitative transfer. The resulting reaction
mixture was stirred at -78 °C for 2 h 20 min. The reaction was quenched with saturated aqueous NH₄Cl (100 mL). The resulting biphasic mixture was transferred to a 1 L separatory funnel using 100 mL H₂O and 300 mL Et₂O. After mixing and phase separation, the aqueous layer was extracted with diethyl ether (2 × 200 mL Et₂O). The combined organic layers were washed with brine (300 mL), dried over Na₂SO₄, and concentrated in vacuo to afford a crude mixture. The same reaction was repeated (23 mmol scale) and crude products were combined for chromatographic purification (10:1 to 8:1 hexanes/EtOAc) to give 3.52-3 as a clear, colorless oil (6.1 g, 51% yield).

TLC (3:1 hexanes/EtOAc)
R_f = 0.52, stained by KMnO₄.

¹H-NMR (500 MHz, CDCl₃)
δ 7.26 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.5 Hz, 2H), 6.03 (dt, J = 7.5 Hz, J = 1.8 Hz, 1H), 4.45 (s, 2H), 3.81 (s, 3H), 3.72 (s, 3H), 3.52 (t, J = 6.0 Hz, 2H), 2.77 (m, 2H), 1.91 (m, 3H).

¹³C-NMR (125 MHz, CDCl₃)
δ 168.5, 159.4, 140.1, 130.7, 129.5, 128.5, 114.0, 72.7, 69.4, 55.5, 53.6, 51.5, 30.4, 20.9.

HRMS (ESI+)
Calculated for C₁₅H₂₁O₄: 265.1440
Found: 265.1436

A 1 L two neck round bottom flask was fitted with a thermometer, sealed with a rubber septum, and vac-filled with N₂. THF (280 mL) and the ester 3.52-3 (6.1 g, 23.1 mmol, 1.0 equiv.) were added to the flask, and the mixture was cooled with to -78 °C in a dry ice / acetone bath. DIBAL-H (1.0 M in hexanes, 69 mL, 3.0 equiv.) was added gradually to the reaction flask over 20 min, and the resulting reaction mixture was stirred at -78 °C for 5 minutes before switching to a -15 °C dry ice / brine cooling bath. After 1.5 h, MeOH (60 mL) was added to quench the reaction at -15 °C. Using Et₂O, the reaction mixture was transferred to a 2 L Erlenmeyer flask, and saturated Rochelle’s salt (280 mL) was added. After stirring overnight to complex aluminum salts, the crude mixture was transferred to a 1 L separatory funnel using Et₂O (50 mL) and water (50 mL). After mixing and phase separation, the aqueous layer was extracted (3 × 250 mL EtOAc). The combined organics were washed with brine (400 mL), concentrated in vacuo to
approximately 50 mL, diluted in Et₂O, dried with Na₂SO₄, vacuum filtered, and concentrated to give a cloudy oil. Chromatographic purification (9 cm diameter column, 500 mL SiO₂, 2:1 hexanes/EtOAc) yielded 3.52-4 (5.3 g, 97% yield).

TLC (2:1 hexanes/EtOAc)

Rₜ = 0.26, stained by KMnO₄.

¹H-NMR (500 MHz, CDCl₃)

δ 7.24 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 5.32 (td, J = 8.0 Hz, J = 1.3 Hz, 1H), 4.44 (s, 2H), 4.01 (s, 2H), 3.80 (s, 3H), 3.43 (t, J = 6.0, 2H), 2.34 (app. q, 2H), 1.82 (s, 3H).

¹³C-NMR (125 MHz, CDCl₃)

δ 159.4, 138.2, 130.0, 129.6, 124.7, 114.0, 73.0, 69.0, 61.4, 55.4, 28.6, 22.4

HRMS (ESI+)

Calculated for C₁₄H₂₁O₃: 237.1491
Found: 237.1494

A 500 mL 3-neck round bottom flask was charged with imidazole (3.67 g, 54.0 mmol, 2.4 eq), sealed with three rubber septa, and vac-filled with N₂. Under N₂, CH₂Cl₂ (200 mL) and allylic alcohol 3.52-4 (5.31 g, 22.5 mmol, 1.0 eq) were added by cannulation with rinsing for quantitative transfer. After cooling to 0 °C in an ice/water bath, TIPSCI (5.8 mL, 27.0 mmol, 1.2 eq) was added dropwise over 7 min. The reaction was allowed to warm to rt with stirring overnight. After 8 h, the reaction mixture was transferred to a 500 mL separatory funnel. The organic layer was washed (2 × 150 mL water), and combined aqueous layers were extracted (250 mL CH₂Cl₂). The combined organic layers were washed with brine (300 mL), dried with MgSO₄, vacuum filtered, and concentrated in vacuo to yield the product as an oil. Chromatographic purification (25:3:1 hexanes / DCM / Et₂O to 25:4:1) gave the pure product 3.5₂-₅ (7.26 g, 82% yield).

TLC (10:1 hexanes/EtOAc)

Rₜ = 0.46, stained by KMnO₄.
**1H-NMR (500 MHz, CDCl3)**

δ 7.26, (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 5.20 (dt, J = 7.3 Hz, J = 1.2 Hz, 1H), 4.43 (s, 2H), 4.23 (s, 2H), 3.80 (s, 3H), 3.41 (t, J = 7.2 Hz, 2H), 2.33 (app q, 2H), 1.78 (d, J = 1.1 Hz, 3H), 1.14-1.04 (m, 21H).

**13C-NMR (125 MHz, CDCl3)**

δ 159.3, 137.5, 130.8, 129.5, 121.8, 114.0, 72.7, 70.1, 62.3, 55.5, 28.5, 21.3, 18.3, 12.2.

**HRMS (ESI+)**

Calculated for C$_{23}$H$_{41}$O$_3$Si: 393.2825

Found: 393.2818

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To a 500 mL round bottom flask were added the PMB-protected alcohol **3.52-5** (7.26 g, 18.5 mmol, 1 eq) chloroform (160 mL), and water (8 mL). The mixture was stirred at room temperature for 10 min before adding 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 12.6 g, 55.5 mmol, 3.0 eq) portionwise over 10 min. After 1 h, the reaction was quenched with the addition of sat. aq. NaHCO$_3$ (100 mL). The mixture was filtered through celite, which was rinsed with EtOAc. The resulting red filtrate was concentrated and then transferred to a 500 mL separatory funnel, rinsing with EtOAc (200 mL) and H$_2$O (150 mL). Brine (60 mL) was added to improve phase separation, and then the aqueous layer was extracted with EtOAc (2 × 200 mL). The combined organics were washed with brine (250 mL), dried with Na$_2$SO$_4$, vacuum filtered, and concentrated to give a dark red oil. Chromatographic purification (8:1 to 5:1 to 3:1 hexanes/Et$_2$O) gave the pure product **3.52-6** (4.55 g, 90% yield).

**TLC (3:1 hexanes/Et$_2$O)**

$R_f$ = 0.46, stained by KMnO$_4$.

**1H-NMR (400 MHz, CDCl3)**

δ 5.26 (t, J = 7.7 Hz, 1H), 4.23 (s, 2H), 3.61 (t, J = 6.2 Hz, 2H), 2.32 (app q, 2H), 1.82 (s, 3H), 1.18-1.04 (m, 21H).
A dry 50 mL Schlenk flask was charged with PPh₃ (4.12 g, 15.7 mmol, 1.1 eq), sealed with a rubber septum, and vac-filled with N₂ (∗3). CH₂Cl₂ (35 mL) was added. The resulting mixture was stirred and cooled to 0 °C. Br₂ (2.39 g, 15.7 mmol, 1.1 eq) was gradually added until the yellow color persisted, and then several additional crystals of PPh₃ were added until the color vanished. The resulting off-white, opaque mixture was treated with a dropwise addition of pyridine (2.26 g, 28.6 mmol, 2.0 eq), followed by a dropwise addition of 3.52-6 (3.89 g, 14.29 mmol, 1.0 eq) as a solution in DCM (5 mL) with rinsing (10 mL DCM) for quantitative transfer. After 1.5 hours TLC showed the reaction was almost complete. The crude mixture was transferred to a rbf and concentrated in vacuo, giving an off-white powder. The solid was triturated with pentane and then filtered. (2.65 g, 47% yield). Along with additional crude bromide product from a parallel reaction, chromatographic purification (hexanes to 10:1 Et₂O/hexanes) gave the pure product 3.528-7 as a colorless oil (5.65 g 93% yield).

TLC (hexanes)

Rᵢ = 0.25, stained by KMnO₄.

¹H-NMR (400 MHz, CDCl₃)

δ 5.21 (dt, J = 7.3 Hz, J = 1.2 Hz, 1H), 4.23 (s, 2H), 3.34 (t, J = 7.2 Hz, 2H), 2.60 (app q, 2H), 1.80 (d, J = 1.0 Hz, 3H), 1.16-1.04 (m, 21H).

¹³C-NMR (100 MHz, CDCl₃)

δ 138.8, 122.4, 62.4, 33.0, 31.5, 21.4, 18.3, 12.2.
In an unoptimized procedure, in the glovebox, alkyl bromide **3.52-7** (2.01 g, 6 mmol, 1 equiv) was weighed into a flame-dried 40 mL vial. Zn dust (1.18 g, 18 mmol, 3 equiv) was weighed into another flame-dried 40 mL vial equipped with a stir bar. 8 mL DMA was added to the vial containing the alkyl bromide to give a colorless solution. The vials were sealed with septum caps and brought out of the glovebox. To the vial containing Zn dust was added I₂ (45.7 mg, 0.18 mmol, 0.03 equiv). The vial was resealed and vac-filled with N₂ (× 3). DMA (2 mL) was added, and the mixture stirred for 2 min during which the brown color of I₂ disappeared. The solution of the alkyl bromide was then cannulated to the Zn dust, rinsing with DMA (2 mL × 2). The mixture was stirred at 80 °C for 14 h, then cooled to rt and taken into the glovebox.

In the glovebox, (E)-ethyl 2,3-dibromoacrylate (52) (430 mg, 1.67 mmol) was weighed into a flame-dried 40 mL vial equipped with a stir bar. THF (15 mL) was added, followed by PdCl₂(PPh₃)₂ (35.1 mg, 0.05 mmol, 0.03 equiv wrt dibromide). 2 of these reactions were prepared in parallel. The organozinc solution (5 mL) was filtered directly into each of the reaction vial. The reactions were sealed with PTFE-lined caps, brought out of the glovebox and stirred at 45 °C for 6 h, then cooled to rt. The reaction mixtures in the 2 vials were combined into a separatory funnel containing 40 mL saturated aq. NH₄Cl solution, rinsing with H₂O and Et₂O. Et₂O (10 mL) was added and the layers mixed and separated. The aqueous layer was extracted with Et₂O (30 mL × 2). The combined organics were washed with H₂O, brine, dried over MgSO₄ and Darco, filtered through celite and concentrated in vacuo. The crude product was purified by silica gel chromatography (20-25-30% CH₂Cl₂/hexanes). The mixed fractions were pooled and re-purified by silica gel chromatography (15-20-25% CH₂Cl₂/hexanes). The fractions containing the pure product were concentrated, then taken up in hexanes and stirred with activated charcoal. The mixture was filtered through celite and concentrated *in vacuo* to give a very slightly brown liquid as the product **E-3.52** (526 mg, 36% yield).

**TLC (30% CH₂Cl₂/hexanes)**

Rₜ = 0.41, visualized with UV, stained with KMnO₄.

**¹H-NMR (500 MHz, CDCl₃)**

δ 6.64 (t, J = 7.7 Hz, 1H), 5.15 (tq, J = 7.3, 1.3 Hz, 1H), 4.26 (q, J = 7.0 Hz, 2H), 4.22 (s, 2H), 2.53 (q, J = 7.5 Hz, 2H), 2.22-2.13 (m, 2H), 1.78 (q, J = 1.3 Hz, 3H), 1.33 (t, J = 7.1 Hz, 3H), 1.22-0.96 (m, 21H).

**¹³C-NMR (125 MHz, CDCl₃)**

δ 162.8, 147.8, 137.0, 123.9, 111.6, 62.1, 62.1, 31.6, 26.6, 21.1, 18.0, 14.1, 12.0.
To a flame-dried 7 mL vial cooled under Argon and equipped was added zinc dust (248.1 mg, 3.79 mmol, 1.5 equiv.) and iodine (32.3 mg, 0.127 mmol, 0.5 equiv.). The vial was sealed with a PTFE-lined cap, purged twice with argon, and charged with DMF (1.0 mL, 2.5 M). After stirring at room temperature for 5 min until I₂ color disappeared, 5-bromo-2-methyl-2-pentene (0.34 mL, 413.8 mg, 2.54 mmol, 1.0 equiv.) was added to the reaction vial via syringe under a positive pressure of argon. The vial was sealed with Teflon tape and parafilm after the gas inlet needle was removed. The reaction mixture was then placed in an 80 °C aluminum heat block and maintained at that temperature with stirring for 4 h. The reaction mixture was then allowed to cool to room temperature and was taken into the glovebox. There the reaction mixture was passed through a 0.2 μm filter to afford a bright yellow solution, which was used immediately. To a flame-dried 40 mL vial was added vinyl iodide 3.47 (351 mg, 1.0 mmol, 1.0 equiv.), PdCl₂(PPh₃)₂ (21.0 mg, 0.03 mmol, 0.03 equiv.), and LiBr (452 mg; 5.2 mmol; 5.2 equiv.) followed by THF (9 mL, 0.1 M total). The resulting mixture was allowed to stir at room temperature for 5 min as a yellow suspension. After 5 min, alkyl zinc 3.46 solution in DMF (1.0 mL, 2.5 M, 2.5 equiv.) was added to the reaction mixture rinsing with THF for quantitative transfer, causing the reaction mixture to turn orange. The vial was sealed with a PTFE-lined cap and removed from the glovebox. The vials were placed in a 60 °C aluminum heat block and maintained at that temperature with stirring for 6 h. The reaction mixture was then cooled to room temperature and quenched with saturated aqueous NH₄Cl (10 mL). The mixture was transferred into a separatory funnel rinsing with EtOAc (10 mL) and H₂O (10 mL) was added. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine:H₂O (1:1) (3 x 20 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo to afford an orange brown oil. The crude material was adsorbed onto Celite from an acetone slurry and purified by silica gel chromatography (Hexanes:Acetone 4:1 to Hexanes:Acetone 1:1) to afford a pale yellow solid. The solid was triturated with Et₂O:Hexanes (1:1) to give the product 3.49 as a white solid after filtration and drying (182 mg, 59%).

TLC (EtOAc)

R_f = 0.41, visualized by UV, stained with KMnO₄.
$^1$H-NMR (500 MHz, acetone-$d_6$)

$\delta$ 5.22 (tq, $J = 7.2$, 1.4 Hz, 1H), 5.11 (tquint, $J = 7.1$, 1.4 Hz, 1H), 4.18 (d, $J = 16.9$ Hz, 2H), 4.02 (d, $J = 16.9$ Hz, 2H), 3.10 (s, 3H), 2.11 – 2.00 (m, 4H), 1.96 (dd, $J = 8.4$, 7.0 Hz, 2H), 1.66 – 1.64 (m, 3H), 1.61 – 1.58 (m, 6H), 0.71 – 0.63 (m, 2H).

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

$\delta$ 168.8, 133.6, 131.5, 128.5, 125.1, 62.6, 46.2, 40.4, 27.4, 25.8, 23.2, 17.7, 15.9.

HRMS (ESI+)

Calculated for $C_{16}H_{26}BNO_4Na$: 330.1853

Found: 330.1852

To a solution of MIDA boronate $^{3.49}$ (307 mg, 1 mmol, 1 equiv) in THF (5 mL) was added 1N NaOH (aq) (5 mL, 5 mmol, 5 equiv) under ambient atmosphere and temperature. The reaction was stirred at room temperature for 20 min. The reaction was concentrated in vacuo to remove THF. With vigorous stirring, saturated NH$_4$Cl (aq.) (5mL) was added. The mixture was extracted with Et$_2$O ($3 \times 5$ mL). The organic extracts were dried over Na$_2$SO$_4$, filtered and concentrated to 1 mL. This solution was then transferred to a 7 mL vial, rinsing with THF (1mL). The vial was sealed with a septum cap and the solution concentrated to 1 mL under a stream of N$_2$. THF (2 mL) was added under N$_2$, and the solution concentrated to 1.25 mL under a stream of N$_2$. This solution of the boronic acid (75% yield) was then taken into the glovebox for the subsequent coupling reaction. $^1$H-NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.28 (br s, 1H), 5.08–4.95 (m, 2H), 1.94 (q, $J = 7.4$ Hz, 4H), 1.83 (dd, $J = 8.7$, 6.2 Hz, 2H), 1.56 (dd, $J = 6.3$ Hz, 3H), 1.48 (s, 6H), 0.58 (dd, $J = 9.1$, 7.0 Hz, 2H); $^{11}$B-NMR (128 MHz, DMSO-$d_6$): $\delta$ 32.5. Note: over-concentration of the boronic acid solution will cause boroxine formation. NMR data for boroxine: $^1$H-NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.28 (br s, 1H), 5.12 (app t, $J = 7.5$ Hz, 1H), 5.03 (dt, $J = 8.9$, 1.5 Hz, 1H), 1.99–1.84 (m, 6H), 1.59 (s, 3H), 1.51 (s, 3H), 1.50 (s, 3H), 0.49 (t, $J = 7.7$ Hz, 2H); $^{11}$B-NMR (128 MHz, DMSO-$d_6$): $\delta$ 24.1.

In the glovebox, a flame-dried 7 mL vial was charged with vinyl bromide $^{E-3.52}$ (108 mg, 0.25 mmol, 1 equiv), Ag$_2$O (261 mg, 1.125 mmol, 4.5 equiv), and a stir bar. The boronic acid solution prepared above was then added, rinsing with THF (1.25 mL). Pd[P(o-tol)$_3$]$_2$ (17.8 mg, 0.025 mmol, 1 equiv) was then
The vial was sealed with a PTFE-lined cap, brought out of the glovebox and stirred at 60 °C in a heating block for 13.5 h. The reaction was then cooled to room temperature and filtered through celite, eluting with Et₂O. The filtrate was concentrated in vacuo, azeotroping once with CH₂Cl₂. The crude product was purified by silica gel column chromatography (20% to 30% CH₂Cl₂/hexanes) to give the product 15 as a slightly yellow oil (73.2 mg, 58% yield).

TLC (40% CH₂Cl₂/hexanes)
\[ R_f = 0.47, \text{ visualized by UV, stained with KMnO}_4. \]

\[ \text{H-NMR (500 MHz, CDCl}_3\]  
\[ \delta 5.83 (t, J = 7.5 \text{ Hz}, 1H), 5.18 (dt, J = 7.0, 1.0 \text{ Hz}, 1H), 5.12-5.08 (m, 2H), 4.23 (s, 2H), 4.20 (q, J = 7.3 \text{ Hz}, 2H), 2.44 (q, J = 7.5 \text{ Hz}, 2H), 2.26 (t, J = 7.0 \text{ Hz}, 1H), 2.14-2.04 (m, 6H), 1.97 (app t, J = 8.5 \text{ Hz}, 2H), 1.77 (d, J = 1.0 \text{ Hz}, 3H), 1.68 (s, 3H), 1.60 (s, 3H), 1.58 (s, 3H), 1.30 (t, J = 7.2 \text{ Hz}, 3H), 1.14-1.05 (m, 21H). \]

\[ \text{C-NMR (125 MHz, CDCl}_3\]  
\[ \delta 168.0, 141.1, 135.9, 135.7, 132.2, 131.3, 125.0, 124.3, 123.3, 62.0, 60.0, 39.7, 34.7, 29.8, 27.7, 27.4, 26.7, 25.7, 18.3, 17.7, 16.0, 14.3, 12.0. \]

HRMS (ESI+)

Calculated for C₃₁H₅₇O₃Si: 505.4077  
Found: 505.4077

In the glovebox, the 40 mL vial containing 3.51 (214 mg, 0.424 mmol, 1 equiv) and a stir bar was charged with Mg turnings (412 mg, 16.96 mmol, 40 equiv). The vial was sealed with a septum cap and brought out of the glovebox and placed under N₂. MeOH (8 mL) was added via syringe and the mixture was sonicated for 2 min, then stirred at rt with an N₂ inlet needle. An exotherm formed as the Mg turnings dissolved. The reaction was cooled in an ice/water bath. The reaction was then stirred for 16 h, gradually warming to room temperature. The reaction was cooled to 0 °C in an ice/water bath, then quenched with the addition of saturated aq. NH₄Cl (8 mL), forming a gelatinous mixture which was agitated manually. A small amount of H₂O was added to dissolve the inorganic salts. The mixture was transferred to a
separatory funnel, rinsing with Et₂O. After mixing and phase separation, the aqueous layer was extracted with Et₂O (15 mL). The aqueous layer was concentrated *in vacuo* to remove most of the MeOH. The resulting aqueous phase was extracted with Et₂O (2 x 15 mL). The combined organics were dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was diluted with benzene (5 mL) and the mixture further dried with Na₂SO₄, filtered into a 40 mL vial and concentrated and dried under high vacuum to give the product 3.57 as a mixture of the ethyl ester and methyl ester in the ratio 7.7 : 1 (200.8 mg, 0.397 mmol, 94% yield). This material was used without further purification.

**TLC (40% CH₂Cl₂/hexanes)**

R⁰ = 0.47, stained by KMnO₄.

**¹H-NMR (500 MHz, CDCl₃)**

δ 5.15 (t, J = 7.0 Hz, 1H), 5.10-5.07 (m, 2H), 4.21 (s, 2H), 4.13 (q, J = 7.1 Hz, 2H), 3.66 (s, 3H for methyl ester), 2.31 (tt, J = 9.0, 5.55 Hz, 1H), 2.08-2.04 (m, 2H), 2.01 (m, 6H), 1.76 (app s, 3H), 1.68 (app s, 3H), 1.68-1.60 (m, 1H), 1.60 (s, 3H), 1.57 (s, 3H), 1.58-1.55 (m, 1H), 1.48-1.40 (m, 2H), 1.30 (quint, J = 7.8 Hz, 2H), 1.26 (t, J = 7.0 Hz, 3H), 1.14-1.05 (m, 21H).

**¹³C-NMR (125 MHz, CDCl₃)**

δ 176.3, 135.8 (Me), 135.7, 135.5, 131.3, 125.6, 125.5 (Me), 124.3, 123.6, 123.5 (Me), 61.9, 60.0, 51.3 (Me), 45.2, 45.1 (Me), 39.7, 32.4, 32.1, 27.8 (Me), 27.7, 26.6, 25.8, 25.7, 21.0, 18.0, 17.7, 15.9, 14.3, 12.0. Note: (Me) = peaks corresponding to the methyl ester.

**HRMS (ESI+)**

Calculated for C₃₁H₅₉O₅Si: 507.4233

Found: 507.4231

The 40 mL vial containing 3.57 (200.8 mg, 0.0544 mmol, 1 equiv) was charged with a stir bar and sealed with a septum cap. The vial was vac-filled with N₂ (x 3). THF (8 mL) was added via syringe and the solution cooled to -20 °C in a dry ice/ethylene glycol/ethanol bath. DIBAl-H (1M in hexanes, 2 mL, 2 mmol, 5.04 equiv) was added dropwise. The reaction was stirred at -20 °C for 2 h. The reaction was quenched by adding saturated Rochelle’s salt solution (10 mL) was dropwise at -20 °C. Et₂O (5 mL) was
then added. The mixture was warmed to room temperature and stirred for 1 h. The mixture was transferred to a separatory funnel, rinsing with H₂O and Et₂O (10 mL). After mixing and phase separation, the aqueous layer was extracted with Et₂O (2 x 5 mL). The combined organics were washed with 1:1 H₂O/brine (20 mL), brine, dried over Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by silica gel chromatography (5% to 10% to 20% Et₂O/hexanes) to give the product **3.58** as a colorless oil (169.9 mg, 90% yield).

TLC (20% Et₂O/hexanes)

Rₖ = 0.24, stained by KMnO₄.

**¹H-NMR** (500 MHz, CDCl₃)

δ 5.19 (app dt,  = 7.0, 1.0 Hz, 1H), 5.11-5.07 (m, 2H), 4.22 (d,  J = 12.5 Hz, 1H), 4.21 (d,  J = 12.5 Hz, 1H), 3.54 (dd,  J = 5.5, 1.5 Hz, 2H), 2.11-1.94 (m, 8H), 1.77 (d,  = 1.0 Hz, 3H), 1.68 (s, 3H), 1.60 (s, 6H), 1.50-1.25 (m, 7H), 1.15-1.06 (m, 21H).

**¹³C-NMR** (125 MHz, CDCl₃)


**HRMS (ESI+)**

Calculated for C₂₉H₅₇O₂Si: 465.4128

Found: 465.4126

To a solution of **3.58** (165.3 mg, 0.356 mmol) in THF (3.6 mL) and pyridine (1.2 mL) in a polyethylene vial equipped with a stir bar was added HF-pyridine (0.4 mL) dropwise at 0 °C. The vial was purged with N₂, and sealed with a screw cap. The reaction was gradually warmed to rt. After 3.5 h, another portion of HF-pyridine (0.4 mL) was added to the reaction at rt. The reaction was then stirred for another 3 h. The reaction was added portionwise to a stirring solution of saturated aqueous NaHCO₃ (10 mL). Et₂O (10 mL) was added. The mixture was transferred to a separatory funnel and another 10 mL saturated aqueous NaHCO₃ was added. After phase separation, the aqueous layer was extracted with Et₂O (2 x 10 mL). The combined organics were washed with H₂O, brine, dried over Na₂SO₄, filtered and concentrated. The crude
product was purified by silica gel chromatography (20% to 30% to 40% EtOAc/hexanes) to give the pure product 3.59 as a colorless oil (98.2 mg, 89% yield).

TLC (40% EtOAc/hexanes)

\[ \text{R}_f = 0.25, \text{stained by KMnO}_4. \]

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

\[ \delta 5.29 \text{ (app t, } J = 7.5 \text{ Hz, } 1\text{H}), 5.12-5.07 \text{ (m, } 2\text{H}), 4.16 \text{ (d, } J = 11.5 \text{ Hz, } 1\text{H}), 4.10 \text{ (d, } J = 11.5 \text{ Hz, } 1\text{H}), 3.58 \text{ (dd, } J = 10.5, 5.0 \text{ Hz, } 1\text{H}), 3.51 \text{ (dd, } J = 11.0, 6.0 \text{ Hz, } 1\text{H}), 2.10-1.97 \text{ (m, } 8\text{H}), 1.80 \text{ (d, } J = 1.3 \text{ Hz, } 3\text{H}), 1.68 \text{ (d, } J = 1.0 \text{ Hz, } 3\text{H}), 1.60 \text{ (s, } 6\text{H}), 1.50-1.25 \text{ (m, } 9\text{H}). \]

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

\[ \delta 135.2, 134.4, 131.3, 128.5, 124.4, 124.3, 65.5, 61.5, 39.7 \text{ (2C), } 30.9, 30.2, 27.6, 26.9, 26.7, 25.7, 25.2, 21.3, 17.7, 16.0. \]

HRMS (ESI+)

Calculated for C_{20}H_{37}O_2: 309.2794

Found: 309.2794

To a Schlenk tube (1 cm diameter) sealed with a rubber septum and vac-filled with N\(_2\) (×3) was added CH\(_2\)Cl\(_2\) (0.2 mL) followed by DMSO (0.015 mL, 0.211 mmol, 8.7 equiv). The solution was cooled to -78 °C in a dry ice/acetone bath. Oxalyl chloride (2.0 M in CH\(_2\)Cl\(_2\), 0.05 mL, 0.1 mmol, 4.1 equiv) was added dropwise via syringe. The resulting solution was stirred at -78 °C for 30 min. A solution of diol 3.59 (7.5 mg, 0.0243 mmol, 1.0 equiv) in CH\(_2\)Cl\(_2\) (0.2 mL) in a 7 mL vial was added dropwise to the reaction flask via syringe, rinsing with CH\(_2\)Cl\(_2\) (0.2 mL). The solution was stirred for 30 min at − 78 °C, then NEt\(_3\) (0.030 mL, 0.215 mmol, 8.8 equiv) was added into the reaction dropwise. The reaction was stirred for 5 min at the same temperature, then the cold bath was removed and the reaction stirred at room temperature for another 45 min. TLC showed complete conversion of the diol. The reaction was cooled to 0 °C in an ice/water bath. Dry MeNH\(_2\) gas was then passed above the reaction solution over 3 min via an inlet needle with an outlet needle, causing an increase in reaction volume and dissolution of the solids. The reaction was stirred for 3.5 h, gradually warming to room temperature in the ice/water bath. The flask was then
opened to the Schlenk line, causing evaporation of the dissolved MeNH₂. The solvent was removed under a stream of N₂, giving an off-white oily solid. The rubber septum was quickly replaced with a new septum under positive N₂ flow. The Schlenk tube was evacuated and filled with N₂, then evacuated again, and the residue was dried under high vacuum overnight. The flask was filled with N₂. Dry AcOH (0.4 mL) was added to dissolve the brown residue. The solution was stirred at 80 °C (oil bath temperature) for 8.5 h. The reaction was cooled to 0 °C in an ice/water bath. CH₂Cl₂ (2 mL) and 3N NaOH were added with stirring until pH>10. The mixture was transferred to a separatory funnel and the layers separated. The aqueous layer was then extracted with CH₂Cl₂ (2 × 2 mL). The organics were dried over Na₂SO₄, filtered and concentrated \textit{in vacuo}. \(^1\)H-NMR showed the crude product as the ammonium salt. The brown residue was taken up in CH₂Cl₂ (5 mL) and added to the aqueous layers were from the extraction which were re-adjusted to pH=14 with 6N NaOH. After mixing and phase separation, the aqueous layer was extracted with CH₂Cl₂ (2 × 5 mL). The combined organics were washed with brine, dried over Na₂SO₄ and concentrated. The crude product was purified by silica gel column chromatography (20% to 50% EtOAc/pentane) to give the product 3.5 as a colorless oil (2.7 mg, 39% yield).

\(^1\)H-NMR (500 MHz, CDCl₃)
\[ \delta 2.89 (s, 1H), 2.54 (d, J = 4.5, 1H), 1.89 (t, J = 5.0 Hz, 1H), 1.74-1.38 (m, 15H), 1.17 (dd, J = 9.5, 3.0, 1H) 0.98-0.92 (m, 1H), 0.88 (d, J = 6.5, 3H), 0.87 (d, J = 7.0, 3H), 0.74 (s, 3H), 0.70 (s, 3H). \]

\(^{13}\)C-NMR (125 MHz, CDCl₃)
\[ \delta 60.3, 54.8, 50.4, 49.7, 47.3, 43.4, 39.4, 38.6, 36.4, 35.6, 34.5, 28.6, 27.8, 26.6, 22.8, 21.1 (2C), 21.0, 18.4, 21.1 (3C), 21.0. \]

HRMS (ESI+)

| Calculated for C\(_{20}\)H\(_{34}\)N: | 288.2691 |
| Found: | 288.2697 |

In an unoptimized procedure, anhydrous K₂CO₃ (36.5 mg, 0.264 mmol, 4 equiv) was weighed into a flame-dried 7 mL vial equipped with a stir bar. The vial was sealed with a septum cap, evacuated and filled with N₂ (×3). Amine 3.5 (19 mg, 0.066 mmol, 1 equiv) was dissolved in PhH (0.75 mL) and added

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to the vial. The suspension was cooled to 0 °C, then bromoacetyl bromide (11.5 µL, 0.132 mmol, 2 equiv)
was added via syringe and the reaction was warmed to room temperature. After 1 h, another portion of
bromoacetyl bromide (11.5 µL, 0.132 mmol, 2 equiv) was added. The reaction was left to stir for another
15 h at room temperature. The reaction was filtered through celite and silica gel, eluting with CH₂Cl₂. The
brown filtrate was treated with Darco and filtered through celite. The filtrate was concentrated in vacuo,
giving a brown residue, which was purified by silica gel chromatography (10-20% EtOAc/hexanes) to
give a white solid as the pure product (6.7 mg, 25%). The solid was taken up in EtOH (~ 1 mL) and H₂O
was added, causing the solution to become cloudy. The precipitate was redissolved in a minimal amount
of EtOH and the solution filtered through a 0.2 µM filter into a 7 mL vial. The solution was then left to
slowly evaporate, giving crystals for X-ray analysis.

TLC (20% EtOAc/hexanes)
\[ R_f = 0.59 \], visualized by UV.

\(^1\)H-NMR (500 MHz, CDCl₃)
\[ \delta \ 4.11 \text{ (br s, 1H)}, \ 4.08 \text{ (d, } J = 11.5 \text{ Hz, 1H)}, \ 3.80 \text{ (d, } J = 11.5 \text{ Hz, 1H)}, \ 3.50 \text{ (d, } J = 4.7 \text{ Hz, 1H)}, \ 2.20 \text{ (t, } J = 5.3 \text{ Hz, 1H)}, \ 1.77-1.13 \text{ (m, 17H)}, \ 1.09 \text{ (d, } J = 6.2 \text{ Hz, 3H)}, \ 0.87 \text{ (s, 3H)}, \ 0.80 \text{ (s, 3H)}, \ 0.78 \text{ (d, } J = 6.5 \text{ Hz, 3H)}. \]

\(^{13}\)C-NMR (126 MHz, CDCl₃)
\[ \delta \ 169.9, \ 61.9, \ 55.4, \ 53.3, \ 51.4, \ 46.6, \ 45.3, \ 39.5, \ 38.4, \ 36.6, \ 36.0, \ 35.6, \ 28.8, \ 27.4, \ 26.0, \ 23.1, \ 21.3, \ 20.6, \ 20.4, \ 19.5. \]

HRMS (ESI+)
\[ \text{Calculated for } \text{C}_{22}\text{H}_{35}\text{NOBr: } 408.1902 \]
\[ \text{Found: } 408.1906 \]

\(X\)-ray Crystal Structure Data for \(N\)-bromoacyl-3.5
Crystal data and structure refinement for **N-bromoacyl-3.15**

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<td>R1 = 0.0334, wR2 = 0.0721</td>
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REFERENCES

CHAPTER 4
SYNTHESIS OF MANY DIFFERENT TYPES OF SMALL MOLECULES USING ONE AUTOMATED PROCESS

Junqi Li, Steven Ballmer, Eric Gillis, Seiko Fujii, Michael Schmidt, Andrea Palazzolo, Jonathan Lehmann, Gregory Morehouse, and Martin D. Burke

Small molecule synthesis usually relies on procedures highly customized for each target. A broadly applicable automated process could greatly increase the accessibility of this class of compounds to enable investigations of their practical potential. In this chapter, we report a small molecule synthesizer that can execute the synthesis of 14 distinct classes of small molecules, including Csp\(^3\)-rich polycyclic natural product frameworks, using the same fully automated process based on the iterative coupling approach described in Chapters 1 to 3. Key to enabling automation is the discovery of a catch-and-release chromatographic purification protocol applicable to all of the corresponding intermediates. This chapter also details the development of a protecting group strategy that is suitable for the synthesis of a library of natural products and derivatives. Investigations in these areas have provided general guidelines on the types of protecting groups suitable for the iterative coupling process. More broadly, the successful synthesis of different types of small molecules using the same automated process illuminates an actionable roadmap to a more general and automated approach for small molecule synthesis.

Dr. Eric Gillis discovered the general binary elution profile of MIDA boronates, constructed the small molecule synthesizer, and wrote the code for the operating software. Dr. Steven Ballmer optimized the synthesizer and operated the synthesizer together with Michael Schmidt. The work described in this chapter was completed in collaboration with Dr. Seiko Fujii. Portions of this chapter were adapted from Li, J.; Ballmer, S. G.; Gillis, E. P.; Fujii, S.; Schmidt, M. J.; Palazzolo, A. M. E.; Lehmann, J. W.; Morehouse, G. F.; Burke, M. D. Science 2015, 347, 1221-1226.
INTRODUCTION

Small molecules perform many important functions in nature, medicine, and technology. However, efforts to discover and optimize new small molecule function are often impeded by limitations in synthetic access to this class of compounds. For peptides and oligonucleotides, the development of automated synthesis platforms removed this bottleneck. The resulting expanded access to these molecules permitted widespread exploration and applications of their functional potential. Substantial progress has also been made towards automating the synthesis of oligosaccharides, and some organic polymers. In each of these cases, automation was enabled by the development of a general building block-based synthesis strategy and a common purification process for the corresponding intermediates. Such standardization reduced the number of processes employed and thus decreased the number of challenges involved in automating the synthesis platform.

In contrast, despite tremendous progress in the field, small molecule syntheses typically employ strategies and purification methods that are highly customized for each target. Automation of small molecule synthesis has thus focused on expanding the types of reactions and purification processes that can be implemented on a synthesizer. While the use of advanced engineering and robotics can assist with such an approach, this approach has two inherent limitations in both the planning and execution stages of synthesis: i) the need for the chemist to design the synthesis to each target or family of targets, and ii) even with the aid of computer programs in searching reaction databases, the conditions for most transformations can often times be highly substrate-dependent, and purification processes need to be optimized for each intermediate. These limitations are a result of the lack of standardization of the way molecules are constructed. Consequently, automation has not received widespread utilization in both academic and industrial settings to the extent seen with peptide and oligonucleotide synthesizers. Synthesis thus has remained a bottleneck in the study of small molecule function, and the exclusive domain of expert chemists.

To enable the more generalized automation of small molecule synthesis, we asked whether many different types of small molecules could be prepared using a common building block-based strategy and a common purification process. Small molecules can be very diverse in structure, and thus automating the synthesis of the entire set of targets shown in Figure 4-1 represents a major challenge. However, like peptides, oligonucleotides and oligosaccharides, most natural products (such as 4.1-4.4) are biosynthesized via the iterative assembly of a small set of building blocks, such as malonyl coenzyme A, isopentenyl pyrophosphate, and pyruvic acid. Many materials and pharmaceuticals (such as 4.5-4.9) comprise collections of aryl and/or heteroaryl components. Even topologically complex natural products containing macrocyclic or polycyclic frameworks (such as 4.10–4.14) are usually biosynthesized via
iterative building block-based assembly of linear precursors, which are then (poly)cyclized to yield more complex molecular architectures.\textsuperscript{11,12,13}

![Figure 4-1](image.png)

This analysis has inspired us to develop the iterative coupling platform that is analogous to peptide synthesis, as described in Chapters 1-3. Supporting the notion that many small molecules might be accessible via a common, biosynthesis-inspired strategy involving the iterative assembly of building blocks, we recently demonstrated that more than 75% of all polyene natural product motifs can be prepared using just 12 building blocks and one coupling reaction.\textsuperscript{14} In Chapter 3, we have also shown that utilizing a linear-to-cyclized strategy, the same platform can be used to access the cyclic targets \textbf{10-14}. Having established the strategy that can potentially access a wide range of complex small molecules, we are now faced with the challenges in translating the chemistry into an automated platform.

4-2 A GENERALIZED PURIFICATION PROTOCOL

The key challenge in automating small molecule synthesis is finding a generalized purification method that can be used for all intermediates during synthesis. Small molecule synthesis typically involves purifications customized for each intermediate, such as chromatography with eluents optimized for each compound. Such customization is incompatible with generalized automated purification. Solid-phase synthesis can address this problem for peptides\textsuperscript{1}, oligonucleotides\textsuperscript{2}, oligosacharides\textsuperscript{3}, and some organic polymers.\textsuperscript{4a} In some cases, syntheses of natural products and pharmaceuticals have also been aided by solid-phase methods.\textsuperscript{15} This approach is well-established, compatible with a wide range of chemistries, and has been employed in industry. However, small molecules do not possess a common functional group handle for attachment to solid support which precludes generalized application of this approach. Thus, a different solution was needed.
We recognized that each iteration of building block assembly in our platform generates a MIDA boronate as the key intermediate (Figure 4-2). This led us to question whether the MIDA boronate motif could serve as a surrogate common handle for purification. In this vein, we discovered that MIDA boronates uniformly possess highly unusual binary affinity for silica gel with certain pairs of eluents (Figure 4-3). Specifically, all MIDA boronates 4.15a-t, with appended fragments representing a wide range of sizes, polarities, and functional group content, show minimal mobility on thin layer silica gel chromatography when eluting with MeOH:Et₂O (Figure 4-3, left). However, all of the same MIDA boronates are rapidly eluted with THF (Figure 4-3, right).

This phenomenon enabled us to develop a new type of catch-and-release purification protocol applicable to any intermediate that contains a MIDA boronate (Figure 4-4). A crude reaction mixture is passed over silica gel and the MIDA boronate is temporarily caught while excess reagents and byproducts are removed via washing with MeOH:Et₂O. The MIDA boronate is then cleanly released by switching the

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**Figure 4-2.** MIDA boronates as key intermediates (highlighted in yellow) in iterative coupling-based syntheses.

**Figure 4-3.** MIDA boronates uniformly show binary elution properties on silica gel thin-layer chromatography.

**Figure 4-4.** New type of catch-and-release purification protocol applicable to any intermediate that contains a MIDA boronate.
eluent to THF. The MIDA boronate motif can thus serve as both a latent reactive functional group for iterative coupling and a traceless common functional group handle for generalized purification.

Figure 4-4. Catch-and-release chromatography purification protocol for MIDA boronates.

4-3 A SMALL MOLECULE SYNTHESIZER

Having established a common purification method, we designed and built a synthesizer that iteratively assembles MIDA boronate building blocks in a fully automated fashion (Fig. 4-5). This device comprises three modules that sequentially execute the deprotection, coupling, and purification steps required for each cycle. All solutions are automatically transferred via computer-controlled syringe pumps running custom designed software. Thus, each automated synthesis simply requires placing pre-packed cartridges onto the synthesizer and pressing “start”.

Figure 4-5. Photograph of the small molecule synthesizer and the 3 modules for deprotection, coupling and purification.

The fully automated synthesis commences at the deprotection module, where THF and water are transferred via a syringe pump into a cartridge containing the MIDA boronate and NaOH. After deprotection, the reaction is quenched and the resulting THF solution of the freshly prepared boronic acid is separated from the water-soluble MIDA ligand. The coupling module then heats and stirs a solution of the next building block and the coupling reagents. The synthesizer then adds the freshly prepared solution of boronic acid to the coupling reaction. At the end of the reaction, the synthesizer filters and transfers the crude reaction mixture to the purification module, which executes the catch-and-release purification.
protocol with MeOH:Et$_2$O followed by THF. The THF solution of the purified product is then transferred directly into the deprotection module to start the next iteration of the synthesis.

To first test the capacity of this synthesizer to execute one cycle of deprotection, coupling, and purification, we subjected a series of commercially available aryl, heteroaryl, vinyl, and alkyl MIDA boronates to automated deprotection and coupling with a model bifunctional building block, 4-bromophenyl MIDA boronate (Table 4-1). Using a standard set of hydrolysis conditions (NaOH, THF:H$_2$O, 23 °C, 20 min), and coupling conditions (PdXPhos$^{16}$, K$_3$PO$_4$), we obtained the desired cross-coupling products in good yields and purities in all cases (entries 1-3). The synthesizer was also capable of executing a Csp$^3$ coupling using Pd[P(o-tol)]$_2$ and Ag$_2$O/K$_2$CO$_3$$^{17}$ (entry 4).

![Diagram of reaction process]

<table>
<thead>
<tr>
<th>Entry</th>
<th>MIDA boronate 4.16</th>
<th>% conversion of 4.16 to 4.17</th>
<th>Boronic acid 4.17</th>
<th>% conversion of 4.18 to 4.19</th>
<th>MIDA boronate 4.19</th>
<th>% isolated yield of 4.19</th>
<th>% purity of 4.19</th>
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<td>99</td>
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<td>99</td>
<td>4.19d</td>
<td>59</td>
<td>80</td>
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Table 4-1. Fully automated cycles of deprotection, coupling, and purification. Coupling conditions: XPhos 2nd generation palladacycle, K$_3$PO$_4$, THF, 55 °C, 16 h for entries 1-3, and Pd[P(o-tol)]$_2$, Ag$_2$O, K$_2$CO$_3$, THF, 55 °C, 16 h for Csp$^3$ coupling in entry 4.

Accessing many pharmaceuticals and materials represented by structures 5-9 requires the flexibility to link building blocks via carbon-heteroatom and/or carbon-carbon bonds. The stability of MIDA boronates towards many reaction conditions$^{18,19}$ and the synthetic versatility of boronic acids$^{20}$ allowed us to add carbon-heteroatom bond formations to the same platform. The synthesizer successfully executed a series of automated carbon-heteroatom bond formation, including a Buchwald-Hartwig amination, O-alkylation, and amide bond formations (Table 4-2). Despite the different reagents and byproducts, the same catch-and-release process purified all of the corresponding MIDA boronate products.
Table 4-2. Fully automated cycles of deprotection, coupling, and purification for carbon-heteroatom bond formation.

### 4-4 AUTOMATED SYNTHESIS OF MATERIALS, PHARMACEUTICALS AND NATURAL PRODUCTS

Having confirmed the capacity to reliably execute single cycles of deprotection, coupling, and purification, we next targeted the automated synthesis of a wide range of linear small molecules (4.1-4.9) via multiple carbon-carbon and/or carbon-heteroatom bond formations (Figure 4-6). These include natural products from major biosynthetic pathways (4.1-4.4), materials components (4.5, 4.6), and pharmaceuticals/biological probes (4.7-4.9). Most of the corresponding building blocks are commercially available. Similar to automated peptide, oligonucleotide, and oligosaccharide syntheses, all of the synthesizer-generated final products were purified using standard chromatographic techniques, and any protecting groups other than MIDA were easily removed in a separate step. In each case, a single automated run successfully delivered the targeted small molecule in multimilligram quantities, fulfilling the requirements of most functional discovery assays.

<table>
<thead>
<tr>
<th>entry</th>
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<th>conditions</th>
<th>% isolated yield of 4.22</th>
<th>% purity of 4.22</th>
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<td>PdXPhos K$_3$PO$_4$, THF 55 °C, 16 h</td>
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<tr>
<td>2</td>
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4-5 AUTOMATED SYNTHESIS OF A NATURAL PRODUCT-DERIVED LIBRARY

The development of small molecules with optimized functions often requires efficient access to many structural derivatives of a parent compound. To test if this platform could enable such access, we
targeted the automated preparation of many derivatives of the complex neolignan natural product ratanhine 4. In this experiment, we did not optimize of any of the deprotection, coupling, or purification conditions used to construct 4.37 (Figure 4-6). We input four sets of building blocks representing common substructural elements found throughout the neolignan family and/or other pharmaceutically relevant motifs (Figure 4-7). These building blocks included variations in oxidation states, methylation patterns, fluorine content, aromatic ring identity, and size. They also represent pre-programmed oligomer lengths of 3 to 4 units based on whether the third building block was a bifunctional halo-MIDA boronate or a capping halide.

Figure 4-7. Targeted automated synthesis of a 20-membered library of ratanhine derivatives by mixing and matching building blocks.

One critical element for a successful library synthesis is a protecting group scheme that is compatible with the coupling chemistry and removal of protecting groups at the end of the synthesis can be carried out without the need for optimization of conditions for each library member. Since the deprotection of the MIDA boronate after each coupling reaction is carried out under aqueous basic conditions, the protecting group must be inert under these conditions. The presence of electron-rich aryl and heteroaryl groups meant that the products are likely to be acid-sensitive, while the C=C functionality preclude the use of catalytic hydrogenolysis during deprotection. In addition, similar to peptide synthesis, it is ideal to have a one-step procedure for global deprotection to minimize manipulations after automated synthesis. Taking into account these considerations, silicon-based protecting groups would be suitable for the protection of the free alcohols and phenols in the target library.

4.63 was first chosen as a model system for initial deprotection studies as it contains the allylic alcohol and phenol functional groups that will be present in the most complex member of the library (Figure 4-8). Preliminary investigations on deprotection of the methoxymethyl acetal (MOM) group, which was used as the protecting group previously in the synthesis of ratanhine, showed that the starting material and/or product decomposed before complete deprotection could be achieved under dilute aqueous HCl conditions.
It was thus decided that silyl groups were the most suitable for protecting the alcohols and phenols as silyl ethers are stable under the conditions in the automated synthesis and can be removed using a variety of fluoride sources. Using TIPS groups on the phenols added significant steric bulk on the aryl bromide coupling partner 4.65, resulting in incomplete conversion from 4.65 to 4.66 and partial deprotection of the more labile silyl aryl ethers under the coupling conditions. Although global deprotection of the mixture of products proceeded with a 60% yield without optimization, the TIPS group was deemed unsuitable for the synthesis of the library members that require an additional coupling step (Figure 4-7, bottom).

The SEM group was tested next. Removal of the SEM groups with MgBr₂ and n-BuSH was successful, however, under the reaction conditions nucleophilic displacement of the protected allylic alcohol occurred, giving 4.69 as the only product. Simultaneously, we tested the TBDPSE group in a simpler and more synthetically accessible model system and found that one of the TBDPSE groups could be removed cleanly using TBAF in THF, but the reaction stalled after the removal of the first TBDPSE group. We reasoned that the phenoxide formed under the basic reaction conditions after the first TBDPSE deprotection electronically deactivated the aryl ring towards the second TBDPSE deprotection.
We proceeded to test the use of TBDPSE groups in three representative library members 4.73, 4.75, and 4.77. Global deprotection of 4.73 resulted in clean formation of the desired product 4.74 using TBAF·3H₂O and DMSO (Scheme 4-3A). The non-polar library members were found to be more soluble in DMPU, so a 1:1 DMSO/DMPU was later used as the solvent mixture. The basic reaction conditions and presence of water were sufficient to cleave the benzoate group in 4.75, so the same conditions were used for the deprotection of 4.75 (Scheme 4-3B).

These conditions were however, not suitable for the deprotection of 4.77 due to competitive deprotection of the benzoate group. An anhydrous source of fluoride was needed. The TBDPSE groups were inert towards HF-pyridine. CsF in DMSO was tested, and it was found that the reaction gave a mixture of the desired product 4.78 and the benzoate cleaved product 4.79 in a 3:1 mixture, which could not be separated by silica gel chromatography (Scheme 4-4).
We also observed that one TBDPSE group was cleaved more quickly than the other, giving 4.81 as the only mono-protected product. When 4.81 was subjected to the same conditions, no benzoate cleavage product was found. We hypothesized that deprotection of the TBDPSE at the terminal position leads to formation of the phenoxide which reduces the electrophilicity of the benzoate group, thus preventing benzoate cleavage (Scheme 4-5).

![Scheme 4-5. Sequential deprotection of the silyl groups of 4.80.](image)

We thus switched the terminal protecting group to the less sterically bulky and thus more labile TMSE protecting group. Indeed, global deprotection of all three silyl groups in a one-pot procedure generated only 4.82 and no benzoate cleavage was observed (Scheme 4-6).

![Scheme 4-6. Deprotection of 4.82 containing a TMSE group in place of the TBDPSE group at the terminal position.](image)

With the conditions optimized for the removal of the silyl groups, we proceeded to construct the library on the synthesizer. Importantly, this synthesis was conducted without any changes to the coupling conditions used in the synthesis of 4.37. In the event, the synthesizer successfully generated 20 out of 20 of the targeted derivatives, collectively representing all possible combinations of this four-component matrix of building blocks (Figure 4-9). Removal of the TIPS, TBDPSE, TMSE or Bz protecting groups were carried out successfully on all library members using the pre-determined conditions.
Figure 4-9. Automated synthesis of ratanhine derivatives. Conditions: deprotection – NaOH, THF:H₂O; coupling – cycle 1: Pd(OAc)₂, SPhos, K₂CO₃, THF, 55 °C, 16h. cycle 2: Pd(OAc)₂, XPhos, K₃PO₄, THF, 55 °C, 14 h. cycle 3: Pd(OAc)₂, SPhos, K₃PO₄, THF, 55 °C, 24 h; purification – SiO₂, MeOH:Et₂O; THF.

4-6 SEMI-AUTOMATED SYNTHESIS OF CYCLIC NATURAL PRODUCTS VIA THE LINEAR-TO-CYCLIZED STRATEGY

Finally, we tested whether the range of macro- and polycyclic natural products and natural product-like cores 4.10-4.14 described in Chapter 3 could be generated using the same automated building block assembly process and the linear-to-cyclized strategy (Figure 4-10). In the event, the Csp³ Suzuki and Negishi couplings optimized manually translated to the automated platform, generating the linear precursors in multimilligram quantities. The linear precursors were then successfully cyclized with a macrocyclization (entry 1), Diels-Alder reactions (entries 2 and 3), a cation-pi cyclization (entry 4) and a cascade sequence involving hetero-Diels-Alder reactions and aza-Prins-cyclization (entry 5). The successful automated synthesis of the linear precursors to complex polycyclic thus has the potential to become a valuable tool for accelerating method development for new types of stereoselective cyclizations by providing facile stereocontrolled access to the linear substrates and their analogs.
4-7 SUMMARY AND CONCLUSIONS

Thus, many different types of small molecules can be synthesized using one automated building block assembly platform. This advance was enabled by standardizing the synthesis and purification processes used to assemble these structures. Importantly, a majority of the building blocks employed herein are already commercially available.

Further expanding the scope of this automated synthesis platform represents an actionable roadmap toward a general and broadly accessible solution to the small molecule synthesis problem. This roadmap includes identifying highly redundant substructural elements found in many small molecules and transforming these substructures into suitable building blocks for synthesis. The identification process can be highly aided by the increasingly comprehensive nature of searchable small molecule databases, for e.g. the Dictionary of Natural Products,21 Pubchem,22 ChemDB,23 etc., as well as databases that aim to map the entire theoretical possible chemical space.24 Developing programs that can carry out global analyses of natural products to identify the most commonly occurring substructures within each class of natural products would be very helpful in this process.
Once substructures are identified, better methods for making these building blocks and iteratively coupling them together. This includes the development of more general methods for Csp²-Csp² couplings, a greater scope in stereospecific Csp³-Csp² couplings, and discovering conditions for stereospecific Csp³-Csp³ couplings. An important third goal is advancing the capacity for biosynthesis-inspired cyclizations of linear precursors to yield complex natural product frameworks. Catalyst-controlled stereoselective cyclizations remains a frontier area in synthesis. Achieving these objectives stands to better enable the scientific community to bring the substantial power of small molecule synthesis to bear upon many important unsolved problems in society.

4-8 REFERENCES

1 Merrifield, R. B. Science 1965, 150, 178-185.
17 These conditions were modified from the conditions used for stereoretentive cross-coupling of chiral, non-racemic boronic acids: Crouch, I. T.; Wang, P.; Burke, M. D., manuscript in preparation
21 http://dnp.chemnetbase.com
23 http://cdb.ics.uci.edu/
CHAPTER 4
EXPERIMENTAL SECTION

Materials. Commercial reagents were purchased from Sigma-Aldrich, Fisher Scientific, Alfa Aesar, TCI America, or Frontier Scientific, and were used without further purification unless otherwise noted. Most of the building blocks used in these studies are available from commercial sources. The following MIDA boronates were purchased from Sigma-Aldrich: 4.15a (697311), 4.15b (700231), 4.15c (721573), 4.15d (710032), 4.15e (MIDA071), 4.15f (698229), 4.15g (697494), 4.15h (698164), 4.15i (698016), 4.15j (698148), 4.15k (704547), 4.15l (MIDA032), 4.15m (736600), 4.15n (748714), 4.15o (723711), 4.15p (738514), 4.15q (699861), 4.15r (MIDA020), 4.15s (MIDA076), 4.15t (704873), 4.16a (730335), 4.16b (733539), 4.16c (703710), 4.18 (698083), 4.21a (RNI00021), 4.21b (698067), 4.23 (MIDA034), 4.27 (MIDA013), 4.30 (698032), 4.33 (701831), 4.54 (MIDA039), 4.60 (MIDA014), 61 (MIDA017), 4.38 (MIDA083), 4.39 (MIDA084), 4.41 (MIDA080), 4.42 (701092), 4.45 (723711), 4.46 (MIDA081), 4.49 (MIDA085), 2-furanyl MIDA boronate (701017). XPhos 2nd generation palladacycle refers to chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (741825, Sigma-Aldrich). Solvents were purified via passage through packed columns as described by Pangborn and coworkers\(^1\) (THF, Et\(_2\)O, CH\(_3\)CN, CH\(_2\)Cl\(_2\): dry neutral alumina; hexane, benzene, and toluene, dry neutral alumina and Q5 reactant; DMSO, DMF: activated molecular sieves). All water was deionized prior to use. Diisopropylethylamine was freshly distilled under an atmosphere of nitrogen from CaH\(_2\). NMR and MS data for the automated synthesis of targets 4.1 – 4.9, library members 4.83 – 4.101, and linear precursors 4.107, 4.111, 4.116, 4.121, and 4.122 have been reported elsewhere.\(^2\)

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

Structural analysis. \(^1\)H NMR and \(^{13}\)C NMR spectra were recorded at 20 \(\circ\)C on Varian Unity 500, Varian Unity Inova 500NB or Varian Unity 500 instruments. Chemical shifts (\(\delta\)) are reported in parts per million (ppm) downfield from tetramethylsilane and referenced to residual protium in the NMR solvent (CHCl\(_3\), \(\delta\)
163

= 7.26; acetone, δ = 2.05, center line) or to added tetramethylsilane (δ = 0.00). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sept = septet, m = multiplet, b = broad, app = apparent), coupling constant (J) in Hertz (Hz), and integration. Chemical shifts (δ) for 13C NMR are reported in ppm downfield from tetramethylsilane and referenced to carbon resonances in the NMR solvent (CDCl3, δ = 77.0, center line; acetone, δ = 39.5, center line). Carbons bearing boron substituents were not observed (quadrupolar relaxation). High resolution mass spectra (HRMS) were performed by Furong Sun and Dr. Haijun Yao at the University of Illinois School of Chemical Sciences Mass Spectrometry Laboratory.

1. Manual deprotections of ratanhine library members

Deprotection condition 1 (for library members 4.83-4.86 and 4.89-4.94)

To a 7-mL vial containing the protected library member and a PTFE-coated magnetic stir bar was added TBAF·3H2O (2.2–15 equiv) followed by 1:1 DMSO/DMPU under ambient atmosphere. The vial was sealed with a Teflon-lined cap and stirred at 50 °C for 30 minutes–6 hours. The reaction was then cooled to room temperature and diluted with a solution of 1:1 saturated NH4Cl/H2O (1.5–2 mL). The layers were mixed and the aqueous layer was removed. The organic layer was washed with H2O (2 × 1.5 mL). The combined aqueous phase was extracted with EtOAc (3 mL). The organic phase was dried over anhydrous MgSO4, filtered, and concentrated in vacuo. The crude product was purified by silica gel chromatography to give the pure product as a white or off-white solid.

Deprotection condition 1 was followed to give deprotected 4.83 (7.1 mg, 50% yield).

TLC (20% EtOAc/hexanes)

Rf = 0.14, visualized by shortwave UV

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

δ 8.77 (br s, 1H), 7.83 (d, J = 8.5 Hz, 1H), 7.54 (d, J = 2.0 Hz, 1H), 7.41 (d, J = 8.5 Hz, 1H), 7.29 (dd, J = 8.5, 2.0 Hz, 1H), 7.16 (d, J = 1.0 Hz, 1H), 6.64 (d, J = 2.0 Hz, 1H), 6.60 (dd, J = 8.0, 2.0 Hz, 1H), 6.51 (d, J = 16, 1.5 Hz, 1H), 6.25 (dq, J = 15.5, 7 Hz, 1H), 3.99 (s, 3H), 1.86 (dd, J = 7.0, 2.0 Hz, 3H).
\[^{13}\text{C-}\text{NMR\ (125 MHz, acetone-}d_6)\]
\[
\delta 160.2, 159.2, 154.2, 153.8, 134.0, 132.3, 131.3, 128.5, 124.5, 122.7, 118.7, 111.9, 111.2, 108.5, 104.6, 100.2, 55.9, 18.6.
\]

HRMS (ESI+)

- Calculated for C\(_{18}\)H\(_{17}\)O\(_3\): 281.1178
- Found: 281.1181

Deprotection condition 1 was followed to give **deprotected 4.84** (11.7 mg, 78% yield).

TLC (30% EtOAc/hexanes)

\(R_f = 0.3\), visualized by shortwave UV.

\[^{1}\text{H-}\text{NMR\ (500 MHz, acetone-}d_6)\]
\[
\delta 8.73 \text{ (br s, 1H)}, 7.84 \text{ (d, } J = 8.5 \text{ Hz, 1H)}, 7.13 \text{ (s, 1H)}, 7.11 \text{ (d, } J = 1.0 \text{ Hz, 1H)}, 6.93 \text{ (d, } J = 1.0 \text{ Hz, 1H)}, 6.64 \text{ (d, } J = 2.0 \text{ Hz, 1H)}, 6.60 \text{ (dd, } J = 8.5, 2.0 \text{ Hz, 1H)}, 6.48 \text{ (dd, } J = 16, 1.5 \text{ Hz, 1H)}, 6.25 \text{ (dq, } J = 16, 6.5 \text{ Hz, 1H)}, 4.03 \text{ (s, 3H)}, 3.98 \text{ (s, 3H)}, 1.86 \text{ (dd, } J = 6.5, 1.5 \text{ Hz, 3H}).
\]

\[^{13}\text{C-}\text{NMR\ (125 MHz, acetone-}d_6)\]
\[
\delta 160.2, 159.1, 154.0, 145.9, 142.9, 135.0, 132.7, 132.6, 128.5, 124.6, 111.9, 111.6, 108.5, 105.1, 104.8, 100.2, 56.4, 55.9, 18.6.
\]

HRMS (ESI+)

- Calculated for C\(_{19}\)H\(_{19}\)O\(_4\): 311.1283
- Found: 311.1277

Deprotection condition 1 was followed to give **deprotected 4.85** (6.0 mg, 56% yield).
TLC (50% EtOAc/hexanes)

$R_f = 0.27$, visualized by shortwave UV.

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

$\delta$ 8.78 (br s, 1H), 7.83 (d, $J = 8.5$ Hz, 1H), 7.61 (d, $J = 1.5$ Hz, 1H), 7.43 (d, $J = 8.5$ Hz, 1H), 7.36 (dd, $J = 9.0$, 2.0 Hz, 1H), 7.18 (d, $J = 0.5$ Hz, 1H), 6.70 (d, $J = 16.0$ Hz, 1H), 6.64 (d, $J = 2.5$ Hz, 1H), 6.60 (dd, $J = 8.5$, 2.5 Hz, 1H), 6.38 (dt, $J = 16$, 5.5 Hz, 1H), 4.25 (t, $J = 5.5$ Hz, 2H), 3.99 (s, 3H), 3.84 (t, $J = 5.5$ Hz, 1H).

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

$\delta$ 160.2, 159.1, 154.2, 153.9, 133.3, 131.3, 130.5, 129.6, 128.5, 123.0, 119.2, 111.8, 111.2, 108.4, 104.5, 100.2, 63.4, 55.8.

HRMS (ESI+)

Calculated for C$_{18}$H$_{17}$O$_4$: 297.1127

Found: 297.1128

Deprotection condition 1 was followed to give **deprotected 4.86** (7.4 mg, 35% yield).

TLC (60% EtOAc/hexanes)

$R_f = 0.22$, visualized by shortwave UV; $^1$H-NMR (500 MHz, acetone-$d_6$): $\delta$ 8.75 (br s, 1H), 7.85 (d, $J = 8.0$ Hz, 1H), 7.18 (d, $J = 1.5$ Hz, 1H), 7.15 (s, 1H), 6.99 (d, $J = 1.0$ Hz, 1H), 6.66 (dt, $J = 17$, 1.5 Hz, 1H), 6.64 (d, $J = 2.0$ Hz, 1H), 6.60 (dd, $J = 8.5$, 2.5 Hz, 1H), 6.38 (dt, $J = 16$, 5.5 Hz, 1H), 4.25 – 4.24 (m, 2H), 4.04 (s, 3H), 3.99 (s, 3H), 3.84 (br s, 1H).

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

$\delta$ 160.2, 159.1, 154.2, 146.0, 143.2, 134.4, 132.8, 130.9, 129.7, 128.5, 112.3, 111.9, 108.5, 105.4, 104.8, 100.2, 63.4, 56.4, 55.9.
HRMS (ESI+)

Calculated for C_{19}H_{19}O_5: 327.1232
Found: 327.1223

Deprotection condition 1 was followed to give **deprotected 4.89** (3.1 mg, 63% yield).

TLC (60% EtOAc/hexanes)

$R_f = 0.36$, visualized by shortwave UV.

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

\[ \delta 8.37 \text{ (dd, } J = 2.5, 0.5 \text{ Hz, } 1\text{H}), 7.90 \text{ (d, } J = 8.5 \text{ Hz, } 1\text{H}), 7.70 \text{ (d, } J = 1.5 \text{ Hz, } 1\text{H}), 7.52 \text{ (d, } J = 8.5 \text{ Hz, } 1\text{H}), 7.50 \text{ (dd, } J = 9.0, 3.0 \text{ Hz, } 1\text{H}), 7.45 \text{ (dd, } J = 8.5, 1.5 \text{ Hz, } 1\text{H}), 7.33 \text{ (d, } J = 1 \text{ Hz, } 1\text{H}), 6.42 \text{ (t, } J = 8.0 \text{ Hz, } 2\text{H}), 3.96 \text{ (s, } 3\text{H}), 3.87 \text{ (br t, } J = 5.0 \text{ Hz, } 1\text{H}). \]

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

\[ \delta 157.1, 156.6, 155.4, 142.4, 139.2, 133.8, 130.4, 130.2, 130.1, 124.1, 121.2, 120.9, 119.8, 111.9, 103.5, 63.3, 56.2. \]

HRMS (ESI+)

Calculated for C_{17}H_{16}NO_3: 282.1130
Found: 282.1132

Deprotection condition 1 was followed to give **deprotected 4.90** (3.9 mg, 67% yield)
TLC (60% EtOAc/hexanes)
\[ R_f = 0.27, \text{ visualized by shortwave UV.} \]

\[^1\text{H-NMR (500 MHz, acetone-}d_6\text{)}\]
\[ \delta \ 8.36 \ (dd, J = 2.5, 0.5 \text{ Hz, } 1\text{H}), 7.90 \ (d, J = 8.5 \text{ Hz, } 1\text{H}), 7.49 \ (dd, J = 9.0, 3.0 \text{ Hz, } 1\text{H}), 7.30 \ (s, 1\text{H}), 7.25 \ (d, J = 1.0 \text{ Hz, } 1\text{H}), 7.08 \ (d, J = 1.5 \text{ Hz, } 1\text{H}), 6.68 \ (app d, J = 15.5 \text{ Hz, } 1\text{H}), 6.41 \ (dt, J = 16, 5.5 \text{ Hz, } 1\text{H}), 4.25 \ (t, J = 5.5 \text{ Hz, } 2\text{H}), 4.06 \ (s, 3\text{H}), 3.95 \ (s, 3\text{H}), 3.86 \ (br t, J = 5.5 \text{ Hz, } 1\text{H}). \]

\[^{13}\text{C-NMR (125 MHz, acetone-}d_6\text{)}\]
\[ \delta \ 159.9, 156.5, 146.3, 144.6, 142.4, 139.2, 134.8, 131.8, 130.4, 130.2, 121.2, 120.8, 112.6, 105.9, 103.8, 63.3, 56.3, 56.2. \]

HRMS (ESI+)
\[ \text{Calculated for C}_{18}\text{H}_{18}\text{NO}_4: 312.1236 \]
\[ \text{Found: 312.1239} \]

Deprotection condition 1 was followed to give **deprotected 4.91** (12.6 mg, 81% yield)

TLC (20% EtOAc/hexanes)
\[ R_f = 0.36, \text{ visualized by shortwave UV.} \]

\[^1\text{H-NMR (500 MHz, acetone-}d_6\text{)}\]
\[ \delta \ 9.30 \ (br s, 1\text{H}), 7.96 \ (d, J = 8.5 \text{ Hz, } 1\text{H}), 7.63 \ (d, J = 1.0 \text{ Hz, } 1\text{H}), 7.47 \ (d, J = 8.5 \text{ Hz, } 1\text{H}), 7.38 \ (dd, J = 8.5, 1.5 \text{ Hz, } 1\text{H}), 7.10 \ (s, 1\text{H}), 7.03 \ (dd, J = 8.5, 2.0 \text{ Hz, } 1\text{H}), 6.98 \ (m, 1\text{H}), 6.52 \ (dd, J = 15.5, 1.5 \text{ Hz, } 1\text{H}), 6.28 \ (dq, J = 15.5, 6.5 \text{ Hz, } 1\text{H}), 1.87 \ (dd, J = 6.5, 1.5 \text{ Hz, } 3\text{H}). \]

\[^{13}\text{C-NMR (125 MHz, acetone-}d_6\text{)}\]
\[ \delta \ 159.7, 154.2, 152.0, 147.2, 134.4, 131.9, 130.5, 130.0, 125.0, 123.7, 121.5 \ (J_{C-F} = 257 \text{ Hz}), 119.1, 115.9, 115.7, 111.5, 109.3, 105.3, 18.5. \]
HRMS (ESI+)

Calculated for C_{18}H_{14}O_{3}F_{3}: 335.0895

Found: 335.0889

Deprotection condition 1 was followed to give deprotected 4.92 (14.3 mg, 77% yield).

TLC (20% EtOAc/hexanes)

R_f = 0.27, visualized by shortwave UV.

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

δ 9.33 (br s, 1H), 7.96 (d, J = 9.0 Hz, 1H), 7.19 (d, J = 0.5 Hz, 1H), 7.07 (s, 1H), 7.03 (dd, J = 8.5, 2.0 Hz, 1H), 7.00 (d, J = 1.5 Hz, 1H), 6.97 (m, 1H), 6.49 (dd, J = 15.5, 1.5 Hz, 1H), 6.28 (dq, J = 16.0, 6.5 Hz, 1H), 4.04 (s, 3H), 1.86 (dd, J = 6.5, 3.0 Hz, 3H).

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

δ 159.7, 151.7, 147.1, 146.0, 143.5, 135.4, 132.2, 131.9, 129.9, 125.0, 121.5 (J_C-F = 256 Hz), 115.9, 115.7, 111.8, 109.2, 105.8, 105.6, 56.3, 18.5.

HRMS (ESI+)

Calculated for C_{19}H_{16}O_{4}F_{3}: 365.1001

Found: 365.0997

Deprotection condition 1 was followed to give deprotected 4.93 (7.1 mg, 73% yield).

TLC (40% EtOAc/hexanes)

R_f = 0.21, visualized by shortwave UV.
$^1$H-NMR (500 MHz, acetone-$d_6$)

$\delta$ 9.30 (br s, 1H), 7.97 (d, $J = 8.5$ Hz, 1H), 7.10 (d, $J = 1.5$ Hz, 1H), 7.50 (d, $J = 8.5$ Hz, 1H), 7.44 (dd, $J = 8.5$, 2.0 Hz, 1H), 7.12 (d, $J = 0.5$ Hz, 1H), 7.04 (dd, $J = 8.5$, 2.5 Hz, 1H), 6.98 (qint, $J = 2$ Hz, 1H), 6.72 (d, $J = 16$ Hz, 1H), 6.41 (dt, $J = 16.0$, 5.0 Hz, 1H), 4.26 (d, $J = 5.0$ Hz, 2H), 3.84 (br s, 1H).

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

$\delta$ 159.8, 154.4, 152.1, 147.2, 133.8, 130.6, 130.1, 130.0 (2C), 124.0, 121.5 ($J_{CF} = 256$ Hz), 119.7, 115.9, 115.7, 111.6, 109.3, 105.3, 63.3.

HRMS (ESI+)

Calculated for C$_{18}$H$_{14}$O$_3$: 351.0844

Found: 351.0849

Deprotection condition 1 was followed to give **deprotected 4.94** (11.4 mg, 67% yield).

TLC (40% EtOAc/hexanes)

$R_f = 0.13$, visualized by shortwave UV.

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

$\delta$ 9.30 (br s, 1H), 7.97 (d, $J = 8.5$ Hz, 1H), 7.26 (d, $J = 0.5$ Hz, 1H), 7.09 (s, 1H), 7.06 (d, $J = 1.0$ Hz, 1H), 7.04 (dd, $J = 8.5$, 2.5 Hz, 1H), 6.97 (m, 1H), 6.68 (d, $J = 15.5$ Hz, 1H), 6.41 (dt, $J = 16.0$, 5.0 Hz, 1H), 4.26 (d, $J = 5.0$ Hz, 2H), 4.06 (s, 3H), 3.85 (br s, 1H).

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

$\delta$ 159.7, 151.8, 147.1, 146.1, 143.7, 134.8, 131.9, 130.4, 130.1, 129.9, 121.5 ($J_{CF} = 256$ Hz), 115.9, 115.7, 112.4, 109.2, 106.0, 105.6, 63.3, 56.4.

HRMS (ESI+)

Calculated for C$_{19}$H$_{16}$O$_3$F$_3$: 381.0950

Found: 381.0946
De protection condition 2 (for library members 4.95-4.98)

To a 1-mL Reacti-vial™ containing the protected tetramer library member and a PTFE-coated magnetic stir bar was added TBAF·3H₂O (15-20 equiv) followed by DMSO under ambient atmosphere. The vial was sealed with a cap and stirred at 50 °C for 5 hours. The reaction was then cooled to room temperature, diluted with 8 mL Et₂O and washed with a solution of 1:1 saturated NH₄Cl/H₂O (4 mL). The aqueous layer was extracted with 4 mL Et₂O. The combined organic layers were washed with H₂O (2 × 4 mL), then with brine (4 mL). The organic phase was dried over anhydrous MgSO₄, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography.

De protection condition 2 was followed to give **deprotected 4.95** (1.0 mg, 48% yield).

**TLC (40% EtOAc/pentane)**

Rᵣ = 0.49, visualized by shortwave UV.

**¹H-NMR (500 MHz, acetone-**d₆**)**

δ 7.77 (s, 1H), 7.53 (d, J = 1.5 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.27 (dd, J = 8.5, 2.0 Hz, 1H), 7.18-7.17 (m, 3H), 6.82 (dd, J = 6.5, 3.0 Hz, 1H), 6.68 (s, 1H), 6.50 (dd, J = 16.0, 1.5 Hz, 1H), 6.31 (dd, J = 15.5, 1.5 Hz, 1H), 6.24 (dq, J = 16.0, 6.5 Hz, 1H), 6.05 (dq, J = 15.5, 7.0 Hz, 1H), 5.69 (d, J = 2.5 Hz, 1H), 5.66 (d, J = 2.5 Hz, 1H), 3.99 (s, 3H), 1.85 (dd, J = 6.5, 1.5 Hz, 1H), 1.78 (dd, J = 6.5, 1.5 Hz, 1H).

**HRMS (ESI+)**

Calculated for C₂₉H₂₇O₄: 439.1909

Found: 439.1904

De protection condition 2 was followed to give **deprotected 4.96** (1.1 mg, 38% yield).
TLC (40% EtOAc/pentane)  
$R_f = 0.46$, visualized by shortwave UV.

$^1$H-NMR (500 MHz, acetone-$d_6$)  
$\delta$ 7.81 (s, 1H), 7.18-7.14 (m, 3H), 7.10 (d, $J = 1.0$ Hz, 1H), 6.90 (d, $J = 1.0$ Hz, 1H), 6.82 (dd, $J = 7.5$, 1.5 Hz, 1H), 6.67 (s, 1H), 6.46 (dd, $J = 16$, 1.5 Hz, 1H), 6.30 (dd, $J = 15.5$, 1.0 Hz, 1H), 6.24 (dq, $J = 15.5$, 6.5 Hz, 1H), 6.04 (dq, $J = 15.5$, 6.5 Hz, 1H), 5.70 (d, $J = 1.5$ Hz, 1H), 5.67 (d, $J = 2.0$ Hz, 1H), 3.98 (s, 3H), 3.96 (s, 3H), 1.85 (dd, $J = 7.0$, 2.0 Hz, 3H), 1.78 (dd, $J = 6.5$, 1.5 Hz, 3H).

HRMS (ESI+)  
Calculated for C$_{30}$H$_{29}$O$_5$: 469.2015  
Found: 469.2014

Deprotection condition 2 was followed to give **deprotected 4.97** (0.039 mg, 14% yield). The yield of the deprotection of 78 was determined by $^1$H-NMR using an internal standard.

$^1$H-NMR (500 MHz, acetone-$d_6$)  
$\delta$ 7.78 (s, 1H), 7.60 (d, $J = 1$ Hz, 1H), 7.40 (d, $J = 8$ Hz, 1H), 7.33 (dd, $J = 8.5$, 1.5 Hz, 1H), 7.19-7.17 (m, 3H), 6.82 (d, $J = 9$ Hz, 1H), 6.70-6.68 (m, 2H), 6.37 (dt, $J = 16$, 5.5 Hz, 1H), 6.31 (dd, $J = 15.5$, 1 Hz, 1H), 6.05 (dq, $J = 15.5$, 6.5 Hz, 1H), 5.69 (d, $J = 2$ Hz, 1H), 5.66 (d, $J = 2$ Hz, 1H), 4.24 (dd, $J = 5$, 2 Hz, 2H), 3.99 (s, 3H), 1.78 (dd, $J = 6.5$, 1.5 Hz, 3H).

HRMS (ESI+)  
Calculated for C$_{29}$H$_{27}$O$_5$: 455.1858  
Found: 455.1866
Deprotection condition 2 was followed to give **deprotected 4.98** (0.3 mg, 21% yield).

TLC (40% EtOAc/pentane)

R<sub>f</sub> = 0.48, visualized by shortwave UV.

<sup>1</sup>H-NMR (500 MHz, acetone-<em>d<sub>6</sub></em>)

δ 7.81 (s, 1H), 7.18 – 7.14 (m, 4H), 6.97 (d, <em>J</em> = 1.0 Hz, 1H), 6.82 (dd, <em>J</em> = 7.0, 1.5 Hz, 1H), 6.67 – 6.63 (m, 2H), 6.37 (dt, <em>J</em> = 16, 5.5 Hz, 1H), 6.30 (dd, <em>J</em> = 15.5, 1.5 Hz, 1H), 6.04 (dq, <em>J</em> = 16.0, 7.0 Hz, 1H), 5.69 (d, <em>J</em> = 2.0 Hz, 1H), 5.66 (d, <em>J</em> = 2.0 Hz, 1H), 4.23 (d, <em>J</em> = 4.5 Hz, 2H), 3.98 (s, 3H), 3.98 (s, 3H), 1.78 (dd, <em>J</em> = 6.5, 2.0 Hz, 3H).

HRMS (ESI+)

Calculated for C<sub>30</sub>H<sub>29</sub>O<sub>6</sub>: 485.1964

Found: 485.1952

**Deprotection condition 3 (for library members 4.37 and 4.99-4.101)**

To a 1-mL Reacti-vial™ containing the protected library member and a PTFE-coated magnetic stir bar was added CsF (25-30 equiv) and 18-crown-6 (2 equiv) followed by DMSO in a glovebox. The vial was sealed with a cap and stirred at 50 °C for 14 hours. The reaction was then cooled to room temperature, diluted with 8 mL EtOAc and washed with a solution of 1:1 saturated NH<sub>4</sub>Cl/H<sub>2</sub>O (8 mL). The aqueous layer was extracted with 4 mL EtOAc. The combined organic layers were washed with H<sub>2</sub>O (2 × 4 mL), then with brine (8 mL). The organic phase was dried over anhydrous MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography.
Deprotection condition 3 was followed to give 4.4 as an off-white solid (0.2 mg, 0.00036 mmol, 7% yield).

TLC (40% EtOAc/pentane)

\( R_f = 0.44 \), visualized by shortwave UV.

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

\( \delta\ 7.83\ (dt, J = 9.0, 2.0 \text{ Hz}, 2\text{H}), 7.77\ (s, 1\text{H}), 7.53\ (s, 1\text{H}), 7.43\ (dd, J = 8.5, 2.0 \text{ Hz}, 1\text{H}), 7.37\ (d, J = 8.5 \text{ Hz}, 1\text{H}), 7.34\ (d, J = 2.5 \text{ Hz}, 1\text{H}), 7.28\ (d, J = 8.0, 1.0 \text{ Hz}, 1\text{H}), 7.17\ (d, J = 8.5 \text{ Hz}, 1\text{H}), 7.14\ (s, 1\text{H}), 6.83\ (dt, J = 8.5, 2.0 \text{ Hz}, 2\text{H}), 6.55\ (s, 1\text{H}), 6.50\ (dd, J = 15.5, 1.5 \text{ Hz}, 1\text{H}), 6.44\ (dd, J = 16.0, 1.5 \text{ Hz}, 1\text{H}), 6.31-6.21\ (m, 2\text{H}), 5.61\ (d, J = 1.5 \text{ Hz}, 1\text{H}), 5.57\ (d, J = 2.0 \text{ Hz}, 1\text{H}), 3.96\ (s, 3\text{H}), 1.87\ (dd, J = 6.5, 1.5 \text{ Hz}, 3\text{H}), 1.84\ (dd, J = 6.5, 1.5 \text{ Hz}, 3\text{H}).

HRMS (ESI+)

Calculated for C_{36}H_{31}O_6: 559.2121

Found: 559.2128

Deprotection condition 3 was followed to give deprotected 4.99 (1.1 mg, 52% yield).

TLC (40% EtOAc/pentane)

\( R_f = 0.39 \), visualized by shortwave UV.

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

\( \delta\ 7.85\ (\text{app d}, J = 9.0 \text{ Hz}, 2\text{H}), 7.81\ (s, 1\text{H}), 7.43\ (dd, J = 8.5, 2.5 \text{ Hz}, 1\text{H}), 7.33\ (d, J = 2.5 \text{ Hz}, 1\text{H}), 7.18\ (d, J = 8.5 \text{ Hz}, 1\text{H}), 7.12 - 7.10\ (m, 2\text{H}), 6.92\ (d, J = 1.5 \text{ Hz}, 1\text{H}), 6.84\ (\text{app d}, J = 9.0 \text{ Hz}, 2\text{H}), 6.55\ (s, 1\text{H}), 6.49 - 6.42\ (m, 2\text{H}), 6.30 - 6.21\ (m, 2\text{H}), 5.62\ (d, J = 2.0 \text{ Hz}, 1\text{H}), 5.58\ (d, J = 1.5 \text{ Hz}, 1\text{H}), 3.97\ (s, 3\text{H}), 3.96\ (s, 3\text{H}), 1.86\ (dd, J = 6.5, 1.5 \text{ Hz}, 3\text{H}), 1.83\ (dd, J = 7.0, 2.0 \text{ Hz}, 3\text{H}).

HRMS (ESI+)

Calculated for C_{37}H_{33}O_7: 589.2226

173
Deprotection condition 3 was followed to give **deprotected 4.100** (0.15 mg, 22% yield).

TLC (60% EtOAc/pentane)

\[ R_f = 0.24, \text{ visualized by shortwave UV.} \]

\[ ^1\text{H-NMR (500 MHz, acetone-}d_6\text{)} \]

\[ \delta 7.82 \text{ (app d, } J = 8.5 \text{ Hz, 2H), 7.77 (s, 1H), 7.60 (d, } J = 1.5 \text{ Hz, 1H), 7.43 (dd, } J = 8.0, 2.0 \text{ Hz, 1H), 7.40 (d, } J = 8.0 \text{ Hz, 1H), 7.35-7.33 (m, 2H), 7.17 (d, } J = 8.5 \text{ Hz, 1H), 7.15 (d, } J = 1.0 \text{ Hz, 1H), 6.83 (app d, } J = 9.0 \text{ Hz, 2H), 6.69 (app d, } J = 16.0 \text{ Hz, 1H), 6.56 (s, 1H), 6.44 (d, } J = 16 \text{ Hz, 1H), 6.38 (dt, } J = 16.0, 5.5 \text{ Hz, 1H), 6.27 (dq, } J = 16, 6.5 \text{ Hz, 1H), 5.61 (d, } J = 1.5 \text{ Hz, 1H), 5.58 (d, } J = 2.0 \text{ Hz, 1H), 4.25-4.24 (m, 2H), 3.97 (s, 3H), 1.84 (dd, } J = 6.5, 1.5 \text{ Hz, 3H).} \]

HRMS (ESI+)

Calculated for C_{36}H_{31}O_7: 575.2070

Found: 575.2070

Deprotection condition 3 was followed to give **deprotected 4.101** (0.3 mg, 14% yield).

TLC (60% EtOAc/pentane)

\[ R_f = 0.23, \text{ visualized by shortwave UV.} \]

\[ ^1\text{H-NMR (500 MHz, acetone-}d_6\text{)} \]
δ 7.85 (dt, J = 8.5, 2.0 Hz, 2H), 7.81 (s, 1H), 7.43 (dd, J = 8.0, 2.0 Hz, 1H), 7.33 (d, J = 2.0 Hz, 1H), 7.18-7.17 (m, 2H), 7.13 (s, 1H), 6.98 (s, 1H), 6.84 (dt, J = 9.0, 2.0 Hz, 2H), 6.66 (app d, J = 16.0 Hz, 1H), 6.55 (s, 1H), 6.44 (dd, J = 16.5, 1.5 Hz, 1H), 6.37 (dt, J = 16.0, 5.5 Hz, 1H), 6.27 (dq, J = 16.0, 6.5 Hz, 1H), 5.62 (d, J = 1.5 Hz, 1H), 5.58 (d, J = 1.5 Hz, 1H), 4.25-4.24 (m, 2H), 3.99 (s, 3H), 3.96 (s, 3H), 1.83 (dd, J = 6.5, 1.5 Hz, 3H)

HRMS (ESI+)

Calculated for C_{37}H_{33}O_{8}: 605.2175

Found: 605.2167

2. Manual synthesis of 4.9-4.14 from linear precursors generated by the synthesizer

A 7 mL vial containing protected seco acid 4.107-1 (85.6 mmol, 0.115 mmol, 1 equiv) and a stir bar was charged with TBAF·3H_{2}O (185 mg, 0.586 mmol, 5.1 equiv) in the glovebox. The vial was sealed with a septum cap and brought out of the glovebox. DMSO (2.3 mL) was added via syringe and the reaction was stirred at 50 °C for 70 min in a heating block. The reaction was cooled to room temperature, then partitioned between H_{2}O (20 mL) and Et_{2}O (20 mL). After mixing thoroughly and separating the phases (both phases should become clear), the aqueous layer was extracted with Et_{2}O (20 mL, then with 10 mL). The combined organics were washed with brine, dried over MgSO_{4}, filtered and concentrated to ~ 5mL. Celite was added to the solution and the crude product was adsorbed onto celite in vacuo. The celite pad was loaded onto a florisil column (5 cm length, 2 cm diameter) equilibrated with 60% EtOAc/hexanes. The impurities were eluted with 80% EtOAc/hexanes + 0.1% AcOH. The product was eluted with 80%
EtOAc/hexanes + 0.2% AcOH. The fractions containing the product were concentrated to ~ 5 mL and then azeotroped with n-heptane to remove residual AcOH. After complete removal of solvent, the residue was triturated with 1:5 DCM:pentane, causing an off-white solid to precipitate. The suspension was then concentrated in vacuo and dried under high vacuum to give an off-white fluffy solid as the product 4.107-1 (41 mg, 73%). $^1$H-NMR matches literature data.$^3$

The following procedure is modified from a known literature procedure.$^3$ A dry 40 mL vial equipped with a stir bar was charged with PPh$_3$ (99.2 mg, 0.378 mmol, 5.05 equiv). The vial was sealed with a septum cap, evacuated and filled with N$_2$ (×3). THF (2.5 mL) was added, followed by PhMe (5 mL). A dry 7 mL vial was charged with seco acid 4.107-1 (36.4 mg, 0.0748 mmol, 1 equiv), sealed with a septum cap, evacuated and filled with N$_2$ (×3). THF (0.4 mL) and PhMe (2 mL) was added. Diethyl azodicarboxylate solution (40 wt% in PhMe, 0.17 mL, 0.374 mmol, 5 equiv) was then added to the 40 mL vial via syringe, giving a very light yellow solution. A 3 mL syringe was charged with 1.2 mL of the seco acid solution, which was added to the 40 mL vial over 6 h with the aid of a syringe pump. The reaction was then stirred for another 1 h. Another portion of PPh$_3$ (99.2 mg, 0.378 mmol, 5.05 equiv) was added as a solid. The vial was flushed briefly with N$_2$ and re-sealed with a septum cap. Another portion of diethyl azodicarboxylate solution (40 wt% in PhMe, 0.17 mL, 0.374 mmol, 5 equiv) was added. The 3 mL syringe was then charged with the remaining seco acid solution and added to the reaction over 5 h. The reaction was then stirred for another 5 h. THF (0.3 mL) was used to rinse out the 7 mL vial, adding the rinse to the reaction over 1h. The reaction was stirred for another 3.5 h, then transferred to a recovery flask, rinsing with EtOAc. Celite was added and the crude product adsorbed in vacuo. The crude product was purified by silica gel column (hexanes to 5% to 10% to 15% EtOAc/hexanes) to give an off-white solid as the pure product 4.107-2 (12.4 mg, 35%). TLC (30% Et$_2$O/hexanes): $R_f$ = 0.28, visualized by short wave UV; $^1$H-NMR matches literature data.$^3$

Supplementary $^1$H-NMR: (500 MHz, CDCl$_3$)

$\delta$ 7.43-7.38 (m, 4H), 7.35-7.31 (m, 4H), 7.29-7.27 (m, 2H), 6.55 (d, $J = 2.5$ Hz, 1H), 6.57 (d, $J = 2.0$ Hz, 1H), 6.31 (d, $J = 3.0$ Hz, 1H), 6.09 (d, $J = 3.0$ Hz, 1H), 5.30-5.24 (m, 1H), 5.09 (d, $J = 11.5$ Hz, 1H), 5.05 (d, $J = 12.5$ Hz, 1H), 5.04 (d, $J = 11.5$ Hz, 1H), 5.00 (d, $J = 12.0$ Hz, 1H), 3.28 (dd, $J = 17.0$, 14.5 Hz, 2H), 2.83 (ddd, $J = 15.5$, 6.5, 2.5 Hz, 1H), 2.73 (ddd, $J = 15$, 11.5, 2.5 Hz, 1H), 2.07-2.03 (m, 1H), 1.86-1.79 (m, 1H), 1.27 (d, $J = 6.5$ Hz, 3H).
In an unoptimized procedure, a solution of the dibenzyl ether \textbf{4.107-2} (12.1 mg, 0.0258 mmol) in a 7 mL vial was charged with 10% Pd/C (2 mg) The vial was sealed with a septum cap and H\textsubscript{2} gas was bubbled through the stirring suspension for 8 min from a balloon. The outlet needle was removed and the reaction was stirred under H\textsubscript{2} atmosphere at room temperature. After 1 h, another portion of 10% Pd/C (1.4 mg) was added to the reaction. The vial was flushed with H\textsubscript{2} for 3 min, then left to stir. After another 2 h, a third portion of 10% Pd/C (5 mg) was added and the reaction was left to stir for another 25 min. The reaction was then purged with N\textsubscript{2} for 5 min, then filtered through celite, rinsing with EtOAc. The filtrate was concentrated in vacuo, azeotroping once with CH\textsubscript{2}Cl\textsubscript{2}. The crude product was purified by silica gel chromatography (20% to 30% to 40% EtOAc/pentane) to give a mixture of citreofuran and the tetrahydrofuran side product arising from reduction of the furan ring. The pure product \textbf{4.10} (0.99 mg, 13%) was obtained after HPLC purification (Agilent Prep-C18, 10 µm, 30 x 150 mm, product number: 413910-302, 25 mL/min, gradient: 40% to 70% EtOH/H\textsubscript{2}O in 25 min) \textsuperscript{1}H-NMR matches literature data.\textsuperscript{3}

To a polyethylene vial containing a solution of \textbf{4.111-1} in THF (0.4 mL) was added HF-pyridine (0.09 mL), followed by THF (0.3 mL). The vial was capped and stirred at room temperature for 3 h. The reaction was quenched with the dropwise addition of saturated aqueous NaHCO\textsubscript{3} (5 mL). The mixture was stirred for 5 min, then transferred to a separatory funnel saturated aqueous NaHCO\textsubscript{3} (3 mL), rinsing with Et\textsubscript{2}O (8 mL). After mixing and phase separation, the aqueous layer was extracted with Et\textsubscript{2}O (4 mL × 2). The combined organics were washed with H\textsubscript{2}O, brine, dried over MgSO\textsubscript{4}, filtered and concentrated \textit{in vacuo}, azeotroping once with CH\textsubscript{2}Cl\textsubscript{2}. The crude product was purified by silica gel chromatography (30% to 40% Et\textsubscript{2}O/pentane) to give a colorless liquid as the product \textbf{4.111-1} (7.3 mg, 60%).
TLC (50% Et$_2$O/hexanes)

R$_f$ = 0.32, visualized by UV, stained by KMnO$_4$

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

$\delta$ 6.63 (td, J = 7.5, 1.5 Hz, 1H), 6.23 (dd, J = 15.0, 10.0 Hz, 1H), 6.04 (dd, J = 15.0 Hz, 10.5 Hz, 1H), 5.73 (dt, J = 15.5 Hz, 6.0 Hz, 1H), 5.67 (dt, J = 15.0, 7.5 Hz, 1H), 4.17 (app d, J = 5.5 Hz, 1H), 2.20-2.08 (m, 3H), 1.99-1.93 (m, 1H), 1.78 (d, J = 1.0 Hz, 3H), 1.56-1.41 (m, 11H), 1.33 (t, J = 9.5 Hz, 1H), 1.27-1.21 (m, 1H), 0.89 (d, J = 6.5 Hz, 3H).

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

$\delta$ 167.6, 141.2, 133.7, 131.9, 130.8, 129.6, 129.0, 79.9, 63.5, 40.0, 35.2, 32.9, 28.1, 26.3, 19.4, 12.3.

HRMS (ESI+)

Calculated for C$_{18}$H$_{30}$O$_3$Na: 317.2093

Found: 317.2096

The following procedure is modified from a known literature procedure$^4$: A Schlenk bomb containing alcohol 4.111-1 (7.3 mg, 0.0248 mmol) and a stir bar was charged with 1,2-dichlorobenzene (2.5 mL) under a stream of N$_2$. Methylen blue (~ 1 mg) was added, forming a blue solution. The solution was degassed with 6 freeze-pump-thaw cycles. The flask was sealed under vacuum, then warmed to room temperature and placed in a sand bath and warmed to ~150 °C. The reaction temperature was allowed to equilibrate for another 15 min before introducing N$_2$ gently into the reaction vessel. The vessel was sealed again and stirred at 200-210 °C (bath temperature). The reaction was stirred for a total of 68 h at that temperature. The reaction was cooled to room temperature, then transferred to a 15 mL rfb, rinsing with CH$_2$Cl$_2$. The CH$_2$Cl$_2$ was removed by rotary evaporation. The remaining solvent was removed by distillation under vacuum, giving a blue residue. The crude product was loaded onto a silica gel column equilibrated with 10% Et$_2$O/pentane. The product was eluted with 20% Et$_2$O/pentane. This semi-purified product was purified on a second silica gel column (100% CH$_2$Cl$_2$) to give oblongolide 4.11 as a white solid (1.3 mg, 24%) in 85-90% purity. $^1$H-NMR matches literature data.$^4$
Supplementary data: $^1$H-NMR (500 MHz, CDCl$_3$)

$\delta$ 5.61 (d, $J = 10.0$ Hz, 1H), 5.55 (ddd, $J = 10.0$, 4.5, 2.5 Hz, 1H), 4.39 (t, $J = 9.0$ Hz, 1H), 3.83 (dd, $J = 11.0$, 8.5 Hz, 1H), 2.75-2.70 (m, 1H), 1.96-1.74 (m, 3H), 1.52-1.45 (m, 1H), 1.35-1.21 (m, 3H), 1.14 (s, 3H), 0.97-0.84 (m, 4H), 0.79 (q, $J = 12.3$ Hz, 1H).

To a solution of ketal 4.116 (18.8 mg, 0.0602 mmol) in THF (2 mL) in a 7 mL vial was added 2N HCl (1 mL) dropwise under ambient atm at 0 °C. The addition was completed in less than 1 min. The vial was capped with a PTFE-lined cap and stirred at 0 °C for 2 h 10 min. The reaction was quenched with the slow addition of saturated aqueous NaHCO$_3$ (2 mL) at the same temperature. The mixture was stirred vigorously until bubbling ceased. The mixture was then transferred to a separatory funnel containing saturated aqueous NaHCO$_3$ (5 mL) and Et$_2$O (5 mL), rinsing with Et$_2$O (5 mL). After mixing and phase separation, the aqueous layer was extracted with Et$_2$O (2 × 5 mL). The combined organics were washed with brine, dried over MgSO$_4$, filtered and concentrated in vacuo at room temperature. The crude product was taken up in a minimum amount of 60% DCM/pentane and loaded onto a silica gel column equilibrated with 60% DCM/pentane. The crude product was purified by silica gel chromatography (60% to 70% DCM/pentane) to afford the product 4.116-1 as a single isomer (8.5 mg, 62%). $^1$H-NMR matches literature data.

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

$\delta$ 9.52 (d, $J = 8.0$ Hz, 1H), 7.38 (app d, $J = 8.0$ Hz, 2H), 7.31 (app t, $J = 7.5$ Hz, 2H), 7.21 (d, $J = 7.5$ Hz, 1H), 6.86 (dt, $J = 15.5$, 6.5 Hz, 1H), 6.75 (dd, $J = 15.5$, 10.0 Hz, 1H), 6.47 (d, $J = 15.5$ Hz, 1H), 6.23 (dd, $J = 15.0$, 10.5 Hz, 1H), 6.14 (ddt, $J = 15.5$, 6.5, 1.0 Hz, 1H), 5.79 (dt, $J = 15.0$, 7.5 Hz, 1H), 2.38 (app q, $J = 7.0$ Hz, 2H), 2.22 (app q, $J = 8.0$ Hz, 2H), 1.67 (quint, $J = 7.5$ Hz, 1H).
The following procedure is modified from a published procedure\(^5\): A solution of imidazolidinone catalyst (29.4 mg, 0.118 mmol) in MeCN (1.2 mL) in a 7 mL vial was cooled to \(-35^\circ C\) in a dry ice/ethylene glycol/EtOH bath with stirring. TFA (9 \(\mu\)L, 0.118 mmol) and H\(_2\)O (24 \(\mu\)L) were added. The solution was stirred for 5 min at the same temperature. 75 \(\mu\)L of this solution was then added to the 2 mL vial containing aldehyde 4.116-1. The vial was capped with a PTFE-lined cap and left to stand in a -18 °C freezer for 39 h. The reaction was then warmed to room temperature and loaded directly onto a silica gel column equilibrated with 5% EtOAc/pentane, rinsing with a small amount of the same solvent mixture. The product was eluted with 5% EtOAc/pentane. The fractions containing the product were concentrated \textit{in vacuo} at room temperature to give the product 4.12 as a crystalline solid (6.7 mg, 79% yield). The d.r. was determined to be 17:1 \(^1\)H-NMR. The e.r. was determined to be 95.5:4.5 by chiral HPLC (Chiralcel-OD-H, 15% IPA/hexane isocratic elution, flow rate = 0.75 mL/min, \(t_r\) (minor) = 5.33 min, \(t_r\) (major) = 5.85 min). \(^1\)H-NMR matches reported literature data.\(^5\)

In the glovebox, the 7 mL vial containing 4.122 (34.6 mg, 0.0685 mmol, 1 equiv) and a stir bar was charged with Mg turnings (70.5 mg, 2.90 mmol, 42.3 equiv). The vial was sealed with a septum cap and brought out of the glovebox and placed under N\(_2\). MeOH (1.4 mL) was added via syringe and the mixture was sonicated for 2 min, then stirred at rt with an N\(_2\) inlet needle. Note: an exotherm formed as the Mg turnings dissolved, but the reaction was not cooled. The reaction was stirred for 16 h, then quenched with the addition of sat. aq. NH\(_4\)Cl (2 mL). The mixture was transferred to a separatory funnel, rinsing with Et\(_2\)O (10 mL) and H\(_2\)O (5 mL). After mixing and phase separation, the aqueous layer was extracted with Et\(_2\)O (2 x 5 mL). The combined organics were washed with H\(_2\)O (10 mL), brine, dried over Na\(_2\)SO\(_4\),
filtered and concentrated \textit{in vacuo}. The residue was taken up in CH$_2$Cl$_2$, filtered through a pad of Na$_2$SO$_4$ and concentrated \textit{in vacuo}. After drying under high vacuum, the material was re-subjected to the above reaction conditions to consume the remaining starting material. After the same work-up procedure described above, the desired reduced product \textbf{4.122-1} was obtained as a 4:1 mixture of ethyl:methyl ester (29.1 mg, 84\% yield). This material was used without further purification. NMR data matches that of product from manual synthesis (Chapter 3).

The 7 mL vial containing ester \textbf{4.122-1} (27.6 mg, 0.0544 mmol, 1 equiv) was charged with a stir bar and sealed with a septum cap. The vial was vac-filled with N$_2$ (× 3). THF (1.1 mL) was added via syringe and the solution cooled to -25 °C in a dry ice/ethylene glycol/ethanol bath. DIBAl-H (1M in hexanes, 0.27 mL, 0.27 mmol, 4.96 equiv) was added dropwise. The reaction was stirred at -20 °C for 2 h. The reaction was quenched by adding sat. Rochelle’s salt solution (1.5 mL) was dropwise at -20 °C. Et$_2$O (1.5 mL) was then added. The mixture was stirred vigorously for 10 min, then H$_2$O (1 mL) and Et$_2$O (1mL) were added. After stirring for another 10 min, the mixture was transferred to a separatory funnel, rinsing with H$_2$O (8mL) and Et$_2$O (8 mL). After mixing and phase separation, the aqueous layer was extracted with Et$_2$O (2 × 5 mL). The combined organics were washed with H$_2$O, brine, dried over Na$_2$SO$_4$, filtered and concentrated \textit{in vacuo}. The crude product was purified by silica gel chromatography (5\% to 10\% to 20\% Et$_2$O/hexanes) to give the product \textbf{4.122-2} as a colorless oil (22.5 mg, 89\% yield). NMR data matches that of product from manual synthesis (Chapter 3).

To a solution of \textbf{4.122-2} (22.3 mg, 0.048 mmol) in THF (0.75 mL) and pyridine (0.25 mL) in a polyethylene vial equipped with a stir bar was added HF-pyridine (0.18 mL) dropwise at 0 °C. The vial was purged with N$_2$, and sealed with a screw cap. The reaction was gradually warmed to rt. After 5 h, another portion of HF-pyridine (0.05 mL) was added to the reaction at rt. The reaction was then stirred for another 1.5 h, then quenched by the slow addition of sat. aqueous NaHCO$_3$ (3 mL). The mixture was transferred to a separatory funnel containing sat. aq. NaHCO$_3$ (10 mL), rinsing with Et$_2$O (10 mL). After mixing and phase separation, the aqueous layer was extracted with Et$_2$O (3 × 5 mL). The combined organics were washed with H$_2$O, brine, dried over Na$_2$SO$_4$, filtered and concentrated. The crude product was purified by silica gel chromatography (20\% to 30\% to 40\% EtOAc/hexanes) to give the pure product.
4.122-3 as a colorless oil (13.7 mg, 93% yield). NMR data matches that of product from manual synthesis (Chapter 3).

The following procedure was modified from a published procedure: To a Schlenk tube sealed with a rubber septum and vac-filled with N₂ (3×) was added CH₂Cl₂ (0.3 mL) followed by DMSO (30 µL, 0.386 mmol, 8.7 equiv). The solution was cooled to -78 °C in a dry ice/acetone bath. Oxalyl chloride (2.0 M in CH₂Cl₂, 90 µL, 0.18 mmol, 4.05 equiv) was added dropwise via syringe. The resulting solution was stirred at -78 °C for 30 min. A solution of diol 4.122-3 (13.7 mg, 0.0444 mmol, 1.0 equiv) in CH₂Cl₂ (0.3 mL) in a 7 mL vial was added dropwise to the reaction flask via syringe, rinsing with CH₂Cl₂ (0.3 mL). The solution was stirred for 20 min at –78 °C, then NEt₃ (45 µL, 0.32 mmol, 7.25 equiv) was added into the reaction dropwise. The reaction was stirred for 5 min at the same temperature, then the cold bath was removed and the reaction stirred at room temperature for another 45 min. TLC showed complete conversion of the diol. The reaction was cooled to 0 °C in an ice/water bath. Dry MeNH₂ gas was then passed above the reaction solution over 4 min via an inlet needle with an outlet needle, causing an increase in reaction volume and dissolution of the solids. The reaction was stirred for 4 h, gradually warming to room temperature in the ice/water bath. The flask was then opened to the Schlenk line, causing evaporation of the dissolved MeNH₂. The solvent was removed under a stream of N₂, giving a yellow oily solid. The rubber septum was quickly replaced with a new septum under positive N₂ flow, and the residue was dried under high vacuum overnight. The flask was filled with N₂. Dry AcOH (0.7 mL) was added to dissolve the brown residue. The solution was stirred at 80 °C (oil bath temperature) for 8.5 h. The reaction was cooled to room temperature and transferred to an Erlenmeyer flask equipped with a stir bar, rinsing with CH₂Cl₂ (10 mL). The solution was cooled to 0 °C in an ice/water bath. 3N NaOH was added dropwise with stirring until pH>10 (approx. 4.4 mL). The mixture was transferred to a separatory funnel, rinsing with CH₂Cl₂ (5 mL). After phase separation the pH was adjusted to 14 with 2 drops of 3N NaOH. The aqueous phase was then extracted with CH₂Cl₂ (2 × 3 mL). The combined organics were washed with saturated NaHCO₃ (aq), dried over Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by silica gel column chromatography (20-40% EtOAc/pentane) to give the product as a colorless oil (6.0 mg, 47% yield). NMR data matches that of product from manual synthesis (Chapter 3)
3. Synthesis of building blocks

a. Synthesis of building blocks for 4.3

To a 500-mL Schlenk flask charged with Sn(OTf)$_2$ (112.5 mmol, 46.9 g) was added CH$_2$Cl$_2$ (500 mL) and triethylamine (120 mmol, 16.7 mL) dropwise. The resulting orange-brown suspension was cooled to -78 °C. To the stirred mixture was added (S)-1-(p-methoxybenzyl)-2-methylpentan-3-one (4.31-1) (75.0 mmol, 17.8 g, 2.00 mL) as a neat liquid over 15 minutes. The mixture was stirred for 2 hours at -78 °C. To the mixture was added 3-(trimethylsilyl)propionaldehyde$^7$ (43) (112.5 mmol, 14.2 g) as a neat liquid over 20 minutes. The mixture was stirred for an additional 3 hours at -78 °C. The reaction was quenched by pouring the mixture slowly into saturated aqueous NH$_4$Cl (300 mL) cooled in an ice bath, rinsing with additional CH$_2$Cl$_2$. The mixture was stirred vigorously for 10 minutes, then filtered through Celite™ to remove the tin(II) salts. The filtrate was transferred to a 2-L separatory funnel and the phases separated. The organic phase was washed with saturated aqueous NH$_4$Cl (200 mL). The combined aqueous phases were extracted with CH$_2$Cl$_2$ (200 mL). The combined organic phases were washed with H$_2$O (200 mL), dried over anhydrous MgSO$_4$, filtered and concentrated in vacuo to afford a yellow-brown oil. This
residue was subjected to flash chromatography on silica gel (EtOAc:hexanes 8:100 → 20:100) to afford 3-2.2 as a colorless oil (36.71 g, 73% yield).

TLC (20% EtOAc/hexanes)
R_f = 0.22, stained by KMnO_4

^1^H-NMR (500 MHz, CDCl_3)
δ 8.5 (app d, J = 8.5 Hz, 2H), 6.87 (app d, J = 8.5 Hz, 2H), 4.78 (d, J = 3.5 Hz, 1H), 4.43 (d, J = 11.5 Hz, 1H), 4.36 (d, J = 11.5 Hz, 1H), 3.79 (s, 3H), 3.58 (app t, J = 9 Hz, 1H), 3.41 (dd, J = 9, 5 Hz, 1H), 3.14 (m, 1H), 2.92, (dq, J = 7.5, 3 Hz, 1H), 1.26 (d, J = 7.5 Hz, 3H), 1.01 (d, J = 7 Hz, 3H), 0.17 (s, 9H).

^13^C-NMR (125 MHz, CDCl_3)
δ 216.1, 159.3, 129.5, 129.3, 113.8, 104.0, 90.2, 73.1, 63.3, 55.2, 51.7, 44.7, 13.5, 10.5, -0.2

HRMS (ESI+)
Calculated for C_{20}H_{30}O_{4}NaSi: 385.1811
Found: 385.1808

To a 1-L, 3-neck, round-bottom flask charged with tetramethylammonium triacetoxyborohydride (298 mmol, 78.30 g) was added dry acetic acid (240 mL) and MeCN (400 mL). The resulting homogeneous solution was cooled to -30 °C and stirred for 30 minutes. To the stirred solution was added 4.31-2 (71.6 mmol, 25.95 g), dropwise over 1 minute, as a solution in MeCN (50 mL + 50 mL rinse). The solution was stirred and allowed to slowly warm to 0 °C over 13 h. The reaction was then poured into aqueous dibasic sodium tartrate solution (0.5 M, 400 mL) and stirred for 1 hour. The solution was transferred into a separatory funnel, and Et_2O was added. After mixing and phase separation, the aqueous layer was extracted with Et_2O. The combined organic phase was washed with saturated aqueous NaHCO_3 (2 × 200 mL), then brine (20 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated _in vacuo_. Toluene was added to azeotrope most of the remaining acetic acid prior to silica gel purification. The residue obtained after concentration was subjected to flash chromatography on silica gel.
(EtOAc:hexanes:AcOH 10:90:2 → 20:80:2) to afford 4.31-3 as a pale yellow oil (18.51 g, 71% yield). Chromatographic purification was carried out again to obtain an analytically pure sample (colorless oil).

TLC (30% EtOAc/hexanes)

\[ R_f = 0.39, \text{stained by KMnO}_4 \]

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

\[ \delta 7.22 \text{ (app d, } J = 8.5 \text{ Hz, } 2\text{H}), 6.87 \text{ (app d, } J = 8.5 \text{ Hz, } 2\text{H}), 4.65 \text{ (d, } J = 2.5 \text{ Hz, } 1\text{H}), 4.46 \text{ (d, } J = 11 \text{ Hz, } 1\text{H}), 4.45 \text{ (d, } J = 11.5 \text{ Hz, } 1\text{H}), 3.80 \text{ (s, } 3\text{H}), 3.73-3.68 \text{ (m, } 2\text{H}), 3.45 \text{ (dd, } J = 9.5, 5.5 \text{ Hz, } 1\text{H}), 2.00-1.94 \text{, (m, } 2\text{H}), 1.03 \text{ (t, } J = 7 \text{ Hz, } 6\text{H}), 0.17 \text{ (s, } 9\text{H}). \]

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

\[ \delta 159.4, 129.4, 129.3, 113.9, 105.6, 89.6, 80.1, 73.6, 73.4, 66.0, 55.2, 40.6, 34.9, 14.8, 12.8, -0.1. \]

HRMS (ESI+)

Calculated for C\(_{20}\)H\(_{33}\)O\(_4\)Si: 365.2148

Found: 365.2152

To a 1-L Schlenk flask charged with 4.31-3 (25.8 mmol, 9.40 g) was added CH\(_2\)Cl\(_2\) (450 mL). To the stirred solution was added Proton Sponge (141.9 mmol, 38.70 g) as a solid in one portion, then trimethylsilyloxonium tetrafluoroborate (180.6 mmol, 38.70 g) as a solid in one portion. The mixture was stirred at 23 °C for 16 hours. The orange mixture was filtered and the solid was rinsed with additional CH\(_2\)Cl\(_2\) (100 mL). The filtrate was concentrated in vacuo to ~50 mL, during which a solid precipitated. To this suspension was added Et\(_2\)O (300 mL), mixed and filtered, rinsing with 150 mL Et\(_2\)O. The filtrate was transferred to a 1-L separatory funnel and washed with 0.5 M HCl (2 × 250 mL). The aqueous phase was extracted with 100 mL Et\(_2\)O. The combined organics were neutralized with saturated aqueous NaHCO\(_3\) (200 mL) and washed with brine, dried over anhydrous MgSO\(_4\), filtered and concentrated to give a yellow oil. The oil was subjected to flash chromatography on silica gel (EtOAc:hexanes 1:20 → 1:10) to afford 4.31-4 as a colorless oil (5.37 g, 53% yield).
TLC (10% EtOAc/hexanes)
\[ R_f = 0.33, \text{stained by KMnO}_4 \]

\(^1\)H-NMR (500 MHz, CDCl\(_3\))
\[ \delta 7.25 (\text{pp d, } J = 8.5 \text{ Hz, } 2\text{H}), \ 6.89 (\text{pp d, } J = 8.5 \text{ Hz, } 2\text{H}), \ 4.44 (\text{d, } J = 11.5 \text{ Hz, } 1\text{H}), \ 4.38 (\text{d, } J = 11.5 \text{ Hz, } 1\text{H}), \ 4.21 (\text{d, } J = 3 \text{ Hz, } 1\text{H}), \ 3.80 (\text{s, } 3\text{H}), \ 3.57 (\text{dd, } J = 9.5, 5 \text{ Hz, } 1\text{H}), \ 3.41 (\text{s, } 3\text{H}), \ 3.39, (\text{s, } 3\text{H}), \ 3.27 (\text{dd, } J = 9.0, 8.0 \text{ H, } 1\text{H}), \ 3.13 (\text{dd, } J = 10.0, 2.5 \text{ Hz, } 1\text{H}), \ 2.10 – 2.04, (\text{m, } 1\text{H}), \ 1.94 – 1.88 (\text{m, } 1\text{H}), \ 1.09 (\text{d, } J = 7.0 \text{ Hz, } 3\text{H}), \ 1.01 (\text{d, } J = 7.5 \text{ Hz, } 3\text{H}), \ 0.18 (\text{s, } 9\text{H}). \]

\(^1\)C-NMR (125 MHz, CDCl\(_3\))
\[ \delta 160.0, 130.8, 129.0, 113.7, 104.7, 90.9, 85.1, 72.7, 72.0, 71.3, 61.2, 56.5 (2\text{C}), 55.2, 41.7, 35.7, 16.4, 11.3, 0.0. \]

HRMS (ESI+)

Calculated for C\(_{22}\)H\(_{36}\)O\(_4\)NaSi: 415.2281

Found: 415.2272

To a stirred solution of 4.31-4 in MeCN and H\(_2\)O was added ceric ammonium nitrate (1.844 mmol, 1.011 g) portion wise over 15 minutes under ambient atmosphere and temperature. The solution was stirred for 60 min at 23 °C, then diluted with Et\(_2\)O (100 mL) and washed H\(_2\)O (150 mL) and saturated NaHSO\(_3\) (2 × 150 mL). The combined aqueous layer was extracted with Et\(_2\)O (100 mL). The organic phase was dried over anhydrous MgSO\(_4\), filtered and concentrated. The resulting oil was subjected to flash chromatography on silica gel (EtOAc:CH\(_2\)Cl\(_2\) 0:100 → 20:100) to afford 4.31-5 as a colorless oil (202 mg, 77% yield).

TLC (20% EtOAc/hexanes)
\[ R_f = 0.37, \text{stained by KMnO}_4 \]

\(^1\)H-NMR (500 MHz, CDCl\(_3\))
δ 4.23 (d, J = 3 Hz, 1H), 3.86 (d, J = 11, 3 Hz, 1H), 3.53 (dd, J = 11.5, 4.5 Hz, 1H), 3.46, (s, 3H), 3.40 (s, 3H), 3.24 (dd, J = 10, 2 Hz, 1H), 2.01-1.95 (m, 1H), 1.88-1.82, (m, 1H), 1.18 (d, J = 7.5 Hz, 3H), 0.99 (d, J = 7 Hz, 3H), 0.18 (s, 9H).

13C-NMR (125 MHz, CDCl3)
δ 104.3, 91.4, 87.7, 71.8, 64.4, 61.4, 56.4, 42.1, 35.6, 16.1, 11.2, -0.1

HRMS (ESI+)
Calculated for C_{14}H_{28}O_{3}NaSi: 295.1705
Found: 295.1708

To a solution of 4.31-5 (15.15 mmol, 4.13 g) in CH2Cl2 (150 mL) in a 300-mL round-bottom flask cooled to 0 °C was added Dess-Martin Periodinane (30.3 mmol, 12.86 g) portionwise over 5 minutes, under ambient atmosphere. The reaction was stirred for 10 minutes after the addition was complete, then the ice/water bath was removed. The reaction was stirred for another 75 minutes, and then transferred to a separatory funnel. The mixture was extracted with 1:1 saturated NaHCO3/1.5 M Na2S2O3 (6 × 50 mL) until TLC indicated that all byproducts have been removed. The aqueous phase was then extracted with CH2Cl2 (100 mL), and the combined organic phases were washed with brine, dried over anhydrous Na2SO4, filtered and concentrated at 27 °C. The resulting oil (4.31-6) was dried briefly under high vacuum (~15 minutes), then used immediately for the next reaction.

To a 500-mL Schlenk flask charged with anhydrous CrCl2 (242.4 mmol, 29.81 g) was added THF (250 mL) and cooled to 10 °C in an ice/water bath. With the exclusion of light, to the stirred suspension was added slowly over 15 minutes via cannula a solution of 4.31-6 (assumed 15.15 mmol) and CHI3 (75.75 mmol, 29.83 g) in THF (80 mL). The resulting red mixture was stirred at 23 °C for 2 hours. The mixture was filtered through Celite™ and washed with Et2O (300 mL). The dark-colored solution was transferred to a separatory funnel and washed with H2O (2 x 200 mL), brine, then dried over anhydrous MgSO4, filtered and concentrated to give a black residue. The residue was absorbed onto Celite™ in vacuo from
an acetone solution. The resulting powder was subjected to flash chromatography on silica gel (hexanes:EtOAc 100:0 → 20:100). The product obtained after chromatography was stirred with saturated Na₂SO₃ and passed through a pad of Darco® to remove residual iodine to afford 4.31-7 as a pale yellow oil (4.06 g, 68% yield over 2 steps).

TLC (20% EtOAc/hexanes)
Rᵣ = 0.52, stained by KMnO₄.

¹H-NMR (500 MHz, CDCl₃)
δ 6.55 (dd, J = 15, 9.5 Hz, 1H), 6.02 (dd, J = 15, 1 Hz, 1H), 4.23 (d, J = 2 Hz, 1H), 3.43, (s, 3H), 3.39 (s, 3H), 3.04 (dd, J = 10, 2 Hz, 1H), 2.49-2.43 (m, 1H), 1.72-1.65 (m, 1H), 1.13 (d, J = 6.5 Hz, 3H), 0.94 (d, J = 7 Hz, 3H), 0.19 (s, 9H); ¹³C-NMR (125 MHz, CDCl₃): δ 147.3, 104.3, 91.3, 85.1, 75.1, 71.8, 61.3, 56.4, 43.2, 42.1, 18.1, 10.8, -0.0.

HRMS (ESI+)
Calculated for C₁₅H₂₇O₂NaISi: 417.0723
Found: 417.0741

In an unoptimized procedure, a dry 200-mL Schlenk flask was charged with THF (46 mL) and 4.31-7 in 10 mL THF. The solution was cooled to -78 °C and n-BuLi (1.6 M in hexanes, 12.3 mmol, 7.7 mL) was added dropwise via cannula over 15 minutes, during which the reaction turned yellow. The reaction was stirred at -78 °C for 25 minutes, then trimethylborate (13.45 mmol, 1.5 mL) was added neat in one portion. Stirring was continued at -78 °C for 20 minutes, then the cooling bath was removed. The reaction was slowly warmed to 23 °C over 2 hours. The reaction was poured into a 1 N HCl solution (200 mL) pre-cooled to 0 °C and stirred for 15 minutes. The mixture was transferred to a separatory funnel, rinsing with 100 mL Et₂O. The mixture was shaken and the phases were separated. The aqueous phase was extracted with Et₂O (2 × 50 mL). The combined organics were washed with H₂O (50 mL), brine, dried over anhydrous MgSO₄, filtered and concentrated to give a yellow oil (4.31-8), which was diluted with toluene (30 mL) and used directly in the next step.
To a solution of 4.31-8 in toluene (50 mL) and DMSO (5 mL) was added N-methyliminodiacetic acid (1.45 g, 9.84 mmol). The round-bottom flask was fitted with a Dean-Stark trap and a reflux condenser and refluxed for 4 hours. The reaction was cooled to 23 °C and transferred into 1:1 saturated NaCl/H₂O (50 mL). The organic phase was washed with another 50 mL 1:1 saturated NaCl/H₂O. The combined aqueous phase was washed with Et₂O (2 × 50 mL), and the organic layer was dried over anhydrous MgSO₄, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (Et₂O:acetone 100:0 → 1:2) to give 4.31-9 as a white solid (1.74 g, 50% yield over 2 steps).

TLC (acetone/hexane 1:1)

Rᵣ = 0.47, stained by KMnO₄.

¹H-NMR (500 MHz, CDCl₃)

δ 6.24 (dd, J = 18, 8 Hz, 1H), 5.41 (dd, J = 18, 1 Hz, 1H), 4.21 (d, J = 3 Hz, 1H), 3.82 (d, J = 16.5 Hz, 2H), 3.66 (dd, J = 16.5, 3 Hz, 2H), 3.40 (s, 3H), 3.38 (s, 3H), 3.08 (dd, J = 10, 2 Hz, 1H), 2.80, (s, 3H), 2.52-2.49 (m, 1H), 1.68-1.61 (m, 1H), 1.13 (d, J = 7 Hz, 3H), 0.95 (d, J = 7 Hz, 3H), 0.17 (s, 9H).

¹³C-NMR (125 MHz, CDCl₃)

δ 167.6, 167.5, 148.9, 104.8, 91.3, 85.6, 72.1, 61.6, 61.2, 56.8, 46.9, 42.8, 42.1, 18.2, 11.2, 0.2.

HRMS (ESI+)

Calculated for C₂₀H₃₅BNO₆Si: 424.2327

Found: 424.2329

To a solution of 4.31-9 (1.69 g, 3.99 mmol) in acetone/H₂O/lutidine (10:10:1, 84 mL) at 0 °C was added AgNO₃ (3.39 g, 20.0 mmol) in one portion. The reaction was gradually allowed to warm to 23 °C over 2.5 hours. The reaction was quenched by transferring the mixture into saturated aqueous NH₄Cl (100 mL) and diluted with EtOAc (50 mL). The mixture was filtered to remove the insoluble salts. The filtrate was transferred to a separatory funnel and the phases were separated. The organic phase was washed with 0.5
M HCl (2 × 50 mL) and the aqueous phase extracted with EtOAc (50 mL). The organic layer was washed with brine, dried over anhydrous MgSO₄, filtered and concentrated to afford a white foam. The foam was dissolved in Et₂O (~10 mL), then 20% Et₂O/hexane (30 mL) was added and the suspension was filtered, washing with additional 20% Et₂O/hexane (20 mL). The filtrate was concentrated in vacuo to give 4.31-10 as a white solid (1.22 g, 87% yield).

TLC (acetone/hexane 1:1)

R_f = 0.34, stained by KMnO₄

¹H-NMR (500 MHz, CDCl₃)

δ 6.24 (dd, J = 17.5, 8 Hz, 1H), 5.41 (dd, J = 17.5, 1 Hz, 1H), 4.23 (t, J = 2 Hz, 1H), 3.79 (d, J = 16 Hz, 2H), 3.66 (dd, J = 16, 1.5 Hz, 2H), 3.42 (s, 3H), 3.40 (s, 3H), 3.09 (dd, J = 10, 2.5 Hz, 1H), 2.81, (s, 3H), 2.55-2.47 (m, 1H), 2.40 (d, J = 2 Hz, 1H), 1.69-1.61 (m, 1H), 1.14 (d, J = 7 Hz, 3H), 0.96 (d, J = 7 Hz, 3H).

¹³C-NMR (125 MHz, CDCl₃)

δ 168.1, 168.0, 148.1, 85.3, 82.6, 74.3, 71.2, 61.4, 61.0, 56.6, 46.9, 42.5, 41.9, 18.0, 10.7

HRMS (ESI+)

Calculated for C_{17}H_{27}BNO₆: 352.1931

Found: 352.1933

Preparation of catalyst stock solution. A dry 7-mL vial equipped with a PTFE-coated magnetic stir bar was charged with RuPhos (9.3 mg, 0.02 mmol). The vial was brought into the glovebox, and Pd₂dba₃ (4.6 mg, 0.005 mmol) was added. CH₂Cl₂ (3 mL) was added, and the mixture was stirred at 23 °C for 25 minutes.

The freshly prepared catalyst stock solution was used immediately for the preparation of 4.31-11: A dry 20-mL vial equipped with a PTFE-coated magnetic stir bar was charged with 4.31-10 (176 mg, 0.5 mmol). The vial was evacuated and filled with argon (x 3), then CH₂Cl₂ (5 mL) was then added, followed by the catalyst stock solution, rinsing with CH₂Cl₂ (2 mL). Tributyltin hydride (0.27 mL, 1.00 mmol) was added neat dropwise to the reaction under argon at 23 °C, over 1 hour 25 minutes. The reaction was stirred at 23
°C for 2 hours after the addition was complete. The reaction was concentrated in vacuo and purified by silica gel chromatography (10% to 50% acetone/hexanes). The yellow solid obtained after concentration was dissolved in 10% acetone/hexanes and passed through a pad of Darco® and Celite™ to give a colorless solution. The solution was concentrated in vacuo to give 4.31-11 as an off-white solid (255 mg, 79% yield).

TLC (acetone/hexane 1:1)
R_f = 0.47, stained by KMnO_4

^1^H-NMR (500 MHz, CDCl_3)
δ 6.27 (dd, J = 18, 7.5 Hz, 1H), 6.12, (d, J = 19 Hz, 1H), 5.84, (dd, J = 19, 6 Hz, 1H), 5.38 (d, J = 18 Hz, 1H), 3.83-3.82 (m, 1H), 3.79 (dd, J = 16.5, 3 Hz, 2H), 3.65 (d, J = 16.5 Hz, 2H), 3.46-3.44 (m, 1H), 3.44 (s, 3H), 3.26 (s, 3H), 3.11 (dd, J = 9.5, 2.5 Hz, 1H), 2.78, (s, 3H), 2.55-2.47 (m, 1H), 1.53-1.47 (m, 6H), 1.31 (sext, J = 7.5 Hz, 6H), 1.13 (d, J = 6.5 Hz, 3H), 0.91-0.87 (m, 15H), 0.77 (d, J = 7.5 Hz, 3H)

^13^C-NMR (125 MHz, CDCl_3)
δ 167.4, 149.1, 147.5, 130.4, 86.1, 84.0, 61.4, 60.8, 56.4, 46.6, 42.0, 41.7, 29.1, 27.2, 18.1, 13.7, 9.8, 9.4

LRMS (ESI+)
Calculated for C_{29}H_{55}BNO_6Sn: 644.3
Found: 644.3

To a solution of 4.31-11 (1.387 g, 2.16 mmol) in CH_2Cl_2 (20 mL) in a 50-mL round-bottom flask was added dropwise a solution of I_2 (0.576 g, 2.27 mmol) in CH_2Cl_2 (30 mL) via a pressure-equalizing funnel at 0 °C under ambient atmosphere over 1 hour. The funnel was rinsed with CH_2Cl_2 (10 mL) and the solution added portion wise to the reaction. The ice bath was removed and the reaction was allowed to gradually warm to 23 °C over 1 hour. The reaction was transferred into a 250-mL separatory funnel, rinsing with additional CH_2Cl_2. The organic layer was washed with 2 × 30 mL 1 M Na_2S_2O_3 solution, then with 2 × 25 mL 3 M KF solution. The combined aqueous layer was extracted with 25 mL CH_2Cl_2.
The organic phase was dried over anhydrous MgSO₄, filtered and concentrated \textit{in vacuo}. The crude product was purified by silica gel chromatography (1:6 to 2:3 acetone/hexanes) to give \textit{4.31} as a white solid (0.827 g, 80%).

TLC (acetone/hexane 1:1)

\[ R_f = 0.32, \text{stained by KMnO}_4 \]

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

\[
\delta 6.46\ (dd, J = 14.5, 7 \text{ Hz, } 1\text{H}),\ 6.26,\ (d, J = 14.5 \text{ Hz, } 1\text{H}),\ 6.19,\ (dd, J = 17.5, 7.5 \text{ Hz, } 1\text{H}),\ 5.39\ (d, J = 17.5 \text{ Hz, } 1\text{H}),\ 3.94\ (d, J = 16.5 \text{ Hz, } 2\text{H}),\ 3.88\ (m, 1\text{H}),\ 3.68\ (dd, J = 16.5, 4.5 \text{ Hz, } 2\text{H}),\ 3.42\ (s, 3\text{H}),\ 3.26\ (s, 3\text{H}),\ 3.07\ (dd, J = 9.5, 1.5 \text{ Hz, } 1\text{H}),\ 2.80,\ (s, 3\text{H}),\ 2.55\ (m, 1\text{H}),\ 1.52\ (m, 1\text{H}),\ 0.76\ (d, J = 7.0 \text{ Hz, } 3\text{H}).
\]

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

\[
\delta 167.7,\ 167.6,\ 148.5,\ 145.8,\ 85.8,\ 82.8,\ 61.4,\ 61.0,\ 56.7,\ 46.8,\ 41.8,\ 41.6,\ 18.0,\ 9.8
\]

HRMS (ESI+):

Calculated for C\textsubscript{17}H\textsubscript{28}BNO\textsubscript{6}I: 480.1054

Found: 480.1053

\[ \text{b. Synthesis of building blocks for the ratanhine library} \]

To a stirred solution of triphenylphosphine (1.10 g, 4.2 mmol, 1.2 equiv) in THF (10 mL) at 0 °C was added dropwise diisopropylazodicarboxylate (DIAD; 830 μL, 4.2 mmol, 1.2 equiv) to generate a yellow suspension. In one portion, 4-bromo-3-methoxyphenol (711 mg, 3.5 mmol, 1 equiv) and 2-(tert-butyldiphenylsilyl)ethanol (1.19 g, 4.2 mmol, 1.2 equiv) were added. The mixture was stirred for 15 minutes, after which the ice bath was then removed and the reaction warmed to ambient temperature. After stirring for 1 hour, the reaction was diluted with diethyl ether and adsorbed onto Celite™ \textit{in vacuo}. The Celite™ pad was loaded onto a silica gel column and eluted with hexanes/DCM gradient (4:1 to 3:7). Fractions containing a minor impurity were re-adsorbed on Celite™ and eluted from a silica gel column.
using a hexanes/DCM gradient (4:1 to 3:1). Purified fractions were combined to afford 4.58 as a colorless amorphous solid (1.19g, 72% yield).

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

\(\delta 7.74 - 7.72\) (m, 4H), 7.50 - 7.44 (m, 6H), 7.34 (d, \(J = 8.5\) Hz, 1H), 6.43 (d, \(J = 2.5\) Hz, 1H), 6.27 (dd, \(J = 9.0, 3.0\) Hz, 1H), 4.08 - 4.05 (m, 2H), 3.81 (s, 3H) 1.86 – 1.83 (m, 2H), 1.11 (s, 9H); \(^1\)C-NMR (125 MHz, acetone-\(d_6\)): \(\delta 160.5, 157.5, 136.6, 134.7, 133.8, 130.3, 128.7, 107.7, 102.4, 101.3, 66.3, 56.4, 28.1, 18.5, 12.5.

HRMS (EI+)

Calculated for C\(_{25}\)H\(_{29}\)O\(_2\)SiBr: 468.11202

Found: 468.11118

\[\begin{array}{c}
\text{F}_3\text{CO} & \text{OH} \\
\text{Br} & \text{TBDPS}
\end{array}\]

\[\text{PPP}_3, \text{DIAD} \]

\[\text{THF, } 0^\circ\text{C to } 23^\circ\text{C}\]

\[\begin{array}{c}
\text{F}_3\text{CO} & \text{Br} \\
\text{OH} & \text{TBDPS}
\end{array}\]

To a stirred solution of triphenylphosphine (765 mg, 3.0 mmol, 1.5 equiv) in THF (7.5 mL) at 0 °C was added dropwise diisopropylazodicarboxylate (DIAD; 570 μL, 3.0 mmol, 1.5 equiv) to generate a yellow suspension. In one portion, 4-bromo-3-(trifluoromethoxy)phenol (500 mg, 2.0 mmol, 1 equiv) and 2-(tert-butyldiphenylsilyl)ethanol (830 mg, 3.0 mmol, 1.5 equiv) were added. The mixture was stirred for 15 minutes, after which the ice bath was then removed and the reaction warmed to ambient temperature. After stirring for 16 hours, the reaction was diluted with diethyl ether and adsorbed onto Celite™ in \textit{vacuo}. The Celite™ pad was loaded onto a silica gel column and eluted with 4:1 hexanes/DCM. The colorless oil from this column was re-adsorbed onto Celite™, loaded onto silica gel, and eluted with a hexanes/DCM gradient (hexanes to 9:1 hexanes/DCM) to afford 4.59 as a colorless oil (785 mg, 77% yield).

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

\(\delta 7.71 - 7.69\) (m, 4H), 7.55 (d, \(J = 8.5\) Hz, 1H), 7.47 – 7.41 (m, 6H), 6.82 – 6.81 (m, 1H), 6.75 (dd, \(J = 8.5, 2.5\) Hz, 1H), 4.11 – 4.07 (m, 2H), 1.86 – 1.83 (m, 2H), 1.08 (s, 9H).

\(^1\)C-NMR (125 MHz, acetone-\(d_6\))


Triphenylphosphine (PPh₃, 7450 mg, 28.4 mmol, 1.8 equiv.) was charged in a 250-mL round-bottom flask equipped with a PTFE-coated magnetic stir bar and back-filled with N₂. THF (70 mL) was added and the reaction mixture was cooled to 0 °C for 10 minutes. Diisopropyl azodicarboxylate (DIAD, 5.6 mL, 28.4 mmol, 1.8 equiv.) was added dropwise to the reaction flask affording a white precipitate. This heterogeneous mixture was stirred at 0 °C for 10 minutes. 2-trimethylsilylethanol (4.1 mL, 28.4 mmol, 1.8 equiv.) was added to the reaction flask and the resulting mixture was stirred at 0 °C for 10 minutes.

Methyl p-hydroxybenzoate (2400 mg, 15.8 mmol, 1.0 equiv.) was added to the flask in one portion followed by THF (10 mL) and the resulting reaction mixture was stirred at 0 °C for 10 minutes. After 10 min, the reaction mixture was warmed to 23 °C with stirring for 16 hours. After 16 hours, the reaction mixture was concentrated in vacuo to afford a clear oil. This crude oil was dissolved in minimum amount of diethyl ether (5 mL). Hexanes (100 mL) were added and the solution was stirred at 23 °C for 5 minutes until white solid precipitated. The solid was filtered through a fritted filter funnel rinsing with hexanes. The filtrate was concentrated in vacuo to afford a clear oil, which was adsorbed onto Celite™ from an acetone solution and purified by SiO₂ chromatography (20% DCM:hexanes → 50% DCM:hexanes) to afford 4.61-1 as a clear oil (434 mg, 11% yield).

TLC (dichloromethane:hexanes 1:1)

Rₜ = 0.28, shortwave UV.

¹H-NMR (500 MHz, CDCl₃)
δ 7.97 (d, J = 9.5 Hz, 2H), 6.88 (d, J = 9.0 Hz, 2H), 4.13 (t, J = 7.5 Hz, 2H), 3.88 (s, 3H), 1.15 (t, J = 8.0 Hz, 2H), 0.09 (s, 9H); ¹³C-NMR (125 MHz, CDCl₃): δ 216.4, 172.1, 163.5, 132.3, 121.4, 114.2, 65.8, 17.6, -1.35.

HRMS (ESI+)

Calculated for C₁₃H₂₀O₃SiNa: 275.1079
Found: 275.1084

A 40-mL vial equipped with a PTFE-coated magnetic stir bar was charged with LiOH·H₂O (722 mg, 17.2 mmol, 10 equiv.) and H₂O (4 mL). The vial was placed in a 60 °C aluminum heating block and stirred at that temperature for 5 minutes until a clear solution was afforded. The vial was removed from the heating block and a solution of 4.61-1 (434 mg, 1.72 mmol, 1.0 equiv.) in THF (9 mL, 0.2 M) was added to the reaction vial. The vial was sealed with a PTFE-lined cap and placed in a 60 °C aluminum heating block and stirred at that temperature for 14 hours. The reaction mixture was cooled to 23 °C, then to 0 °C for 10 minutes. 6 N HCl was added dropwise to the crude reaction mixture with stirring until pH ≤ 1. The reaction mixture was transferred to a separatory funnel with H₂O (20 mL) and EtOAc (40 mL). The phases were separated and the aqueous layer was extracted with EtOAc (40 mL x 2). The combined organic layers were washed with brine (50 mL), dried over anhydrous MgSO₄, and concentrated in vacuo to afford a white solid. The crude solid was adsorbed onto Celite™ from an acetone solution and purified by SiO₂ chromatography (1:4 EtOAc:hexanes → 2:1:7 EtOAc:EtOH:hexanes) to afford 4.61-2 as a white solid (361 mg, 88% yield).

TLC (EtOAc:hexanes 1:4)

Rₜ = 0.22, shortwave UV.

¹H-NMR (500 MHz, CDCl₃)

δ 8.03 (d, J = 9.0 Hz, 2H), 6.91 (d, J = 8.5 Hz, 2H), 4.15 (t, J = 7.5 Hz, 2H), 1.16 (t, J = 8.0 Hz, 2H), 0.09 (s, 9H).

¹³C-NMR (125 MHz, CDCl₃)

δ 172.2, 163.5, 132.3, 121.4, 114.2, 65.8, 17.6, -1.35
A 100-mL flask equipped with a PTFE-coated magnetic stir bar was charged with **4.61-2** (361 mg, 1.51 mmol, 1.0 equiv.) and back-filled with N₂. **4.61-3** (447 mg, 1.82 mmol, 1.2 equiv.), DMAP (222 mg, 1.82 mmol, 1.2 equiv.), and dichloromethane (20 mL, 0.08 M) were added to the reaction flask. The clear, colorless solution was cooled to 0 °C and stirred at that temperature for 10 minutes. DCC (375 mg, 1.82 mmol, 1.2 equiv.) was added in one portion at 0 °C under N₂ and stirred at that temperature for 10 minutes. The ice bath was removed after 10 minutes and the reaction flask was allowed to warm to 23 °C with stirring over 15 hours. After 15 hours, the reaction mixture was concentrated *in vacuo* to afford a yellow sludge. The crude material was adsorbed onto Celite™ from an acetone solution and purified by SiO₂ chromatography (30% DCM:hexanes → 40% DCM:hexanes) to afford **4.61-4** as a clear oil (575 mg, 81% yield).

**TLC (30% DCM:hexanes)**

R<sub>f</sub> = 0.21, shortwave UV.

**¹H-NMR (500 MHz, CDCl₃)**

δ 8.14 (d, J = 8.5 Hz, 2H), 7.92 (s, 1H), 7.61 (d, J = 8.5 Hz, 1H), 6.96 (d, J = 9.0 Hz, 2H), 6.92 (d, J = 8.5 Hz, 1H), 6.70 (dd, J = 11.0 Hz, J = 14.5 Hz, 1H), 5.78 (s, 1H), 5.74 (s, 1H), 5.32 (d, J = 11.0 Hz, 1H), 4.17 (t, J = 8.0 Hz, 2H), 1.18 (t, J = 7.5 Hz, 2H), 0.10 (s, 9H).

**¹³C-NMR (125 MHz, CDCl₃)**

δ 164.4, 163.6, 148.2, 137.5, 135.3, 132.8, 132.4, 129.2, 124.9, 120.8, 117.5, 114.4, 90.4, 65.9, 17.5, -1.33.

**HRMS (ESI+)**

Calculated for C<sub>20</sub>H<sub>24</sub>O<sub>3</sub>Si: 467.0540

Found: 467.0534
A 50-mL flask equipped with a PTFE-coated magnetic stir bar was charged with 4.61-4 (575 mg, 1.23 mmol, 1.0 equiv.), sealed with a septum, and back-filled with N₂. Dichloromethane (12 mL, 0.1 M) was added to afford a clear, colorless solution. This solution was cooled to 0 °C and stirred at that temperature for 10 minutes. Bromine (0.14 mL, 2.71 mmol, 2.2 equiv.) was added dropwise to the reaction mixture at 0 °C over the course of 20 minutes until a bright red color persisted. The crude reaction mixture was concentrated in vacuo in a 50-mL round-bottom flask and azeotroped with DCM (3 x 15 mL) to afford the dibromide as a yellow foamy solid (721 mg, 93% crude yield). The flask was charged with a PTFE-coated magnetic stir bar, sealed with a septum, and back-filled with N₂. Acetonitrile (11.5 mL, 0.1 M) was added and the reaction mixture was stirred at 23 °C for 5 minutes. DBU (0.2 mL, 1.34 mmol, 1.2 equiv.) was added dropwise and the resulting mixture was stirred for 10 minutes. After 10 minutes, incomplete conversion was observed by TLC analysis, so another 0.3 mL of DBU was added dropwise. After 20 minutes of stirring at 23 °C, the reaction mixture was cooled to 0 °C and 1 N HCl (10 mL) was added. The reaction mixture was transferred to a separatory funnel with EtOAc (15 mL) and H₂O (15 mL) and the layers were separated. The phases were separated and the aqueous layer was extracted with EtOAc (10 mL x 2). The combined organic layers were dried over anhydrous MgSO₄ and concentrated in vacuo to afford a clear oil. The crude material was adsorbed onto Celite™ from an acetone solution and purified by SiO₂ chromatography (40% DCM:hexanes) to afford 4.61-5 as a pale yellow oil (503 mg, 75% yield over two steps).

TLC (1:3 DCM:hexanes)

Rₐ = 0.25, shortwave UV.

¹H-NMR (500 MHz, CDCl₃)

δ 8.13 (d, J = 9.0 Hz, 2H), 7.78 (s, 1H), 7.70 (d, J = 8.5 Hz, 1H), 6.98 (d, J = 8.5 Hz, 1H), 6.96 (d, J = 9.0 Hz, 2H), 5.91 (d, J = 1.5 Hz, 1H), 5.84 (d, J = 2.0 Hz, 1H), 4.17 (t, J = 8.0 Hz, 2H), 1.17 (t, J = 8.0 Hz, 2H), 0.10 (s, 9H).

¹³C-NMR (125 MHz, CDCl₃)

δ 164.1, 163.6, 147.8, 138.9, 138.9, 135.4, 132.5, 125.3, 123.0, 122.7, 120.7, 114.4, 89.4, 65.9, 17.5, -1.34.
HRMS (ESI+)

Calculated for C_{20}H_{23}O_{3}SiBr: 544.9645
Found: 544.9646

In a glove box, to a 7-mL vial equipped with a PTFE-coated magnetic stir bar and containing 4.61-5 (20 mg, 0.037 mmol, 1.0 equiv.) and trans-propenyl boronic acid (4.73 mg, 0.055 mmol, 1.5 equiv.) was added ground potassium phosphate (23 mg, 0.11 mmol, 3.0 equiv.) and PdCl_{2}dppf·CH_{2}Cl_{2} (1.5 mg, 0.002 mmol, 5 mol%) followed by THF (0.7 mL, 0.05 M). The vial was sealed with a cap and removed from the glove box. The vial was placed in a 45 °C aluminum heating block and stirred at that temperature for 24 hours. After 24 hours, the reaction mixture was cooled to 23 °C, filtered through a pad of Celite™, and concentrated in vacuo. The crude material was adsorbed onto Celite™ from an acetone solution and purified by SiO_{2} chromatography (30% DCM:hexanes) to afford 4.61 as a pale yellow oil (13.5 mg, 80% yield).

TLC (1:1 DCM:hexanes)

R_f = 0.31, shortwave UV.

^1H-NMR (500 MHz, CDCl_{3})

δ 8.15 (d, J = 8.5 Hz, 2H), 7.40 (s, 1H), 7.35 (d, J = 8.5 Hz, 1H), 7.13 (d, J = 8.5 Hz, 1H), 6.96 (d, J = 9.0 Hz, 2H), 6.39 (d, J = 16.0 Hz, 1H), (dq, J = 15.5 Hz, J = 6.5 Hz, 1H), 5.89 (d, J = 1.5 Hz, 1H), 5.82 (d, J = 1.5 Hz, 1H), 4.17 (t, J = 8.0 Hz, 2H), 1.90 (d, J = 7.0 Hz, 3H), 1.17 (t, J = 8.0 Hz, 2H), 0.10 (s, 9H).

^13C-NMR (125 MHz, CDCl_{3})

δ 164.6, 163.4, 146.4, 135.8, 133.2, 132.4, 129.6, 127.6, 127.2, 126.8, 124.6, 123.2, 122.1, 121.2, 114.3, 65.9, 18.5, 17.5, -1.33.

HRMS (ESI+)

Calculated for C_{23}H_{28}O_{3}SiBr: 459.0991
Found: 459.0987
A dry 25-mL Schlenk flask equipped with a PTFE-coated magnetic stir bar was charged with phenol 4.61-3 (738 mg, 3 mmol) and DMAP (73.3 mg, 0.6 mmol) under N₂. The flask was sealed with a rubber septum and CH₂Cl₂ (15 mL) was added via syringe. To this solution was added DIPEA (2.1 mL, 12.1 mmol) in one portion. Benzylo chloride (0.7 mL, 6.03 mmol) was then added neat dropwise over 5 minutes. The reaction was stirred for another 19 hours at room temperature, then transferred into a separatory funnel containing 1 N HCl (10 mL). After mixing and phase separation, the organic layer was washed with another portion of 1 N HCl (10 mL) and then with H₂O (20 mL). The combined aqueous layer was extracted with CH₂Cl₂ (20 mL). The organic phase was washed with brine (20 mL), dried over anhydrous MgSO₄, filtered and concentrated. The crude product was purified by silica gel chromatography (30 - 35% CH₂Cl₂/hexanes) to afford 4.62-1 as a colorless viscous oil (643 mg, 61% yield).

TLC (50% DCM/hexanes)  
R_f = 0.44, visualized by shortwave UV.

¹H-NMR (500 MHz, CDCl₃)  
δ 8.21 (d, J = 7 Hz, 2H), 7.94 (d, J = 2 Hz, 1H), 7.66 (tt, J = 7.5, 1.5 Hz, 1H), 7.63 (dd, J = 8, 1.5 Hz, 1H), 7.56 (t, J = 7.5 Hz, 2H), 6.94 (d, J = 8.5 Hz, 1H), 6.71 (dd, J = 17.5, 11 Hz, 1H), 5.77 (dd, J = 18, 1 Hz, 1H), 5.34 (d, J = 11 Hz, 1H).

¹³C-NMR (125 MHz, CDCl₃)  
δ 164.6, 148.0, 137.5, 135.4, 133.9, 132.7, 130.2, 129.0, 128.9, 128.7, 124.7, 117.7, 90.6.

HRMS (ESI+)  
Calculated for C₁₅H₁₂O₂I: 350.9882  
Found: 350.9890
A solution of 4.62-1 (3.37 g, 9.62 mmol) in CH₂Cl₂ (120 mL) in a 200-mL round-bottom flask was cooled to 0 °C under N₂. Bromine (0.49 mL, 9.6 mmol) was added neat dropwise over 15 minutes. After the addition was complete, the reaction was stirred for a further 5 minutes. The reaction was concentrated in vacuo to give an orange solid. Residual bromine was removed by azeotroping the residue with CH₂Cl₂ (15 mL × 2). The round bottom flask containing the crude product and equipped with a PTFE-coated magnetic stir bar was sealed with a rubber septum and back-filled with N₂ twice. MeCN (120 mL) was added to dissolve most of the solid. DBU (1.4 mL, 9.5 mmol) was then added neat dropwise via syringe over 15 minutes. The reaction was stirred for 15 minutes before being charged with another portion of DBU (0.2 mL, 1.34 mmol) added neat dropwise into the reaction. After another 15 minutes, another portion of DBU (0.2 mL, 1.34 mmol) was added. The reaction was poured slowly into 2 N HCl solution (100 mL) cooled to 0 °C with vigorous stirring. EtOAc (50 mL) was added and the mixture stirred. After phase separation, the aqueous layer was extracted with EtOAc (50 mL). The combined organic phase was washed with brine (100 mL), then dried over anhydrous MgSO₄, filtered and concentrated in vacuo. The crude product was purified by silica gel chromatography (30-35% CH₂Cl₂/hexanes) to afford 4.62-2 as an off-white solid (2.67 g, 66% yield over 2 steps).

TLC (40% CH₂Cl₂/hexanes)
  Rₚ = 0.47, visualized by shortwave UV.

¹H-NMR (500 MHz, CDCl₃)
  δ 8.20 (d, J = 7.5 Hz, 2H), 7.79 (d, J = 2 Hz, 1H), 7.72 (dd, J = 8.5, 2 Hz, 1H), 7.66 (t, J = 7.5 Hz, 1H), 7.52 (tt, J = 8, 1.5 Hz, 2H), 6.99 (d, J = 8.5 Hz, 1H), 5.92 (d, J = 2 Hz, 1H), 5.85 (d, J = 1.5 Hz, 1H).

¹³C-NMR (125 MHz, CDCl₃)
  δ 164.4, 147.6, 138.9, 135.4, 133.9, 130.3, 128.8, 128.6, 125.1, 123.1, 122.5, 89.7.

HRMS (ESI+)
  Calculated for C₁₅H₁₀O₂BrINa: 450.8807
  Found: 450.8809
A dry 40-mL vial equipped with a PTFE-coated magnetic stir bar was charged with 4.62-2 (858 mg, 2.0 mmol) and trans-propenyl boronic acid (223 mg, 2.6 mmol). The vial was brought into a glovebox and charged with K₃PO₄ (1.27 g, 3 equiv.), PdCl₂dpff.CH₂Cl₂ (849 mg, 4 mmol) and THF (20 mL, 0.1 M). The vial was sealed with a Teflon-lined cap and stirred at 60 °C for 18 hours. The reaction was cooled to 23 °C and filtered through a pad of Celite™ and concentrated in vacuo. The crude product was purified by silica gel chromatography (30-40% CH₂Cl₂/hexanes) to give 4.62 as an off-white solid (268 mg, 39% yield).

TLC (40% CH₂Cl₂/hexanes)

Rₖ = 0.43, visualized by shortwave UV.

¹H-NMR (500 MHz, CDCl₃)

δ 8.22 (dd, J = 8.0, 1.0 Hz, 2H), 7.65 (t, J = 7.5 Hz, 1H), 7.52 (app t, J = 8.0 Hz, 2H), 7.41 (d, J = 2.0 Hz, 1H), 7.36 (dd, J = 8.5, 2.0 Hz, 1H), 7.15 (d, J = 8.5 Hz, 1H), 6.40 (dd, J = 16.0, 1.5 Hz, 1H), 6.26 (dq, J = 15.5, 6.5 Hz, 1H), 5.90 (d, J = 1.5 Hz, 1H), 5.83 (d, J = 2.0 Hz, 1H), 1.90 (dd, J = 7.0, 1.5 Hz, 3H).

¹³C-NMR (125 MHz, CDCl₃)

δ 164.8, 146.2, 136.0, 133.6, 133.3, 130.3, 129.5, 129.3, 128.6, 127.6, 127.2, 127.0, 124.5, 123.1, 122.2, 18.5.

HRMS (ESI+)

Calculated for C₁₈H₁₆O₂Br: 343.0334
Found: 343.0336

c. Synthesis of building blocks for 4.9
A mixture of p-nitrophenyl boronic acid (1.53 g, 9.17 mmol, 1 equiv), N-methylaminodiacetic acid (1.62 g, 11.0 mmol, 1.2 equiv) in toluene (90 mL) and DMSO (9 mL) in a 200 mL rbf fitted with a Dean-Stark trap and a condenser was heated to reflux. The reflux was maintained for 1 h 50 min, emptying the Dean-Stark trap once. The reaction was cooled to room temperature. Toluene was removed in vacuo and the residue was partitioned between 1:1 H$_2$O/brine (100 mL) and 2:1 EtOAc/acetone (2:1). The aqueous layer was extracted with 2:1 EtOAc/acetone (90 mL). The combined organics were washed with brine (~ 50 mL). The organic layer containing grey solids was filtered to separate the solids, rinsing with acetone. The grey solid was washed with H$_2$O to remove any inorganic salts, then dried under air. The filtrate was dried over MgSO$_4$ and Darco, then filtered through celite and concentrated in vacuo. To the solid residue was added ~ 10 mL of acetone. 100 mL Et$_2$O was layered on top of the mixture and left to stand overnight. The crystals formed were isolated by vacuum filtration, rinsing with Et$_2$O. The crystals were combined with the grey solids to give the desired product 16-1 (2.16 g, 85% yield).

TLC (50% acetone/hexanes)

R$_f$ = 0.35, visualized by UV.

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

$\delta$ 8.28-8.21 (m, 2H), 7.84 (app d, $J = 8.5$ Hz, 2H), 4.45 (d, $J = 17.1$ Hz, 2H), 4.25 (d, $J = 17.1$ Hz, 2H), 2.83 (s, 3H).

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

$\delta$ 169.0, 161.4, 151.4, 134.8, 123.2, 63.1, 48.5

HRMS (EI+)

Calculated for C$_{11}$H$_{11}$O$_6$N$_2$B: 278.07103

Found: 278.07115
In an unoptimized procedure, a 100 mL recovery flask was charged with a stir bar, **16-1** (500 mg, 1.80 mmol), THF (36 mL) and MeCN (12 mL). The solution was stirred to dissolve the solids. Pd/C (10 wt%, 287 mg) was added. The flask was sealed with a rubber septum and N\textsubscript{2} was bubbled through the mixture for 5 min. The N\textsubscript{2} inlet was replaced with a H\textsubscript{2} balloon. H\textsubscript{2} was bubbled through the solution for 5 min. The outlet needle was removed and the reaction stirred under a H\textsubscript{2} atmosphere at rt for 36 h. The flask was opened briefly to atmosphere and another portion of Pd/C (10 wt%, 63 mg) was added. The flask was re-sealed and H\textsubscript{2} was bubbled through the mixture for 5 min. The outlet needle was removed and the reaction heated to 45 °C for 14 h to consume the remaining starting material. The reaction was cooled to rt, then purged with N\textsubscript{2} for 10 min before filtering through celite, rinsing with MeCN (3 x 10 mL). The filtrate was concentrated in vacuo. The residue was taken up in MeCN (10 mL). Et\textsubscript{2}O (50 mL) was layered on top. The mixture was left to stand overnight. The crystals formed were isolated by vacuum filtration and dried under high vac to give **16** as a crystalline solid (341 mg, 76% yield).

**TLC (50% acetone/hexanes)**  
R\textsubscript{f} = 0.30, visualized by UV, stained by KMnO\textsubscript{4}

\[ ^1H-NMR \text{ (500 MHz, acetone-d}_6\text{): } \delta 7.24-7.18 \text{ (m, 2H), 6.69-6.61 (m, 2H), 4.69 (br s, 2H), 4.25 (d, J = 17.0 Hz, 2H), 4.04 (d, J = 2H), 2.69 (s, 3H).} \]

**HRMS (ESI+)**  
Calculated for C\textsubscript{11}H\textsubscript{14}N\textsubscript{2}O\textsubscript{4}B: 249.1047  
Found: 249.1048

**REFERENCES**


