DESIGN OF A SECOND GENERATION MIDA BORONATE: ITERATING C(sp^3) BASED SUZUKI CROSS COUPLINGS

BY

MICHAEL JOSEPH SCHMIDT

THESIS

Submitted in partial fulfillment of the requirements
for the degree of Master of Science in Chemistry
in the Graduate College of the
University of Illinois at Urbana-Champaign, 2016

Urbana, Illinois

Adviser:

Professor Martin D. Burke

ABSTRACT

Small molecules have had a tremendous positive impact on human health and society in general. Despite this, small molecule synthesis is still a time and cost intensive process practiced primarily by highly trained specialists. Inspired by the impact of general, automated synthesis platforms for peptides and other biomolecules, we have pioneered iterative cross coupling (ICC) as an analogous platform for small molecules. Enabled by both a building block based synthesis strategy and a general purification protocol, our group has designed and built a small molecule synthesizer. We have demonstrated the ability of this synthesizer to access a wide variety of small molecules, including natural products, pharmaceuticals, and materials components. Further, the synthesizer is able to access complex, polycyclic, $C(sp^3)$ rich natural products through the use of the "linear-to-cyclized" strategy wherein linear precursors are prepared on the machine in an automated fashion and then manually cyclized.

Given the ubiquity of stereogenic $C(sp^3)$ carbons in natural products, the ability to stereospecifically couple secondary alkyl fragments iteratively would be highly enabling. However, all currently known methods for such transformations require conditions which hydrolyze MIDA boronates (aqueous base, high heat, strong base, etc.). In this thesis I describe the development of a second generation iminodiacetic acid ligand for boronic acids which is refractory to hydrolysis and has enabled the first examples of coupling unactivated, secondary alkyl boronic acids in the context of an iterative cross coupling cycle.

To Yia Yia,
for teaching me hard work, generosity, and decency, all by example

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CHAPTER 1

INTRODUCTION

1.1 ITERATIVE SYNTHESIS METHODS

The impact of small molecules on society is vast and, as such, methods which enable rapid and flexible access to small molecules are highly impactful. Despite this, small molecule syntheses still typically rely on synthetic routes and purification procedures that are developed on a *de novo* basis, requiring time- and cost-intensive efforts of highly trained specialists. In contrast, the chemical synthesis of important biological macromolecules like peptides[1] and oligonucleotides[2] is performed using generalized and automated synthesis platforms. This has enabled widespread access to these molecules and shifted the focus away from their synthesis and primarily towards their function and application.

In solid phase peptide synthesis, an amino acid loaded onto a polymeric support via the C-terminus is coupled to a second amino acid protected at its N-terminus as the Fmoc carbmamate. This crucial protecting group strategy[3] prevents random oligomerization of the bifunctional amino acid. The use of a solid support allows for very rapid and convenient purification between coupling steps via simple washing of the resin and filtration. Deprotection with the mild base piperidine reveals the free amine group, ready to undergo further rounds of coupling (Figure 1.1, A). Once the desired peptide is prepared, it is cleaved from the solid support, globally deprotected, and purified via traditional chromatographic methods. The laboratory synthesis of oligonucleotides is performed in a similar manner, wherein a polymer loaded nucleotide is coupled with a bifunctional nucleotide building block protected at the 5'-O as the dimethoxytrityl (DMT) ether. After coupling, any unreacted nucleophile is capped using acetic anhydride/DMAP, and the newly formed phosphite ester linkage is oxidized to the desired

phosphate ester linkage. Following purification, deprotection with dichloracetic acid (DCL) thus reveals the free hydroxyl group ready for further coupling (Figure 1.1, B). An analogous strategy for the synthesis of oligosaccharides has also been also been developed more recently by Seeberger.[4]

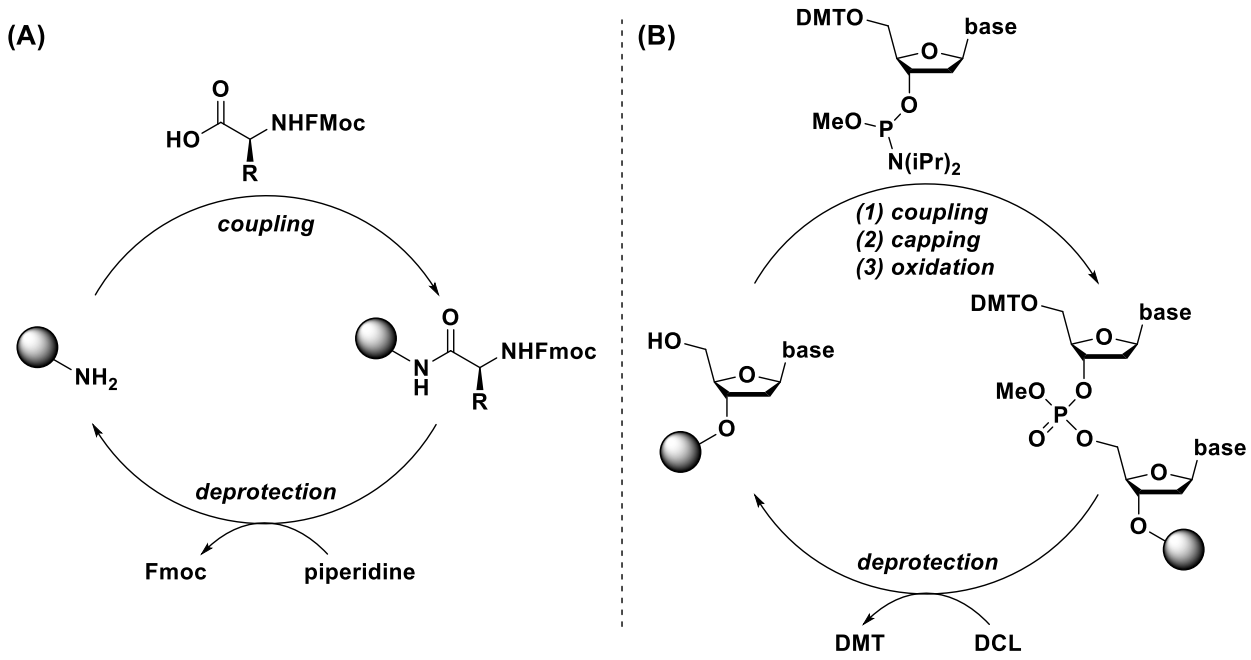

Figure 1.1. Schematic representations of (A) solid phase peptide synthesis, (B) solid phase oligonucleotide synthesis

The development of these automated platforms was enabled primarily by two main strategic and tactical advances: (i) generalized, building block-based synthetic methods and (ii) purification methods which are agnostic to the specific chemical structure of the corresponding intermediates. Building block-based strategies for the synthesis of biopolymers are readily apparent due to their inherently modular structure and the iterative nature of their biosynthesis. Additionally, common functional group motifs on their building blocks allowed the development of efficient strategies for their loading onto and removal from solid supports, a key advance which allowed the use of the solid phase purification strategy.

In some select cases, similar strategies have been employed in the synthesis of organic polymers and small molecules. Moore and coworkers[5] demonstrated the controlled synthesis of sequence specific phenylacetylene oligomers. In this nonlinear growth strategy, each iterative cycle doubles the length of the oligomers by cleaving a portion of the growing polymer from its solid support and coupling it to the remaining supported sequence (Figure 1.2, A). While one could easily imagine the automation of such chemistry, the coupling reactions used are highly customized to these specific Sonogashira couplings, and as such, the scope of motifs which are accessible is lacking. Hiyama[6] also showed that bifunctional [(2-hydroxymethyl)phenyl]dimethylsilanes could be used to the prepare oligoarenes. In this system, treatment with mild base forms the activated pentavalent silicon coupling partner which undergoes coupling with the O-protected bifunctional silane (Figure 1.2, B). While the broader scope of this method is attractive, Hiyama has only thus far demonstrated the use of aryl and heteroaryl coupling partners. Additionally, the challenge of common purification remains in the way automation.

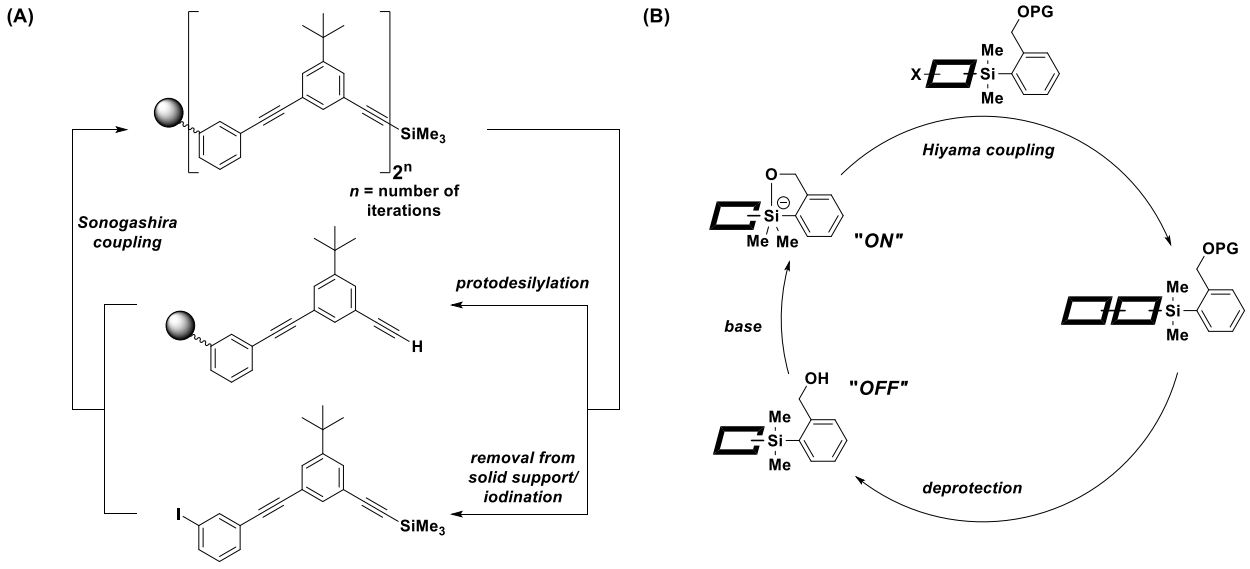

Figure 1.2. (A) Solid supported iterative synthesis of phenylacetylene polymers using Sonogashira couplings and (B) Hiyamas iterative silicon-based couplings to make oligoarenes

1.2 ITERATIVE CROSS COUPLING WITH MIDA BORONATES

At first glance, small molecule synthesis seems refractory to an automated, generalized building block based synthesis platform. Unlike peptides, oligonucleotides, and oligosaccharides, small molecules contain no obvious, inherent modularity to lend themselves to building block based deconstructions. However, despite their incredibly diverse structures, most small molecule natural products are analogously biosynthesized by the iterative assembly of a small set of building blocks like malonyl-CoA, isopentenyl pyrophosphate, and pyruvic acid.[7] Natural products containing complex macro- and polycyclic frameworks, which at first seem refractory to such a building block-based strategy, are also typically biosynthesized by iterative building block assembly of a linear precursor followed by cyclization(s) to yield the final product.[8-10] In addition, many pharmaceuticals and materials components are made up of repeating units of aryl and/or heteroaryl motifs.[11] This latent modularity suggests that a biosynthesis inspired, building block-based strategy could enable access to a majority of small molecules.

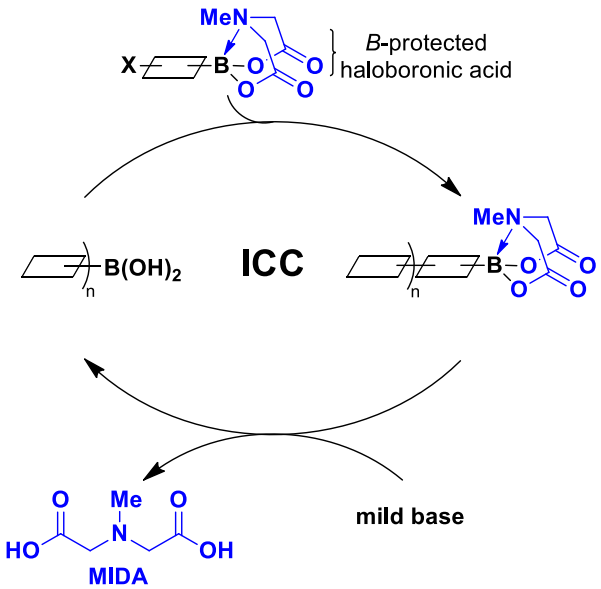

Figure 1.3. A general schematic of iterative cross coupling using bifunctional MIDA boronates

In this vein, our group has pioneered the use of iterative cross-coupling (ICC) in which bifunctional *N*-methyliminodiacetic acid (MIDA) boronates are sequentially assembled in a manner analogous to iterative peptide coupling (Figure 1.3).[12] The MIDA ligand enables this iterative assembly by reversibly attenuating the transmetalation activity of boronic acids in the same way that Fmoc attenuates the nucleophilicity of amines in peptide coupling. The mild and stereospecific nature of the Suzuki coupling allows for stereochemistry, oxidation states, and functional groups to be built into the building blocks and translated faithfully into the products. Reflecting the power of this approach, iterative cross-coupling and MIDA boronates have been used by our group[12-16] and others[17-19] in the syntheses of many different natural products and their derivatives (Figure 1.4). In fact, this platform was the basis of a recent study in which our group showed that over 75% of all known polyene natural product motifs can be prepared using just 12 building blocks and one coupling reaction.[20] Additionally, around 200 MIDA boronates and thousands of halide and boronic acid building blocks are currently commercially available, and in at least one case, a MIDA boronate has been used on the process scale to prepare a new drug candidate for phase II clinical trials. The widespread use of MIDA boronates can at least partially be attributed to their highly desirable physical properties. MIDA Boronates are almost universally well behaved crystalline solids which are indefinitely stable to storage under air on the benchtop.

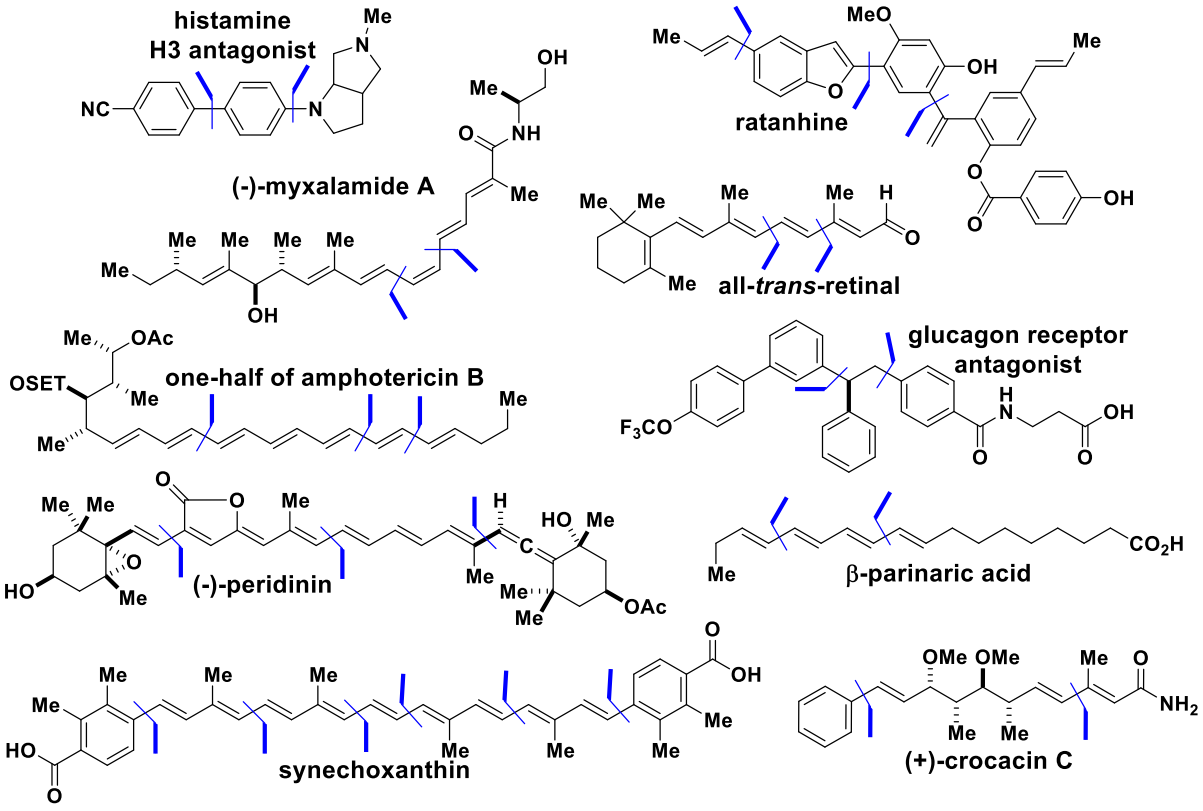

Figure 1.4. Select examples of total syntheses which utilized bifunctional MIDA boronate building blocks

With the ICC synthesis platform in place, our group next aimed to develop a common purification protocol for all of the intermediates, an advance which would enable automation. As previously discussed in the cases of biopolymers,[1,2,4] small organic polymers,[5] and even some select small molecules,[6] this challenge has been overcome through the use of solid-phase synthesis. However, small molecules do not generally possess a common functional group handle which would allow such an approach to be used. Quite serendipitously, our group discovered that MIDA boronates possess nearly universal binary elution properties on standard silica gel. Regardless of the polarity, size, or functional groups present in the organic fragments, MIDA boronates remain at the baseline when eluting with 1.5% MeOH in Et_2O during thin-layer chromatography. However, switching the eluent to THF rapidly elutes the same MIDA boronates (Figure 1.5). This unique elution profile enabled the development of a new type of catch-and-

release purification where a crude reaction mixture is passed over silica gel with MeOH/Et_2O and any MIDA boronates are retained while excess reagents and byproducts are washed away. The clean MIDA boronate product is then obtained by eluting with THF.

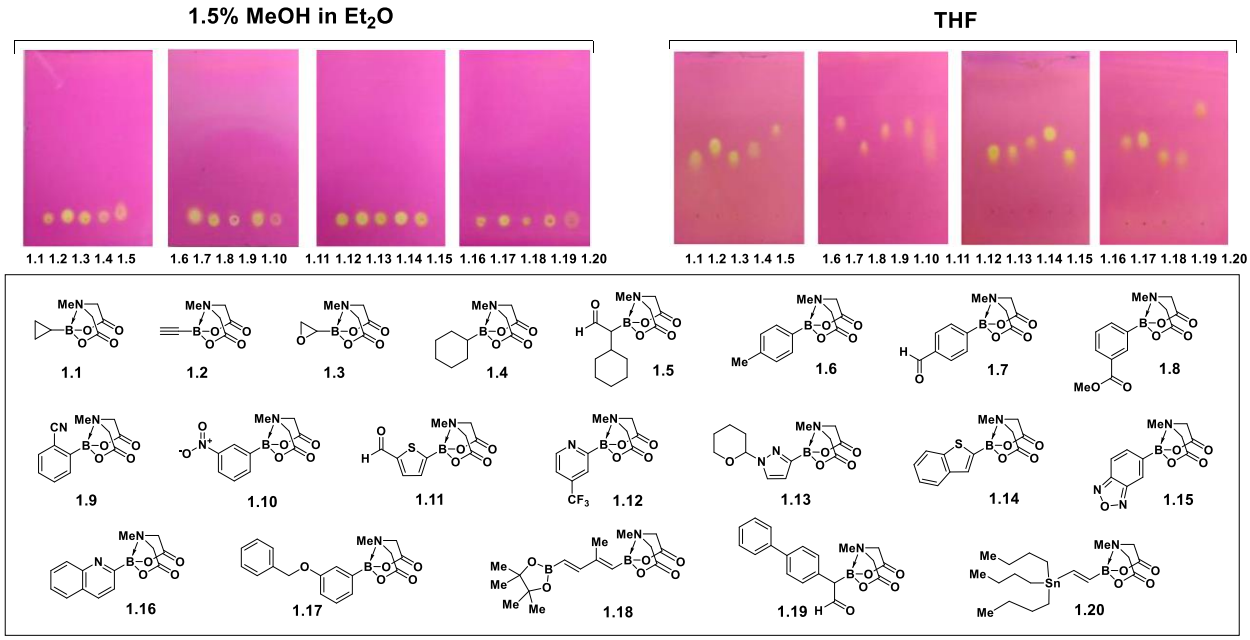

Figure 1.5. MIDA boronates uniformly show binary elution properties on silica gel thin-layer chromatography

1.3 SUMMARY

Modern laboratory syntheses of large biomolecules like peptides and oligonucleotides are accomplished using automated, generalized synthetic platforms. Collectively, these platforms have drastically increased the efficiency and flexibility with which researchers can access these important classes of molecules. This has led to a shift in the bottleneck in these areas of research from their synthesis to the study of their function. The development of these platforms was enabled by (i) building block based synthesis strategies and (ii) general purification techniques. An analogous platform for the synthesis of small molecules would be highly enabling, but also represents significant unique challenges. The latent modularity of small molecule natural products,[7-10] pharmaceuticals, and materials components[11] suggests that the iterative cross

coupling of bifunctional MIDA boronates could access the majority of small molecule chemical space. Additionally, despite the lack of a common functional group handle for solid phase purification, MIDA boronates exhibit almost universal elution properties on silica gel which has allowed the development of a general "catch-and-release" purification protocol, suggesting that a solution to automatable purification of intermediates regardless of their structure is possible.

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CHAPTER 2

SYNTHESIS OF MANY DIFFERENT TYPES OF ORGANIC SMALL MOLECULES USING ONE AUTOMATED PROCESS[‡]

2.1 A SMALL MOLECULE SYNTHESIZER

With both a common building block–based synthesis platform and a common purification method, we designed and built a synthesizer that iteratively assembles MIDA boronate building blocks in a fully automated fashion (Figure 2.1, A).[1] This device comprises three modules that sequentially execute the deprotection, coupling, and purification steps required for each cycle (Figure 2.1, B). All solutions are automatically transferred via computer controlled syringe pumps running custom-designed software. Thus, each automated synthesis simply requires placing prepacked cartridges onto the synthesizer and pressing "start."

The fully automated synthesis commences at the deprotection module, where THF and water are syringed into a cartridge containing the first MIDA boronate building block and solid NaOH. Sparging the cartridge with argon from the bottom provides sufficient mixing for the system, and upon completion of the deprotection (typically less than 20 minutes), the reaction is quenched and diluted with diethyl ether. Aqueous extraction separates the freshly prepared boronic acid from the water soluble MIDA ligand, and the ethereal boronic acid solution is dried by sequentially passing it over $MgSO_4$ and molecular sieves. Solvent switch to THF and concentration to the appropriate volume yields the dry boronic acid solution ready for the upcoming reaction. The coupling module then heats and stirs a solution of the next building block and the coupling reagents while the synthesizer adds the freshly prepared THF solution of boronic acid to the coupling reaction. This slow addition is particularly crucial in the coupling of

[‡] Reproduced with modifications from Li, J.; Ballmer, S.G.; Gillis, E.P.; Schmidt, M.J.; Palazzolo, A.M.E.; Lehmann, J.W.; Morehouse, G.F.; Burke, M.D. *Science* **2015**, *347*, 1221-1226. Reprinted with permission from AAAS. Found online at http://science.sciencemag.org/content/347/6227/1221.abstract

boronic acids sensitive to decomposition, such as 2-heterocyclic, vinyl, cyclopropyl, and alkyl boronic acids.[2] 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:Et2O 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.

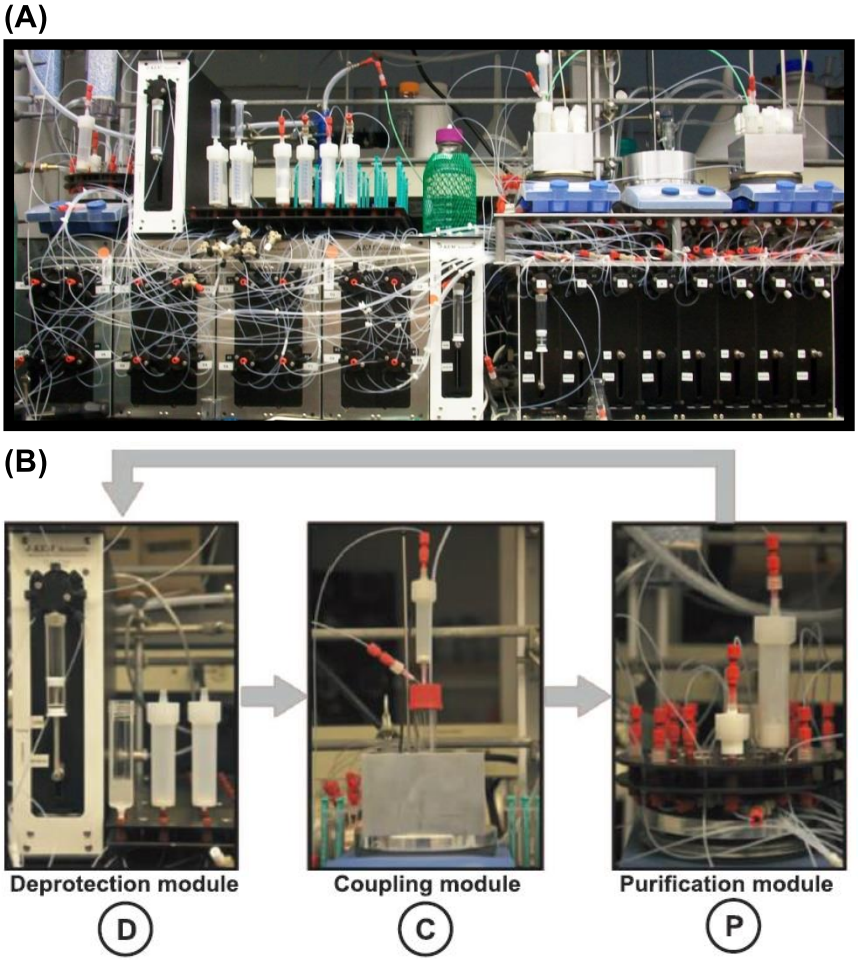
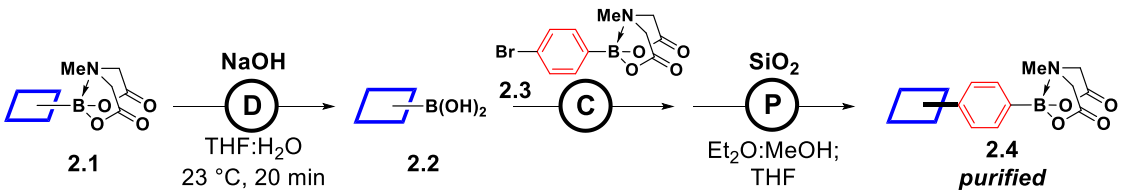


Figure 2.1. (A) A photograph of the small molecule synthesizer and (B) close ups of the deprotection, coupling, and purification modules

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, and vinyl MIDA boronates to automated deprotection and coupling with a model bifunctional building block, 4-bromophenyl MIDA boronate **2.3** (Table 2.1). Using a standard set of

hydrolysis conditions (NaOH, THF:H_2O, 23 °C, 20 min) and coupling conditions (PdXPhos, K_3PO_4),[3] we obtained the desired cross-coupling products in good yields and purities in all cases (Table 2.1, entries 1 to 3). The synthesizer was also capable of executing a C(sp^3) coupling using $Pd[P(o\text{-}tol_3)]_2$ and Ag_2O/K_2CO_3 (Table 2.1, entry 4). Accessing many pharmaceuticals and materials requires the flexibility to link building blocks via carbon heteroatom and/or carbon-carbon bonds. The stability of MIDA boronates toward many reaction conditions[4,5] and the synthetic versatility of boronic acids[6] allowed us to add carbon-heteroatom bond formations to the same platform. The synthesizer successfully executed a series of automated carbon-heteroatom bond formations, including a Buchwald-Hartwig amination, O-alkylation, and amide bond formations (Table 2.2). Despite the different reagents and by-products, the same catch-and-release process purified all of the corresponding MIDA boronate products.



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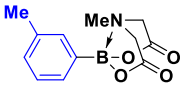
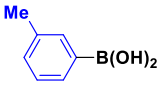
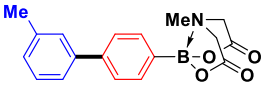
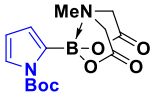
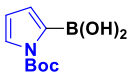
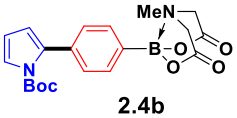
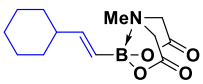
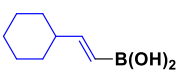
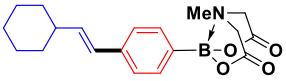
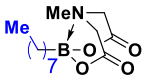
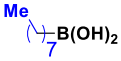
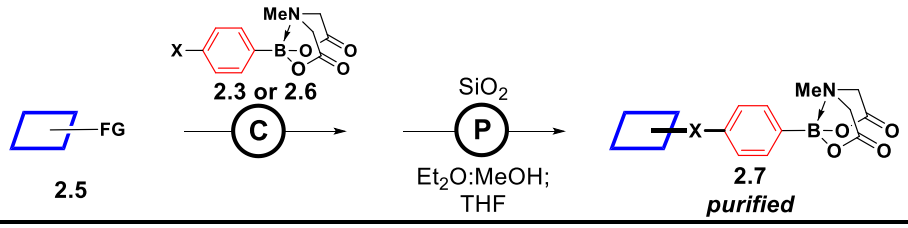
1	 **2.1a**	99	 **2.2a**	98	 **2.4a**	61	**>95**
2	 **2.1b**	99	 **2.2b**	99	 **2.4b**	83	**>95**
3	 **2.1c**	98	 **2.2c**	99	 **2.4c**	67	**>95**
4	 **2.1d**	99	 **2.2d**	99	 **2.4d**	59	**80**

Table 2.1. Single cycles of deprotection, coupling, and purification performed by the automated synthesizer



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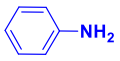
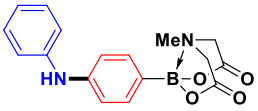
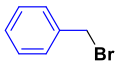
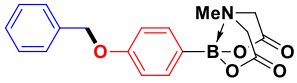
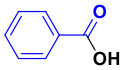
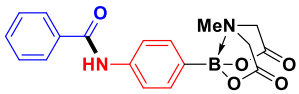
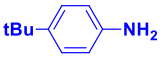
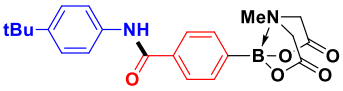
1	 2.5a	**X** = Br 2.3	PdXPhos K_3PO_4, THF 55 °C, 16 h	 2.7a	75	**88**
2	 2.5b	**X** = OH 2.6a	K_2CO_3 30% MeCN/THF 60 °C, 16 h	 2.7b	83	**>95**
3	 2.5c	**X** = NH_2 2.6b	TATU, DIPEA 30% MeCN/THF 40 °C, 13 h	 2.7c	80	**90**
4	 2.5d	**X** = CO_2H 2.6c	TATU, DIPEA 30% MeCN/THF 23 °C, 1h	 2.7d	88	**90**

Table 2.2. Carbon heteroatom bond formations accomplished by the automated synthesizer

2.2 AUTOMATED SYNTHESIS OF LINEAR SMALL MOLECULES

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 (**2.8** to **2.19**) via multiple carbon-carbon and/or carbon heteroatom bond formations (Figure 2.2). These include natural products from major biosynthetic pathways (**2.8**, **2.10**, **2.11**, **2.13**), materials components (**2.15**, **2.16**), and pharmaceuticals and biological probes (**2.17** to **2.19**). 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.

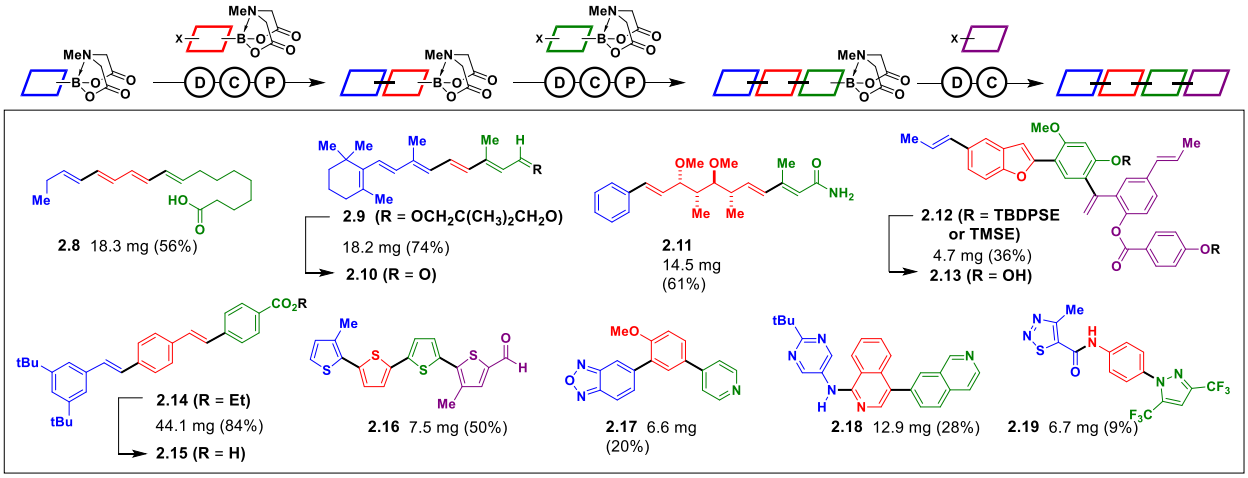


Figure 2.2. Automated synthesis of natural products, materials, pharmaceuticals, and biological probes via iterative coupling of building blocks indicated by different colors

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 **2.13**. In this experiment, we did not optimize any of the deprotection, coupling, or purification conditions used to construct **2.12** (Figure 2.2). We input four sets of building blocks representing common substructural elements found throughout the neolignan family and/or other pharmaceutically relevant motifs (Figure 2.3). These building blocks included variations in oxidation states, methylation patterns, fluorine content, aromatic ring identity, and size. They also represent preprogrammed oligomer lengths of 3 to 4 units, based on whether the third building block was a bifunctional halo-MIDA boronate or a capping halide. 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 2.3).

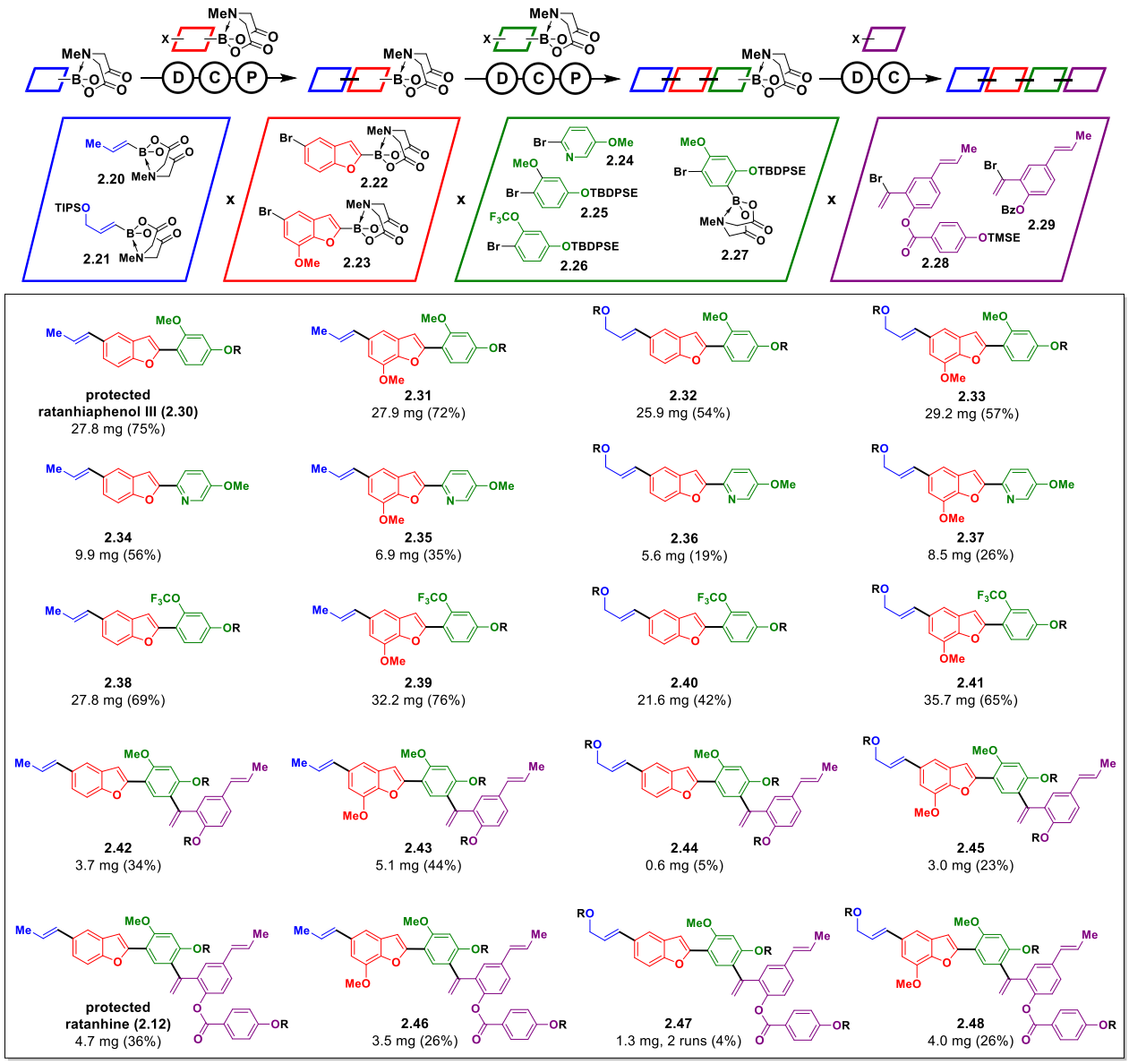


Figure 2.3. Conditions: Deprotection – NaOH, THF:H_2O. Coupling – cycle 1: $Pd(OAc)_2$, SPhos, K_2CO_3, THF, 55 °C, 16 hours; cycle 2: $Pd(OAc)_2$, XPhos, K_3PO_4, THF, 55 °C, 14 hours; cycle 3: $Pd(OAc)_2$, SPhos, K_3PO_4, THF, 55 °C, 24 hours. Purification – SiO_2, MeOH:Et_2O; THF. All protecting groups other than MIDA [R: TIPS, TBDPSE, TMSE, or Bz] were successfully removed in a separate step

2.3 AUTOMATED SYNTHESIS OF POLYCYCLIC NATURAL PRODUCTS

Having shown the synthesizers capacity to prepare many different linear small molecule, we decided to test whether a wide range of macro- and polycyclic natural products and natural product–like cores (Figure 2.4) could be generated using the same automated building block assembly process and a strategy dubbed "linear-to-cyclized". In this strategy, linear precursors are prepared in an automated fashion and are then manually cyclized in an enantio- and diastereoselective fashion. The macrocyclic natural product citreofuran possesses both $C(sp^3)$ and atropisomerism stereochemical elements (Figure 2.4, entry 1). This complex target can be derived from linear precursor **2.53**,[7] which can, in theory, be assembled from building blocks **2.49** to **2.51**. All of the required stereochemical information for citreofuran is preencoded in the chiral nonracemic MIDA boronate building block **2.49**. On the synthesizer, fully automated deprotection of **2.49**, $C(sp^3)$ coupling with **2.50**, and purification yielded intermediate **2.52**. A second round of deprotection and coupling of the resulting 2-furanyl boronic acid with **2.51** produced linear precursor **2.53**. This linear precursor was then deprotected and atropdiastereoselectively macrocyclized to generate citreofuran.

Oblongolide is a norsesquiterpene γ-lactone natural product containing a 6,6,5-tricyclic core with five $C(sp^3)$ stereogenic centers, one of which is quaternary (Figure 2.4, entry 2). The three building blocks **2.55** to **2.57** were automatically assembled via iterative $C(sp^2)$ and $C(sp^3)$ couplings to produce linear precursor **2.59**. After deprotection, the linear precursor was subjected to a cascade intramolecular substrate-controlled diastereoselective Diels-Alder reaction and lactonization process,[8] which defined the four contiguous stereogenic centers in oblongolide.

In cases where no $C(sp^3)$ stereogenic centers are present in the linear precursors, the enantioselectivity of cyclizations can be controlled using a rapidly expanding toolbox of chiral

catalysts.[9] This approach allows the stereoselective construction of the natural product–like hexahydroindene and steroid-like core structures **2.66** and **2.72** using the same linear-to-cyclized strategy (Figure 2.4, entries 3 and 4). Specifically, building blocks **2.61** to **2.63**, all possessing olefins with predefined geometries required for cyclization, were assembled on the synthesizer to produce linear precursor **2.65**. This precursor was then subjected to deprotection and a chiral imidazolidinone-promoted organocatalytic enantio- and diastereoselective Diels-Alder reaction to generate **2.66** (Figure 2.4, entry 3).[10] Similarly, iterative C(sp^3) coupling of building blocks **2.67** to **2.69** generated linear precursor **2.71**, which then underwent catalyst-promoted enantio- and diastereoselective cation-π cyclization[11] followed by reduction to generate **2.72** (Figure 2.4, entry 4). Finally, by simply replacing building block **2.69** with **2.73** and using the same automated platform, even the highly complex pentacyclic secodaphnane core **(±)-2.75** was readily prepared (Figure 2.4, entry 5).[12]

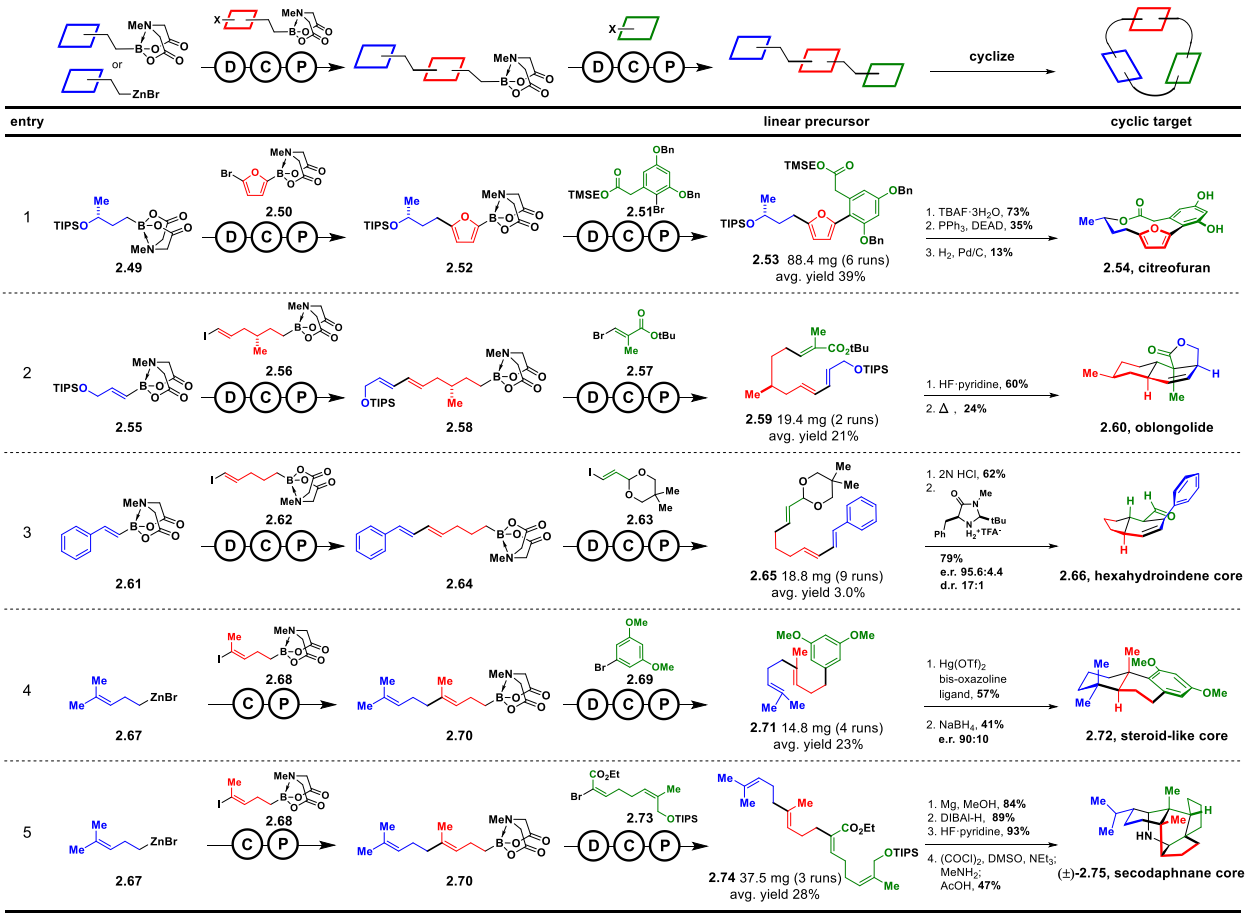


Figure 2.4. Modular linear precursors assembled via automated C(sp^2) and C(sp^3) couplings are diastereo- and/or enantioselectively cyclized

Initial difficulties in the synthesis of secodaphnane core **2.75** nicely illustrate the need for strategic building block design. A first generation version of building block **2.73** is shown in Figure 2.5 (**2.76**). After many failed efforts to couple **2.76** with dimer **2.70**, investigation into side reactions revealed two serious issues. The first was that the benzoyl protected allylic alcohol formed the π-allyl complex due to the leaving group capacity of the benzoate group. Changing to a silyl protected alcohol obviated this issue. Second, upon oxidative addition, the alkenyl Pd(II) species underwent facile intramolecular Heck reaction to form a kinetically favored 5-membered ring. By simply switching the stereochemistry of the vinyl bromide from *cis* to *trans*, the geometry required for the Heck reaction was no longer present and the reaction was shut down

entirely. Building block **2.73** underwent smooth Suzuki coupling with dimer **2.70** to provide linear precursor **2.74**, both on the bench and on the synthesizer.

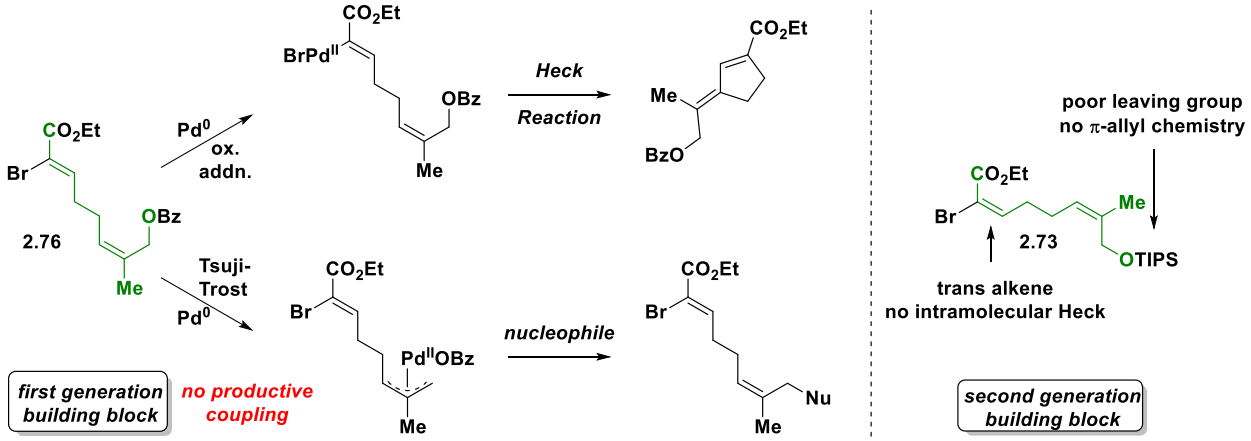


Figure 2.5. Strategic design of building block **2.73** enabled synthesis of secodaphnane core **2.75**

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 creating building blocks representing the highly redundant substructural elements found in many small molecules,[13] developing better methods for iteratively coupling those building blocks together, and advancing the capacity for biosynthesis inspired cyclizations of linear precursors to yield complex natural product frameworks. 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.

2.4 EXPERIMENTAL SECTION

General Materials and Methods

Commercial reagents were purchased from Sigma-Aldrich, EMD Millipore, Fisher Scientific, Alfa Aesar, Frontier Scientific, Oakwood Products, or Strem and were used without further purification unless otherwise noted. Unless otherwise noted, manual building block syntheses were carried out in oven- or flame-dried glassware under a dry inert atmosphere. Unless otherwise noted: Celite™ refers to Celite™ 545 filter aid (not acid washed); Darco® refers to activated carbon, Darco® G-60, -100 mesh, powder; and K_3PO_4 and K_2CO_3 were both anhydrous and were freshly and finely ground in a 120 °C mortar and pestle. 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[14] (THF, Et_2O, CH_3CN, CH_2Cl_2: dry neutral alumina; hexanes, benzene, toluene: dry neutral alumina and Q5 reactant; DMSO, DMF: activated molecular sieves. Water was deionized.

Thin layer chromatography (TLC) was performed using the indicated eluent on E. Merck silica gel 60 F254 plates (0.25 mm). Compounds were visualized by exposure to a UV lamp (λ = 254 and/or 366 nm) and/or a basic solution of $KMnO_4$ followed by brief heating with a Varitemp® heat gun. Flash chromatography was performed as described by Still and coworkers (*35*) using EM Merck silica gel 60 (230-400 mesh). ^1H NMR spectra were recorded at room temperature on one of the following instruments: Varian Unity 500, Varian VXR 500, or Varian Unity Inova 500NB. Chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane and referenced to residual protium in the NMR solvent ($CDCl_3$, δ = 7.26; $(CD_3)_2CO$, δ = 2.05, center line; CD_2Cl_2, δ = 5.32, center line; $(CD_3)_2SO$, δ = 2.50, center line).

Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sept = septet, m = multiplet, br = broad, app = apparent, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets), coupling constant (*J*) in Hertz (Hz), and integration. ^{13}C NMR spectra were recorded at room temperature on one of the following instruments: Varian Unity 500 or Varian VXR 500. Chemical shifts (δ) are reported in ppm downfield from tetramethylsilane and referenced to carbon resonances in the NMR solvent ($CDCl_3$, δ = 77.16, center line; $(CD_3)_2CO$, δ = 29.84, center line; CD_2Cl_2, δ = 53.84; $(CD_3)_2SO$, δ = 39.52, center line). High resolution mass spectra (HRMS) were performed by Furong Sun and Elizabeth Eves at the University of Illinois School of Chemical Sciences Mass Spectrometry Laboratory.

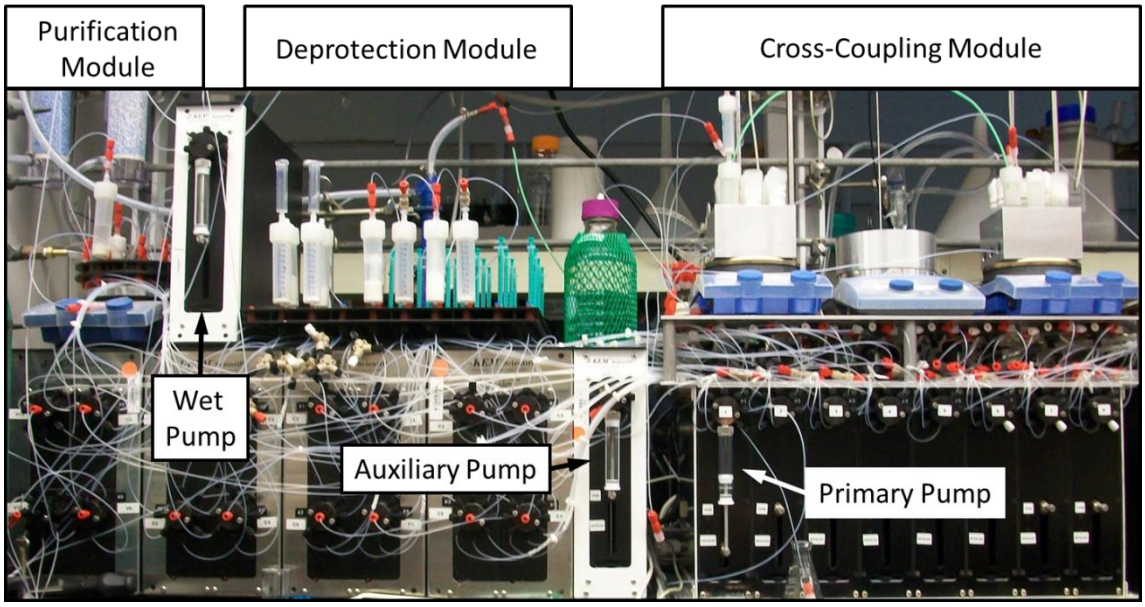


Figure 2.6. Photograph of the automated synthesizer

Design of the Deprotection Module

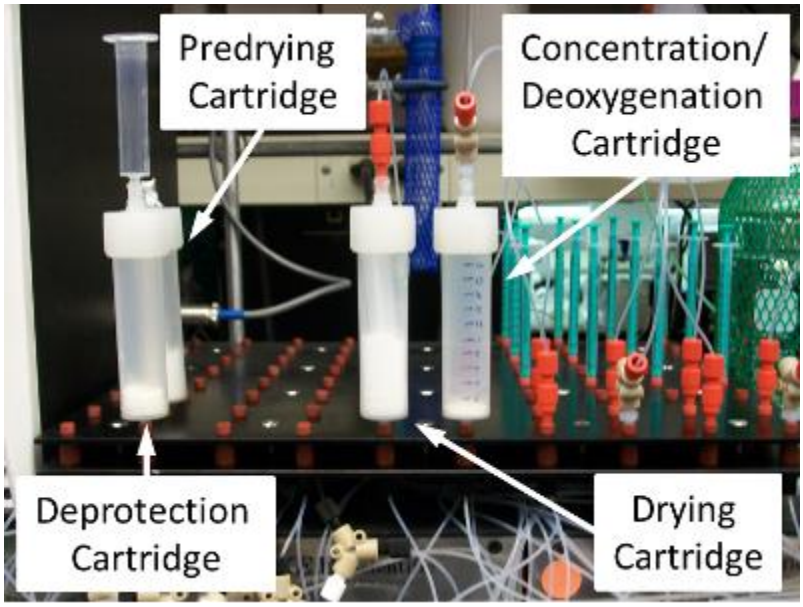


Figure 2.7. Photograph of the deprotection module

The deprotection module consists of two J-KEM® Scientific V6 programmable syringe pumps (part # SYR-1400PC). Both are fitted with a 10-mL glass/PTFE syringe (part # SPGS-10000) and an 8-port distribution valve (part # SPDV-8). One pump (the Primary Pump) is utilized as the organic liquid handling pump and the other (the Wet Pump) is used exclusively as the aqueous liquid handling pump. The module utilizes an additional five 8-port distribution valves (part # SPDV-CS8) housed in four separate quad stack KEM select distribution modules (part # SYR-CS4) for liquid handling. A source of dry nitrogen and dry argon are used for liquid handling and deoxygenation/concentration processes. Connections between valves are made with FEP tubing (1/16'' OD, 0.030'' ID).

To the Deprotection Cartridge, the Primary Pump adds THF and the Wet Pump adds water. The reaction is then agitated with pulses of argon gas. The Wet Pump then adds a quenching reagent (either pH=6 phosphate buffer or saturated NH_4Cl) and the Primary Pump

adds Et_2O. The resulting biphasic system is agitated with pulses of nitrogen gas and the aqueous layer is drawn off and disposed of by the Wet Pump. The Wet Pump adds 50% saturated aqueous NaCl. The resulting biphasic system is agitated with pulses of nitrogen and the aqueous layer is drawn off and disposed of by the Wet Pump. The Primary Pump transfers the wet organic solution to a Predrying Cartridge (if applicable), and subsequently Drying Cartridge, containing drying agents and agitates the mixture by repeatedly withdrawing/injecting the solution. The Primary Pump transfers the dried organic solution to a Concentration/Deoxygenation Cartridge and concentrates/deoxygenates the solution with pulses of argon gas.

Design of the Coupling Module

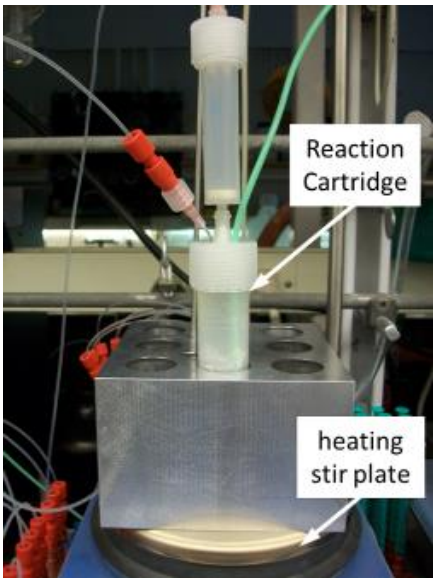


Figure 2.8. Photograph of the coupling module

The coupling module consists of one J-KEM® Scientific V6 programmable syringe pump (part # SYR-1400PC), the Primary Pump described above. The module utilizes one additional 8-port distribution valve (part # SPDV-CS8) housed in one separate quad stack KEM select distribution module (part # SYR-CS4) for liquid handling (shared with the deprotection module). A source of dry nitrogen and dry argon are used for liquid handling and deoxygenation processes

(shared with the deprotection module). Two IKA® RET control visc IKAMAG® safety control heating stir plates (part # 3364001) and one IKA® RCT basic IKAMAG® safety control heating stir plate (part # 3810001) are used for reaction stirring and temperature control. Connections between valves are made with FEP tubing (1/16'' OD, 0.030'' ID).

The Reaction Cartridge, agitated with a magnetic stir bar, is typically deoxygenated with pulses of argon gas. The Primary Pump adds THF to the reaction cartridge and then slowly adds the dried/deoxygenated THF solution of boronic acid. After the addition, the reaction is allowed to agitate.

Design of the Purification Module

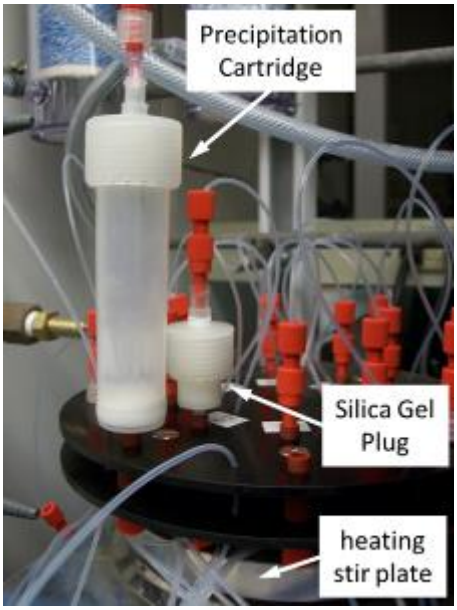


Figure 2.9. Photograph of the purification module

The purification module consists of two J-KEM® Scientific V6 programmable syringe pumps (part # SYR-1400PC). One is the Primary Pump described above. The other pump (the Auxillary Pump) is used exclusively as the column eluent and waste handling pump. The module utilizes an additional six 8-port distribution valves (part # SPDV-CS8) housed in three separate quad stack KEM select distribution modules (part # SYR-CS4) for liquid handling. Five of these

distribution valves are shared with the deprotection and coupling modules. Two IKA® RET control visc IKAMAG® safety control heating stir plates (part # 3364001), shared with the coupling module, and one IKA® RCT basic IKAMAG® safety control heating stir plate (part # 3810001) are used. Connections between valves are made with FEP tubing (1/16'' OD, 0.030'' ID).

The Auxillary Pump adds hexanes to the Precipitation Cartridge, agitated with a magnetic stir bar. The Primary Pump adds portions of the crude reaction solution to the Precipitation Cartridge. The Auxillary Pump then withdraws the solvent through the Silica gel Plug. This process is repeated until the Reaction Cartridge is empty. The Primary Pump then adds 1.5% MeOH in Et_2O to the Precipitation Cartridge and then the Auxillary Pump withdraws the solvent through the Silica Gel Plug. The Primary Pump then adds Et_2O to the Precipitation Cartridge and then the Auxillary Pump withdraws the solvent through the Silica Gel Plug. The Auxillary Pump then adds THF to the Precipitation Cartridge and the Primary Pump removes the resulting solution and transfers it to the next Deprotection Cartridge.

Description of software

The synthesizer is controlled remotely on a Windows-based computer by a custom software program written in VB.NET (based on code written for the J-KEM® Scientific V6 programmable syringe pumps). The software program is designed to interpret instructions to the synthesizer written in a simple custom scripting language. Pre-set series of instructions enable all of the steps required for a synthesis to be executed in a fully automated fashion after the operator simply presses "Start."

Single-Step C-C Bond Formation (Table 2.1) (**Automated Procedure I**)

Unless otherwise noted, "cartridge" refers to a 12-g Luknova column capped with a 12-g Luknova column screw cap.

Automated Procedure I – Cartridge Preparation

First Deprotection Cartridges contain solid NaOH and the starting MIDA boronate.

Predrying Cartridges contain Celite™ (800 mg) and anhydrous $MgSO_4$ (2.1 g). These solids are mixed thoroughly and a plastic 5-mL syringe plunger is placed on top of the mixed solids. This is topped with an aluminum foil cover.

Drying Cartridges contain Celite™ (300 mg) with 4 Å molecular sieves (activated, powder, -325 mesh) (3.6 g) layered on top. A plastic 5-mL syringe plunger is placed on top of the layered solids.

Concentration/Deoxygenation Cartridges are empty.

First Reaction Cartridges contain a PTFE-coated magnetic stir bar, coupling partner, catalyst and ligand, and base. For this cartridge, the factory-supplied fiber frit has been removed and a medium porosity glass frit installed. The cap is pierced with a 1.5-inch 18 G needle and topped with an empty 4-g Luknova column (capped with a 4-g Luknova column screw cap). This cap is tethered to another cap PTFE tubing (1/16-inch I.D., 1/8-inch O.D.). This additional cap, pierced with a 1.5-inch 18 G needle, is attached to the Reaction Filtration Cartridge. The PTFE tubing is adjusted to place the end of the tubing approximately 5 mm above the frit of the First Reaction Cartridge and approximately 20 mm below the screw cap of the Reaction Filtration Cartridge. The luer ports of both screw caps are packed with a small ball of rolled Kimberly-Clark® Kimwipes™.

Reaction Filtration Cartridges contain a PTFE-coated magnetic stir bar and a mixture of Celite™ (2.5 g) and Florisil® (1.25 g). This is tethered to the First Reaction Cartridge as described above.

Precipitation Cartridges contain a PTFE-coated magnetic stir bar, Celite™ (150 mg), and 3-aminopropyl functionalized silica gel (250 mg). Hexanes (10 mL) is added and the cartridge is swirled vigorously to suspend and homogenize the mixture of solids. The stir bar and solids are allowed to settle over 30 seconds and the supernatant hexanes is pushed out of the cartridge with an overhead pressure of air. The stir bar is now embedded in the mixture of solids wet with hexanes.

Silica Gel Plugs contain silica gel, tightly packed, and topped with a 4-g Luknova column frit. This is capped with a 4-g Luknova column screw cap, using four layers of PTFE tape on the sealing insert to ensure a leak-free seal.

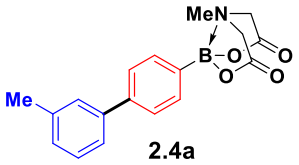
Automated Procedure I - *Experimental Procedure*

Deprotection In the deprotection module, to a Deprotection Cartridge containing starting MIDA boronate **2.1** (1.0 mmol) and NaOH (3.0 mmol, 120 mg) is added 12 mL THF followed by 3 mL water. This solution is then agitated by bubbling argon through the solution for 20 minutes at room temperature. After agitation, 3 mL aqueous potassium phosphate buffer (pH=6, 0.5 M) and 5 mL Et_2O are added. The layers are briefly mixed (again, via argon sparging) before being allowed to separate. Then, the Wet Pump disposes of the aqueous layer before adding 3 mL 50% saturated aqueous NaCl, mixing the layers, and allowing them to separate. Again, the Wet Pump disposes of the aqueous layer. The THF/Et_2O solution of boronic acid is then dried using the Predrying and Drying Cartridges. This is accomplished by the repeated injection and withdrawal of the solution into the cartridges (20 repetitions for the Predrying

Cartridge, followed by 20 repetitions for the Drying Cartridge). The solution is then passed into the Concentration/Deoxygenation Cartridge before washing the contents of the Predrying and Drying Cartridges with 6 mL THF and adding the wash to the Concentration/Deoxygenation Cartridge. This organic solution is then concentrated to 10 mL (evaporating most of the Et_2O) before washing the drying agents with a further 6 mL THF. The organic solution (now only THF) is concentrated to 9 mL. This deoxygenated, dry solution is used directly in the subsequent coupling reaction.

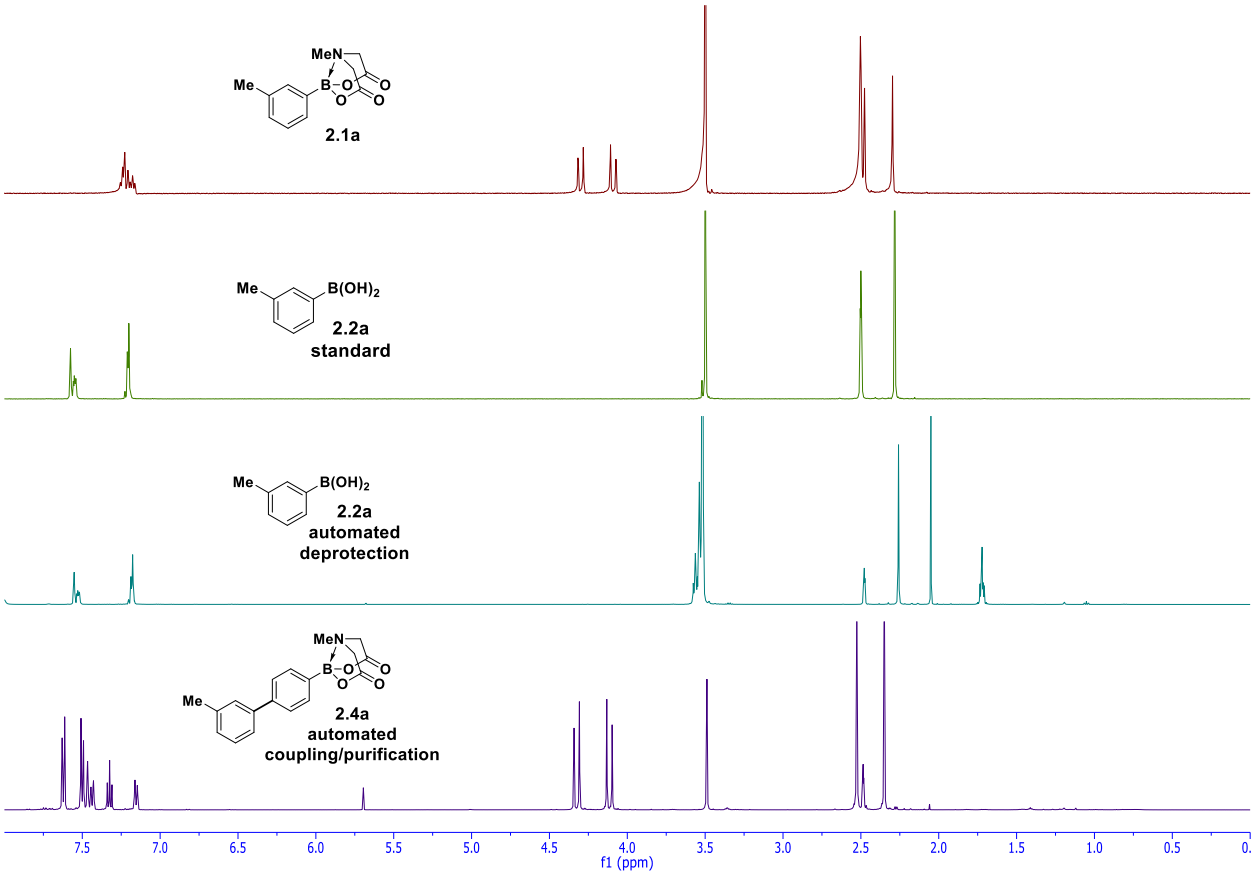
Coupling In the coupling module, a First Reaction Cartridge is charged with bifunctional MIDA boronate **2.3** (0.33 mmol), XPhos 2nd generation palladacycle (0.017 mmol, 13.1 mg, 5 mol%), and K_3PO_4 (3.0 mmol, 637 mg) and warmed to 55 °C before being deoxygenated by flushing with argon for 10 minutes. To this cartridge is added 3 mL THF with stirring. The THF solution of boronic acid **2.2** is added over 4 hours (0.0375 mL/min). At the end of the addition, the reaction is stirred for an additional 12 hours.

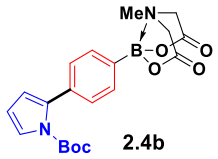
Purification In the purification module, the crude reaction mixture is added to a Reaction Filtration Cartridge and 12 mL hexanes is added to the Precipitation Cartridge/Silica Gel Plug. Then, a 3 mL portion of the filtered crude reaction mixture is added to the Precipitation Cartridge and the solvent is removed from the cartridge, loading any crude reaction product onto the Silica Gel Plug ("catch"). This process is performed a total of 10 times, using 3 mL THF to wash the Reaction and Reaction Filtration Cartridges for each cycle. Then, 12 mL of 1.5% MeOH in Et_2O are added and the solvent is removed three times (36 mL total). Then, 12 mL of Et_2O are added and the solvent is removed 3 times (36 mL total). Finally, 12 mL THF are added and slowly removed (to increase residence time in the column), giving a purified solution of MIDA boronate **2.4**.



2.4a

Automated Procedure I was followed using 251.7 mg (1.02 mmol) aryl MIDA boronate **2.1a** and 104.0 mg (0.333 mmol) bifunctional MIDA boronate **2.3**. The conversion for the deprotection step was 99% and the conversion for the coupling step was 98%. The desired aryl MIDA boronate **2.4a** was obtained as a white solid of >95% purity (65.3 mg, 0.202 mmol, 61% yield). TLC (20% MeCN in Et_2O): R_f = 0.37, visualized by UV and $KMnO_4$ stain; ^{1}H-NMR (500 MHz, DMSO-d_6:D_2O, 95:5): δ 7.64 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 8.5 Hz, 2H), 7.48 (s, 1H), 7.45 (dd, *J* = 7.5, 0.5 Hz, 1H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.17 (dd, *J* = 7.5, 0.5 Hz, 1H), 4.34 (d, *J* = 17.5 Hz, 2H), 4.13 (d, *J* = 17 Hz, 2H), 2.54 (s, 3H), 2.37 (s, 3H); ^{13}C-NMR (125 MHz, DMSO-d_6:D_2O, 95:5): δ 169.1, 140.7, 140.1, 138.0, 132.9, 128.7, 128.0, 127.2, 125.9, 123.7, 61.8, 47.6, 21.0; HRMS (EI+) calculated for $C_{18}H_{18}BNO_4$ $[M]^+$ *m/z* 323.13289, found 323.13253.

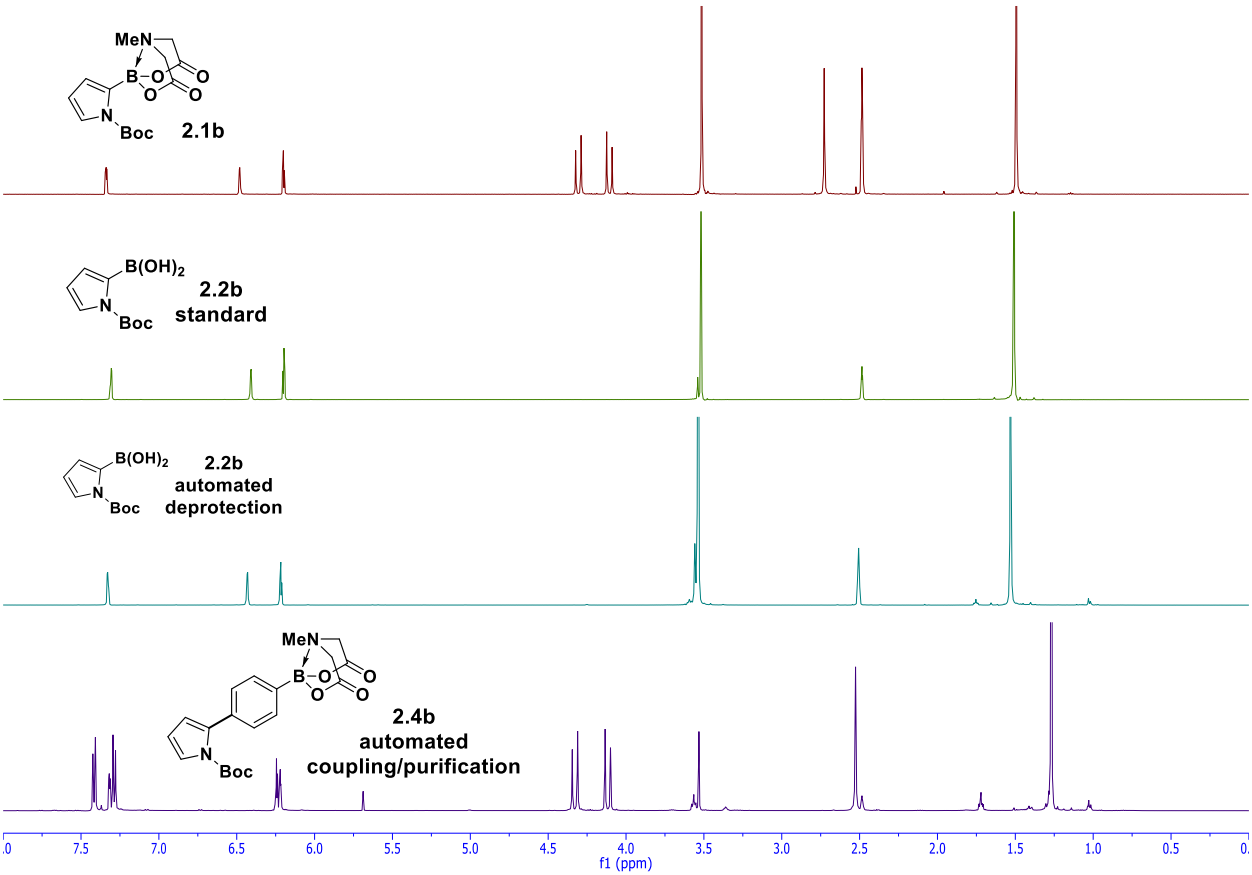


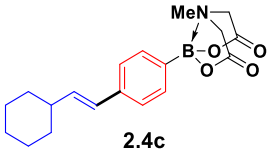


2.4b

Automated Procedure I was followed using 325.4 mg (1.01 mmol) aryl MIDA boronate **2.1b** and 104.4 mg (0.335 mmol) bifunctional MIDA boronate **2.3**. The conversion for the deprotection step was 99% and the conversion for the coupling step was 99%. The desired aryl MIDA boronate **2.4b** was obtained as an off-white solid of >95% purity (110.9 mg, 0.278 mmol, 83% yield). TLC (20% MeCN in Et_2O): R_f = 0.46, visualized by UV and $KMnO_4$ stain; ^{1}H-NMR (500 MHz, DMSO-d_6:D_2O, 95:5): δ 7.43 (d, J = 8 Hz, 2H), 7.33 (dd, J = 3, 1.5 Hz, 1H), 7.30 (d, J = 8.5 Hz, 2H), 6.26 (t, J = 3.5 Hz, 1H), 6.23 (dd, J = 3, 1.5 Hz, 1H), 4.34 (d, J = 17 Hz, 2H), 4.13 (d, J = 17 Hz, 2H), 2.54 (s, 3H), 1.28 (s, 9H); ^{13}C-NMR (125 MHz, DMSO-d_6:D_2O, 95:5): δ

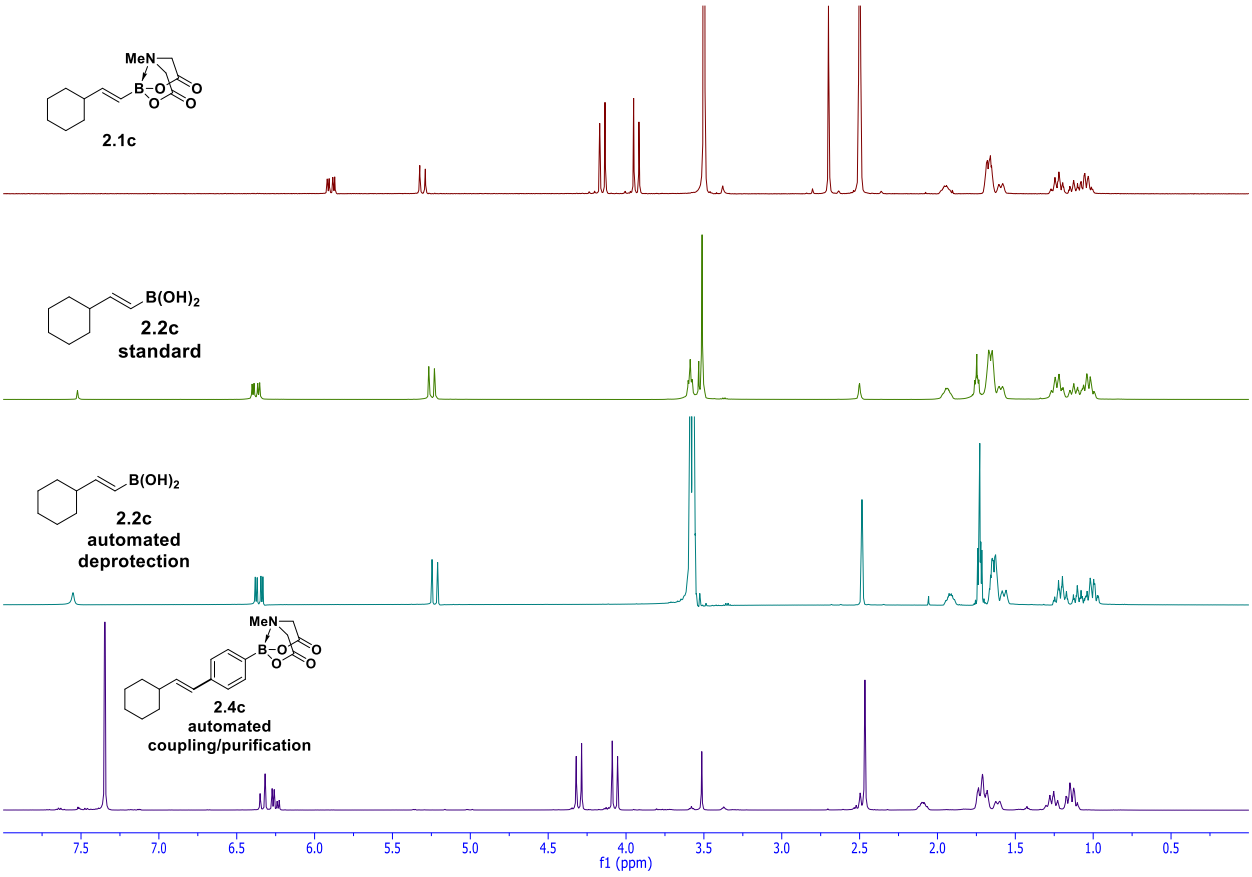
169.7, 149.1, 134.7, 134.4, 132.0, 128.2, 123.0, 114.7, 111.2, 83.9, 62.1, 47.9, 27.3; HRMS (ESI+) calculated for $C_{20}H_{24}BN_2O_6$ $[M+H]^+$ *m/z* 399.1727, found 399.1723.

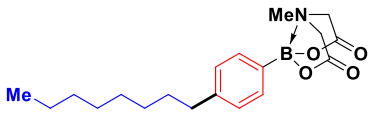




Automated Procedure I was followed using 265.9 mg (1.00 mmol) aryl MIDA boronate **2.1c** and 105.6 mg (0.339 mmol) bifunctional MIDA boronate **2.3**. The conversion for the deprotection step was 98% and the conversion for the coupling step was 99%. The desired aryl MIDA boronate **2.4c** was obtained as an off-white solid of >95% purity (77.7 mg, 0.228 mmol, 67% yield). TLC (20% MeCN in Et_2O): R_f = 0.44, visualized by UV and $KMnO_4$ stain; ^{1}H-NMR (500 MHz, DMSO-d_6:D_2O, 95:5): δ 7.35 (s, 4H), 6.34 (d, *J* = 16.5 Hz, 1H), 6.25 (dd, *J* = 16.5, 7

Hz, 1H), 4.31 (d, *J* = 17 Hz, 2H), 4.08 (d, *J* = 17 Hz, 2H), 2.47 (s, 3H), 2.13-2.06 (m, 1H), 1.74-1.68 (m, 4H), 1.63-1.60 (m, 1H), 1.31-1.23 (m, 2H), 1.18-1.11 (m, 3H); ^{13}C-NMR (125 MHz, DMSO-d_6:D_2O, 95:5): δ 169.6, 138.1, 136.8, 132.7, 127.3, 125.4, 61.9, 47.7, 40.6, 32.6, 25.8, 25.6; HRMS (EI+) calculated for $C_{19}H_{24}BNO_4$ $[M]^+$ *m/z* 341.17984, found 341.18030.

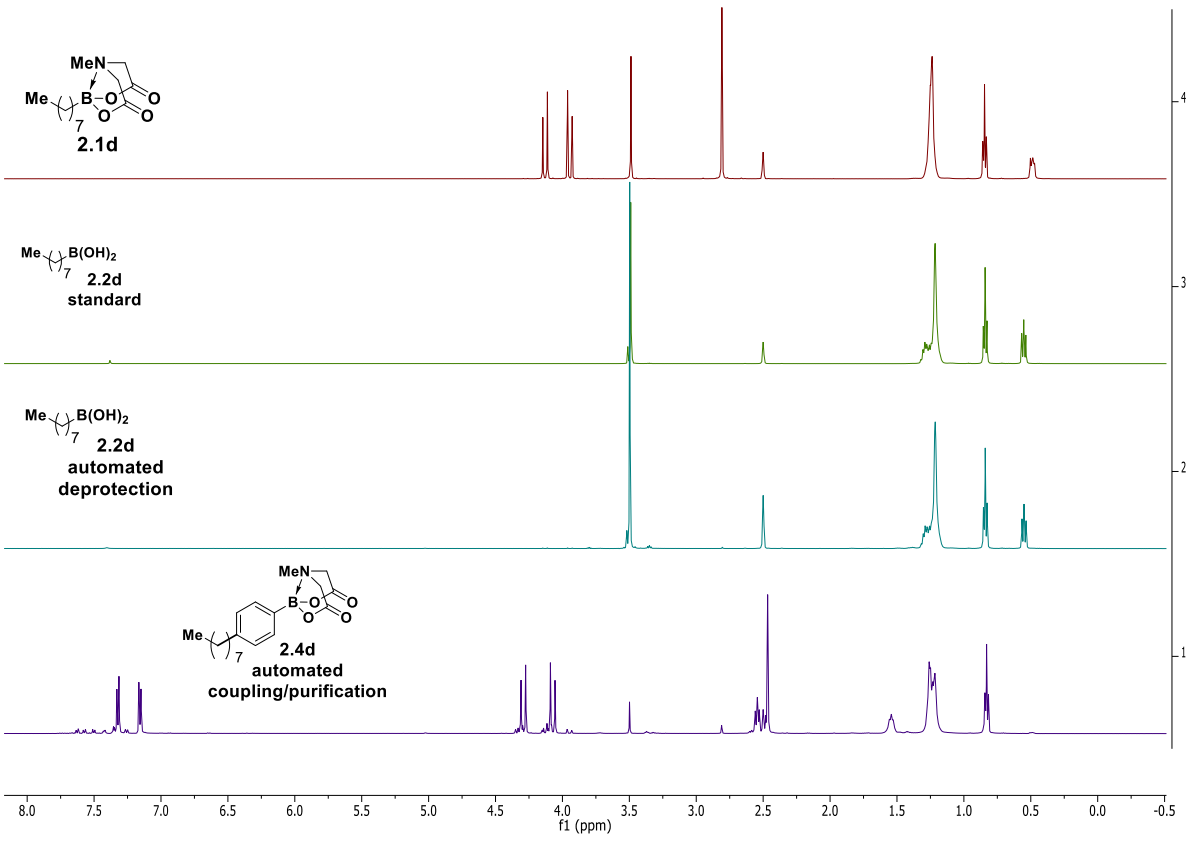




2.4d

Automated Procedure I was followed with modifications: 268.4 mg (0.997 mmol) octyl MIDA boronate **2.1d**, 105.2 mg (0.337 mmol) *p*-bromophenyl MIDA boronate **2.3**, an increased

catalyst loading of 25.6 mg (10 mol%) $Pd[P(o\text{-tol})_3]_2$, and 237.6 mg Ag_2O (1.03 mmol) and 277.7 mg K_2CO_3 (2.01 mmol) were used. The conversion for the deprotection step was 99% and the conversion for the coupling step was 99%. The desired aryl MIDA boronate **2.4d** was obtained as an off-white solid of 80% purity (68.9 mg, 0.200 mmol, 59% yield). TLC (50% acetone/hexanes) R_f = 0.48, visualized by UV and $KMnO_4$ stain; ^{1}H-NMR (500 MHz, DMSO-d_6:D_2O, 95:5): δ 7.32 (d, *J* = 7.6 Hz, 2H), 7.16 (d, *J* = 7.7 Hz, 2H), 4.29 (d, *J* = 17.3 Hz, 2H), 4.07 (d, *J* = 17.3 Hz, 2H), 2.57-2.52 (m, 2H), 2.47 (s, 3H), 1.54 (quint, *J* = 7.4 Hz, 2H), 1.29-1.19 (m, 10H), 0.83 (t, *J* = 6.8 Hz, 3H); ^{13}C-NMR (125 MHz, DMSO-d_6:D_2O, 95:5): δ 169.8, 134.8, 132.9, 128.4, 128.1, 62.3, 57.5, 42.6, 35.8, 31.9, 31.4, 29.4, 29.3, 22.7, 14.6.; HRMS (ESI+) calculated for $C_{19}H_{29}BNO_4$ $[M+H]^+$ *m/z* 346.2190, found 346.2180.



Single-Step C-X Bond Formation (Table 2.2) (**Automated Procedure II**)

Unless otherwise noted, "cartridge" refers to a 12-g Luknova column capped with a 12-g Luknova column screw cap.

Automated Procedure II – *Cartridge Preparation*

Drying Cartridges contain 4.2 g Na_2SO_4, topped with the plunger from a 5 mL syringe.

Concentration/Deoxygenation Cartridges are empty.

First Reaction Cartridges are the 40 mL reaction vials described above, and contain a PTFE-coated magnetic stir bar, coupling partner, coupling reagent (where applicable) and base. These cartridges have no frit at their base. The Luer port at the bottom is packed with a small piece of Kimwipe (so that solids are retained in the vial during weighing). The top of the vial is capped with a screw-top rubber septum cap. This septum is pierced with a 1.5 inch 18 G needle which is connected to an empty 4 g Luknova column (capped with a 4 g Luknova column screw cap connected to a source of dry nitrogen). Additionally, the cap is tethered to the screw cap topping the Reaction Filtration Cartridge via PTFE tubing (1/16-inch I.D., 1/8-inch O.D.) This tubing is adjusted in such a way to be ~5 mm above the base of the reaction vessel, and is used to transfer the crude reaction mixture to the Reaction Filtration Cartridge.

Reaction Filtration Cartridges contain 1.0 g Celite™ and 0.5 g Florisil® which have been thoroughly mixed. This is tethered to the First Reaction Cartridge as described above.

Precipitation Cartridges contain a PTFE-coated magnetic stir bar, Celite™ (150 mg), and 3-aminopropyl functionalized silica gel (250 mg). Hexanes (10 mL) is added and the cartridge is swirled vigorously to suspend and homogenize the mixture of solids. The stir bar and solids are allowed to settle over 30 seconds and the supernatant hexanes is pushed out of the

cartridge with an overhead pressure of air. The stir bar is now embedded in the mixture of solids wet with hexanes.

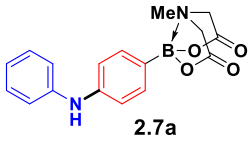
Silica Gel Plugs contain silica gel, tightly packed, and topped with a 4-g Luknova column frit. This is capped with a 4-g Luknova column screw cap, using four layers of PTFE tape on the sealing insert to ensure a leak-free seal.

Automated Procedure II - *Experimental Details*

Coupling The First Reaction Cartridge is charged with all solid reagents (MIDA boronates, coupling reagents, etc.) before sealing, placing into an appropriately warmed heating block, and flushing with argon (10 minutes). To this is added THF (12 mL, unless otherwise noted) with stirring. After stirring briefly, any necessary liquid reagents are added via syringe through the septum cap. The reaction is then stirred in an appropriately warmed heating block until complete, at which point it is transferred to the Reaction Filtration Cartridge before workup/purification.

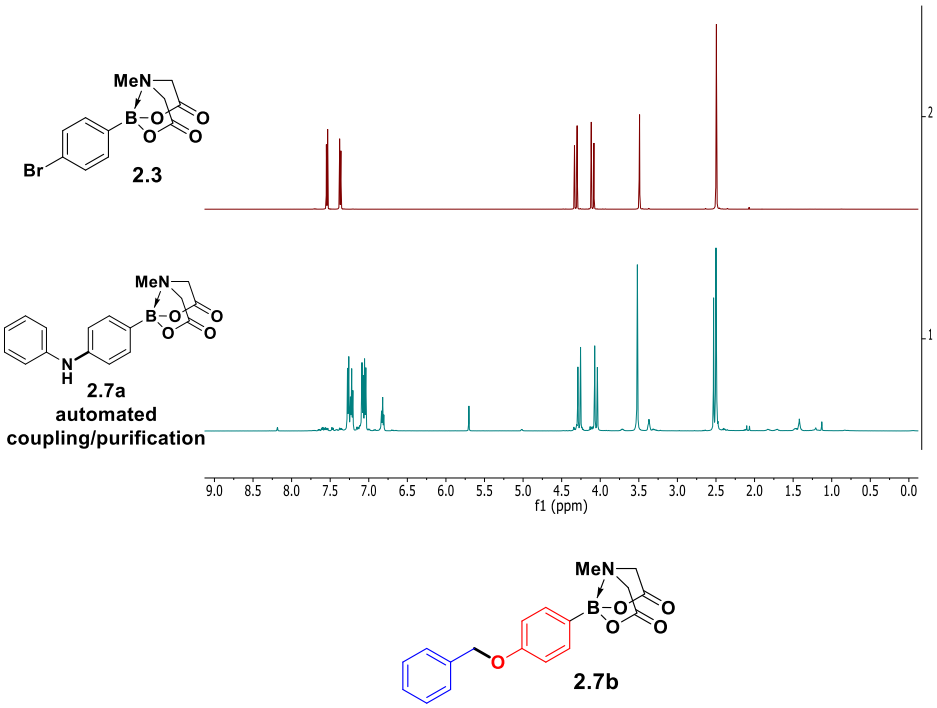
Purification After filtration, the crude reaction mixture is added to the Extraction/Workup Cartridge. To this cartridge is then added 5 mL 50% saturated aqueous NaCl. The layers are mixed via argon sparging (60 seconds) before removing and disposing of the aqueous layer. This is repeated twice more, for a total of three aqueous washes before the organic layer is dried in the Predrying Cartridge. This is accomplished through the repeated injection and withdrawal of the solution into the cartridge (20 repetitions). Then, a 3 mL portion of the filtered and washed crude reaction mixture is added to the Precipitation Cartridge and the solvent is removed from the Precipitation Cartridge, loading any crude reaction product onto the Silica Gel Plug ("catch"). This process is performed a total of 10 times, washing the Predrying Cartridge with 2 mL THF for the final two repetitions. Then, 12 mL of 1.5% MeOH in Et_2O are

added and the solvent is removed 3 times (36 mL total). Then, 12 mL of Et_2O are added and the solvent is removed 3 times (36 mL total). Finally, 12 mL THF are added and slowly removed (to increase residence time in the column), giving a purified solution of the product MIDA boronate. In the case of a single-step coupling experiment this solution is added to an empty Deprotection Cartridge where it can be retrieved for analysis or further use. In the case of multi-step experiments, the solution is moved to a Deprotection Cartridge containing NaOH, concentrated to 10 mL, and another cycle of deprotection begins.

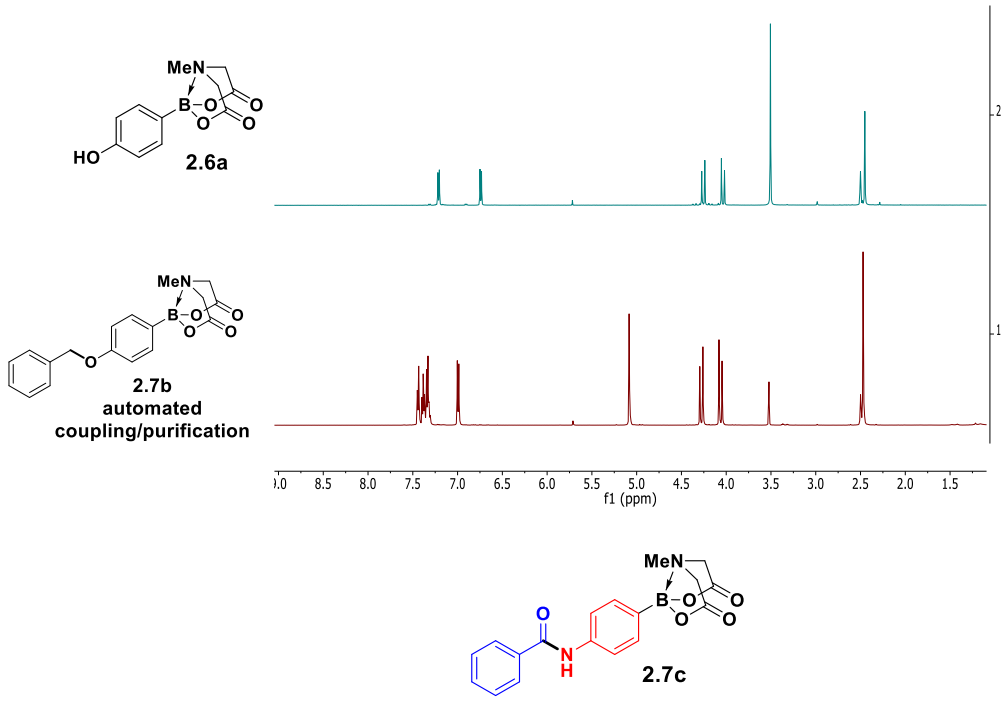


2.7a

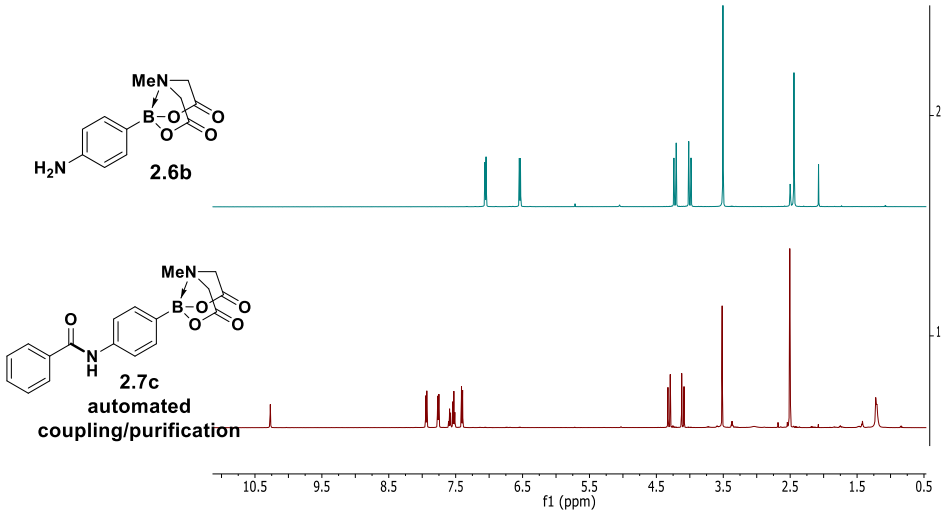
Automated Procedure II was followed using 95 µL aniline **2.5a** (1.04 mmol), 105.2 mg (0.337 mmol) *p*-bromophenyl MIDA boronate **2.3**, 638.4 mg K_3PO_4 (3.01 mmol), and 13.5 mg (5 mol%) 2nd generation XPhos palladacycle. The reaction was run at 55°C for 16 h. The desired aryl MIDA boronate **2.7a** was obtained as an off-white solid (82.3 mg, 0.254 mmol, 75% yield) of 88% purity. ^{1}H-NMR (500 MHz, DMSO-d_6:D_2O, 95:5): δ 7.27 (d, J = 8.3 Hz, 2H), 7.22 (dd, J = 8.5 and 7.2 Hz, 2H), 7.08 (d, J = 7.3 Hz, 2H), 7.05 (d, J = 8.5 Hz, 2H), 6.82 (t, J = 7.2 Hz, 1H), 4.27 (d, J = 17.2 Hz, 2H), 4.05 (d, J = 17.2 Hz, 2H), 2.50 (s, 3H). ^{13}C-NMR (125 MHz, DMSO-d_6:D_2O, 95:5): δ 169.6, 144.3, 143.1, 133.5, 129.3, 120.1, 117.2, 115.8, 61.7, 47.6; HRMS (ESI+) calculated for $C_{17}H_{18}BN_2O_4$ $[M+H]^+$ *m/z* 325.1360, found 325.1358.

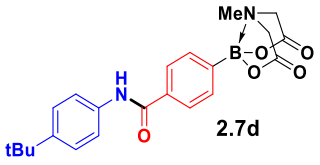


Automated Procedure II was followed using 82.9 mg (0.333 mmol) *p*-hydroxyphenyl MIDA boronate **2.6a**, 120 µL benzyl bromide **2.5b** (1.01 mmol), and 416.4 mg (3.01 mmol) K_2CO_3. After automated addition of THF (8.4 mL), MeCN (3.6 mL) was added as a co-solvent. The reaction was run at 60 °C for 16 h. The desired aryl MIDA boronate **2.7b** was obtained as a solid (93.5 mg, 0.276 mmol, 83% yield) of >95% purity. ^{1}H-NMR (500 MHz, DMSO-d_6:D_2O, 95:5): δ 7.46 – 7.42 (m, 2H), 7.41 – 7.36 (m, 2H), 7.36 – 7.30 (m, 3H), 6.99 (d, J = 8.4 Hz, 2H), 5.08 (s, 2H), 4.28 (d, J = 17.2 Hz, 2H), 4.06 (d, J = 17.2 Hz, 2H), 2.47 (s, 3H); ^{13}C-NMR (125 MHz, DMSO-d_6:D_2O, 95:5): δ 169.7, 159.3, 137.3, 134.0, 128.7, 128.1, 127.9, 114.4, 69.2, 61.8, 47.7; HRMS (ESI+) calculated for $C_{18}H_{19}NO_5B$ $[M+H]^+$ *m/z* 340.1356, found 340.1355.

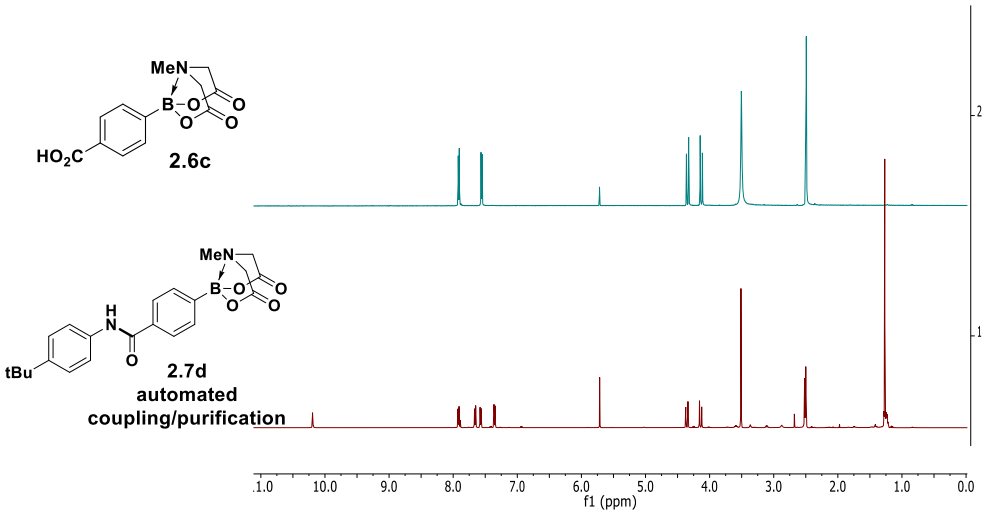


Automated Procedure II was followed using 82.2 mg (0.331 mmol) *p*-aminophenyl MIDA boronate **2.6b**, 60.7 mg (0.497 mmol) benzoic acid **2.5c**, 170.7 mg (0.532 mmol) TATU, and 90 µL (0.517 mmol) DIPEA. After automated addition of THF (8.4 mL), MeCN (3.6 mL) was added as a co-solvent. The reaction was run at 40 °C for 13 h. The desired aryl MIDA boronate **2.7c** was obtained as an off-white solid (93.7 mg, 0.266 mmol, 80% yield) of 90% purity. ^{1}H-NMR (500 MHz, DMSO-d_6:D_2O, 95:5): δ 10.27 (s, 1H), 7.96 – 7.92 (m, 2H), 7.78 – 7.74 (m, 2H), 7.62 – 7.57 (m, 1H), 7.55 – 7.50 (m, 2H), 7.40 (d, J = 8.3 Hz, 2H), 4.31 (d, J = 17.2 Hz, 2H), 4.10 (d, J = 17.2 Hz, 2H), 2.51 (s, 3H); ^{13}C-NMR (125 MHz, DMSO-d_6:D_2O, 95:5): δ169.6, 165.8, 139.8, 135.0, 132.9, 131.8, 128.6, 127.8, 119.7, 61.9, 47.7; HRMS (ESI+) calculated for $C_{18}H_{18}N_2O_5B$ $[M+H]^+$ *m/z* 353.1309, found 353.1310.





Automated Procedure II was followed using 91.7 mg (0.331 mmol) *p*-carboxyphenyl MIDA boronate **2.6c**, 55 µL (0.345 mmol) *p*-(*tert*-butyl)aniline, 118.3 mg (0.367 mmol) TATU, and 60 µL (0.344 mmol) DIPEA. After automated addition of THF (8.4 mL), MeCN (3.6 mL) was added as a co-solvent. The reaction was run at room temperature for 1 h. The desired aryl MIDA boronate **2.7d** was obtained as an off-white solid (118.7 mg, 0.291 mmol, 88% yield) of 90% purity. ^{1}H-NMR (500 MHz, DMSO-d_6:D_2O, 95:5): δ 10.19 (s, 1H), 7.92 (d, J = 8.2 Hz, 2H), 7.66 (d, J = 8.7 Hz, 2H), 7.57 (d, J = 8.1 Hz, 2H), 7.36 (d, J = 8.7 Hz, 2H), 4.35 (d, J = 17.3 Hz, 2H), 4.14 (d, J = 17.2 Hz, 2H), 2.52 (s, 3H), 1.27 (s, 9H); ^{13}C-NMR (125 MHz, DMSO-d_6:D_2O, 95:5): δ169.6, 165.7, 146.4, 136.7, 135.5, 134.2, 132.6, 127.0, 125.4, 120.5, 62.1, 47.9, 34.3, 31.4; HRMS (ESI+) calculated for $C_{22}H_{26}BN_2O_5$ $[M+H]^+$ *m/z* 409.1935, found: 409.1931.



Syntheses Involving Multiple ICC Cycles (Figure 2.2) (**Automated Procedure III**)

Automated Procedure III - *Cartridge Preparation*

For multi-step syntheses, cartridges are prepared in the same manner as outlined in **Automated Procedure I** (for C-C coupling reactions) and **Automated Procedure II** (for C-X bond forming reactions). Each ICC cycle requires one set of the above described cartridges.

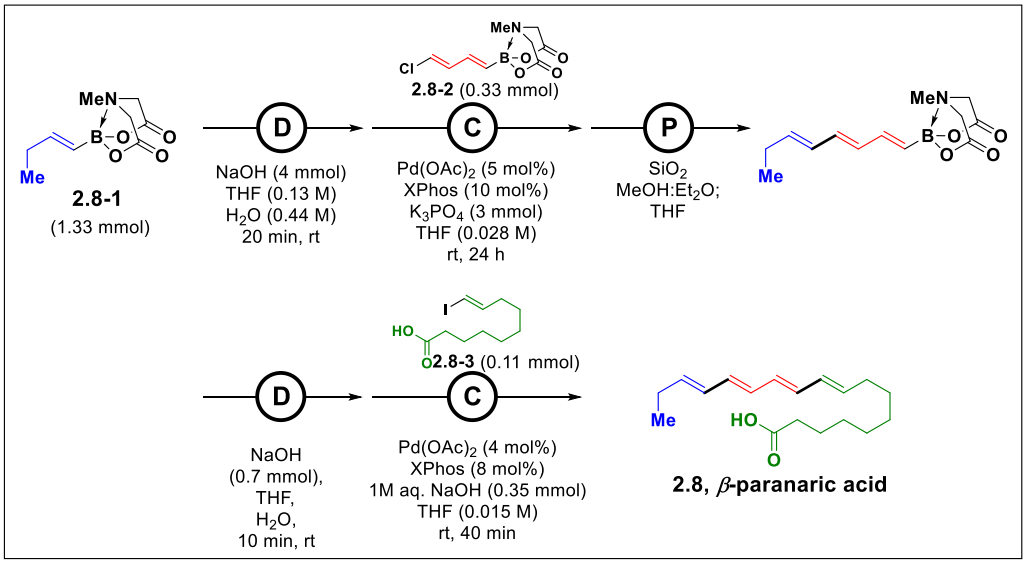
Automated Procedure III - *Experimental Details*

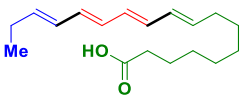
Automated Procedures I and **II** are followed with the following addendums:

For two-step syntheses, after eluting the product from the Silica Gel Plug with 12 mL THF, the purified MIDA boronate solution is added to the Second Deprotection Cartridge which already contains solid NaOH (1.0 mmol, 40 mg). The Second Reaction Cartridge contains the capping building block (0.11 mmol), XPhos 2nd generation palladacycle (0.0056 mmol, 4.4 mg, 5 mol%), and K_3PO_4 (1.0 mmol, 212 mg). The coupling reactions are run at the concentrations noted in the following procedures. This cartridge is identical to a First Reaction Cartridge, but is not tethered to a Reaction Filtration Cartridge.

For three-step syntheses, the Third Deprotection Cartridge contains NaOH (0.33 mmol, 13.3 mg) and no Drying Cartridge is used for the third reaction. The Third Reaction Cartridge is a 7-mL glass vial containing a PTFE-coated magnetic stir, the capping building block (0.037 mmol), XPhos 2nd generation palladacycle (0.00185 mmol, 1.5 mg, 5 mol%), and K_3PO_4 (0.33 mmol, 71 mg). The coupling reactions are run at the concentrations noted in the following procedures. The vial is sealed under argon with a septum-top screw cap.

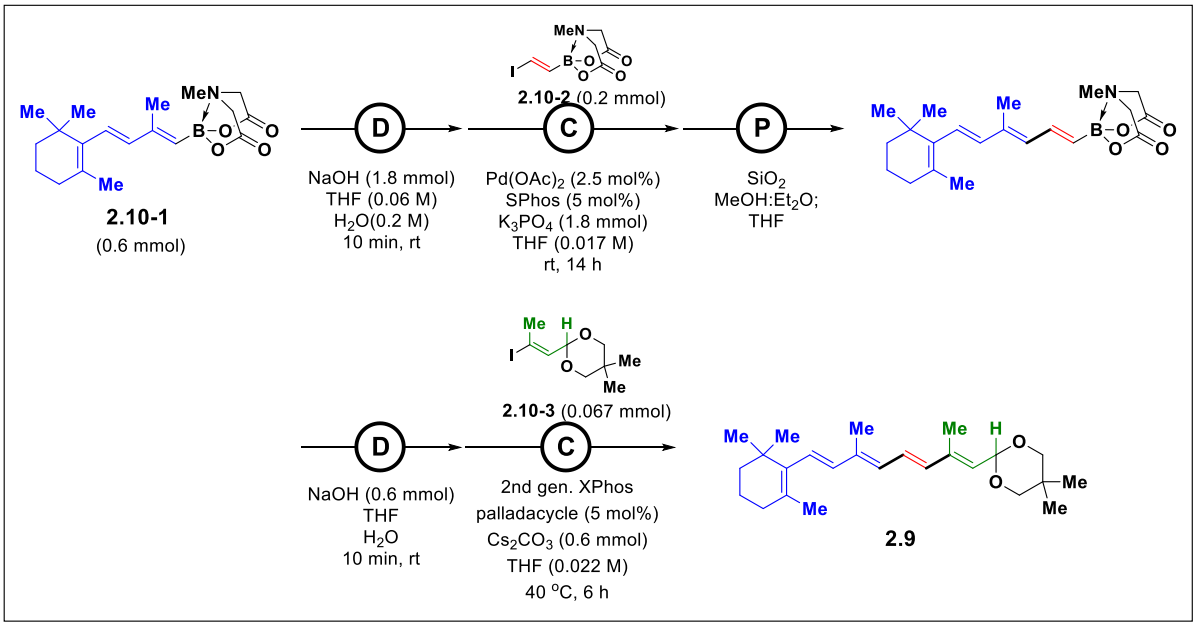
At the end of the synthesis, the crude reaction mixture is purified by either silica gel chromatography or preparative HPLC.

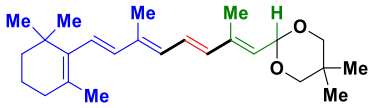




Automated Procedure III was followed with the following modifications: The first coupling reaction was run at room temperature for 24 hours. The second deprotection reaction was run for 10 minutes, and the second coupling reaction was run in a 20-mL glass vial at room temperature using aqueous NaOH as the base for 40 minutes. The procedure was also conducted

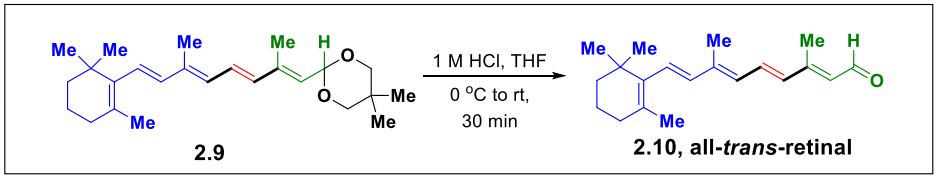
under subdued light conditions to protect against isomerization of the polyene framework. **2.8** was afforded as a fluorescent solid (18.3 mg, 0.0662 mmol, 56% yield). ^{1}H NMR indicated a 10:1 mixture of the desired β-parinaric acid (**2.8**):9-(*Z*)-parinaric acid (arising from 10:1 *E*:*Z* mixture of starting material vinyl iodide **2.8-3**). TLC (50% Et_2O in hexanes): R_f = 0.13, visualized by UV; HPLC (Agilent Prep-C18, 10 µm, 30 x 150 mm (product number: 413910-302), 25 mL/min, gradient: A = water, B = acetonitrile, 0 min: 95% A, 5% B; 2 min: 95% A, 5% B; 15 min: 0% A, 100% B; 30 min: 0% A, 100% B): 23.7 min; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.21-6.05 (m, 6H), 5.76-5.63 (m, 2H), 2.34 (t, *J* = 7 Hz, 2H), 2.15-2.07 (m, 4H), 1.66-1.60 (m, 2H), 1.43-1.26 (m, 8H), 1.01 (t, *J* = 7.5 Hz, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 179.2, 136.7, 135.1, 132.6, 132.6, 131.0, 131.0, 130.8, 129.8, 34.0, 33.0, 29.4, 29.2, 29.1, 29.1, 26.0, 24.8, 13.7; HRMS (ESI+) calculated for $C_{18}H_{29}O_2$ $[M+H]^+$ *m/z* 277.2168, found 277.2175.



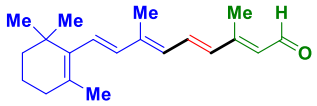


2.9

Automated Procedure III was followed with the following modifications: In the first coupling reaction, SPhos was used as the ligand and the reaction was run for 14 hours at room temperature. Both deprotection reactions were run for 10 minutes. The second coupling reaction was run in a 7-mL glass vial at 40 °C for 6 hours using Cs_2CO_3 as the base. The procedure was also conducted under subdued light conditions to protect against isomerization of the polyene framework. Crude **2.9** was purified via silica gel chromatography (100% hexanes to 30% EtOAc in hexanes) to afford **2.9** as a single stereoisomer and a yellow oil (18.2 mg, 0.0491 mmol, 74% yield). TLC (petroleum ether: ether 4:1): R_f = 0.86, stained by $KMnO_4$; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.66 (dd, *J* = 14.8, 11.2 Hz, 1H), 6.27 (d, *J* = 15.2 Hz, 1H), 6.19-6.08 (m, 3H), 5.54 (d, *J* = 6 Hz, 1H), 5.21 (d, *J* = 6.4 Hz, 1H), 3.66 (d, *J* = 11.2 Hz, 2H), 3.53 (d, *J* = 10.8 Hz, 2H), 2.01 (t, *J* = 6.4 Hz, 2H), 1.95 (s, 3H), 1.91 (s, 3H), 1.70 (s, 3H), 1.62-1.59 (m, 2H), 1.47-1.44 (m, 2H), 1.23 (s, 3H), 1.01 (s, 6H), 0.75 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$):δ 139.3, 137.8, 137.6, 136.6, 135.8, 130.0, 129.3, 127.2, 127.0, 126.2, 109.8, 98.8, 39.6, 34.2, 33.0, 30.0, 28.9, 23.0, 22.0, 21.7, 19.2, 13.4, 12.7; HRMS (ESI+) calculated for $C_{25}H_{39}O_2$ $[M+H]^+$ *m/z* 371.2950, found 371.2950.

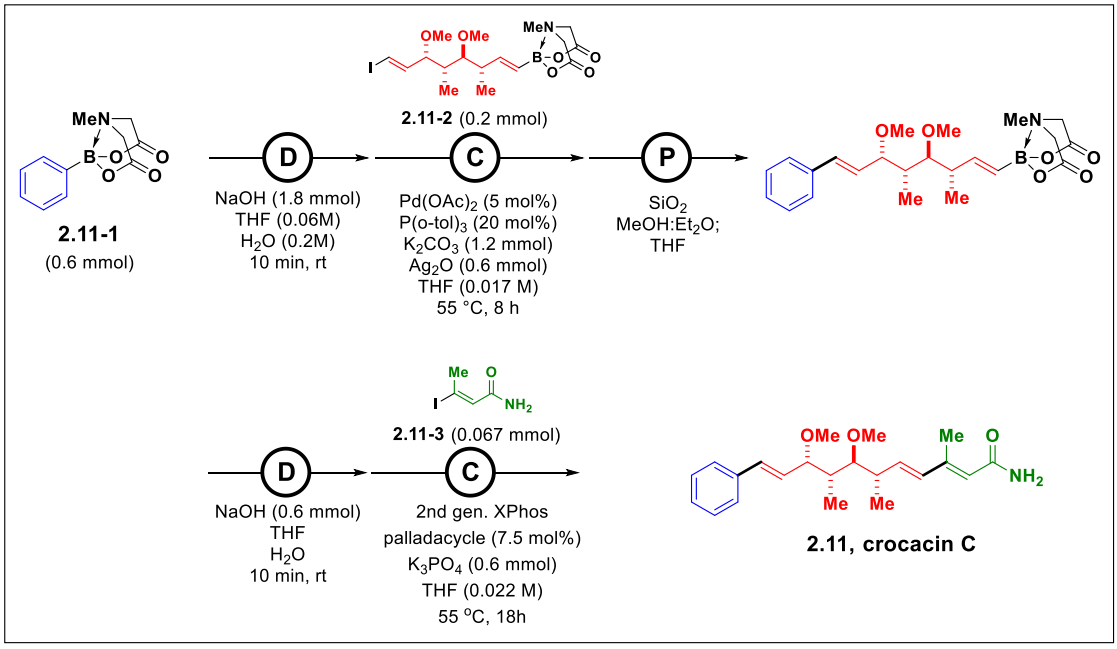


2.9 **2.10, all-*trans*-retinal**



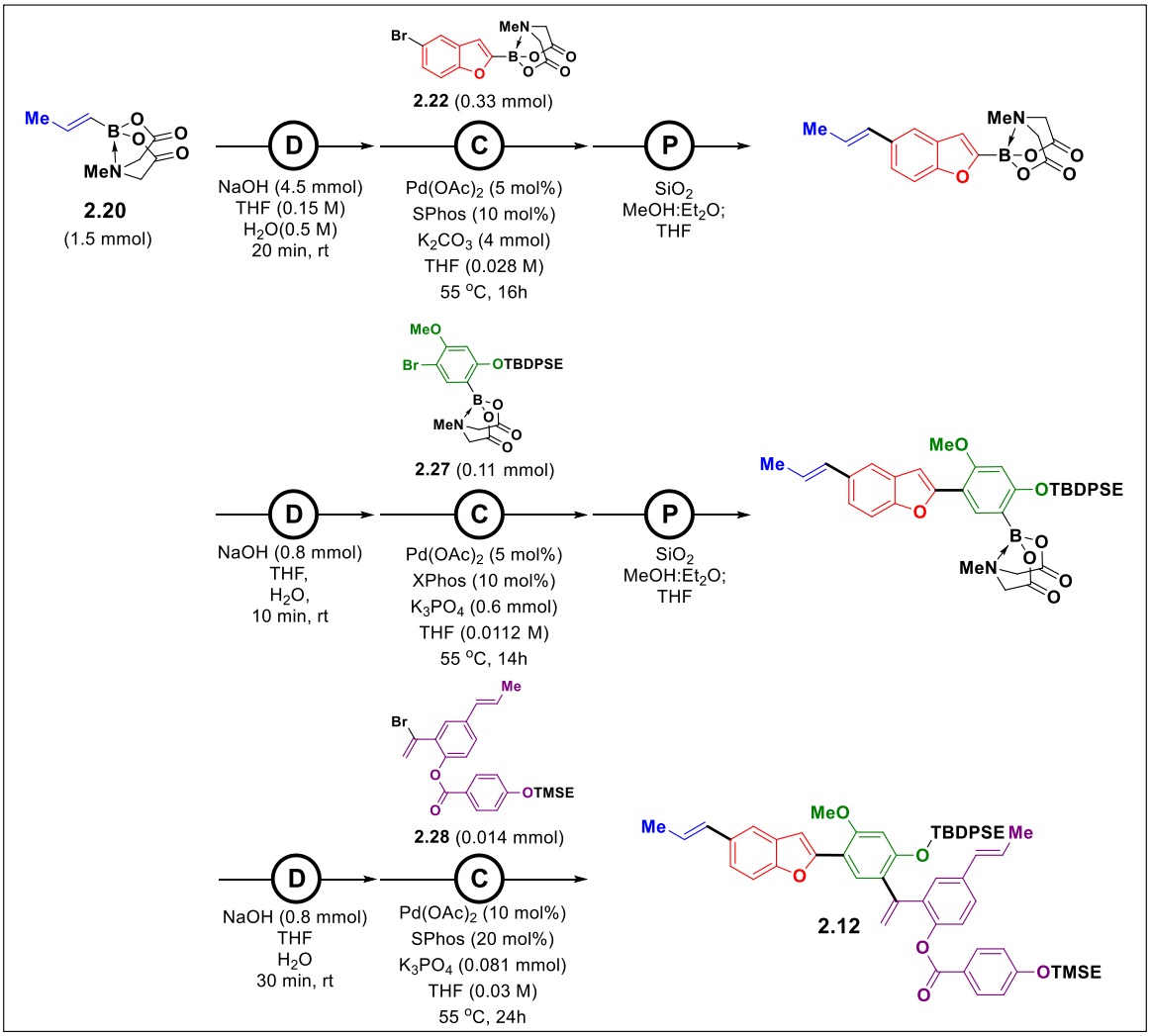
2.10, all-*trans*-retinal

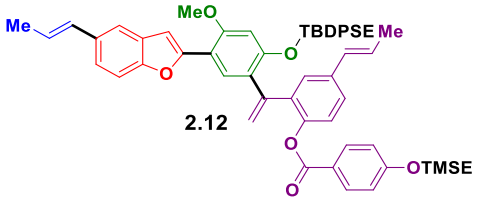
A 7-mL vial charged with **2.9** (18.2 mg, 0.049 mmol, 1.0 equiv.) was sealed with a PTFE-lined cap and purged with N_2 and THF (1.0 mL, 0.05M) was added to afford a clear yellow solution. The vial was cooled to 0 $^{\circ}$C in an ice bath for 5 minutes. Aqueous HCl (1M, 0.5 mL) was added dropwise to the reaction vial and the reaction mixture was allowed to warm to 23 $^{\circ}$C with stirring over 30 minutes. After 30 minutes, the reaction mixture was transferred to a separatory funnel containing aqueous saturated $NaHCO_3$ (5 mL), rinsing with diethyl ether (10 mL) and the phases were separated. The aqueous layer was back-extracted with diethyl ether (5 mL) and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to afford a yellow-orange oil. The resulting crude material (4:1 ratio of all-*trans* retinal (**2.10**):13-*cis*-retinal) was adsorbed onto Celite™ from an acetone solution and purified by silica gel chromatography (32:1 hexanes: EtOAc) to afford **2.10** as an orange solid (8.9 mg, 0.0313 mmol, 64% yield). ^{1}H-NMR (500 MHz, $CDCl_3$):δ 10.11 (d, *J* = 8 Hz, 1H), 7.14 (dd, *J* = 15, 11.5 Hz, 1H), 6.37 (d, *J* =15 Hz, 1H), 6.34 (d, *J* = 15 Hz, 1H), 6.19 (d, *J* = 9.5 Hz, 1H), 6.16 (d, *J* = 16 Hz, 1H), 5.97 (d, *J* = 8.5 Hz, 1H), 2.33 (d, *J* = 1 Hz, 3H), 2.04-2.02 (m, 2H), 2.03 (s, 3H), 1.72 (s, 3H), 1.63-1.60 (m, 2H), 1.49-1.46 (m, 2H), 1.03 (s, 6H).



Automated Procedure III was followed with the following modifications: In the first coupling reaction, P(*o*-tol)$_3$ was used as the ligand and K_2CO_3 and Ag_2O were used as the base and the reaction was run for 8 hours. Both deprotection reactions were run for 10 minutes. The second coupling reaction was run for 18 hours in a 7-mL glass vial. Crude **2.11** was purified via silica gel chromatography (40% EtOAc in hexanes to 50% EtOAc in hexanes) to afford **2.11** as an off-white solid (14.5 mg, 0.0406 mmol, 61% yield). TLC (20% EtOAc in hexanes): R_f = 0.08, visualized by UV; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.39 (d, *J* = 7.5 Hz, 2H), 7.32 (t, *J* = 7 Hz, 2H), 7.23 (t, *J* = 7 Hz, 1H), 6.56 (d, *J* = 16.5 Hz, 1H), 6.17-6.01 (m, 3H), 5.63 (s, 1H), 5.38 (br s, 2H), 4.08 (dd, *J* = 7.5, 1 Hz, 1H), 3.54 (s, 3H), 3.32 (s, 3H), 3.19 (dd, *J* = 10, 2 Hz, 1H), 2.56-2.53 (m, 1H), 2.25 (d, *J* = 1 Hz, 3H), 1.56-1.52 (m, 1H), 1.19 (d, *J* = 7 Hz, 3H), 0.84 (d, *J* = 7 Hz, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 169.4, 149.7, 137.2, 136.8, 134.1, 132.1, 129.3, 128.7,

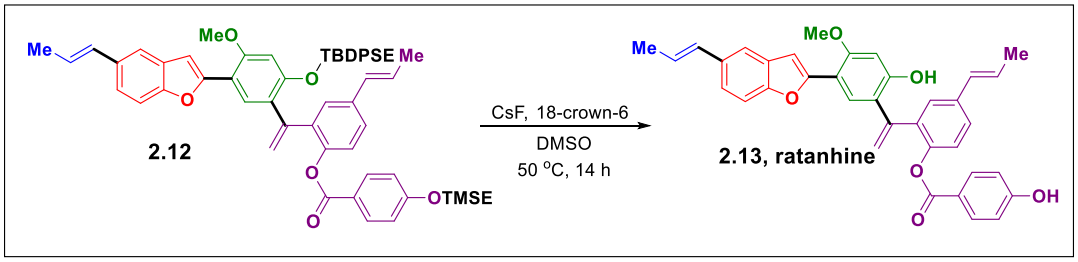
127.7, 126.5, 119.7, 86.5, 81.1, 61.6, 56.6, 42.7, 40.2, 18.9, 13.9, 9.8; HRMS (ESI+) calculated for $C_{22}H_{32}NO_3$ $[M+H]^+$ *m/z* 358.2382, found 358.2392.

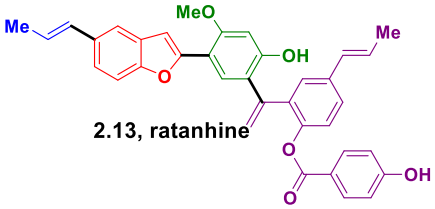




Automated Procedure III was followed with the following modifications: The first coupling reaction was run using SPhos (10 mol%), $Pd(OAc)_2$ (5 mol%) and K_2CO_3 as the base. The second and third deprotection reactions were run for 10 and 30 minutes, respectively. The second coupling reaction was run for 14 hours and the third coupling reaction was run for 24

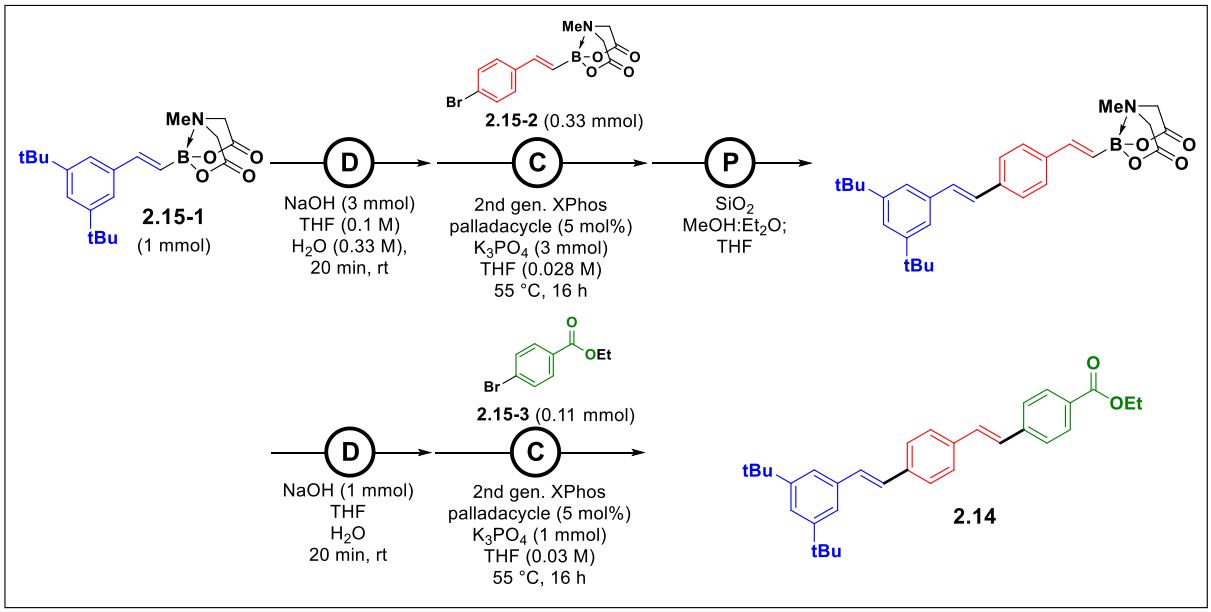
hours using SPhos as the ligand. **2.12** was isolated as a colorless oil (4.7 mg, 36% yield), the ^{1}H NMR of which contained small amounts of hydrocarbon impurities presumed to represent some leaching from the HPLC column. HPLC (Agilent Prep-C18, 10 µm, 30 x 150 mm (product number: 413910-302), 25 mL/min, gradient: A = water, B = 20% THF in MeCN, 0 min: 80% A, 20% B; 5 min: 0% A, 100% B; 50 min: 0% A, 100% B): 13.4 min; ^{1}H-NMR (500 MHz, acetone-d_6): δ 7.67 (s, 1H), 7.64-7.62 (m, 4H), 7.54 (d, *J* = 9 Hz, 2H), 7.50 (s, 1H), 7.45-7.43 (m, 8H), 7.25 (d, *J* = 2 Hz, 1H), 7.21 (d, *J* = 8.5 Hz, 1H), 7.10 (d, *J* = 8.5 Hz, 1H), 6.95 (d, *J* = 1 Hz, 1H), 6.56 (dd, *J* = 16, 2 Hz, 1H), 6.51-6.46 (m, 3H), 6.38 (dq, *J* = 15.5, 6.5 Hz, 1H), 6.35 (s, 1H), 6.26 (dq, *J* = 15.5, 6.5 Hz, 1H), 5.46 (s, 2H), 3.86-3.83 (m, 2H), 3.81 (s, 3H), 3.57-3.54 (m, 2H), 1.91 (dd, *J* = 6.5, 1.5 Hz, 3H), 1.88 (dd, *J* = 5, 1.5 Hz, 3H), 1.20-1.17 (m, 2H), 0.99 (s, 9H), 0.89-0.86 (m, 2H), 0.02 (s, 9H); HRMS (ESI+) calculated for $C_{59}H_{65}O_6Si_2$ $[M+H]^+$ *m/z* 925.4320, found 925.4316.

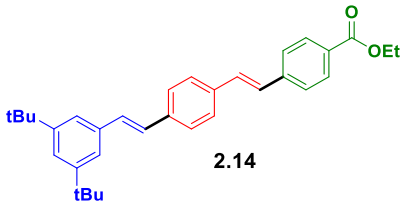




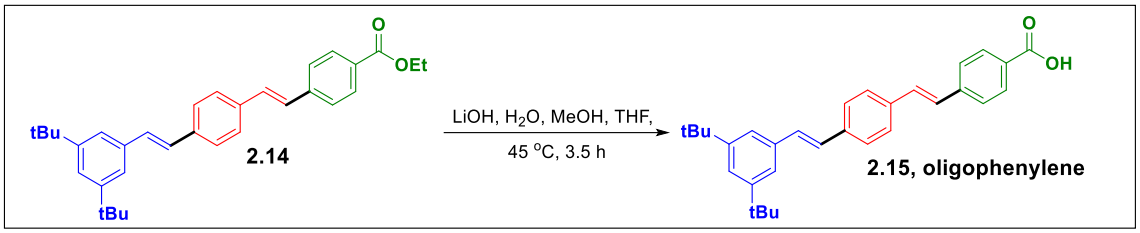
To a 1-mL Reacti-vial™ containing **2.12** and a PTFE-coated magnetic stir bar was added CsF (8.2 mg, 0.054 mmol) and 18-crown-6 (1.1 mg, 0.00416) followed by DMSO (0.15 mL) in a glovebox. The vial was sealed with a cap and stirred at 50 °C for 14 hours. The reaction was then cooled to room temperature, diluted with 8 mL EtOAc and washed with a solution of 1:1

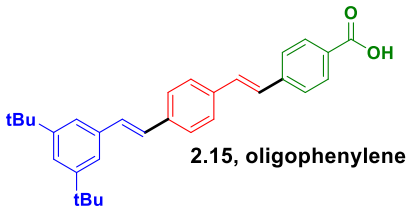
saturated aqueous NH_4Cl/H_2O (8 mL). The aqueous layer was extracted with 4 mL EtOAc. The combined organic layers were washed with H_2O (2 × 4 mL), then with brine (8 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography to afford **2.13** 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}H-NMR (500 MHz, acetone-d_6): δ 7.83 (dt, *J* = 9.0, 2.0 H, 2H), 7.77 (s, 1H), 7.53 (s, 1H), 7.43 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.37 (d, *J* = 8.5 Hz, 1H), 7.34 (d, *J* = 2.5 Hz, 1H), 7.28 (d, *J* = 8.0, 1.0 Hz, 1H), 7.17 (d, *J* = 8.5 Hz, 1H), 7.14 (s, 1H), 6.83 (dt, *J* = 8.5, 2.0 Hz, 2H), 6.55 (s, 1H), 6.50 (dd, *J* = 15.5, 1.5 Hz, 1H), 6.44 (dd, *J* = 16.0, 1.5 Hz, 1H), 6.31-6.21 (m, 2H), 5.61 (d, *J* = 1.5 Hz, 1H), 5.57 (d, *J* = 2.0 Hz, 1H), 3.96 (s, 3H), 1.87 (dd, *J* = 6.5, 1.5 Hz, 3H), 1.84 (dd, *J* = 6.5, 1.5 Hz, 3H); HRMS (ESI+) calculated for $C_{36}H_{31}O_6$ $[M+H]^+$ *m/z* 559.2121, found 559.2128.





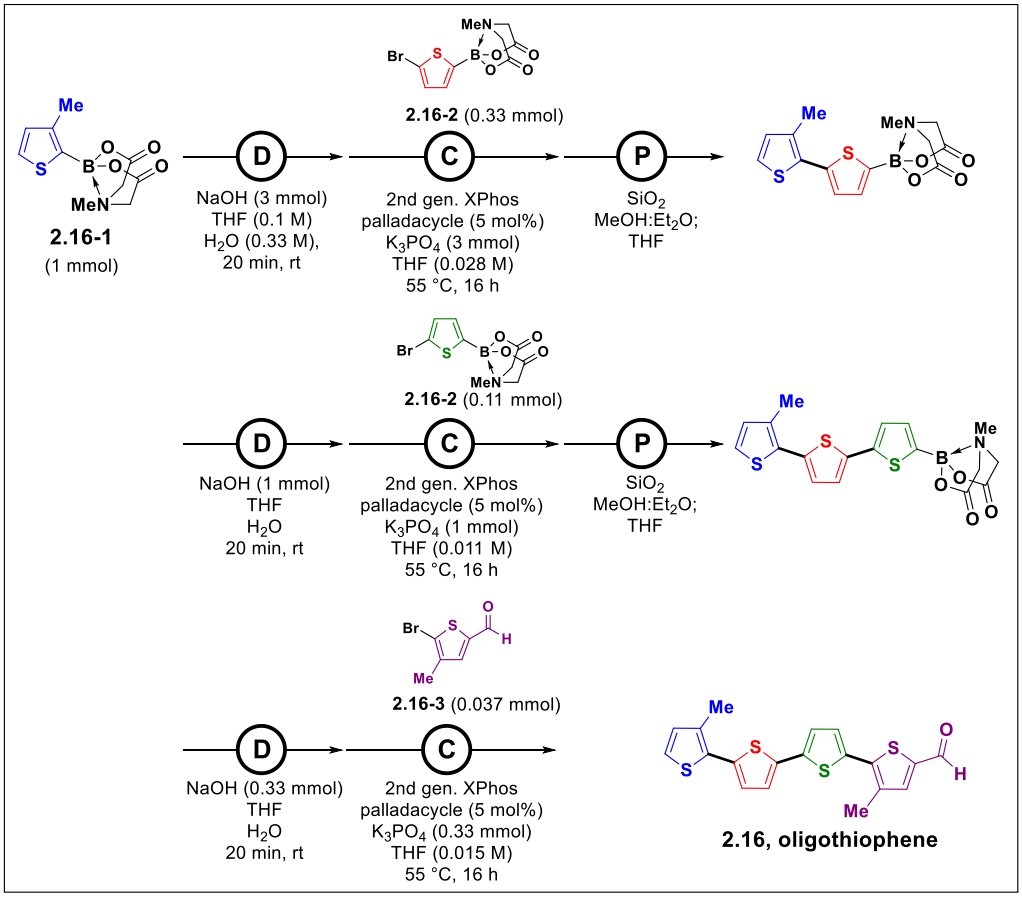
Automated Procedure III was followed with the following modifications: In the second coupling reaction, the addition of the boronic acid was performed over 1 minute and the coupling was run in a 7-mL glass vial. **2.14** was afforded as a yellow solid (44.1 mg, 0.0945 mmol, 84% yield). TLC (40% DCM in hexanes): R_f = 0.31, visualized by UV; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.06 (d, J = 8 Hz, 2H), 7.59-7.54 (m, 6H), 7.41-7.39 (m, 3H), 7.23 (d, J = 16.5 Hz, 1H), 7.22 (d, J = 16 Hz, 1H), 7.15 (d, J = 15.5 Hz, 1H), 7.12 (d, J = 16 Hz, 1H), 4.40 (q, J = 7 Hz, 2H), 1.42 (t, J = 7.5 Hz, 3H), 1.40 (s, 18H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 166.5, 151.2, 141.9, 137.8, 136.5, 136.0, 130.9, 130.2, 130.1, 129.3, 127.5, 127.4, 127.3, 127.0, 126.4, 122.4, 121.0, 61.0, 35.0, 31.6, 14.5; HRMS (ESI+) calculated for $C_{33}H_{39}O_2$ $[M+H]^+$ *m/z* 467.2950, found 467.2943.

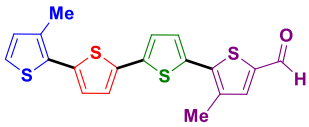




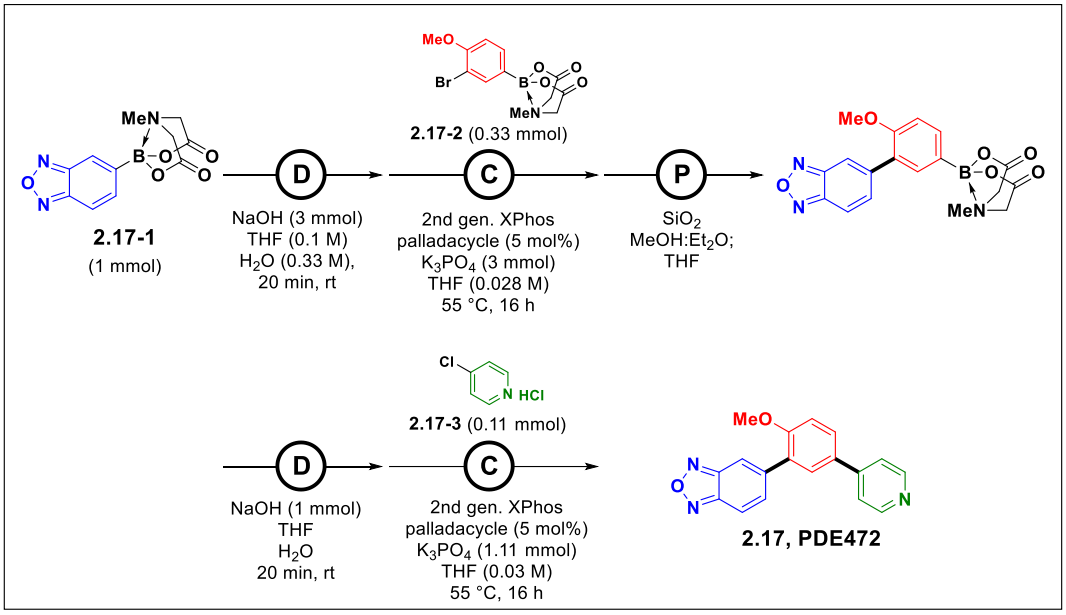
To a solution of ethyl ester **2.14** (44.1 mg, 0.0945 mmol) in MeOH/THF 1:1 (2 mL) was added LiOH solution (18 mg, 0.752 mmol in 0.4 mL H_2O) in one portion. The mixture was stirred vigorously at 45 °C for 3.5 hours. The reaction was cooled briefly in an ice-water bath

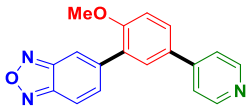
and 0.2 mL of 2 N HCl was added. The mixture was diluted with 5 mL H_2O and extracted with EtOAc (10 mL, then 2 × 5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by recrystallization from hot toluene. A second crop was obtained by precipitation from toluene/hexanes and combined with the first crop to afford **2.15** as a bright yellow solid (20.5 mg, 0.047 mmol, 50% yield). ^{1}H-NMR (500 MHz, DMSO-d_6): δ 12.88 (s, 1H), 7.92 (d, J = 8 Hz, 2H), 7.70 (d, J = 8.5 Hz, 2H), 7.64 (s, 3H), 7.43 (d, J = 1.5 Hz, 2H), 7.40 (d, J = 16.5 Hz, 1H), 7.34 (d, J = 16.5 Hz, 1H), 7.32 (d, J = 17 Hz, 1H), 7.30 (s, 2H), 7.26 (d, J = 16.5 Hz, 1H), 1.31 (s, 18 H); ^{13}C-NMR (125 MHz, DMSO-d_6): δ 167.0, 150.5, 141.5, 137.2, 136.2, 135.7, 130.6, 129.7 (2C), 129.4, 127.2, 127.1, 126.8, 126.4, 121.6, 120.8, 34.5, 31.2; HRMS (EI+) calculated for $C_{31}H_{34}O_2$ $[M]^+$ *m/z* 438.25588, found: 438.25538.





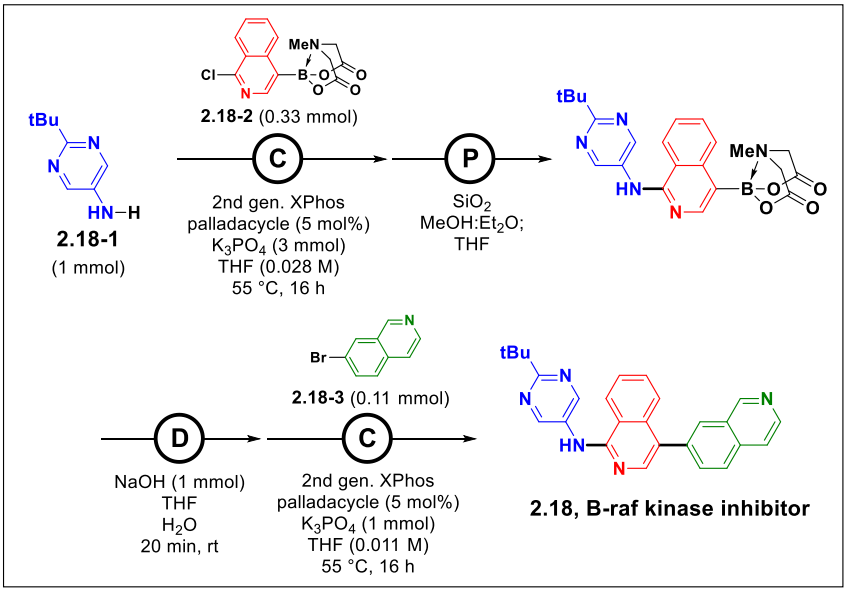
Automated Procedure III was followed. Crude **2.16** was purified via silica gel chromatography (100% hexanes to 20% EtOAc in hexanes) to afford **2.16** as a red/orange solid (7.5 mg, 0.0194 mmol, 50% yield). TLC (20% EtOAc in hexanes): R_f = 0.29, visualized by longwave UV; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 9.81 (s, 1H), 7.54 (s, 1H), 7.24 (d, *J* = 3.5 Hz, 1H), 7.17 (m, 3H), 7.06 (d, *J* = 3.5 Hz, 1H), 6.90 (d, *J* = 5.0 Hz, 1H), 2.48 (s, 3H), 2.43 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 182.6, 141.6, 140.6, 139.7, 139.2, 136.7, 135.8, 134.8, 134.5, 134.2, 131.7, 130.7, 128.2, 126.2, 124.8, 124.2, 123.8, 16.1, 15.7; HRMS (EI+) calculated for $C_{19}H_{14}OS_4$ $[M]^+$ *m/z* 385.99277, found 385.99217.

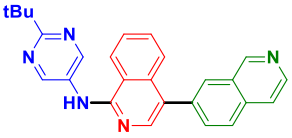




2.17, PDE472

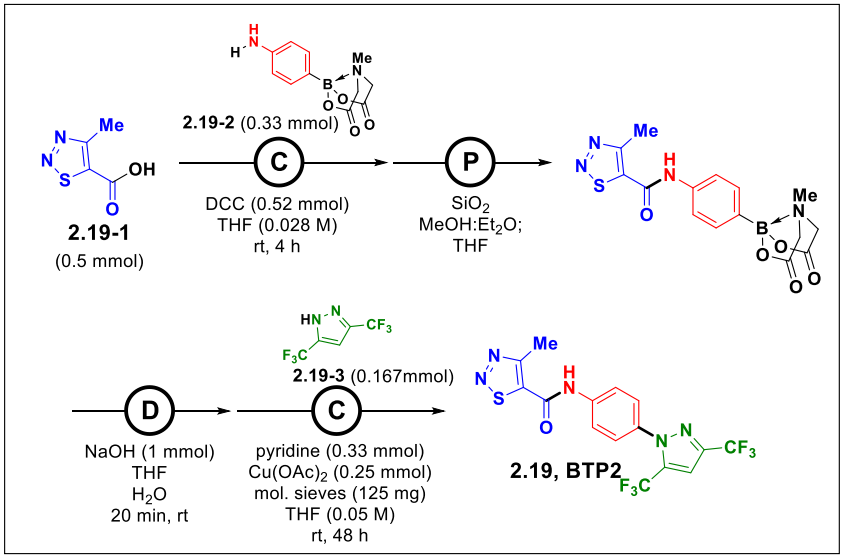
Automated Procedure III was followed with the following modifications: In the second coupling reaction: 1.11 mmol of K_3PO_4 were used, the addition of the boronic acid was performed over 1 minute, and the coupling was run in a 7-mL glass vial. **2.17** was afforded as a colorless solid (6.6 mg, 0.0218 mmol, 20% yield). TLC (EtOAc): R_f = 0.30, visualized by UV; HPLC (Agilent Prep-C18, 10 µm, 30 x 150 mm (product number: 413910-302), 25 mL/min, gradient: A = water, B = acetonitrile, 0 min: 95% A, 5% B; 20 min: 5% A, 95% B): 17.5 min; ^{1}H-NMR (500 MHz, acetone-d_6): δ 8.63 (br s, 2H), 8.12 (t, J = 1 Hz, 1H), 7.97 (dd, J = 9.5, 1 Hz, 1H), 7.96 (d, J = 2.5 Hz, 1H), 7.93 (dd, J = 9, 2.5 Hz, 1H), 7.87 (dd, J = 9.5, 1.5 Hz, 1H), 7.74 (app d, J = 6 Hz, 2H), 7.35 (d, J = 9 Hz, 1H), 3.98 (s, 3H); ^{13}C-NMR (125 MHz, DMSO-d_6): δ 157.3, 150.1, 149.3, 148.1, 146.1, 142.2, 135.8, 129.8, 129.1, 129.0, 128.2, 120.9, 114.9 (2C), 112.7, 56.1; HRMS (ESI+) calculated for $C_{18}H_{14}N_3O_2$ $[M+H]^+$ *m/z* 304.1086, found 304.1081.

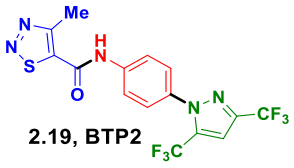




2.18, B-raf kinase inhibitor

Automated Procedure III was followed. Crude **2.18** was purified via silica gel chromatography (50% hexanes in EtOAc to 100% EtOAc) to afford **2.18** as a tan-orange solid (12.9 mg, 0.0318 mmol, 28% yield). TLC (EtOAc): R_f = 0.25, visualized by UV; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 9.31 (br s, 1H), 9.19 (s, 2H), 8.58 (d, *J* = 5 Hz, 1H), 8.16 (d, *J* = 8 Hz, 1H), 8.10 (s, 1H), 8.05 (s, 1H), 7.95 (d, *J* = 8.5 Hz, 1H), 7.87-7.81 (m, 2H), 7.74 (d, *J* = 5.5 Hz, 1H), 7.68-7.60 (m, 2H), 7.56 (br s, 1H), 1.44 (s, 9H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 171.2, 152.5, 151.6, 148.5, 143.2, 140.9, 136.9, 135.9, 135.2, 133.2, 132.7, 130.8, 128.9, 128.6, 127.2, 126.8, 126.3, 125.6, 121.9, 120.6, 118.2, 39.0, 29.9; HRMS (ESI+) calculated for $C_{26}H_{24}N_5$ $[M+H]^+$ *m/z* 406.2032, found 406.2031.



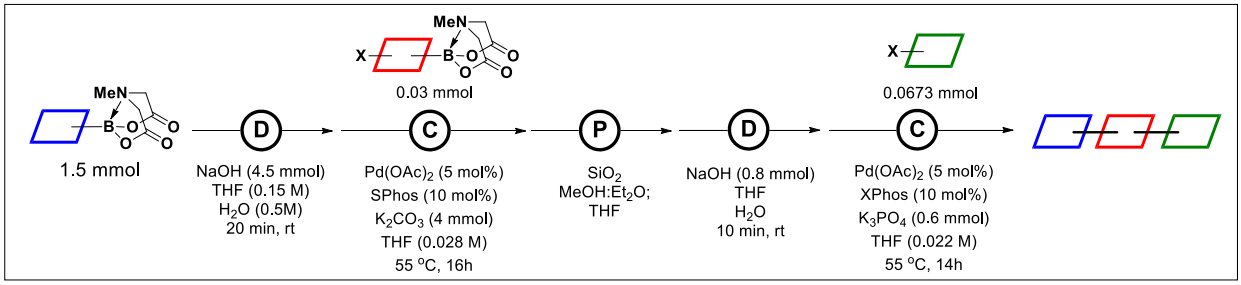


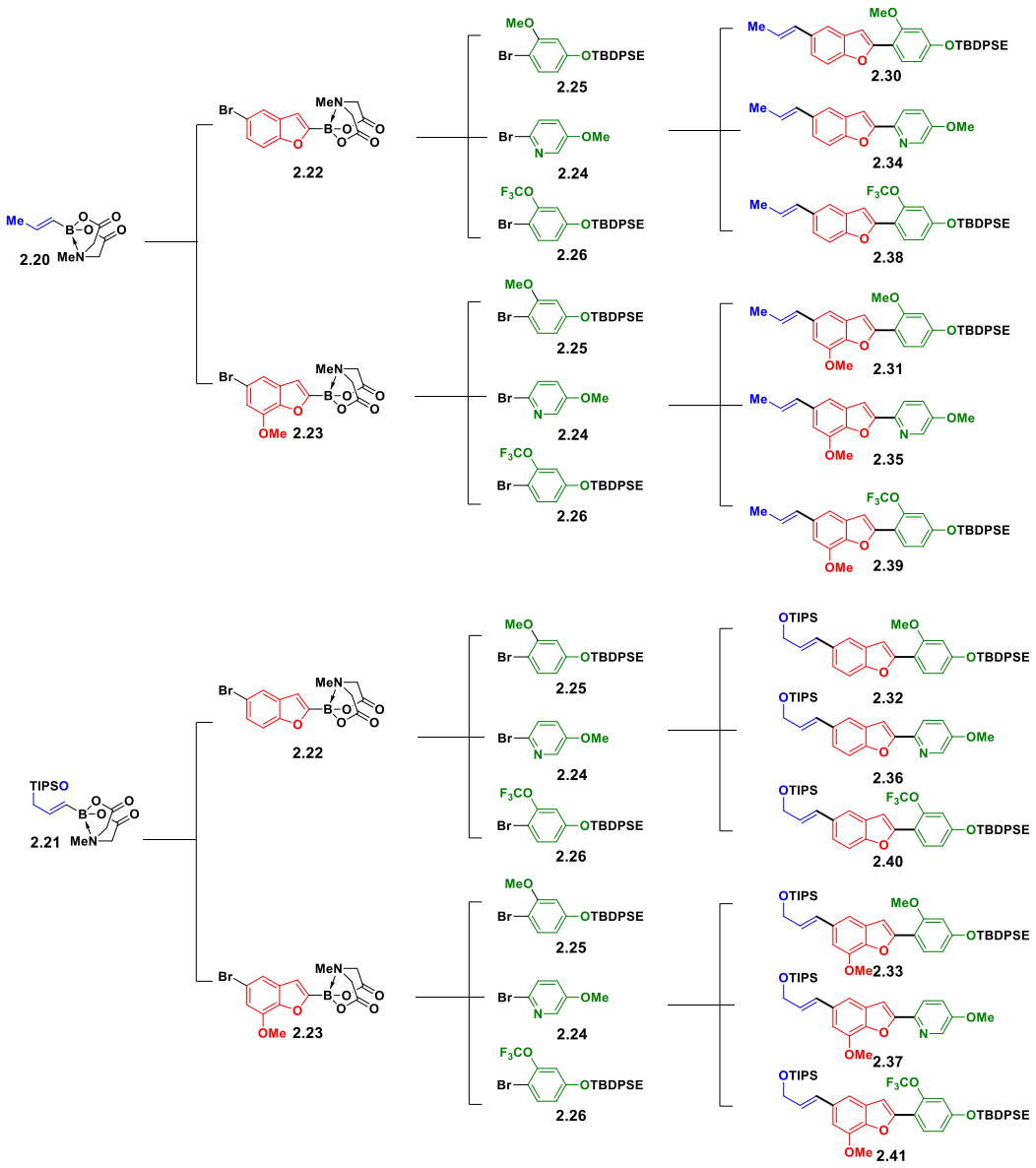
Automated Procedure III was followed with the following modifications: In the first coupling reaction, *N*,*N*'-dicyclohexylcarbodiimide (DCC) was used as a coupling agent. The DCC, carboxylic acid **2.19-1**, and amine MIDA boronate **2.19-2** all began in the First Reaction Cartridge and the coupling was run at room temperature for 4 hours. In the second coupling reaction, 0.167 mmol of pyrazole **2.19-3**, 0.33 mmol of pyridine, 0.25 mmol of $Cu(OAc)_2$, and 125 mg of activated 4 Å powdered molecular sieves were used, the addition of the boronic acid was performed over 1 minute, and the coupling was run at room temperature for 48 hours in a 7-mL glass vial. **2.19** was afforded a colorless solid (6.7 mg, 0.0159 mmol, 9% yield). TLC (20% EtOAc in hexanes): R_f = 0.22, visualized by UV; HPLC (Agilent Prep-C18, 10 µm, 30 x 150 mm (product number: 413910-302), 25 mL/min, gradient: A = water, B = MeCN, 0 min: 95% A, 5% B; 10 min: 5% A, 95% B; 15 min: 5% A, 95% B; 15.5 min: 95% A, 5% B; 20.5 min: 95% A, 5% B): 11.6 min; TLC (20% EtOAc in hexanes): R_f = 0.22, visualized by UV. ^{1}H-NMR (500 MHz, acetone-d_6): δ 10.15 (br s, 1H), 8.01 (d, *J* = 9.0 Hz, 2H), 7.66 (d, *J* = 8.5 Hz, 2H), 7.52 (s, 1H),

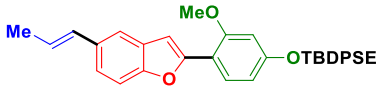
2.92 (s, 3H); ^{13}C-NMR (125 MHz, acetone-d_6): δ 160.8, 159.0, 144.5, 143.1 ($J_{C\text{-}F}$ = 39.2 Hz), 141.1, 135.2, 135.1 ($J_{C\text{-}F}$ = 40.1 Hz), 127.7, 121.7, ($J_{C\text{-}F}$ = 268.6 Hz), 121.5, 120.1 ($J_{C\text{-}F}$ = 269.6 Hz), 108.3, 13.6; HRMS (ESI+) calculated for $C_{15}H_{10}N_5OSF_6$ $[M+H]^+$ *m/z* 422.0510, found 422.0504.

Library Synthesis (Figure 2.3)

General Scheme for Automated Synthesis of Library Members **2.30** to **2.41**

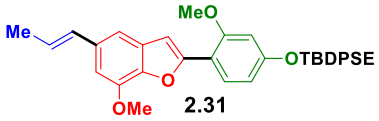






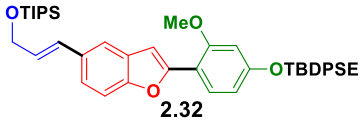
protected ratanhiaphenol III (2.30)
(27.8 mg, 75% yield)

Automated Procedure III as modified for **2.12** was followed to give **2.30** (27.8 mg, 75% yield). TLC (50% DCM in hexanes): R_f = 0.51, stained by $KMnO_4$; ^{1}H-NMR (500 MHz, acetone-d_6): δ 7.82 (d, *J* = 8.5 Hz, 1H), 7.74-7.71 (m, 4H), 7.53 (d, *J* = 1.5 Hz, 1H), 7.47-7.42 (m, 6H), 7.39 (d, *J* = 8.5 Hz, 1H), 7.29 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.17 (d, *J* = 1 Hz, 1H), 6.52-6.46 (m, 3H), 6.24 (dq, *J* = 15.5, 6.5 Hz, 1H), 4.14-4.11 (m, 2H), 3.93 (s, 3H), 1.88-1.84 (m, 5H), 1.09 (s, 9H); ^{13}C-NMR (125 MHz, acetone-d_6): δ 161.3, 158.8, 153.8 (2C), 136.7, 134.8, 134.0, 132.2, 131.2, 130.3, 128.7, 128.3, 124.5, 122.8, 118.7, 112.8, 111.2, 106.6, 105.0, 100.0, 66.2, 55.9, 28.1, 18.6, 18.5, 12.6; HRMS (ESI+) calculated for $C_{36}H_{39}O_3Si$ $[M+H]^+$ *m/z* 547.2668, found 547.2673.



2.31
(27.9 mg, 72% yield)

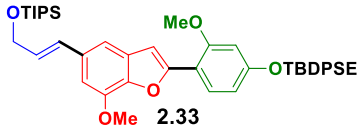
Automated Procedure III as modified for **2.12** was followed to give **2.31** (27.9 mg, 72% yield). TLC (50% DCM in hexanes): R_f = 0.23, visualized by UV; ^{1}H-NMR (500 MHz, acetone-d_6): δ 7.84 (dd, *J* = 8, 0.5 Hz, 1H), 7.74-7.72 (m, 4H), 7.47-7.43 (m, 6H), 7.14 (s, 1H), 7.10 (d, *J* = 1.5 Hz, 1H), 6.93 (d, *J* = 1.5 Hz, 1H), 6.50-6.45 (m, 3H), 6.24 (dq, *J* = 15.5, 6.5 Hz, 1H), 4.14-4.10 (m, 2H), 4.01 (s, 3H), 3.93 (s, 3H), 1.87-1.84 (m, 5H), 1.09 (s, 9H); ^{13}C-NMR (125 MHz, acetone-d_6): δ 161.3, 158.7, 153.7, 145.9, 143.0, 136.7, 135.0, 134.8, 132.6, 132.5, 130.3, 128.7, 128.3, 124.6, 112.8, 111.6, 106.6, 105.2 (2C), 100.0, 66.2, 56.3, 56.0, 28.1, 18.5 (2C) 12.6; HRMS (ESI+) calculated for $C_{37}H_{41}O_4Si$ $[M+H]^+$ *m/z* 577.2774, found 577.2767.



2.32

(25.9 mg, 54% yield)

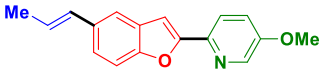
Automated Procedure III as modified for **2.12** was followed to give **2.32** (25.9 mg, 54% yield). TLC (50% DCM in hexanes): R_f = 0.49, stained by $KMnO_4$; ^{1}H-NMR (500 MHz, acetone-d_6): δ 7.83 (d, *J* = 8.5 Hz, 1H), 7.74-7.72 (m, 4H), 7.61 (d, *J* = 1.5 Hz, 1H), 7.47-7.42 (m, 7H), 7.35 (dd, *J* = 8.5, 2 Hz, 1H), 7.19 (d, *J* = 0.5 Hz, 1H), 6.77 (dt, *J* = 16, 1.5 Hz, 1H), 6.51-6.47 (m, 2H), 6.35 (dt, *J* = 15.5, 5 Hz, 1H), 4.47 (dd, *J* = 4.5, 1.5 Hz, 2H), 4.14-4.11 (m, 2H), 3.94 (s, 3H), 1.88-1.84 (m, 2H), 1.22-1.08 (m, 30H); ^{13}C-NMR (125 MHz, acetone-d_6):δ 161.4, 158.8, 154.1, 154.0, 136.7, 134.8, 133.2, 131.3, 130.3, 130.2, 128.8, 128.7, 128.3, 123.3, 119.3, 112.8, 111.3, 106.7, 105.0, 100.0, 66.2, 64.8, 56.0, 28.1, 18.6, 18.4, 12.8, 12.6; HRMS (ESI+) calculated for $C_{45}H_{59}O_4Si_2$ $[M+H]^+$ *m/z* 719.3952, found 719.3925.



2.33

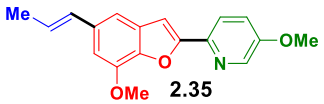
(29.2 mg, 57% yield)

Automated Procedure III as modified for **2.12** was followed to give **2.33** (29.2 mg, 57% yield). TLC (50% DCM in hexanes): R_f = 0.40, visualized by UV; ^{1}H-NMR (500 MHz, acetone-d_6):δ 7.84 (app d, *J* = 9 Hz, 1H), 7.74-7.71 (m, 4H), 7.48-7.43 (m, 6H), 7.17 (d, *J* = 1 Hz, 1H), 7.16 (s, 1H), 7.00 (d, *J* = 1.5 Hz, 1H), 6.73 (dt, *J* = 15.5, 1.5 Hz, 1H), 6.50 (s, 1H), 6.50--6.48 (m, 1H), 6.36 (dt, *J* = 16, 4.5 Hz, 1H), 4.47 (dd, *J* = 5, 1.5 Hz, 2H), 4.14-4.11 (m, 2H), 4.02 (s, 3H), 3.93 (s, 3H), 1.88-1.84 (m, 2H), 1.20-1.09 (m, 30H); ^{13}C-NMR (125 MHz, acetone-d_6): δ 161.3, 158.7, 153.8, 146.0, 143.2, 136.7, 143.7, 134.2, 132.7, 130.5, 130.3, 128.8, 128.7, 128.3, 112.8, 112.3, 106.6, 105.5, 105.2, 100.0, 66.2, 64.8, 56.3, 55.9, 28.1, 18.6, 18.4, 12.8, 12.6; HRMS (ESI+) calculated for $C_{46}H_{61}O_5Si_2$: $[M+H]^+$ *m/z* 749.4058, found 749.4056.



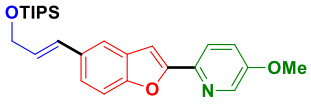
2.34
(9.9 mg, 56% yield)

Automated Procedure III as modified for **2.12** was followed to give **2.34** (9.9 mg, 56% yield). TLC (20% EtOAc in hexanes): R_f = 0.28, stained by $KMnO_4$; ^{1}H-NMR (500 MHz, acetone-d_6): δ 8.37 (dd, *J* = 3, 0.5 Hz, 1H), 7.89 (dd, *J* = 8.5, 0.5 Hz, 1H), 7.63 (dd, *J* = 2 Hz, 1H), 7.50 – 7.48 (m, 2H), 7.39 (dd, *J* = 8.5, 2 Hz, 1H), 7.31 (d, *J* = 1 Hz, 1H), 6.53 (dd, *J* = 16, 1.5 Hz, 1H), 6.29 (dq, 15.5, 6.5 Hz, 1H), 3.95 (s, 3H), 1.87 (dd, *J* = 6.5, 1.5 Hz, 3H); ^{13}C-NMR (125 MHz, acetone-d_6):δ 157.0, 156.6, 155.2, 142.5, 139.2, 134.5, 132.0, 130.4, 125.1, 123.7, 121.2, 120.9, 119.3, 111.9, 103.6, 56.2, 18.6; HRMS (ESI+) calculated for $C_{17}H_{16}NO_2$ $[M+H]^+$ *m/z* 266.1181, found 266.1180.



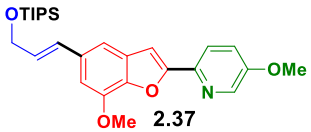
2.35
(6.9 mg, 35% yield)

Automated Procedure III as modified for **2.12** was followed to give **2.35** (6.9 mg, 35% yield). TLC (20% EtOAc in hexanes): R_f = 0.23, stained by $KMnO_4$; ^{1}H-NMR (500 MHz, acetone-d_6): δ 8.36 (dd, *J* = 3, 0.5 Hz, 1H), 7.89 (dd, *J* = 8.5, 0.5 Hz, 1H), 7.49 (dd, *J* = 8.5, 3.0 Hz, 1H), 7.28 (s, 1H), 7.19 (d, *J* = 1.5 Hz, 1H), 7.01 (d, *J* = 1.5 Hz, 1H), 6.50 (d, *J* = 15.5, 1.5 Hz, 1H), 6.29 (dq, *J* = 16, 6.5 Hz, 1H), 4.05 (s, 3H), 3.95 (s, 3H), 1.87 (dd, *J* = 6.5, 1.5 Hz, 3H); ^{13}C-NMR (125 MHz, acetone-d_6): δ 156.9, 156.6, 146.3, 144.5, 142.5, 139.2, 135.5, 132.3, 131.8, 125.1, 121.2, 120.8, 112.0, 105.8, 103.9, 56.3, 56.2, 18.5; HRMS (ESI+) calculated for $C_{18}H_{18}NO_3$ $[M+H]^+$ *m/z* 296.1287, found 296.1282.



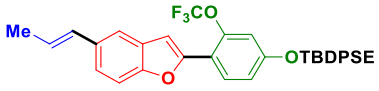
2.36
(5.6 mg, 19% yield)

Automated Procedure III as modified for **2.12** was followed to give **2.36** (5.6 mg, 19% yield). TLC (20% EtOAc in hexanes): R_f = 0.33, visualized by UV; ^{1}H-NMR (500 MHz, acetone-d_6): δ 8.37 (dd, *J* = 3, 1 Hz, 1H), 7.89 (dd, *J* = 9, 1 Hz, 1H), 7.71 (d, *J* = 1.5 Hz, 1H), 7.52 (d, *J* = 8.5, 1H), 7.49 (dd, *J* = 8.5, 3 Hz, 1H), 7.46 (dd, *J* = 8.5, 1H), 7.34 (d, *J* = 1 Hz, 1H), 6.80 (dt, *J* = 15.5, 2 Hz, 1H), 6.40 (dt, *J* = 15.5, 5 Hz, 1H), 4.50 (dd, *J* = 4.5, 2 Hz, 2H), 3.96 (s, 3H), 1.22-1.10 (m, 21H); HRMS (ESI+) calculated for $C_{26}H_{36}NO_3Si$ $[M+H]^+$ *m/z* 438.2464, found 438.2468.



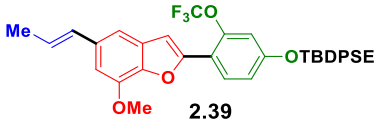
2.37
(8.5 mg, 26% yield)

Automated Procedure III as modified for **2.12** was followed to give **2.37** (8.5 mg, 26% yield). TLC (20% EtOAc in hexanes): R_f = 0.26, visualized by UV; ^{1}H-NMR (500 MHz, acetone-d_6): δ 8.36 (dd, *J*= 3, 0.5 Hz, 1H), 7.90 (dd, *J* = 9, 0.5 Hz, 1H), 7.49 (dd, *J* = 8.5, 3 Hz, 1H), 7.30 (s, 1H), 7.26 (d, *J* = 1.5 Hz, 1H), 7.08 (d, *J* = 1.5 Hz, 1H), 6.76 (dt, *J* = 15.5, 2 Hz, 1H), 6.41 (dt, *J* = 16, 4.5 Hz, 1H), 4.49 (dd, *J* = 5, 2 Hz, 2H), 4.06 (s, 3H), 3.95 (s, 3H), 1.21-1.11 (m, 21H); ^{13}C-NMR (125 MHz, acetone-d_6):δ 157.0, 156.6, 146.4, 144.7, 142.5, 139.2, 134.8, 131.9, 130.2, 129.3, 121.2, 120.8, 112.8, 106.0, 103.9, 64.7, 56.4, 56.2, 18.4, 12.8; HRMS (ESI+) calculated for $C_{27}H_{38}NO_4Si$ $[M+H]^+$ *m/z* 468.2570, found 468.2572.



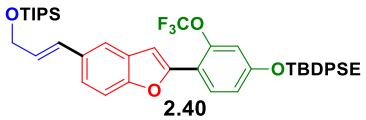
2.38
(27.8 mg, 69% yield)

Automated Procedure III as modified for **2.12** was followed to give **2.38** (27.8 mg, 69% yield). TLC (20% DCM in hexanes): R_f = 0.27, visualized by UV; ^{1}H-NMR (500 MHz, acetone-d_6): δ 7.94 (d, *J* = 9 Hz, 1H), 7.74-7.72 (m, 4H), 7.62 (d, *J* = 1.5 Hz, 1H), 7.48-7.42 (m, 7H), 7.37 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.10 (d, *J* = 0.5 Hz, 1H), 6.91 (dd, *J* = 9, 2.5 Hz, 1H), 6.82 (quint, *J* = 1.5 Hz, 1H), 6.51 (dd, *J* = 16, 2 Hz, 1H), 6.27 (dq, *J* = 16, 7 Hz, 1H), 4.17-4.14 (m, 2H), 1.90-1.87 (m, 2H), 1.86 (dd, *J* = 6.5, 1.5 Hz, 3H), 1.10 (s, 9H); ^{13}C-NMR (125 MHz, acetone-d_6): δ 160.7, 154.2, 151.7, 147.0, 136.7, 134.6, 134.5, 132.0, 130.4, 130.3, 129.8, 128.7, 125.1, 123.8, 121.5 ($J_{C\text{-}F}$ = 257 Hz), 119.2, 116.8, 114.2, 111.6, 109.0, 105.7, 67.0, 28.1, 18.6 (2C), 12.4; HRMS (ESI+) calculated for $C_{36}H_{36}F_3O_3Si$ $[M+H]^+$ *m/z* 601.2386, found 601.2386.



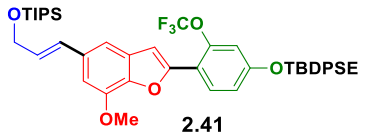
2.39
(32.2 mg, 76% yield)

Automated Procedure III as modified for **2.12** was followed to give **2.39** (32.2 mg, 76% yield). TLC (20% DCM in hexanes): R_f = 0.09, visualized by UV; ^{1}H-NMR (500 MHz, acetone-d_6): δ 7.94 (d, *J* = 9 Hz, 1H), 7.74-7.72 (m, 4H), 7.48-7.42 (m, 6H), 7.18 (d, *J* = 1.5 Hz, 1H), 7.07 (s, 1H), 7.00 (d, *J* = 1.5 Hz, 1H), 6.92 (dd, *J* = 9, 2.5 Hz, 1H), 6.81 (quint, *J* = 2 Hz, 1H), 6.48 (dd, *J* = 16, 2 Hz, 1H), 6.27 (dq, *J* = 16, 6.5 Hz, 1H), 4.17-4.14 (m, 2H), 4.03 (s, 3H), 1.90-1.86 (m, 2H), 1.86 (dd, *J* = 6.5, 1.5 Hz, 3H), 1.09 (s, 9H); ^{13}C-NMR (125 MHz, acetone-d_6): δ 160.7, 151.5, 146.9, 146.1, 143.6, 136.7, 135.5, 134.6, 132.3, 131.9, 130.3, 129.7, 128.7, 125.1, 121.5 ($J_{C\text{-}F}$ = 257 Hz), 116.8, 114.2, 111.8, 109.0, 105.9 (2C), 67.0, 56.4, 28.1, 18.6, 18.5, 12.4; HRMS (ESI+) calculated for $C_{37}H_{38}O_4F_3Si$ $[M+H]^+$ *m/z* 631.2491, found 631.2488.



2.40
(21.6 mg, 42% yield)

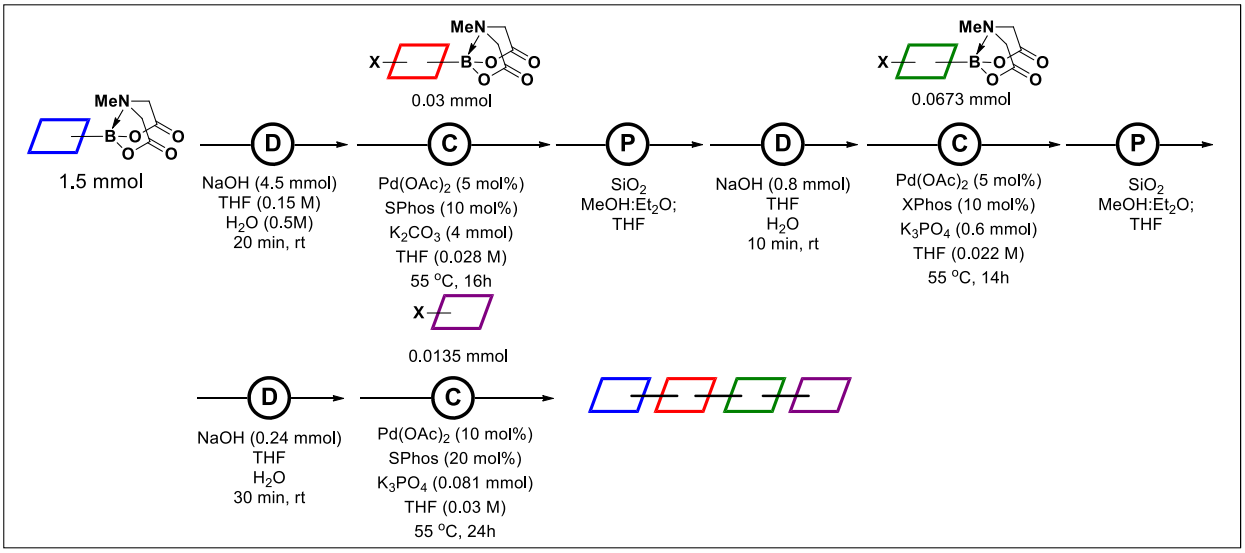
Automated Procedure III as modified for **2.12** was followed to give **2.40** (21.6 mg, 42% yield). TLC (10% DCM in hexanes): R_f = 0.11, visualized by UV; ^{1}H-NMR (500 MHz, acetone-d_6): δ 7.95 (d, *J* = 9 Hz, 1H), 7.74-7.70 (m, 5H), 7.50-7.41 (m, 8H), 7.13 (d, *J* = 0.5 Hz, 1H), 6.92 (dd, *J* = 9, 2.5 Hz, 1H), 6.82 (quint, *J* = 1.5 Hz, 1H), 6.79 (dt, *J* = 16, 1.5 Hz, 1H), 6.39 (dt, *J* = 16, 4.5 Hz, 1H), 4.48 (dd, *J* = 5, 2 Hz, 2H), 4.18-4.14 (m, 2H), 1.90-1.87 (m, 2H), 1.21-1.08 (m, 30H); HRMS (ESI+) calculated for $C_{45}H_{54}F_3O_4Si_2$ $[M+H]^+$ *m/z* 771.3513, found 771.3550.

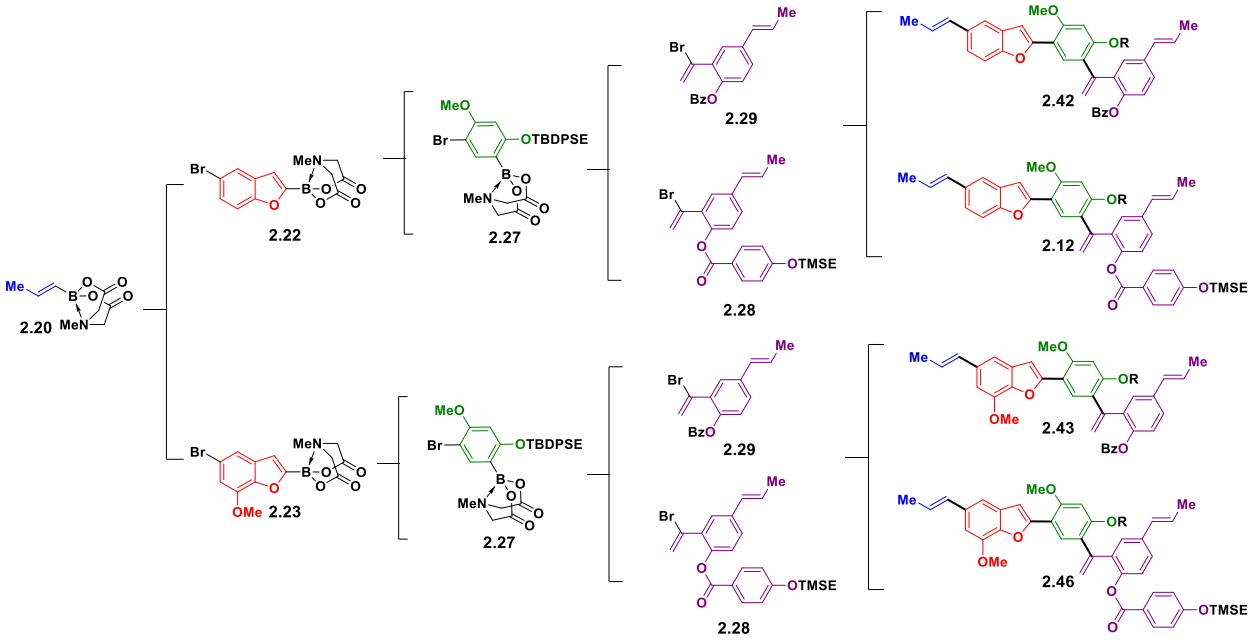


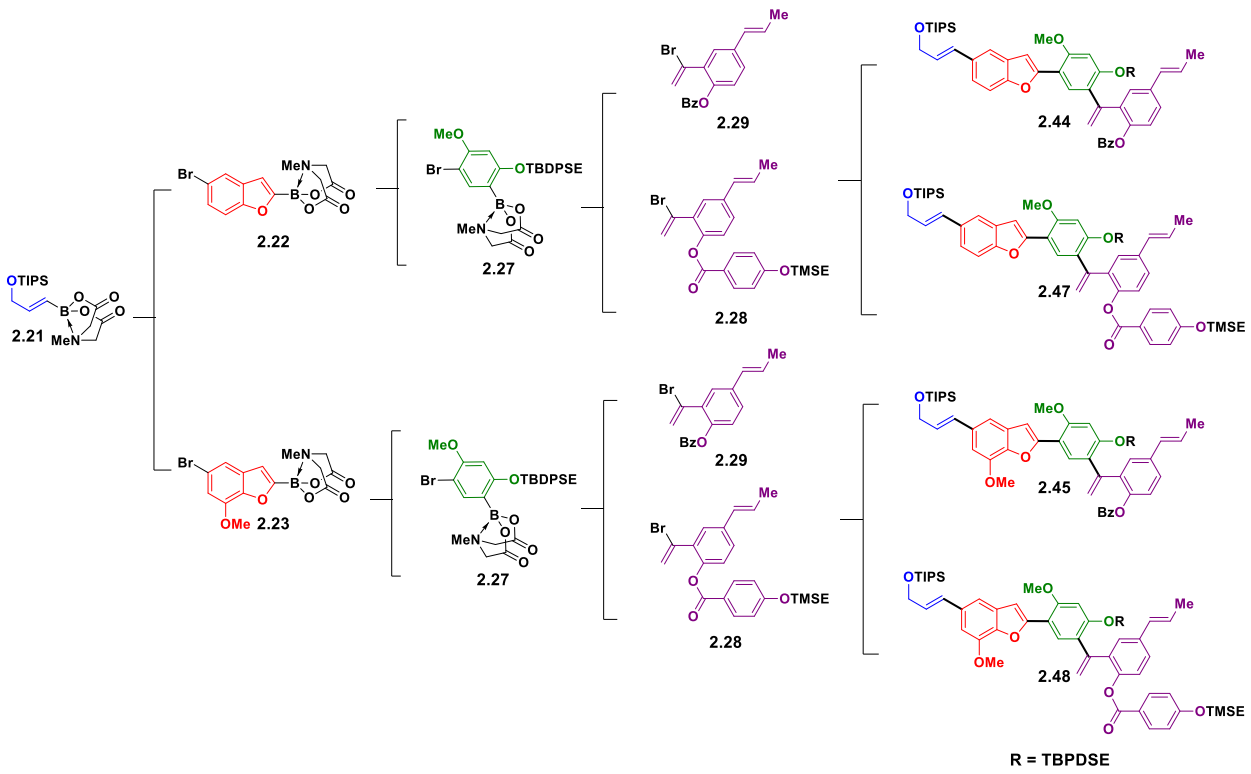
2.41
(35.7 mg, 65% yield)

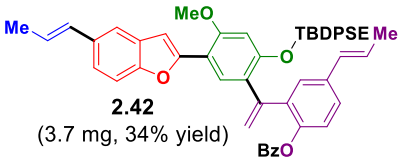
Automated Procedure III as modified for **2.12** was followed to give **2.41** (35.7 mg, 65% yield). TLC (20% DCM in hexanes): R_f = 0.11, visualized by UV; ^{1}H-NMR (500 MHz, acetone-d_6): δ 7.95 (d, *J* = 8.5 Hz, 1H), 7.74-7.72 (m, 4H), 7.46-7.42 (m, 6H), 7.26 (d, *J* = 1.5 Hz, 1H), 7.09 (s, 1H), 7.06 (d, *J* = 1 Hz, 1H), 6.93 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.81 (quint, *J* = 1.5 Hz, 1H), 6.79 (dt, *J* = 15.5, 2 Hz, 1H), 6.39 (dq, *J* = 16, 4.5 Hz, 1H), 4.47 (dd, *J* = 4.5, 1.5 Hz, 2H), 4.17-4.14 (m, 2H), 4.04 (s, 3H), 1.90-1.86 (m, 2H), 1.20-1.09 (m, 30H); ^{13}C-NMR (125 MHz, acetone-d_6): δ 160.7, 151.6, 146.9, 146.2, 143.8, 136.7, 134.8, 134.6, 132.0, 130.3, 130.2, 129.8, 129.3, 128.7, 121.5 ($J_{C\text{-}F}$ = 257 Hz), 116.8, 114.2, 112.6, 109.0, 106.2, 106.0, 67.0, 64.7, 56.4, 28.1, 18.5, 18.4, 12.8, 12.4; HRMS (ESI+) calculated for $C_{46}H_{57}F_3O_5Si_2Na$ $[M+H]^+$ *m/z* 825.3594, found 825.3600.

General Scheme for Automated Synthesis of Library Members **2.12** and **2.42** to **2.48**





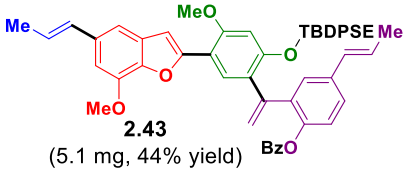




2.42
(3.7 mg, 34% yield)

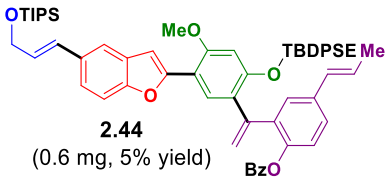
Automated Procedure III as modified for **2.12** was followed to give **2.42** (3.7 mg, 34% yield). HPLC (Agilent Prep-C18, 10 µm, 30 x 150 mm (product number: 413910-302), 25 mL/min, gradient: A = water, B = 10% THF in MeCN, 0 min: 80% A, 20% B; 5 min: 0% A, 100% B; 50 min: 0% A, 100% B): 17.1 min; ^{1}H-NMR (500 MHz, acetone-d_6): δ 7.71 (s, 1H), 7.68-7.61 (m, 6H), 7.60 (d, J = 2.5 Hz, 1H), 7.50 (d, J = 1.5 Hz, 1H), 7.47-7.41 (m, 7H), 7.36 (d, J = 8.5 Hz, 1H), 7.29 (dd, J = 8.5, 1.5 Hz, 1H), 7.17-7.13 (m, 2H), 7.10-7.06 (m, 2H), 6.95 (d, J = 1 Hz, 1H), 6.56 (dd, J = 16, 2 Hz, 1H), 6.51 (dd, J = 16, 1.5 Hz, 1H), 6.38 (dq, J = 16, 6.5 Hz, 1H), 6.34 (s, 1H), 6.25 (dq, J = 15.5, 7 Hz, 1H), 5.50 (d, J = 1.5 Hz, 1H), 5.49 (d, J = 2 Hz, 1H), 3.88-3.86 (m, 2H), 3.79 (s, 3H), 1.90 (dd, J = 6.5, 1.5 Hz, 3H), 1.87 (dd, J = 6.5, 1.5 Hz, 3H),

1.27-1.23 (m, 2H), 0.99 (s, 9H); HRMS (ESI+) calculated for $C_{54}H_{53}O_5Si$ $[M+H]^+$ *m/z* 809.3662, found 809.3658.



2.43
(5.1 mg, 44% yield)

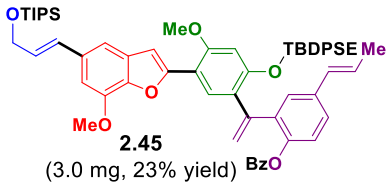
Automated Procedure III as modified for **2.12** was followed to give **2.43** (5.1 mg, 44% yield). HPLC (Agilent Prep-C18, 10 µm, 30 x 150 mm (product number: 413910-302), 25 mL/min, gradient: A = water, B = 10% THF in MeCN, 0 min: 80% A, 20% B; 5 min: 0% A, 100% B; 50 min: 0% A, 100% B): 14.3 min; TLC (70% DCM in hexanes): R_f = 0.5, visualized by UV; ^{1}H-NMR (500 MHz, acetone-d_6): δ 7.75 (s, 1H), 7.68-7.63 (m, 6H), 7.59 (d, *J* = 2.5 Hz, 1H), 7.47-7.41 (m, 8H), 7.17-7.14 (m, 2H), 7.10-7.07 (m, 3H), 6.93 (s, 1H), 6.55 (dd, *J* = 16, 1.5 Hz, 1H), 6.48 (dd, *J* = 16, 1.5 Hz, 1H), 6.38 (dq, *J* = 16, 6.5 Hz, 1H), 6.34 (s, 1H), 6.26 (dq, *J* = 15.5, 6.5 Hz, 1H), 5.51 (d, *J* = 2 Hz, 1H), 5.50 (d, *J* = 2 Hz, 1H), 4.00 (s, 3H), 3.88-3.85 (m, 2H), 3.78 (s, 3H), 1.90 (dd, *J* = 6.5, 1.5 Hz, 3H), 1.87 (dd, *J* = 6.5, 1.5 Hz, 3H), 1.27-1.23 (m, 2H), 0.99 (s, 9H); HRMS (ESI+) calculated for $C_{55}H_{55}O_6Si$ $[M+H]^+$ *m/z* 839.3768, found 839.3772.



2.44
(0.6 mg, 5% yield)

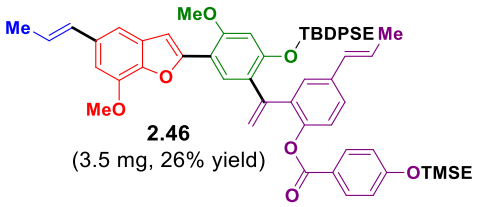
Automated Procedure III as modified for **2.12** was followed to give **2.44** (0.6 mg, 5% yield). HPLC (Agilent Prep-C18, 10 µm, 30 x 150 mm (product number: 413910-302), 25 mL/min, gradient: A = water, B = 10% THF in MeCN, 0 min: 80% A, 20% B; 5 min: 0% A, 100% B; 50 min: 0% A, 100% B): 48.3 min; ^{1}H-NMR (500 MHz, acetone-d_6): δ 7.71 (s, 1H), 7.67-7.58 (m, 7H), 7.47-7.37 (m, 10H), 7.16-7.14 (m, 2H), 7.10-7.07 (m, 2H), 6.97 (s, 1H), 6.78 (app d, *J* = 16 Hz, 1H), 6.56 (dd, *J* = 15.5, 1.5 Hz, 1H), 6.41-6.36 (m, 2H), 6.35 (s, 1H), 5.51 (d,

J = 1.5 Hz, 1H), 5.50 (d, *J* = 1.5 Hz, 1H), 4.50 (dd, *J* = 5, 2 Hz, 2H), 3.88-3.85 (m, 2H), 3.79 (s, 3H), 1.91 (dd, *J* = 6.5, 1.5 Hz, 3H), 1.29-1.07 (m, 23H), 0.94 (s, 9H); HRMS (ESI+) calculated for $C_{63}H_{73}O_6Si_2$ $[M+H]^+$ *m/z* 981.4946, found 981.4949.



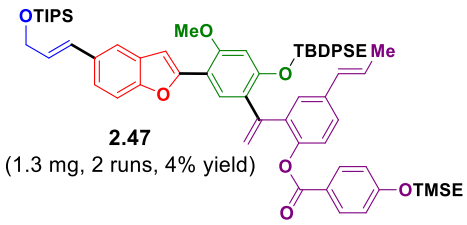
2.45
(3.0 mg, 23% yield)

Automated Procedure III as modified for **2.12** was followed to give **2.45** (3.0 mg, 23% yield). Library member **2.45** was isolated as a colorless oil (3.0 mg), the ^{1}H NMR of which contained small amounts of hydrocarbon impurities presumed to represent some leaching from the HPLC column. HPLC (Agilent Prep-C18, 10 µm, 30 x 150 mm (product number: 413910-302), 25 mL/min, gradient: A = water, B = 10% THF in MeCN, 0 min: 80% A, 20% B; 5 min: 0% A, 100% B; 50 min: 0% A, 100% B): 33.4 min; TLC (50% DCM in hexanes): R_f = 0.18, visualized by UV; ^{1}H-NMR (500 MHz, acetone-d_6):δ 7.75 (s, 1H), 7.69-7.62 (m, 6H), 7.60 (d, *J* = 2.5 Hz, 1H), 7.47-7.40 (m, 7H), 7.17-7.13 (m, 3H), 7.10-7.06 (m, 2H), 7.00 (d, *J* = 1.5 Hz, 1H), 6.95 (s, 1H), 6.76 (dt, *J* = 15.5, 1.5 Hz, 1H), 6.56 (dd, *J* = 15.5, 1.5 Hz, 1H), 6.40-6.35 (m, 2H), 6.34 (s, 1H), 5.52 (d, *J* = 1.5 Hz, 1H), 5.50 (d, *J* = 1.5 Hz, 1H), 4.49 (dd, *J* = 5, 2 Hz, 2H), 4.02 (s, 3H), 3.88-3.85 (m, 2H), 3.78 (s, 3H), 1.90 (dd, *J* = 6.5, 2.5 Hz, 3H), 1.29-1.23 (m, 2H), 1.23-1.08 (m, 21H), 0.99 (s, 9H); HRMS (ESI+) calculated for $C_{64}H_{74}O_7Si_2Na$ $[M+Na]^+$ *m/z* 1033.4871, found 1033.4895.



2.46
(3.5 mg, 26% yield)

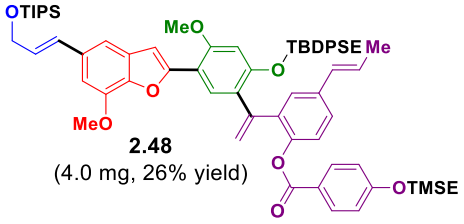
Automated Procedure III as modified for **2.12** was followed to give **2.46** (3.5 mg, 26% yield). HPLC (Agilent Prep-C18, 10 µm, 30 x 150 mm (product number: 413910-302), 25 mL/min, gradient: A = water, B = 20% THF in MeCN, 0 min: 80% A, 20% B; 5 min: 0% A, 100% B; 50 min: 0% A, 100% B): 12.2 min; ^{1}H-NMR (500 MHz, acetone-d_6): δ 7.71 (s, 1H), 7.64-7.62 (m, 4H), 7.56-7.53 (m, 2H), 7.46-7.41 (m, 8H), 7.10 (d, *J* = 8 Hz, 1H), 7.08 (d, *J* = 1 Hz, 1H), 6.94 (d, *J* = 1.5 Hz, 1H), 6.93 (s, 1H), 6.56 (dd, *J* = 15.5, 1.5 Hz, 1H), 6.51-6.47 (m, 3H), 6.38 (dq, *J* = 15.5, 6.5 Hz, 1H), 6.34 (s, 1H), 6.27 (dq, *J* = 15.5, 6.5 Hz, 1H), 5.46 (s, 2H), 4.02 (s, 3H), 3.87-3.84 (m, 2H), 3.80 (s, 3H), 3.56 (app t, *J* = 8 Hz, 2H), 1.90 (dd, *J* = 6.5, 1.5 Hz, 3H), 1.88 (dd, *J* = 6.5, 1.5 Hz, 3H), 1.23-1.20 (m, 2H), 0.98 (s, 9H), 0.91-0.88 (m, 2H), 0.03 (s, 9H); HRMS (ESI+) calculated for $C_{60}H_{67}O_7Si_2$ $[M+H]^+$ *m/z* 955.4425, found 955.4437.



2.47
(1.3 mg, 2 runs, 4% yield)

Automated Procedure III as modified for **2.12** was followed to give **2.47** (1.3 mg, 4% yield). HPLC (Agilent Prep-C18, 10 µm, 30 x 150 mm (product number: 413910-302), 25 mL/min, gradient: A = water, B = 20% THF in MeCN, 0 min: 80% A, 20% B; 5 min: 0% A, 100% B; 50 min: 0% A, 100% B): 26.8 min; ^{1}H-NMR (500 MHz, acetone-d_6): δ 7.69 (s, 1H), 7.64-7.61 (m, 5H), 7.57 (s, 1H), 7.55 (d, *J* = 9 Hz, 2H), 7.46-7.34 (m, 9H), 7.10 (d, *J* = 8.5 Hz, 1H), 6.97 (s, 1H), 6.80 (dt, *J* = 16, 1.5 Hz, 1H), 6.56 (dd, *J* = 15.5, 1.5 Hz, 1H), 6.49 (d, *J* = 7 Hz, 2H), 6.41-6.34 (m, 3H), 5.46 (s, 2H), 4.51 (dd, *J* = 5, 2 Hz, 2H), 3.90-3.85 (m, 2H), 3.81 (s, 3H), 3.58 (app t, *J* = 8 Hz, 2H), 1.91 (dd, *J* = 6.5, 1 Hz, 3H), 1.24-1.17 (m, 5H), 1.15-1.12 (m, 18H),

0.99 (s, 9H), 0.88 (m, 2H), 0.03 (s, 9H); HRMS (ESI+) calculated for $C_{68}H_{85}O_7Si_3$ $[M+H]^+$ *m/z* 1097.5603, found 1097.5591



Automated Procedure III as modified for **2.12** was followed to give **2.48** (4.0 mg, 26% yield). Library member **2.48** was isolated as a colorless oil (4.0 mg), the ^{1}H NMR of which contained small amounts of hydrocarbon impurities presumed to represent some leaching from the HPLC column. HPLC (Agilent Prep-C18, 10 µm, 30 x 150 mm (product number: 413910-302), 25 mL/min, gradient: A = water, B = 20% THF in MeCN, 0 min: 80% A, 20% B; 5 min: 0% A, 100% B; 50 min: 0% A, 100% B): 22.3 min; ^{1}H-NMR (500 MHz, acetone-d_6): δ 7.72 (s, 1H), 7.64-7.62 (m, 5H), 7.55 (d, *J* = 8.5 Hz, 2H), 7.46-7.41 (m, 7H), 7.14 (d, *J* = 1 Hz, 1H), 7.10 (d, *J* = 8 Hz, 1H), 7.00 (d, *J* = 1.5 Hz, 1H), 6.95 (s, 1H), 6.76 (dt, *J* = 15.5, 1.5 Hz, 1H), 6.56 (dd, *J* = 16, 2 Hz, 1H), 6.49 (d, *J* = 8.5 Hz, 2H), 6.42-6.34 (m, 3H), 5.44 (d, *J* = 2 Hz, 1H), 5.43 (d, *J* = 2 Hz, 1H), 4.50 (dd, *J* = 5, 2 Hz, 2H), 4.03 (s, 3H), 3.88-3.82 (m, 2H), 3.80 (s, 3H), 3.59 (app t, *J* = 8 Hz, 2H), 1.91 (dd, *J* = 6.5, 1.5 Hz, 3H), 1.24-1.17 (m, 5H), 1.15-1.13 (m, 18H), 0.99 (s, 9H), 0.91-0.88 (m, 2H), 0.03 (s, 9H); HRMS (ESI+) calculated for $C_{69}H_{86}O_8Si_3Na$ $[M+Na]^+$ *m/z* 1149.5528, found 1149.5552.

Semi-Automated Synthesis of Cyclic Targets (Figure 2.4) Using **Automated Procedures III** and **IV**

Automated Procedure IV - *Cartridge Preparation*

Unless otherwise noted, "cartridge" refers to a 12-g Luknova column capped with a 12-g Luknova column screw cap. Additionally, the Second-Generation procedure makes use of custom 40 mL reaction vials which are fitted at their bottom with ground-glass joints designed to fit into a Luer lock and at their tops with threads to allow for sealing with septum-top screw caps.

First Deprotection Cartridges are the 40 mL reaction vials described above. They contain solid starting MIDA boronate and solid NaOH.

Second and Third Deprotection Cartridges are the 40 mL reaction vials described above. They contain solid NaOH.

Predrying Cartridges are not used in **Automated Procedure IV**.

Drying Cartridges contain 4.2 g Na_2SO_4, topped with the plunger from a 5 mL syringe.

Concentration/Deoxygenation Cartridges are empty.

First Reaction Cartridges are the 40 mL reaction vials described above, and contain a PTFE-coated magnetic stir bar, coupling partner, catalyst, ligand, and base. These cartridges have no frit at their base. The Luer port at the bottom is packed with a small piece of Kimwipe (so that solids are retained in the vial during weighing). The top of the vial is capped with a screw-top rubber septum cap. This septum is pierced with a 1.5 inch 18 G needle which is connected to an empty 4 g Luknova column (capped with a 4 g Luknova column screw cap connected to a source of dry nitrogen). Additionally, the cap is tethered to the screw cap topping the Reaction Filtration Cartridge via PTFE tubing (1/16-inch I.D., 1/8-inch O.D.) This tubing is

adjusted in such a way to be ~5 mm above the base of the reaction vessel, and is used to transfer the crude reaction mixture to the Reaction Filtration Cartridge.

Reaction Filtration Cartridges contain 1.0 g Celite™ and 0.5 g Florisil® which have been thoroughly mixed. This is tethered to the First Reaction Cartridge as described above.

Second and Third Reaction Cartridges contain a PTFE-coated magnetic stir bar, coupling partner, catalyst and ligand, and base.

Precipitation Cartridges contain a PTFE-coated magnetic stir bar, Celite™ (150 mg), and 3-aminopropyl functionalized silica gel (250 mg). Hexanes (10 mL) is added and the cartridge is swirled vigorously to suspend and homogenize the mixture of solids. The stir bar and solids are allowed to settle over 30 seconds and the supernatant hexanes is pushed out of the cartridge with an overhead pressure of air. The stir bar is now embedded in the mixture of solids wet with hexanes.

Silica Gel Plugs contain silica gel, tightly packed, and topped with a 4-g Luknova column frit. This is capped with a 4-g Luknova column screw cap, using four layers of PTFE tape on the sealing insert to ensure a leak-free seal.

Automated Procedure IV - *Experimental Details*

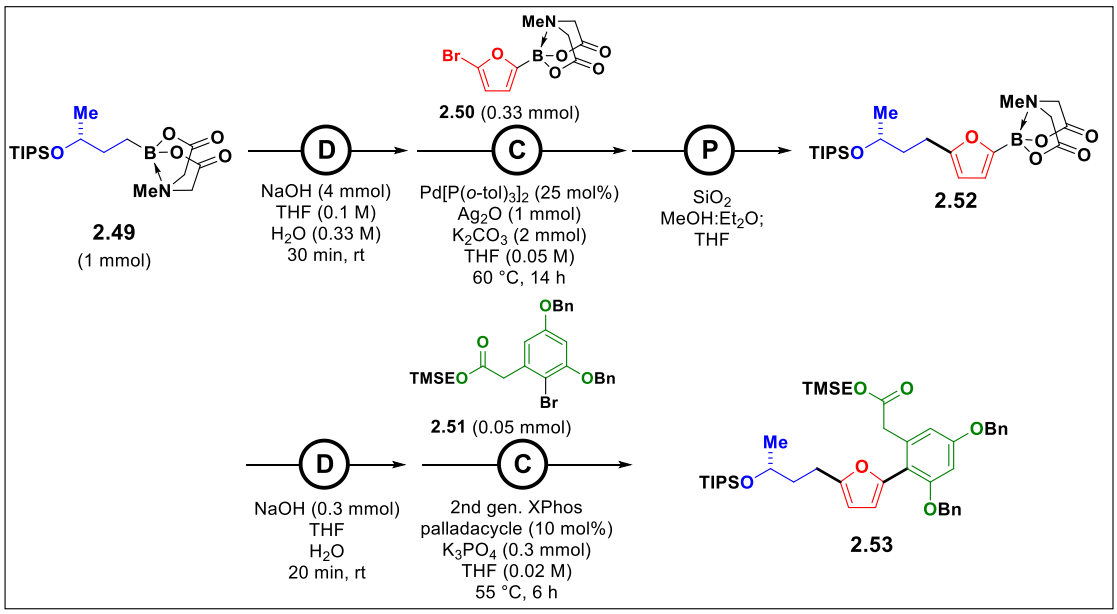
Deprotection In the deprotection module, to a Deprotection Cartridge containing starting MIDA boronate (1.0 mmol) and NaOH (3.0 mmol, 120 mg) is added 3 mL THF followed by 3 mL water. This solution is then agitated by bubbling argon through the solution for 20 minutes at room temperature while open to the air. After the reaction is completed, argon is then continually bubbled through the solution for 1 hour to remove THF, leaving a primarily aqueous solution of what is presumed to be the trihydroxyborate salt. After concentration, sat. NH_4Cl (3 mL) is added to quench the reaction, causing a white precipitate to form. After briefly agitating,

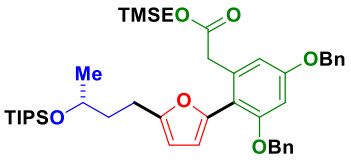
diethyl ether (4 mL) is added to extract the boronic acid from the aqueous layer. This biphasic mixture is then agitated via argon sparging (60 seconds) before removing the aqueous layer from the Deprotection Cartridge. The organic layer is then moved to the Drying Cartridge via the primary pump. The aqueous layer is then replaced into the Deprotection Cartridge. The ether extraction procedure is repeated twice more (12 mL total) before disposing of the aqueous layer. The ethereal boronic acid solution is then dried in the Drying Cartridge via the repeated injection and withdrawal of the solution (20 repetitions). The solution is then passed into the Concentration/Deoxygenation Cartridge before washing the contents of the Drying Cartridge with 2 mL diethyl ether. The solution is then concentrated to ~2 mL before solvent switching by adding THF (4 mL) and then concentrating to ~2 mL. Another portion of THF (4 mL) is added before concentrating to the volume required for the subsequent coupling reaction.

Coupling In the coupling module, a Reaction Cartridge is charged with bifunctional halo-MIDA boronate or capping halide building block, ligand and/or catalyst in a glovebox. The Cartridge is warmed to the appropriate temperature before having the THF solution of boronic acid added in a single portion.

Purification In the purification module, the crude reaction mixture is added to a Reaction Filtration Cartridge and 12 mL hexanes is added to the Precipitation Cartridge/Silica Gel Plug. Then, a 3 mL portion of the filtered crude reaction mixture is added to the Precipitation Cartridge and the solvent is removed from the cartridge, loading any crude reaction product onto the Silica Gel Plug ("catch"). This process is performed a total of ten times, using 3 mL THF to wash the Reaction and Reaction Filtration Cartridges for each cycle. Then, 12 mL of 1.5% MeOH in Et_2O are added and the solvent is removed three times (36 mL total). Then, 12 mL of Et_2O are added and the solvent is removed three times (36 mL total). Finally, 12 mL THF are added and slowly

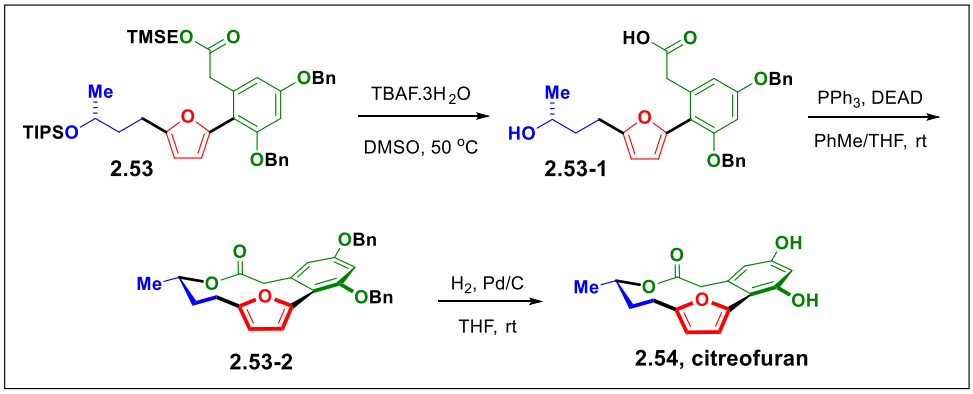
removed (to increase residence time in the column), giving a purified solution of MIDA boronate. The solution is then moved to an empty Concentration/Deoxygenation Cartridge and concentrated to 3 mL before being added to the next Deprotection Cartridge.

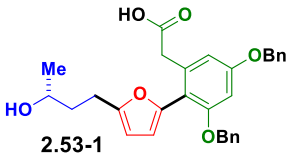




Automated Procedure III was followed with the following modifications: In the first deprotection reaction, 4 mmol of NaOH were used and the reaction was run for 30 minutes. In the first coupling reaction, the concentration was 0.05 M with respect to **2.50**, 1 mmol of Ag_2O, 2 mmol of K_2CO_3, and 25 mol% of $Pd[P(o\text{-tol})_3]_2$ were used, the addition of the boronic acid was performed over 1 minute, and the reaction was run at 60 °C for 14 hours. In the second deprotection reaction, 0.3 mmol of NaOH were used. In the second coupling reaction, the concentration was 0.02 M with respect to **2.51**, 0.3 mmol of K_3PO_4 and 10 mol% of 2nd generation XPhos palladacycle were used, and the reaction was run for 6 hours in a 7-mL glass

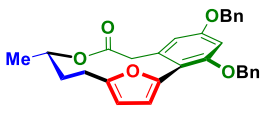
vial. For the purification steps, the Et_2O:MeOH eluent (1.5% MeOH in Et_2O) was diluted 50% with hexanes. This automated cycle was performed 6 times to accumulate **2.53** as a slightly yellow residue (88.4 mg total; average of 14.7 mg, 0.020 mmol, 39% yield). HPLC (Agilent Prep-C18, 10 µm, 30 x 150 mm (product number: 413910-302), 25 mL/min, gradient: A = MeCN, B = EtOAc, 0 min: 100% A, 0% B; 1 min: 100% A, 0% B; 10 min: 90% A, 10% B; 25 min: 90% A, 10% B; 25.5 min: 100% A, 0% B): 18.5 min; ^{1}H-NMR (500 MHz, acetone-d_6): 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); ^{13}C-NMR (125 MHz, acetone-d_6): δ171.6, 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 $C_{44}H_{63}O_6Si_2$ $[M+H]^+$ *m/z* 743.4163, found 743.4166.





2.53-1

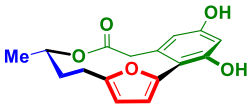
A 7 mL vial containing protected seco acid **2.53** (85.6 mmol, 0.115 mmol, 1 equiv) and a stir bar was charged with TBAF·3H_2O (185 mg, 0.586 mmol, 5.1 equiv) in the glovebox. The vial was sealed with a septum cap and brought out of the glovebox. DMSO (2.3 mL) was added via syringe and the reaction was stirred at 50 °C for 70 min in a heating block. The reaction was cooled to room temperature, then partitioned between H_2O (20 mL) and Et_2O (20 mL). After mixing thoroughly and separating the phases (both phases should become clear), the aqueous layer was extracted with Et_2O (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 **2.53-1** (41 mg, 73%). ^{1}H-NMR matches literature data.[15]



2.53-2

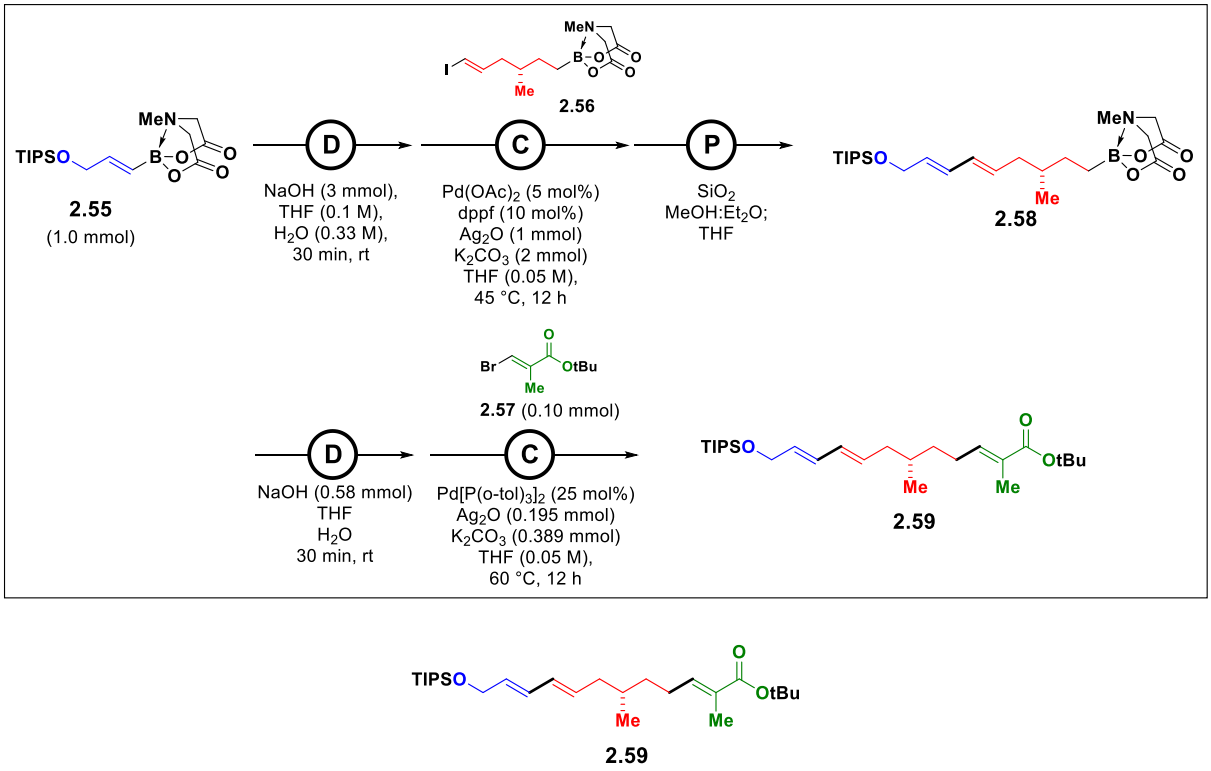
The following procedure is modified from a known literature procedure.[15] A dry 40 mL vial equipped with a stir bar was charged with PPh_3 (99.2 mg, 0.378 mmol, 5.05 equiv). The vial

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 **2.53-1** (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 **2.53-2** (12.4 mg, 35%). TLC (30% Et_2O/hexanes): R_f = 0.28, visualized by short wave UV; ^{1}H-NMR matches literature data.[15] Supplementary ^{1}H-NMR: (500 MHz, $CDCl_3$): δ 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).



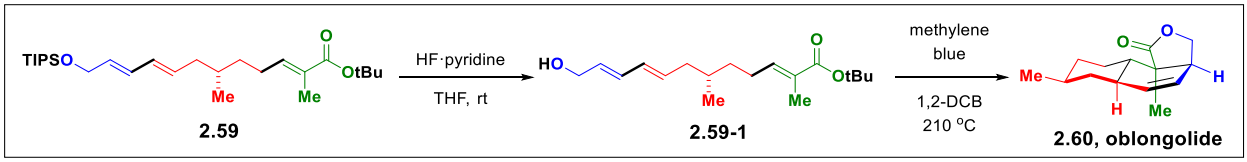
2.54, citreofuran

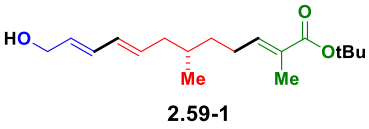
In an unoptimized procedure, a solution of the dibenzyl ether **2.53-2** (12.1 mg, 0.0258 mmol) in a 7 mL vial was charged with 10% Pd/C (2 mg) The vial was sealed with a septum cap and H_2 gas was bubbled through the stirring suspension for 8 min from a balloon. The outlet needle was removed and the reaction was stirred under H_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_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_2 for 5 min, then filtered through celite, rinsing with EtOAc. The filtrate was concentrated in vacuo, azeotroping once with CH_2Cl_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 **2.54** (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_2O in 25 min) ^{1}H-NMR matches literature data.[15]



Automated Procedure III was followed with the following details/modifications: In the first coupling reaction, the concentration was 0.05 M with respect to building block **2.56** (0.33 mmol), 5 mol% of $Pd(OAc)_2$, 10 mol% of dppf, 1 mmol of Ag_2O, and 2 mmol of K_2CO_3 were used, the addition of the boronic acid was performed over 1 minute, and the reaction was run at 45 °C for 12 hours. In the second deprotection reaction, 0.58 mmol of NaOH was used and the reaction was run for 30 minutes. In the second coupling reaction, 25 mol% of $Pd[P(o\text{-}tol)_3]_2$, 0.195 mmol of Ag_2O, and 0.389 mmol of K_2CO_3 were used. The addition of the boronic acid was performed over <1 minute, and the reaction was run at 60 °C for 12 hours. The crude reaction mixture was purified by two rounds of column chromatography (10% Et_2O/hexanes; 20% to 30% to 35% to 45% DCM/hexanes). This automated procedure was performed 2 times to accumulate **2.59** as a slightly yellow residue (19.4 mg total, average 9.7 mg, 0.022 mmol, 21% average yield). TLC (40% CH_2Cl_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); ^{13}C-NMR (125 MHz, $CDCl_3$): 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 $C_{27}H_{50}O_3SiNa$ $[M+Na]^+$ *m/z* 473.3427, found 473.3430.

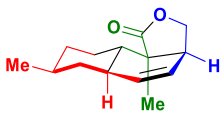




2.59-1

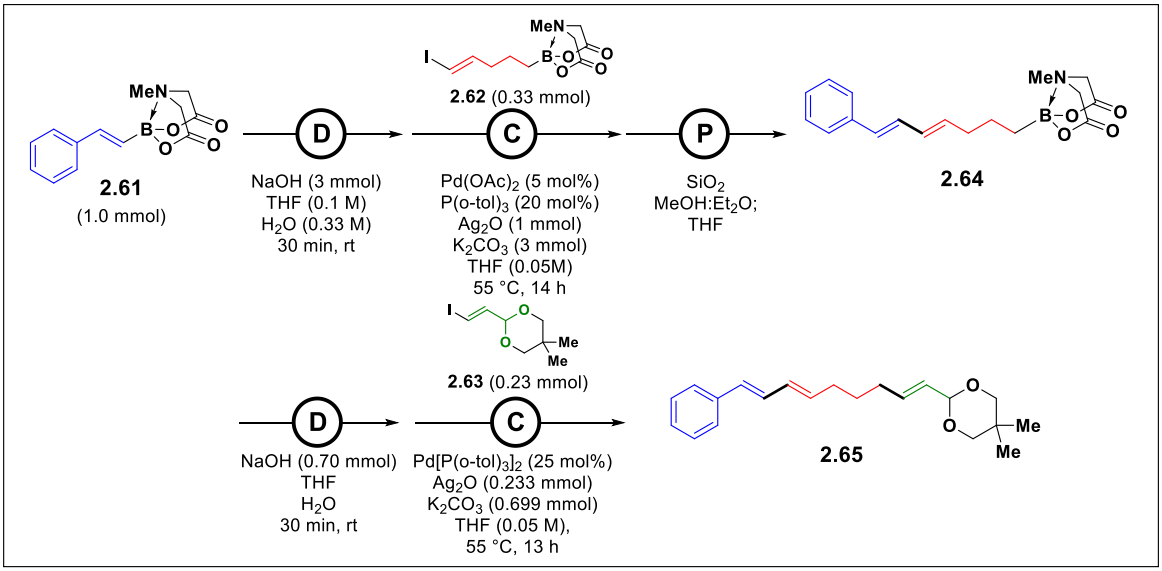
To a polyethylene vial containing a solution of **2.59** in THF (0.4 mL) was added HF·pyridine (0.09 mL), followed by THF (0.3 mL). The vial was capped and stirred at room temperature for 3 h. The reaction was quenched with the dropwise addition of saturated aqueous $NaHCO_3$ (5 mL). The mixture was stirred for 5 min, then transferred to a separatory funnel saturated aqueous $NaHCO_3$ (3 mL), rinsing with Et_2O (8 mL). After mixing and phase separation, the aqueous layer was extracted with Et_2O (4 mL × 2). The combined organics were washed with H_2O, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*, azeotroping once with CH_2Cl_2. The crude product was purified by silica gel chromatography (30% to 40% Et_2O/pentane) to give a colorless liquid as the product **2.59-1** (7.3 mg, 60%). TLC (50% Et_2O/hexanes): R_f = 0.32, visualized by UV, stained by $KMnO_4$; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 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,

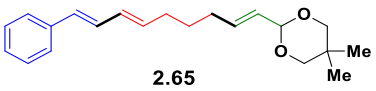
J = 9.5 Hz, 1H), 1.27-1.21 (m, 1H), 0.89 (d, *J* = 6.5 Hz, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 167.6, 141.2, 133.7, 131.9, 130.8, 129.6, 129.0, 79.9, 63.5, 40.0, 35.2, 32.9, 28.1, 26.3, 19.4, 12.3; HRMS (ESI+) calculated for $C_{18}H_{30}O_3Na$ $[M+Na]^+$ *m/z* 317.2093, found 317.2096.



2.60, oblongolide

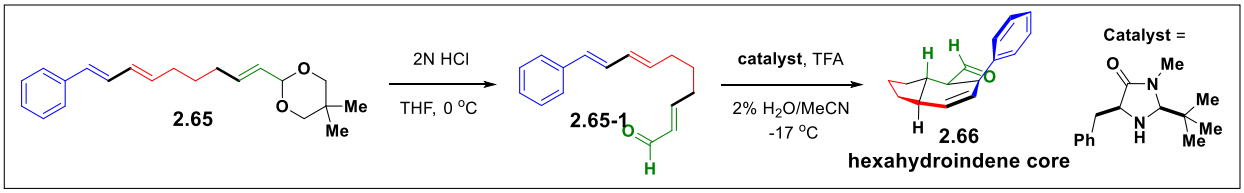
The following procedure is modified from a known literature procedure:[16] A Schlenk bomb containing alcohol **2.59-1** (7.3 mg, 0.0248 mmol) and a stir bar was charged with 1,2-dichlorobenzene (2.5 mL) under a stream of N_2. Methlyene blue (~ 1 mg) was added, forming a blue solution. The solution was 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 rbf, rinsing with CH_2Cl_2. The CH_2Cl_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_2O/pentane. The product was eluted with 20% Et_2O/pentane. This semi-purified product was purified on a second silica gel column (100% CH_2Cl_2) to give oblongolide **2.60** as a white solid (1.3 mg, 24%) in 85-90% purity. ^{1}H-NMR matches literature data.[16] Supplementary data: ^{1}H-NMR (500 MHz, $CDCl_3$): δ 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)

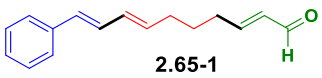




Automated Procedure III was followed with the following modifications: In the first coupling reaction, the concentration was 0.05 M with respect to **2.62**, 1 mmol of Ag_2O, 3 mmol of K_2CO_3, 5 mol% of $Pd(OAc)_2$, and 20 mol% of P(*o*-tol)$_3$ were used, the addition of the boronic acid was performed over 1 minute, and the reaction was run at 55 °C for 14 hours. In the second deprotection reaction, 0.7 mmol NaOH were used and the reaction was run for 30 minutes. In the second coupling reaction, vinyl iodide **2.63** was weighed into a clean, dry 7 mL vial in a glove box, sealed and removed immediately prior to the reaction, and was then washed into the reaction vial using THF (1 mL) in an automated fashion. The concentration was 0.05 M with respect to **2.63** (0.233 mmol), 0.233 mmol of Ag_2O, 0.699 mmol of K_2CO_3, and 25 mol% of Pd[P(*o*-tol)$_3$]$_2$ were used, the addition of the boronic acid was performed over <1 minute, and the reaction was run at 55 °C for 13 hours in a 7-mL glass vial. For the purification steps, the Et_2O:MeOH eluent (1.5% MeOH in Et_2O) was diluted 50% with hexanes. This automated cycle was performed 9 times to give 48.9 mg of crude linear precursor **2.65** as a slightly yellow

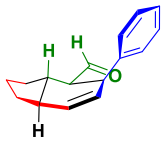
residue. This was purified by two rounds of column chromatography (5% to 10% to 20% Et_2O/hexanes; 5% acetone/hexanes) to yield 18.8 mg of linear precursor **2.65**. TLC (80% CH_2Cl_2/hexanes): R_f = 0.35, visualized by UV, stained by $KMnO_4$; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.37 (app d, *J* = 8 Hz, 2H), 7.30 (app t, *J* = 7.5 Hz, 2H), 7.19 (t, *J* = 7.0 Hz, 1H), 6.74 (dd, *J* = 15.5, 10.5 Hz, 1H), 6.44 (d, *J* = 16 Hz, 1H), 6.21 (dd, *J* = 15, 10.5 Hz, 1H), 5.93 (dt, *J* = 15.5, 7.0 Hz, 1H), 5.80 (dt, *J* = 15.5, 7.0 Hz, 1H), 5.59 (ddt, *J* = 16.0, 5.5, 1.0 Hz, 1H), 4.85 (d, *J* = 5.0 Hz, 1H), 3.65 (d, *J* = 11.5 Hz, 2H), 3.50 (d, *J* = 10.5 Hz, 2H), 2.17 (q, *J* = 7.0 Hz, 2H), 2.12 (q, *J* = 7.0 Hz, 2H), 1.55 (quint, *J* = 7.5 Hz, 2H), 1.22 (s, 3H), 0.74 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 137.8, 135.6, 135.3, 131.0, 130.3, 129.5, 128.7, 127.3, 127.2, 126.3, 101.4, 77.4, 32.4, 31.7, 30.2, 28.3, 23.1 22.1; HRMS (ESI+) calculated for $C_{21}H_{29}O_2$ $[M+H]^+$ *m/z* 313.2168, found 313.2156.





To a solution of ketal **2.65** (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_2O (5 mL), rinsing with Et_2O (5 mL). After mixing and phase separation, the aqueous layer was extracted with Et_2O (2 × 5 mL). The combined organics were washed with brine, dried over

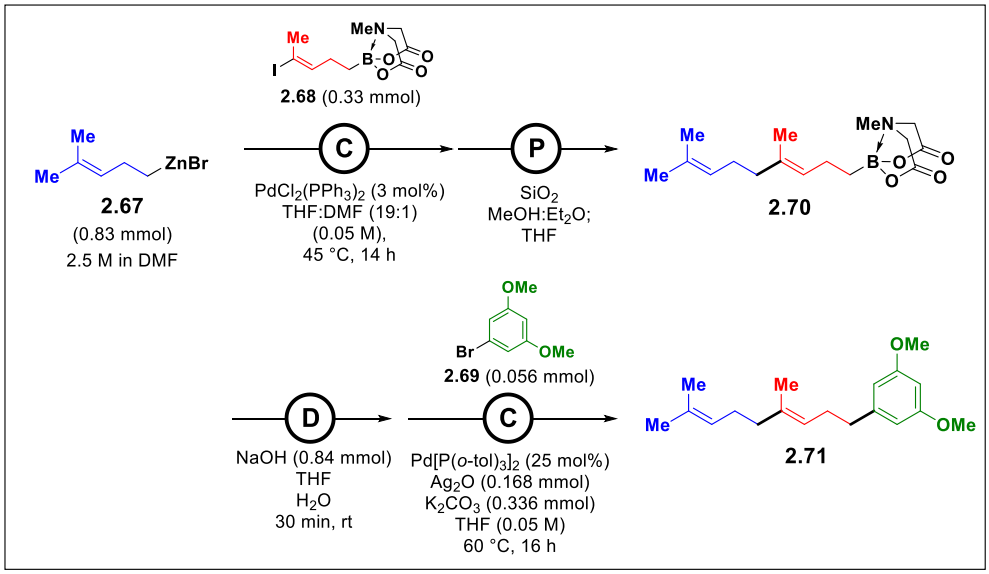
$MgSO_4$, filtered and concentrated *in vacuo* at room temperature. The crude product was taken up in a minimum amount of 60% DCM/pentane and loaded onto a silica gel column equilibrated with 60% DCM/pentane. The crude product was purified by silica gel chromatography (60% to 70% DCM/pentane) to afford the product **2.65-1** as a single isomer (8.5 mg, 62%). ^{1}H-NMR matches literature data (*32*). Supplementary ^{1}H-NMR (500 MHz, $CDCl_3$): δ 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).

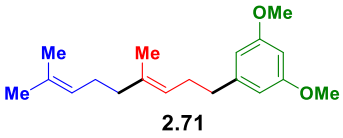


2.66, hexahydroindene core

The following procedure is modified from a published procedure:[17] 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 °C in a dry ice/ethylene glycol/EtOH bath with stirring. TFA (9 µL, 0.118 mmol) and H_2O (24 µL) were added. The solution was stirred for 5 min at the same temperature. 75 µL of this solution was then added to the 2 mL vial containing aldehyde **2.65-1**. 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 *in vacuo* at room temperature to give the product **2.66** 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

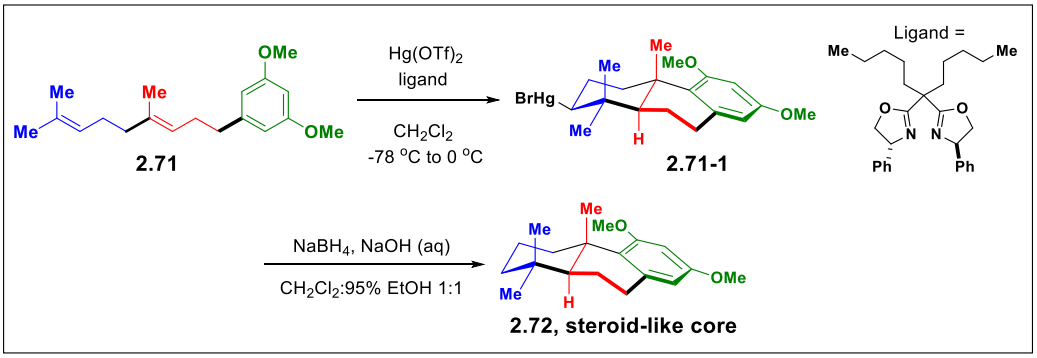
(Chiralcel-OD-H, 15% IPA/hexane isocratic elution, flow rate = 0.75 mL/min, t_r (minor) = 5.33 min, t_r (major) = 5.85 min). ^{1}H-NMR matches reported literature data.[17]

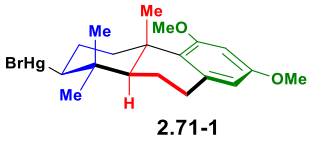




Automated Procedure III was followed with the following modifications: In the first coupling reaction, 0.33 mL of a freshly prepared solution of **2.67** in DMF (~2.5 M) was added manually to the First Reaction Cartridge, the concentration was 0.05 M with respect to **2.68**, 3 mol% of $PdCl_2(PPh_3)_2$ was used, and the reaction was run at 45 °C for 14 hours. Furthermore, the Reaction Filtration Cartridge contained only 300 mg of Celite™ and after filtration, the crude reaction underwent an automated aqueous quench (6 mL saturated aqueous NH_4Cl + 1 mL water) followed by an automated drying process before being purified. In the second deprotection reaction, 0.84 mmol of NaOH were used and the reaction was run for 30 minutes. In the second coupling reaction, 0.168 mmol of Ag_2O, 0.336 mmol of K_2CO_3, and 25 mol% of $Pd[P(o\text{-tol})_3]_2$ were used, the addition of the boronic acid was performed over 1 minute, and the reaction was run at 60 °C in a 7-mL glass vial. For the purification steps, the Et_2O:MeOH eluent

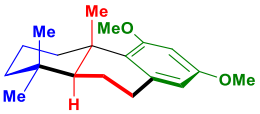
(1.5% MeOH in Et_2O) was diluted 50% with hexanes. This automated cycle was performed 4 times to accumulate **2.71** as a slightly yellow residue (14.8 mg total; average of 3.7 mg, 0.013 mmol, 23% yield). TLC (hexanes): R_f = 0.31, visualized by UV, stained with $KMnO_4$; HPLC (Sunfire Prep-C18, 5 µm, 30 x 150 mm (product number: 186002797), 25 mL/min, gradient: A = water, B = MeCN, 0 min: 50% A, 50% B; 15 min: 5% A, 95% B; 25 min: 5% A, 95% B; 25.5 min: 50% A, 50% B): 19.5 min; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.36 (d, *J* = 2.5 Hz, 2H), 6.30 (t, *J* = 2.5 Hz, 1H), 5.18 (tq, *J* = 7.0, 1.5 Hz, 1H), 5.09 (tdt, *J* = 6.0, 1.9, 1.0 Hz, 1H), 3.78 (s, 6H), 2.58 (dd, *J* = 9.1, 6.7 Hz, 2H), 2.29 (q, *J* = 8.0 Hz, 2H), 2.09-1.96 (m, 4H), 1.68 (d, *J* = 1.0 Hz, 3H), 1.60 (s, 3H), 1.58 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 160.8, 145.0, 135.9 131.5, 124.4, 123.7, 106.6, 97.8, 55.4, 39.9, 36.6, 29.9, 26.9, 25.8, 17.8, 16.2; HRMS (ESI+) calculated for $C_{19}H_{29}O_2$ $[M+H]^+$ *m/z* 289.2168, found 289.2175.





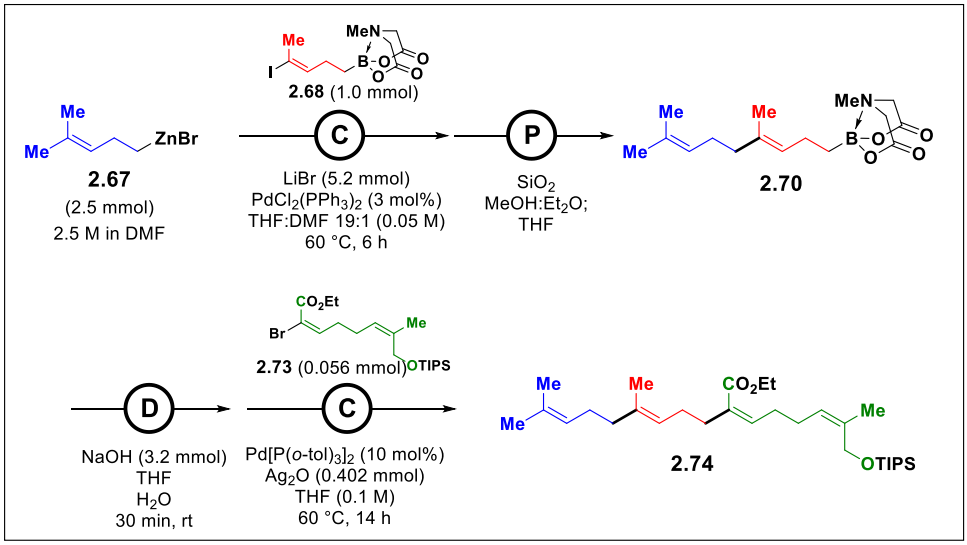
To an oven-dried 20 mL vial equipped with a magnetic stir bar was added $Hg(OTf)_2$ (28.2 mg, 0.057 mmol, 1.1 equiv.) and ligand (28.2 mg, 0.063 mmol, 1.2 equiv.). The vial was purged with Ar thrice and charged with CH_2Cl_2 (4.7 mL). The catalyst solution was then allowed to stir vigorously at room temperature for 20 min at which point it was cooled to -78 °C in an IPA/dry ice bath. After 7 min, linear precursor **2.71** (14.8 mg, 0.051 mmol, 1.0 equiv.) in CH_2Cl_2

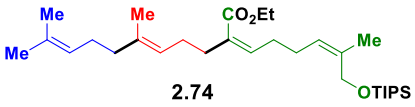
(0.5 mL) was added to the reaction mixture dropwise via syringe over 3 min, giving a bright yellow solution. The reaction mixture was allowed to stir at -78 °C for 1 h at which point the IPA/dry ice bath was replaced with a water/ice bath. The reaction mixture was allowed to slowly warm to 0 °C with stirring over 2 h then quenched with the addition of a pre-mixed solution of sat. NaBr (aq): sat. $NaHCO_3$ (aq) : H_2O (5 mL, 1:2:2) at 0 °C. The ice bath and Ar inlet were removed and reaction mixture was allowed to warm to room temperature with stirring over 45 min. The mixture was transferred to a 40 mL vial, rinsing with CH_2Cl_2 and H_2O. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford a pale yellow solid which was loaded onto Celite as a CH_2Cl_2 slurry and purified by SiO_2 chromatography (hexanes to 4:1 hexanes:EtOAc) to afford organomercury bromide **2.71-1** as a white crystalline solid (23.1 mg; 79% yield). Enhancement of ee by recrystallization was achieved by dissolving the solid organomercury bromide in warm EtOAc (5 mL) and diluting with warn hexanes (50 mL), and storing at -20 °C for 24 h. The resulting mother liquor was concentrated *in vacuo* to afford enantioenriched **2.71-1** (16.7 mg; 57% yield). TLC (4:1 Hexanes:EtOAc): R_f = 0.50, visualized by UV, stained with CAM; ^{1}H-NMR matches literature data.[18] Supplementary ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.27 (d, J = 2.7 Hz, 1H), 6.18 (d, J = 2.7 Hz, 1H), 3.75 (s, 6H), 3.18 (dt, J = 13.5, 3.6 Hz, 1H), 2.92 – 2.78 (m, 3H), 2.27 (qd, J = 13.7, 3.4 Hz, 1H), 1.97 (dq, J = 14.0, 3.8 Hz, 1H), 1.81 (dd, J = 12.9, 5.7 Hz, 1H), 1.67 – 1.57 (m, 1H), 1.38 (d, J = 11.6 Hz, 1H), 1.31 (s, 3H), 1.20 (td, J = 13.4, 3.7 Hz, 1H), 1.15 (s, 3H), 1.13 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 159.6, 158.1, 138.7, 129.2, 104.8, 97.7, 56.5, 55.3, 55.1, 40.2, 39.8, 38.9, 37.2, 33.6, 29.9, 27.6, 26.5, 20.9, 19.9; HRMS (ESI+) calculated for $C_{19}H_{28}O_2BrHg$ $[M+H]^+$ *m/z* 569.0979, found 569.0980.



2.72, steroid-like core

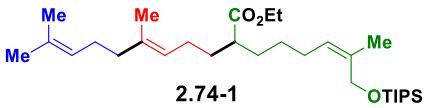
To an oven-dried 2 mL vial containing organomercury bromide **2.71-1** (16.7 mg, 29.5 μmol, 1.0 equiv), equipped with a magnetic stir bar, and purged with Argon thrice was added CH_2Cl_2 (147 μL) and EtOH (147 μL). $NaBH_4$ (4.4M in 14M NaOH, 33.4 μL; 5.0 equiv) was added dropwise via syringe at room temperature causing the reaction mixture to turn dark gray. The reaction mixture was allowed to stir at room temperature for 2 hours at which point it was diluted with Et_2O and transferred to a 40 mL vial rinsing with H_2O and Et_2O. The layers were separated and aqueous layers extracted with Et_2O (2 × 10 mL). The combined organics were washed with brine (2 × 10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford a yellow oil with white precipitate. This crude material was loaded onto Celite as a CH_2Cl_2 slurry and purified by SiO_2 chromatography (hexanes to 2.5% EtOAc in hexanes) to afford **2.72** as a white solid (3.5 mg; 41% yield, 90:10 e.r.) (*36*). The e.r. was determined by chiral HPLC (Chiralcel OD-H, t_r = 17.70 min (major); 18.97 min (minor); flow rate = 0.3 mL/min, 0.3% IPA in Hexanes for 30 min. Detected at λ= 254 nm.). TLC (5% EtOAc in hexanes): R_f = 0.31, visualized by UV, stained with CAM; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.28 (d, J = 2.6 Hz, 1H), 6.19 (d, J = 2.6 Hz, 1H), 3.75 (s, 6H), 3.09 – 3.01 (app dt, J = 13.2, 3.2 Hz, 1H), 2.89 – 2.77 (m, 2H), 1.79 (app dd, J = 6.0, 13.2 Hz, 1H), 1.70 (qt, J = 13.5, 3.6 Hz, 1H), 1.60 – 1.40 (m, 3H), 1.27 (s, 3H), 1.33-1.25 (m, 1H), 1.18 (dtd, J = 30.0, 13.0, 3.9 Hz, 2H), 0.95 (s, 3H), 0.92 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 159.8, 157.9, 139.0, 130.5, 104.9, 97.7, 55.2 (2C), 53.5, 41.7, 39.2, 36.9, 34.0, 33.9, 33.7, 22.3, 20.2, 19.6, 19.1; HRMS (ESI+) calculated for $C_{19}H_{29}O_2$ $[M+H]^+$ *m/z* 289.2162, found 289.2168.





Automated Procedure IV was followed with the following modifications: In the first coupling reaction, 1.0 mL of a freshly prepared solution of **2.67** in DMF (2.5 M, 2.5 mmol) was added manually to the First Reaction Cartridge, the concentration was 0.05 M with respect to **2.68** (1 mmol), 3 mol% of $PdCl_2(PPh_3)_2$ and 5.2 eq LiBr was used, and the reaction was run at 60 °C for 6 hours. Furthermore, the Reaction Filtration Cartridge contained only 300 mg of Celite™ and after filtration, the crude reaction underwent an automated aqueous quench (6 mL saturated aqueous NH_4Cl + 1 mL water) followed by an automated drying process before being purified. In the second deprotection reaction, 3 mmol of NaOH were used and the reaction was run for 30 minutes. In the second coupling reaction, 0.402 mmol of Ag_2O and 10 mol% of $Pd[P(o\text{-tol})_3]_2$ were used, the addition of the boronic acid was performed over 1 minute, and the reaction was run at 60 °C for 14 hours in a 7-mL glass vial. This automated cycle was performed 3 times to accumulate **2.74** as a slightly yellow residue (37.5 mg total; average of 12.5 mg, 0.025 mmol, 28% yield). TLC (40% CH2Cl2/hexanes): Rf = 0.47, visualized by UV, stained with KMnO4;

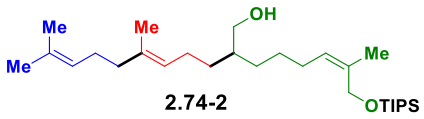
1H-NMR (500 MHz, CDCl3): δ 5.83 (t, J = 7.5 Hz, 1H), 5.18 (dt, J = 7.0, 1.0 Hz, 1H), 5.12-5.08 (m, 2H), 4.23 (s, 2H), 4.20 (q, J = 7.3 Hz, 2H), 2.44 (q, J = 7.5 Hz, 2H), 2.26 (t, J = 7.0 Hz, 1H), 2.14-2.04 (m, 6H), 1.97 (app t, J = 8.5 Hz, 2H), 1.77 (d, J = 1.0 Hz, 3H), 1.68 (s, 3H), 1.60 (s, 3H), 1.58 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H), 1.14-1.05 (m, 21H); 13C-NMR (125 MHz, CDCl3): δ 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 [M+H]+ m/z 505.4077, found 505.4077.



2.74-1

In the glovebox, the 7 mL vial containing **2.74** (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_4Cl (2 mL). The mixture was transferred to a separatory funnel, rinsing with Et_2O (10 mL) and H_2O (5 mL). After mixing and phase separation, the aqueous layer was extracted with Et_2O (2 x 5 mL). The combined organics were washed with H_2O (10 mL), brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was taken up in CH_2Cl_2, filtered through a pad of Na_2SO_4 and concentrated *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 **2.74-1** was obtained as a 4:1 mixture of ethyl:methyl ester (29.1 mg, 84% yield). This material was used without further purification.

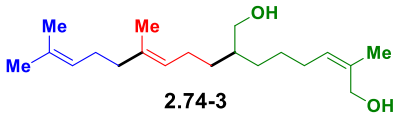
TLC (40% CH2Cl2/hexanes): Rf = 0.47, stained by KMnO4; 1H-NMR (500 MHz, CDCl3): δ 5.15 (t, J = 7.0 Hz, 1H), 5.10-5.07 (m, 2H), 4.21 (s, 2H), 4.13 (q, J = 7.1 Hz, 2H), 3.66 (s, 3H for methyl ester), 2.31 (tt, J = 9.0. 5.55 Hz, 1H), 2.08-2.04 (m, 2H), 2.01 (m, 6H), 1.76 (app s, 3H), 1.68 (app s, 3H), 1.68-1.60 (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; HRMS (ESI+) calculated for C31H59O3Si [M+H]+ m/z 507.4233, found 507.4231. Note: (Me) = peaks corresponding to the methyl ester.



2.74-2

The 7 mL vial containing ester **2.74-1** (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_2O (1.5 mL) was then added. The mixture was stirred vigorously for 10 min, then H_2O (1 mL) and Et_2O (1mL) were added. After stirring for another 10 min, the mixture was transferred to a separatory funnel, rinsing with H_2O (8mL) and Et_2O (8 mL). After mixing and phase separation, the aqueous layer was extracted with Et_2O (2 x 5 mL). The combined organics were washed with H_2O, brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (5% to 10% to 20% Et_2O/hexanes) to give the product **2.74-2** as a colorless oil (22.5 mg, 89% yield). TLC

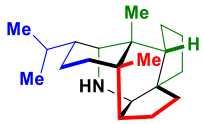
(20% Et2O/hexanes): Rf = 0.24, stained by KMnO4; 1H-NMR (500 MHz, CDCl3): δ 5.19 (app dt, = 7.0, 1.0 Hz, 1H), 5.11-5.07 (m, 2H), 4.22 (d, J = 12.5 Hz, 1H), 4.21 (d, J = 12.5 Hz, 1H), 3.54 (dd, J = 5.5, 1.5 Hz, 2H), 2.11-1.94 (m, 8H), 1.77 (d, = 1.0 Hz, 3H), 1.68 (s, 3H), 1.60 (s, 6H), 1.50-1.25 (m, 7H), 1.15-1.06 (m, 21H); 13C-NMR (125 MHz, CDCl3): δ 135.3, 135.1, 131.3, 126.0, 124.5, 124.3, 65.6, 62.0, 40.1, 39.7, 30.9, 30.5, 27.9, 27.2, 26.7, 25.7, 25.2, 21.0, 21.0, 18.0, 17.7, 16.0; HRMS (ESI+) calculated for C29H57O2Si [M+H]+ m/z 465.4128, found 465.4126.



2.74-3

To a solution of **2.74-2** (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_2O (10 mL). After mixing and phase separation, the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organics were washed with H_2O, brine, dried over Na_2SO_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 **2.74-3** as a colorless oil (13.7 mg, 93% yield). TLC (40% EtOAc/hexanes): Rf = 0.25, stained by KMnO4; 1H-NMR (500 MHz, CDCl3): δ 5.29 (app t, J = 7.5 Hz, 1H), 5.12-5.07 (m, 2H), 4.16 (d, J = 11.5 Hz, 1H), 4.10 (d, J = 11.5 Hz, 1H), 3.58 (dd, J = 10.5, 5.0 Hz, 1H), 3.51 (dd, J = 11.0, 6.0 Hz, 1H), 2.10-1.97 (m, 8 H), 1.80 (d, J = 1.3 Hz, 3H), 1.68 (d, J = 1.0 Hz, 3H), 1.60 (s, 6H), 1.50-

1.25 (m, 9H) 13C-NMR (125 MHz, CDCl3): δ 135.2, 134.4, 131.3, 128.5, 124.4, 124.3, 65.5, 61.5, 39.7 (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 C20H37O2 [M+H]+ m/z 309.2794, found 309.2794.



(±)-2.75, secodaphnane core

The following procedure was modified from a published procedure: To a Schlenk tube sealed with a rubber septum and vac-filled with N_2 (3×) was added CH_2Cl_2 (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 CH_2Cl_2, 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 **2.74-3** (13.7 mg, 0.0444 mmol, 1.0 equiv) in CH_2Cl_2 (0.3 mL) in a 7 mL vial was added dropwise to the reaction flask via syringe, rinsing with CH_2Cl_2 (0.3 mL). The solution was stirred for 20 min at –78 °C, then NEt_3 (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 $MeNH_2$ 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 $MeNH_2$. The solvent was removed under a stream of N_2, giving a yellow oily solid. The rubber septum was quickly replaced with a new septum under positive N_2 flow, and the residue was dried under high vacuum overnight. The

flask was filled with N_2. 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 CH_2Cl_2 (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 CH_2Cl_2 (5 mL). After phase separation the pH was adjusted to 14 with 2 drops of 3N NaOH. The aqueous phase was then extracted with CH_2Cl_2 (2 × 3 mL). The combined organics were washed with saturated $NaHCO_3$ (aq), dried over Na_2SO_4, 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). 1H-NMR (500 MHz, CDCl3): δ 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); 13C-NMR (125 MHz, CDCl3): δ 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 C20H34N [M+H]+ m/z 288.2691, found 288.2697.

2.5 REFERENCES

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CHAPTER 3

DESIGN AND SYNTHESIS OF A MORE HYDROLYTICALLY STABLE MIDA BORONATE

3.1 BACKGROUND

Small molecule natural products serve as potent sources of new pharmaceutical agents.[1-3] The coevolution of secondary metabolites with the targets they affect serves as natures "pre-optimization" of these compounds, and while some of these natural compounds serve as medicines themselves, they often require derivatization and/or optimization.[4,5] In fact, 42% of all new chemical entities approved as drugs from 1981 to 2006 are natural products, derivatives of natural products, or have pharmacophores derived from natural products.[6] Recognizing this, there have been a number of synthetic strategies developed towards rapidly and efficiently preparing compounds or libraries of compounds which more closely match the structural complexity, number of stereogenic centers, and C(sp^3) richness of many natural products.[7-9] Despite this, synthesis still stands as a major bottleneck in fully utilizing the functional potential of small molecule natural products. The advent of general and automated iterative synthesis platforms has largely removed this bottleneck in the case of peptides,[10] oligonucleotides,[11] and increasingly, oligosaccharides.[12] As described in Chapters 1 and 2, our group has pioneered the use of iterative cross coupling as an analogous approach to broadly enable the potential of small molecules. While the coupling of organoboron reagents is well developed and robust in the case of coupling C(sp^2) fragments, the general use of C(sp^3) boronates is still a major challenge. Due to the ubiquity of stereogenic C(sp^3) centers in small molecule natural products, the development of the stereospecific coupling of chiral non-racemic C(sp^3) boronates in a manner compatible with ICC stands to be a highly enabling advance.

In the past decade, a number of important advances have been made towards the development of such methods (Figure 3.1). The first major advance came in 2009 when Crudden[13] reported the stereoretentive coupling of chiral non-racemic secondary benzylic pinacol boronates. Similarly, Molander[14] later reported the stereoretentive coupling of 1-(benzyloxy)alkyltrifluoroborate salts. Molander[15] and Hall[16] also separately reported the stereoinvertive coupling of secondary boronates which contain pendant carbonyl groups (amides and esters). These Lewis basic groups are believed to coordinate to the boron center and thus influence the mechanism by which they transmetalate. In 2011, Suginome[17] showed in a similar system containg pendant Lewis basic groups that different acidic additives can influence which transmetalation pathway is dominant. Addition of the Lewis acid $Zn(OiPr)_4 \cdot iPrOH$ interrupts the intramolecular amide coordination, leading to the retentive pathway being dominant. Alternatively, addition of phenol leads to H-bonding with an oxygen of the pinacol ester, leading to stronger amide coordination and invertive transmetalation as the dominant pathway. While all of these results show major progress towards coupling secondary boronates, they all require pendant activating/directing for the reactions to work efficiently. In an ideal version of the ICC platform, building blocks have all functional groups and stereocenters preinstalled, so the requirement for such groups is inherently limiting. Excitingly, our group has discovered the first stereoretentive coupling of *unactivated* secondary boronic acids,[18,19] while Biscoe and coworkers[20] more recently demonstrated the stereoinvertive coupling of unactivated secondary trifluoroborate salts. All of these methods, both stereoretentive and invertive, would be highly impactful if they were incorporated with the ICC platform, allowing for secondary alkyl fragments to be used as building blocks.

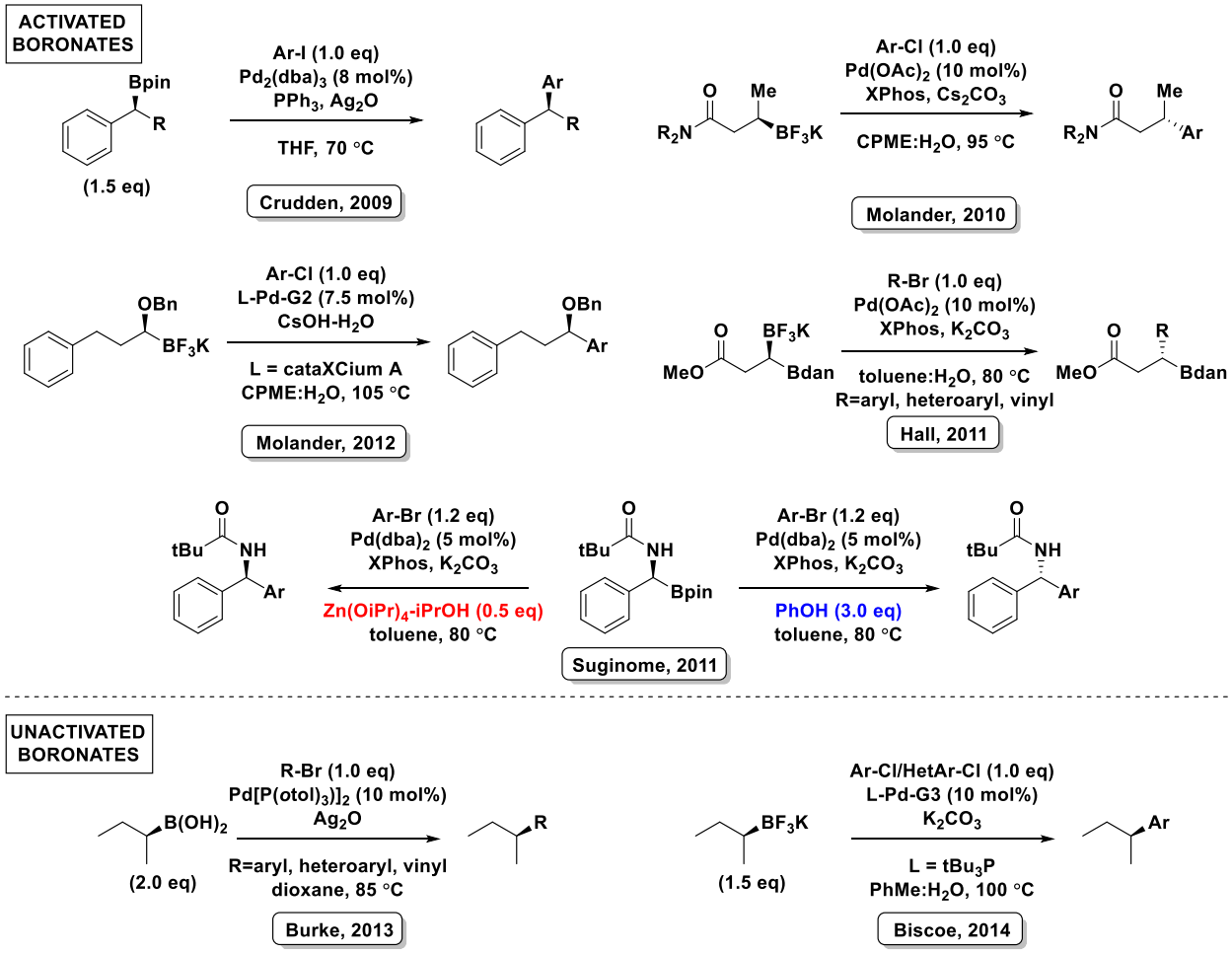


Figure 3.1. A collection of stereoretentive and stereoinvertive methods for the coupling of secondary alkyl boron fragments

One major challenge lies in the way of the utilization of these methods: *all of them are currently incompatible with the MIDA boronate functional group*. Most notably, the use of biphasic, aqueous basic conditions leads to deprotection of the MIDA boronate to the corresponding boronic acid. The use of high temperatures, strong bases, and long reaction times, even in rigorously anhydrous conditions, leads to similar decomposition. In addition, challenging C(sp^2) couplings that require long reaction times and/or high temperatures, while achievable, have been shown to be accompanied by undesired MIDA hydrolysis. Access to complex building blocks from simple MIDA boronate precursors[21] can also be hindered by such competitive

hydrolysis during reactions and/or purification. To collectively address these challenges, I aimed to develop a more hydrolytically stable derivative of the MIDA boronate framework.

3.2 THE MECHANISMS OF MIDA BORONATE HYDROLYSIS

To rationally design a MIDA boronate derivative which is refractory to hydrolysis, understanding the mechanism of the hydrolysis reaction is critical. Our group has collaborated with the groups of Lloyd-Jones and Houk[22] to probe this mechanism utilizing a combination of kinetic isotope effects in the MIDA framework (including ^{13}C, ^{15}N, and ^{11}B), ^{18}O labeling of water and hydroxide, rapid injection kinetics, and computation. The results reveal that MIDA boronates hydrolyze by two distinct mechanisms depending upon the reaction conditions—"basic" (or "fast release") hydrolysis and "neutral" (or "slow release") hydrolysis.

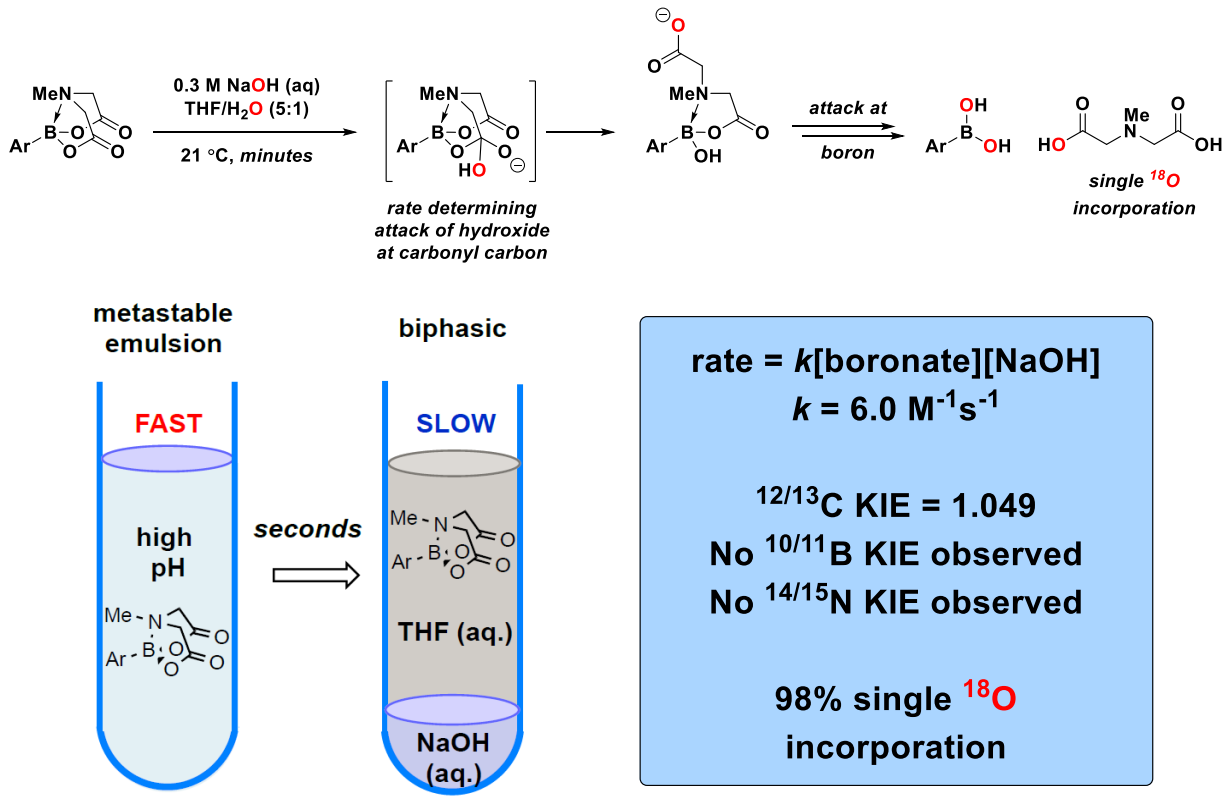


Figure 3.2. Basic hydrolysis mechanism of MIDA boronates ("fast release")

Primarily basic hydrolysis (Figure 3.2) occurs when MIDA boronates are treated with aqueous NaOH in THF at room temperature. Upon addition of the aqueous base to the organic solution, a metastable emulsion is formed between the two layers and hydrolysis occurs rapidly in this medium. At concentrations tested (0.01 to 0.1 M), this emulsion separates into a neutral organic upper layer and a basic aqueous lower layer within minutes. Hydrolysis occurs so quickly that full conversion is typically observed prior to phase separation; however, if hydrolysis is incomplete at this point, the mechanism switches over to the much slower neutral hydrolysis in the organic layer (*vide infra*). The fast, basic hydrolysis begins with rate-limiting attack of hydroxide at the carbonyl carbon of MIDA which is followed by subsequent attacks at boron to liberate the free ligand. In support of this, a significant $^{12/13}C$ KIE of 1.049 was observed, while no such KIEs were observed upon labeling of boron or nitrogen. Additionally, when ^{18}O-labelled water and NaOH were used, the MIDA ligand recovered from the hydrolysis reaction showed 98% incorporation of a single ^{18}O atom, consistent with initial attack at carbon followed solely by attack at boron.

In contrast, primarily neutral hydrolysis (Figure 3.3) occurs when MIDA boronates are treated with aqueous K_3PO_4 (7.5 equivalents) in THF at elevated temperatures (55 to 60 °C). These are conditions based upon those initially developed by our group for the slow release cross coupling of MIDA boronates as surrogates for unstable boronic acids.[23] Much like in the case of basic hydrolysis, upon addition of the aqueous K_3PO_4 to the THF boronate solution, an emulsion is formed which quickly separates into layers; however, unlike the basic hydrolysis, less than 3% of hydrolysis is observed prior to phase separation. The majority of hydrolysis occurs via a water-mediated process in the organic layer post-separation. This neutral hydrolysis was independently confirmed by rate measurements of aqueous THF mixtures containing no base (ie.

no phase separation). Attempts to determine an overall rate law for this process, however, were complicated by the non-ideal behavior of THF/water mixtures, and required introduction of a term for the thermodynamic activity of water (a_w) to account for an apparent plateau in rate with respect to the formal concentration of water ([H_2O]). The rate law thus obtained (presented in Figure 3.3), along with a negative entropy of activation ($\Delta S^{\ddagger} = -16$ e.u.), is consistent with attack by a neutral cluster of water molecules, $(H_2O)_n$, with an average $n = 2.8$. The site of attack by such a water cluster was elucidated through KIE experiments similar to those performed for the basic hydrolysis, showing significant KIEs at boron ($^{10/11}$B KIE = 1.032) and nitrogen ($^{14/15}$N KIE = 1.017) while showing no KIE at carbon. Collectively, these data are consistent with slow release hydrolysis beginning with rate-limiting attack of a cluster of between two and three neutral water molecules at the N-B bond to open the MIDA "cage", followed by subsequent attacks at boron to liberate the free ligand. The use of ^{18}O-labelled water in the neutral hydrolysis reaction led to no incorporation of ^{18}O in the MIDA ligand recovered, again consistent with no direct attack of water at the carbonyl carbons of the MIDA framework. Given the divergent nature of these ^{18}O-labelling experiments, percentage ^{18}O incorporation in recovered MIDA ligand can serve as a powerful mechanistic readout when undesired hydrolysis is observed in any given reaction.

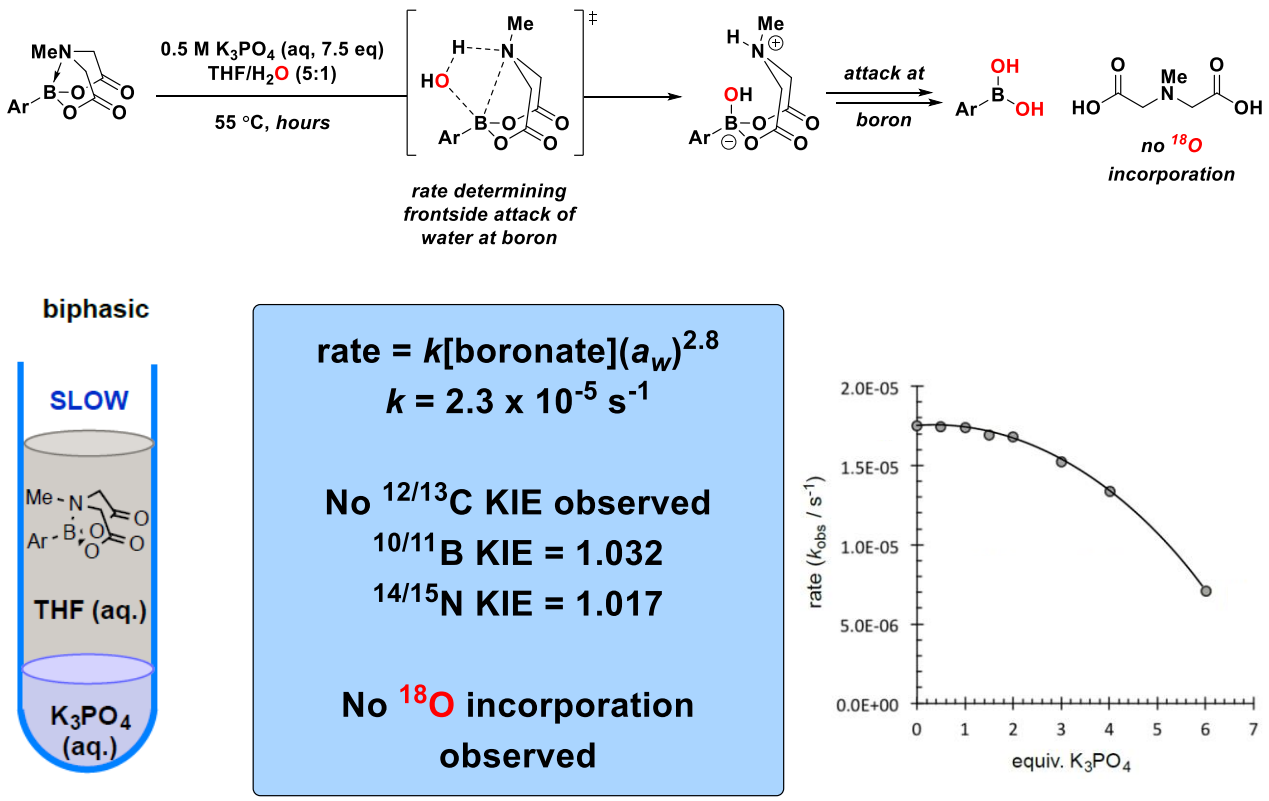


Figure 3.3. Basic hydrolysis mechanism of MIDA boronates ("fast release")

3.3 DEVELOPMENT OF A NEW IMINODIACETIC ACID LIGAND

With a clear mechanistic picture of MIDA boronate hydrolysis in hand, we set out to design a more hydrolytically stable iminodiacetic acid framework. Given that both of the above mechanisms involve rate determining attack of a nucleophile, it stands to reason that increase of steric bulk around the center(s) of attack would decrease the rate of hydrolysis. Towards this goal, I became interested in preparing and testing derivatives of MIDA which have (i) alkyl groups appended to the α-carbon of the acetate groups and (ii) larger alkyl groups appended to the nitrogen. Modifications at the α-methylenes of the MIDA framework seem particularly attractive, as they are proximal to both sites of nucleophilic attack. As shown in Figure 3.4, MIDA boronate derivatives in which the *N*-Me group had been replaced with cyclohexyl (**3.1**)

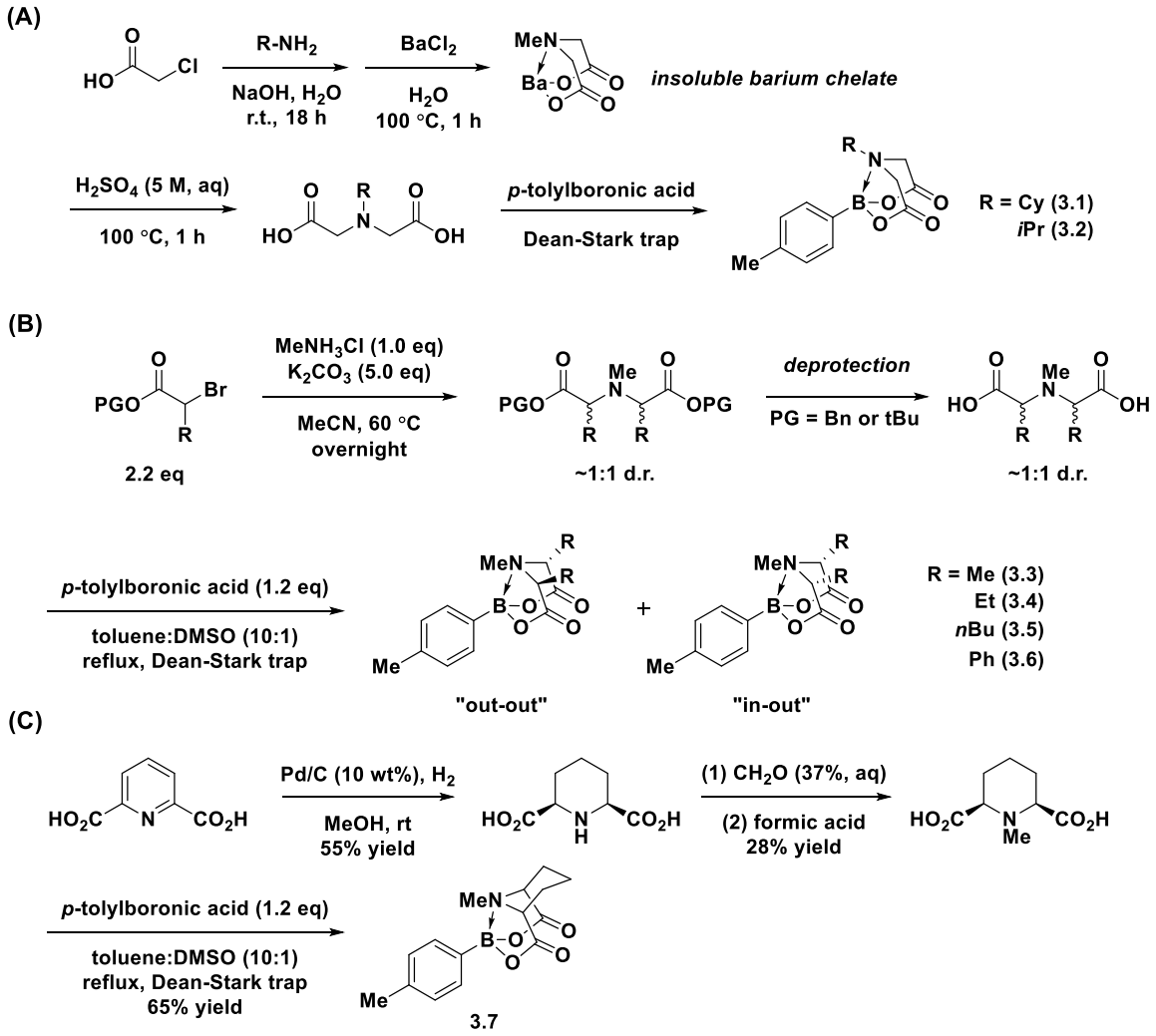


Figure 3.4. Synthetic routes towards new iminodiacetic acid ligand frameworks

and isopropyl (**3.2**) groups had been previously synthesized by former graduate student Dr. Eric Gillis and quantities sufficient for hydrolysis studies were already on hand. In conjunction with undergraduate student Robert Pipal, I then synthesized a collection of α-substituted derivatives (R = Me, Et, *n*Bu, Ph, **3.3** to **3.6**). Double S_N2 displacement of the appropriate α-bromo esters followed by deprotection and complexation with *p*-tolylboronic acid under standard Dean-Stark azeotrope conditions gave the desired boronates as mixtures of the "out-out" and "in-out" diastereomers which were easily separable by column chromatography. Finally, a piperidine-derived ligand in which the two α-substituents were tethered into a 6-membered ring was

prepared from 2,6-dipicolinic acid. Hydrogenation with Pd/C yielded the desired *cis* diastereomer of the resulting piperidine which was then methylated using the Eschweiler-Clarke reaction. Again, standard Dean-Stark azeotrope conditions yielded the desired boronate **3.7.**

To test these new derivatives, an assay was developed based upon our previously reported slow release cross coupling conditions.[23] In this assay, a THF-d_8 solution of the *p*-tolylboronate (0.067 M) is treated with a D_2O solution of K_3PO_4 (3.0 M, 7.5 eq) and stirred for between 0 and 6 hours at 60 °C. At the indicated time point, the reaction vessel is briefly cooled under a stream of air before being diluted with DMSO-d_6 containing an internal standard. Proton NMR is then immediately obtained and integration gives the amount of boronate remaining relative to the initial time point.

A number of useful and surprising trends emerged from this data set. First, in opposition to what was expected, boronates with more sterically bulky *N*-substituents (*N*-Cy, **3.1** and *N*-iPr, **3.2**) hydrolyze more quickly than the parent MIDA boronate (Figure 3.5). One possible mechanistic explanation for this trend is that steric clash between the bulky *N*-substituents and the organic group on boron results in lengthening and weakening of the N-B bond. Given that attack of water at the N-B bond is the rate determining step under slow release conditions, a longer/weaker N-B would be more susceptible to attack. While faster hydrolysis was not the initial goal of this study, a collection of boronates with hydrolysis rates that are tunable to be both faster *and* slower could prove useful in the context of selectively coupling polyborylated building blocks.

Previous studies by former graduate student Greg Morehouse had shown that the α-dimethyl substituted derivative of *p*-bromophenyl MIDA boronate (analogous to compound **3.3**) hydrolyzed more slowly than the parent compound under slow release conditions. To confirm

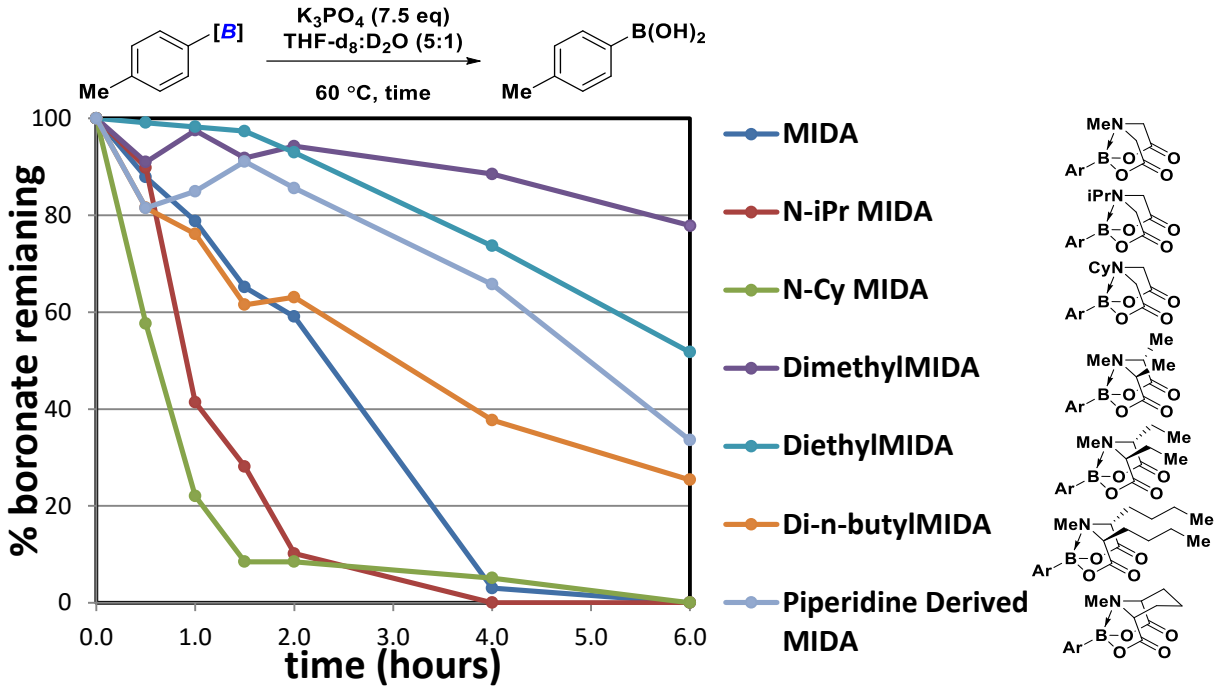


Figure 3.5. Slow release hydrolysis studies of MIDA boronate derivatives. Data points represent the average of two duplicate runs, except in the case of *N*-Cy and *N*-iPr MIDA where $n = 1$. Ar = *p*-tolyl

this data, I prepared diastereomerically pure samples of the "out-out" and "in-out" dimethylMIDA boronates **3.3** and repeated the hydrolysis experiment with both yielding the same result—they hydrolyzed slightly over one order of magnitude slower than the corresponding parent MIDA boronate. While the slowed hydrolysis was welcome and expected, the identical rate profiles of the two diastereomers was intriguing, as it was expected that the "in-out" diastereomer would have less protective capacity towards the rate-determining nucleophilic attack. A closer look at the NMR spectra of these two experiments revealed that these compounds rapidly equilibrated to a thermodynamic mixture of the two diastereomers (<30 minutes), presumably through an enol or enolate intermediate as shown in Figure 3.6. The "in-out" diastereomer was actually preferred by a factor of 8, which was also a surprising result as this isomer was presumed to have more unfavorable steric interactions in the internal cavity of the MIDA framework.

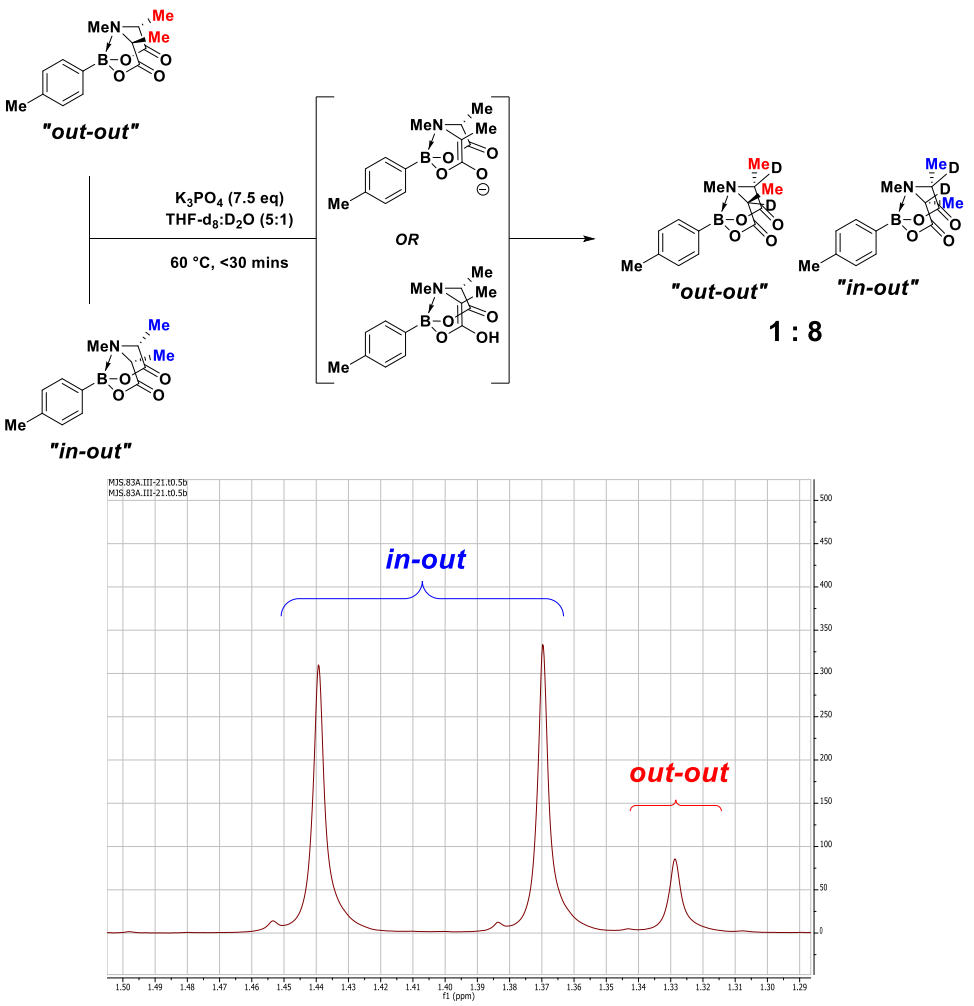


Figure 3.6. Both diastereomers of dimethylMIDA boronate **3.3** rapidly equilibrate to a thermodynamic mixture of the two isomers

Encouraged by these results, I then measured the hydrolysis rates of the diethyl- and dibutylMIDA boronates (**3.4** and **3.5**). Given that the dimethylMIDA boronate had slowed hydrolysis rates, it was expected that increasing the size of the alkyl groups attached to the backbone would result in even slower rates. Quite surprisingly, the opposite trend was observed (Figure 3.5). Of the compounds in this series, dibutylMIDA boronate **3.5** hydrolyzed the fastest, followed by diethylMIDA boronate **3.4** and then the aforementioned dimethylMIDA boronate **3.3**. The current leading hypothesis stems from the fact that the rate of slow release hydrolysis is dependent on the concentration (or, more formally, the activity) of neutral water in the organic

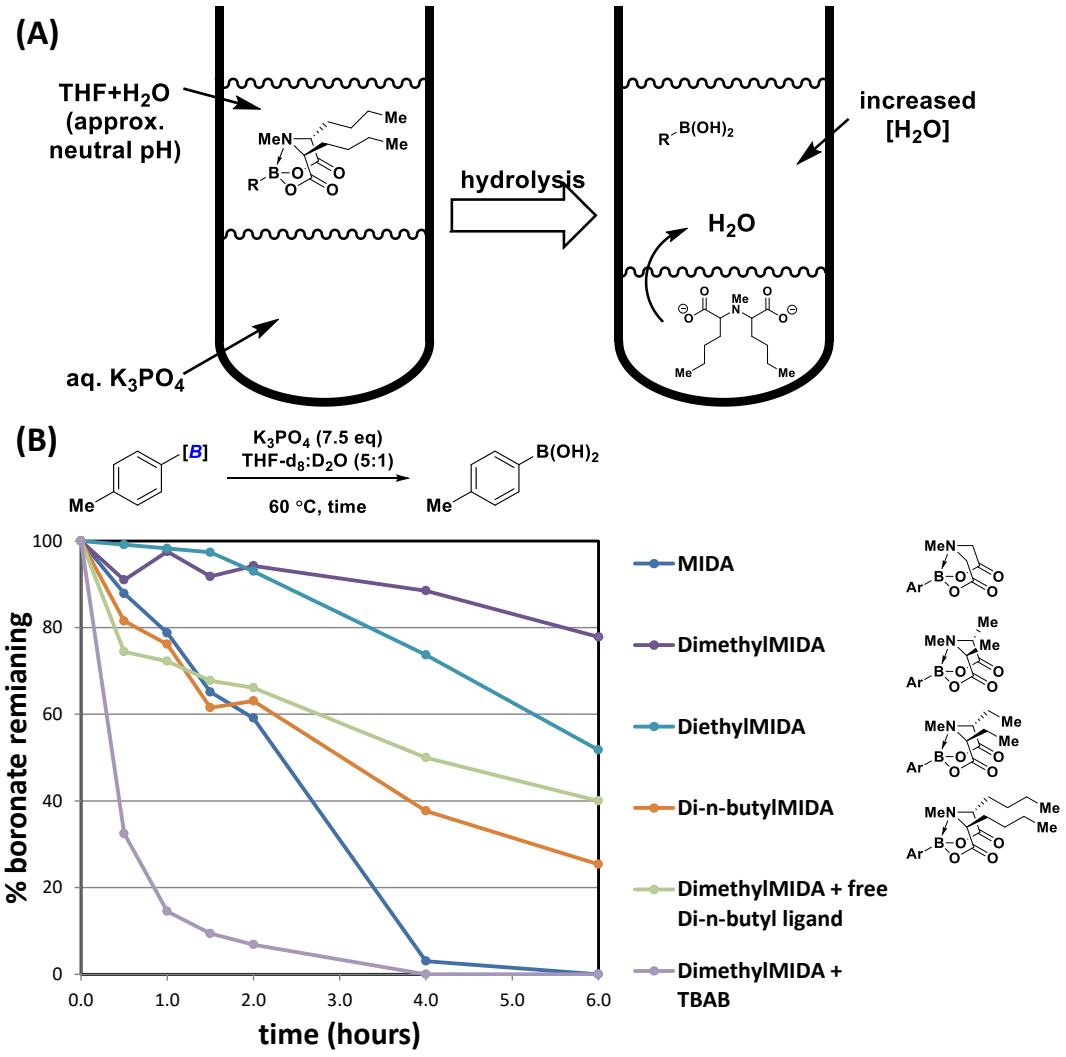


Figure 3.7. (A) Surfactant/phase transfer hypothesis for increasing hydrolysis rate with increasing alkyl chain length (B) Adding free dibutylMIDA ligand to the hydrolysis of dimethylMIDA results in a drastic increase in rate

phase post phase separation. As hydrolysis proceeds, free ligand is released into the reaction mixture and likely primarily exists in the aqueous layer as the dicarboxylate salt. This free ligand can then act as a surfactant that increases the concentration of water in the organic layer, and thus increases the rate of neutral hydrolysis (Figure 3.7, A). With this in mind, the observed trend begins to make sense—ligands with longer alkyl chains appended would be more lipophilic and would therefore be more efficient surfactants, ultimately leading to faster neutral hydrolysis. The

structural similarity of the free ligands to molecules known to act as surfactants (that is, molecules with distinct hydrophilic and hydrophobic regions such as phospholipids) provides further support. In support of this hypothesis, addition of one equivalent of the free dibutylMIDA ligand to the slow release hydrolysis of dimethylMIDA boronate resulted in a nearly 10-fold increase in rate (Figure 3.7, B).

Having shown that simply increasing the length of alkyl chains on the MIDA backbone actually has detrimental effects on its hydrolytic stability, we next became interested in the effect of permethylating the backbone. There are two primary rationales for this interest. First, increasing the number of alkyl groups attached to the alpha carbons of simple alkyl esters results in reduced rates of basic hydrolysis, while simply increasing the length of alkyl chains has a far lesser effect.[24] Our boronate esters have thus far followed a similar trend, so by analogy, we expected tetramethylMIDA (TIDA) to have a decrease in hydrolysis rate relative to dimethylMIDA. Second, epimerization of the dimethylMIDA boronates results in mixtures of diastereomers that would complicate the isolation and characterization of building blocks and synthetic intermediates. Permethylation of the α carbons would remove this complication entirely. TIDA was synthesized in a manner analogous to dimethylMIDA—double S_N2 displacement of *tert*-butyl 2-bromopropionate yielded protected dimethylMIDA which was treated with 2.2 eq of LDA followed by trapping with excess methyl iodide. Treatment of the resulting material with formic acid yielded tetramethylMIDA (TIDA) in 55% yield over 3 steps (Figure 3.8, A). Despite their sterically congested nature, TIDA boronates are easily prepared from the corresponding boronic acids using previously discussed Dean-Stark conditions. Excitingly, hydrolysis of *p*-tolylTIDA boronate (Figure 3.8, B) proceeded much slower than the corresponding MIDA boronate under these conditions. More detailed rate studies will be

required to accurately determine their relative rates. This result represented the first MIDA derivative which has the potential to have the broadened synthetic utility we initially sought, so we decided to further investigate the physical and chemical properties of TIDA boronates.

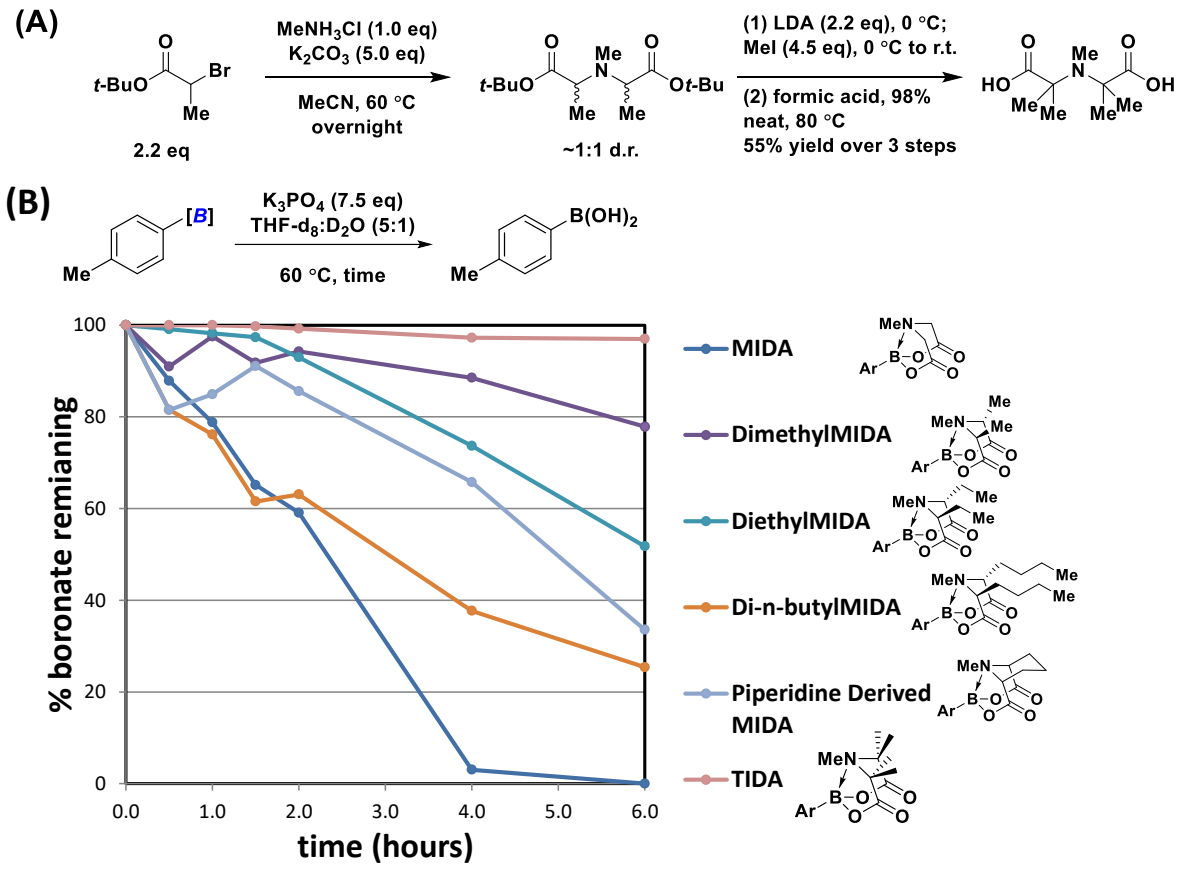


Figure 3.8. (A) Synthesis of tetramethylMIDA (B) Hydrolysis studies of a collection of MIDA boronate derivatives representing a wide range of tunable rates. Ar = *p*-tolyl

The first noticeable difference between *p*-tolyl TIDA boronate and its MIDA counterpart was its reduced solubility in THF. Despite sonication, extended stirring, and warming, a solution of the TIDA boronate in THF that was sufficiently concentrated (0.08 M) for the hydrolysis assay wasn't able to be obtained. In addition to necessitating the boronate to be delivered as a THF slurry (a potential source of experimental error), we recognized that insolubility could be the primary factor behind the lack of hydrolysis observed. To address this concern, I synthesized

octyl TIDA boronate which proved to be completely soluble in THF at the concentration utilized in the hydrolysis reaction. Gratifyingly, no loss of boronate or generation of the corresponding boronic acid was observed by ^{1}H NMR over the course of 6 hours. More detailed studies will be required in the future to fully understand how the nature of the organic fragment on boron affects both the kinetic and thermodynamic solubility of TIDA boronates. Satisfyingly, large transparent crystals of octylTIDA boronate were easily obtained by slow evaporation from THF, allowing the structure to be unambiguously determined by x-ray crystallography. Interestingly, the sterically congested nature of the TIDA boronate causes it to skew away from the symmetrical structure seen in MIDA boronates. As seen in Figure 3.9, one of the α carbons (in this case, the right hand carbon) dips down and inward toward the boron atom, while the other (the left hand carbon) shifts up and out away from the boron atom. These boronates exist as pairs of conformers which rapidly interconvert at room temperature as evidenced by the coalescence of the α-methyl peaks in the ^{1}H NMR spectrum, leading to two singlets (one each for the internal and external sets of methyl groups).

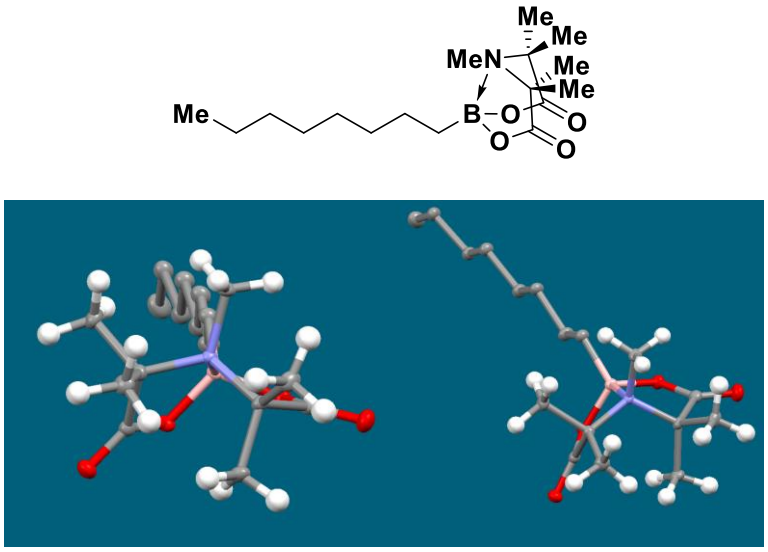


Figure 3.9. X-ray crystal structure of octylTIDA boronate

I then became interested in testing the capacity of the TIDA boronate functional group to withstand conditions previously incompatible with the ICC platform. Excitingly, our groups anhydrous conditions developed for coupling secondary, unactivated boronic acids were successfully used to couple boronic acid **3.9** with 3-iodo-5-trifluoromethylphenylTIDA boronate **3.10** in a modest 14% isolated yield (Figure 3.10, A). With a successfully coupled intermediate, we next looked at conditions for deprotection of the TIDA boronates to allow iteration. Treatment with aqueous NaOH at room temperature, the conditions used to deprotect MIDA boronates, TIDA boronates tested saw no conversion. Increasing the temperature to 60 °C led to full conversion after 60 minutes. Interestingly, it was found that addition of MeOH to the reaction mixture greatly increased the rate of deprotection. Treatment of TIDA intermediate **3.11** with MeOH and aqueous NaOH led to complete, clean deprotection in 15 minutes at 45 °C. Finally, this boronic acid was taken on and coupled with benzyl 4-bromobenzoate to give the final product in 73% isolated yield. This is the first complete cycle of iterative cross coupling which utilized a secondary alkyl boronic acid coupling partner successfully.

Finally, I tested the capacity of TIDA boronates to survive aqueous, biphasic coupling conditions. Coupling of *p*-tolylboronic acid with TIDA boronate **3.10** under conditions developed for slow release cross coupling[23] gave 50% isolated yield of the desired product. Additionally, coupling of either potassium 2-butyltrifluoroborate or 2-butylMIDA boronate with *meta*chlorophenylTIDA boronate **3.13** gave the desired coupling products in 48% and 25% isolated yields respectively. These are the first successful couplings of a benchtop stable boronate with a bifunctional TIDA boronate, representing a major step forward for the iterative cross-coupling platform.

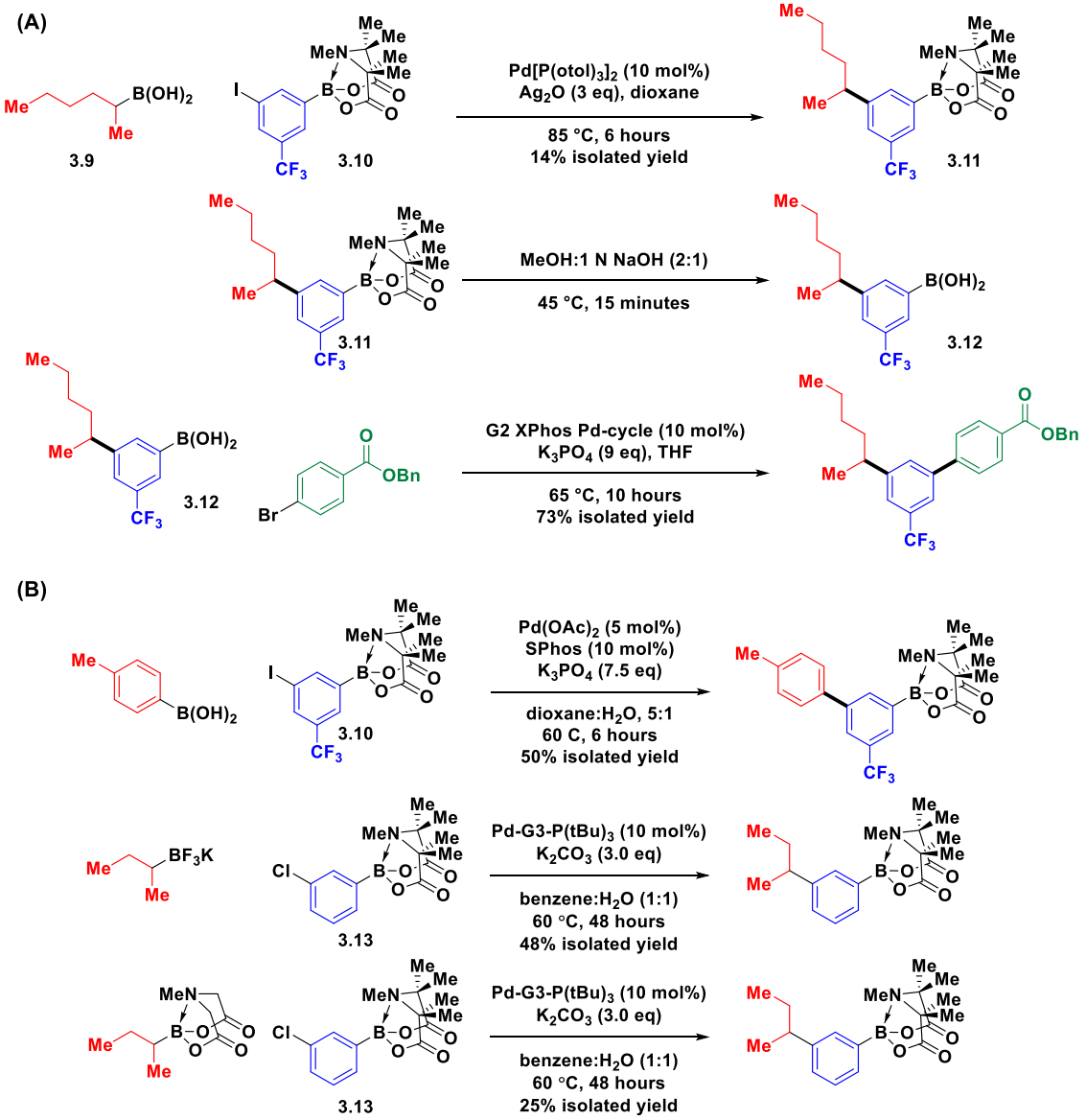


Figure 3.10. (A) A complete iterative cross coupling cycle using an unactivated secondary boronic acid (B) TIDA boronates survive aqueous biphasic coupling conditions in synthetically useful yields

In summary, we have developed a second generation iminodiacetic acid based ligand which is substantially more stable to hydrolysis relative to MIDA. Initial results show that these boronates are also much more stable to a range of conditions for cross coupling. These new conditions will enable unique disconnections to be used with the iterative cross coupling platform, namely in the coupling of unactivated secondary boronates. Given the prevalence of

stereogenic C(sp^3) centers in small molecule natural products, these disconnections stand to enable the ICC platform to access new and important chemical space.

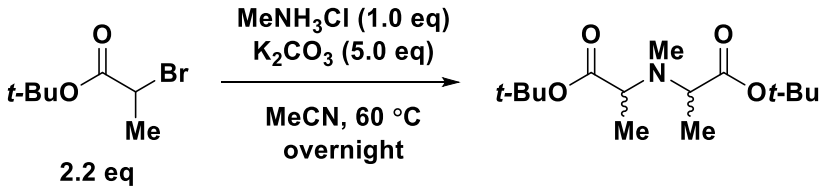
3.4 EXPERIMENTAL SECTION

General Methods and Materials

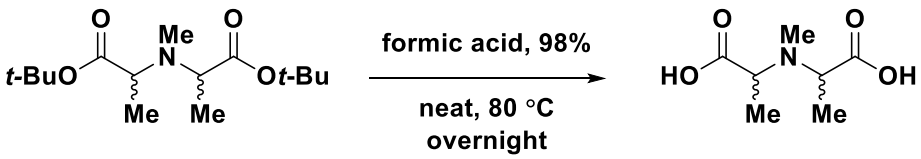
Commercial reagents were purchased from Sigma-Aldrich, TCI America, Alfa Aesar, Strem Chemicals Inc., Fisher Scientific, or Combi Blocks and used without further purification unless otherwise noted. Solvents were purified via passage through packed columns as described by Pangborn and coworkers[25] (THF, 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.

All reactions were performed in flame- or oven (125 °C)-dried glassware under an atmosphere of dry nitrogen or argon unless otherwise stated. Organic solutions were concentrated via rotary evaporation under reduced pressure with a bath temperature of 30-40 °C. Reactions were monitored by analytical thin layer chromatography (TLC) on Merck silica gel 60 F254 plates (0.25 mm) using the indicated solvent system. Compounds were visualized by exposure to UV light (254 nm), or by treatmeant with a basic potassium permanganate (KMnO4) solution followed by brief heating with a Varitemp heat gun. MIDA boronates are compatible with standard silica gel chromatography, include standard loading techniques. Column chromatography was performed on silica gel (Merck Grade 938, pore size 60 Å, 230-400 mesh particle size, Ald. #227196) with indicated solvent systems).

Ligand Synthesis

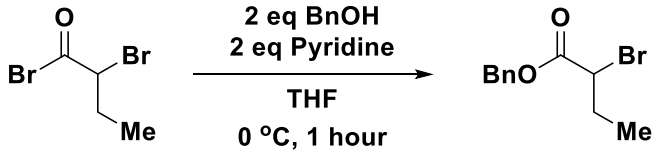


Under ambient atmosphere, methylamine hydrochloride (3.76 g, 55.7 mmol), potassium carbonate (38.48 g, 278.5 mmol), and MeCN (80 mL) were charged into a 250 mL roundbottom flask containing a stir bar. Tert-butyl 2-bromopropionate (25.62 g, 122.5 mmol) was then weighed into a small beaker and poured into the flask, rinsing with further 20 mL of MeCN. The flask was then fit with a rubber septum and flushed with dry nitrogen for 10 minutes. The flask was then stirred in 60 °C oil bath overnight while under a positive pressure of nitrogen. The next day, the crude reaction mixture was filtered through a ~2 cm silica gel plug, rinsing with EtOAc (~50 mL) and acetone (~20 mL). The solvent was then removed *in vacuo* to give 17.13 g of a yellow oil which was primarily product as a ~1:1 mixture of diastereomers. For large scale preparation, this crude material was taken onto the next step without further purification, although purified material can be obtained by column chromatography (10% EtOAc/hexanes). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.43 (app dq, 2H), 2.40 (app d, 3H), 1.45 (app d, 18H), 1.27 (app dd, 6H). *Note: This spectrum is that of the 1:1 mixture of diastereomers—all peaks appear to split as "doublets" but its really just the two diastereomers resolving.*



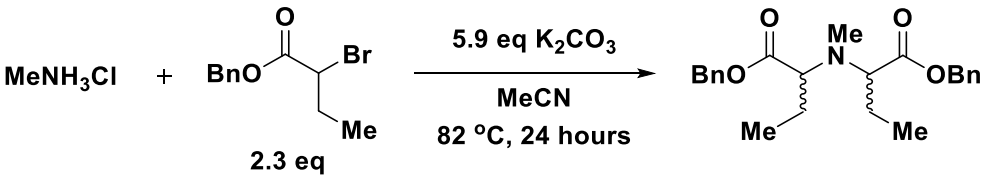
Crude dimethylMIDA *t*-butyl ester (17.13 g, approximately 60 mmol) was charged into a 200 mL roundbottom flask, followed by formic acid (60 mL). The flask was fitted with a rubber

septum and briefly flushed with nitrogen before being stirred in an 80 °C overnight. The next day, TLC (100% EtOAc, $KMnO_4$) showed no remaining starting material and a large smear at the baseline (presumably product and formic acid). Formic acid was then removed by rotary evaporation in a 50 °C bath, followed by being placed under high vacuum in an 80 °C heat block, giving a tacky tan solid. This solid was then taken up in EtOH (~15 mL) with warming via heatgun. To this solution was added acetone (75 mL) dropwise with stirring over ~10 minutes, causing precipitation of a white solid. The solid was then collected by vacuum filtration and washed copiously with acetone (~100 mL). The resulting white crystalline solid was then dried under high vacuum overnight to give 8.62 g (88% yield over two steps) of product as a 1:1 mixture of diastereomers. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 3.48 (app dq, 2H), 2.28 (app d, 3H), 1.20 (app dd, 6H). *Note: This spectrum is that of the 1:1 mixture of diastereomers—all peaks appear to split as "doublets" but its really just the two diastereomers resolving.*

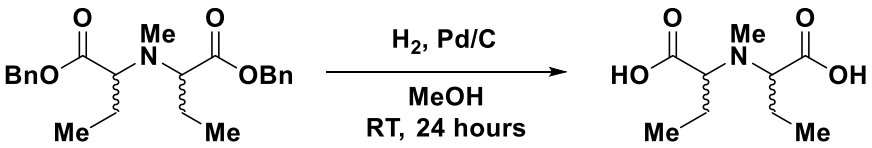


A 100 mL Schlenk flask with a stir bar and stoppered with a rubber septum was vac/filled three times with nitrogen. Benzyl alcohol (5.2 mL, 50 mmol, 2 eq), THF (50 mL), and pyridine (4.05 mL, 50 mmol, 2 eq) were added via syringe while stirring. The reaction was cooled to 0 ºC in an ice bath, and 2-bromobutyrl bromide (3.02 mL, 25 mmol) was added dropwise to the stirring solution over 10 minutes, producing a yellow color. After 1 hour of stirring in the ice bath, the reaction was quenched with the addition of water (50 mL) via syringe. The mixture was transferred to a separatory funnel, and the aqueous layer was extracted with diethyl ether (3 x 30 mL). The combined organics were washed with saturated NH_4Cl (2 x 25 mL), water (25 mL),

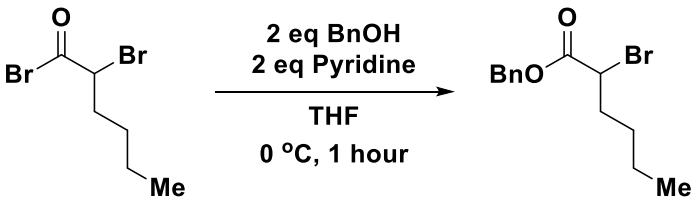
saturated $NaHCO_3$ (25 mL) and brine (25 mL). The organics were dried with $MgSO_4$, filtered over a pad of Celite, and solvent was removed via rotary evaporation, producing a clear oil (8.80 g crude). The crude product was dry loaded on Celite and placed atop a silica gel column equilibrated with 20 % ethyl acetate in hexanes. A clear oil was obtained (96% yield). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.38 (m, 5H), 5.21 (s, 2H), 4.22 (dd, 1H), 2.13 (dq, *J* = 14.2, 7.1 Hz, 1H), 2.03 (dq, *J* = 14.8, 7.5 Hz, 1H), 1.02 (app t, *J* = 7.3 Hz, 3H).



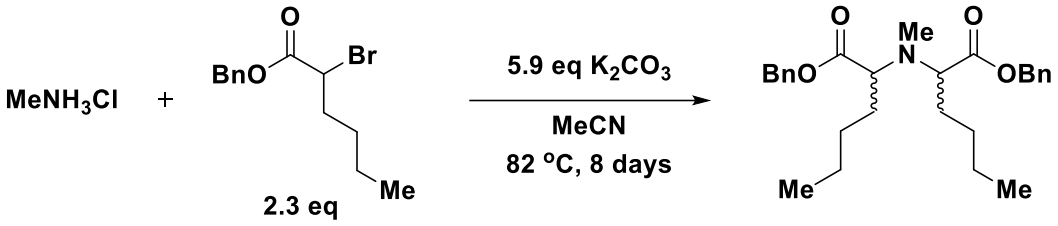
A 20 mL vial with a stir bar was charged with potassium carbonate (2.743 g, 19.81 mmol, 5.86 eq) and methylamine hydrochloride salt (224.5 mg, 3.38 mmol, 1 eq). The vial was capped and purged with nitrogen for 10 minutes. Acetonitrile (3.9 mL) and the 2-bromobenzyl ester (2.008 g, 7.78 mmol, 2.3 eq) were added subsequently with stirring via syringe. The nitrogen inlet was removed and the vial was sealed with Teflon tape. The reaction was heated at 82 ºC in a heat block for 24 hours. The solvent had evaporated off in the vial, leaving a white paste. The mixture was filtered over a pad of Celite and washed with ethyl acetate. The solvent was removed via rotary evaporation, producing a pale, yellow oil (1.50 g crude). A gradient silica column was run with 7.5-10% ethyl acetate in hexanes. A clear oil was isolated (441.3 mg, 15% yield) as a mixture of diastereomers. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.33 (app m, 10H), 5.04 (app ddd, 4H), 3.33 (app dt, 2H), 2.50 (app d, 3H), 1.76 (m, 4H), 0.88 (app dd, 6H). *Note: This spectrum is that of the 1:1 mixture of diastereomers—all peaks appear to split as "doublets" but it's really just the two diastereomers resolving.*



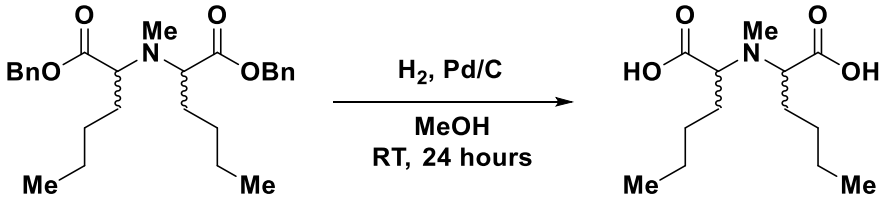
A 40 mL vial was charged with a stir bar and the DEMIDA dibenzyl ester (441.3 mg, 1.151 mmol, 1 eq) was added anhydrous methanol (8.1 mL). The vial was capped and purged for 10 minutes with nitrogen gas bubbling through the solution while stirring. 10% palladium on carbon (21.4 mg) was added by replacing the cap. The vial was purged once more with nitrogen for 10 minutes. One balloon filled with hydrogen gas was bubbled through the reaction mixture. The vial was placed under one balloon of hydrogen for 24 hours with stirring. The balloon was removed and the reaction purged for 20 minutes with nitrogen. The reaction was filtered over a pad of Celite, and washed with methanol (3 x 30 mL). Solvent was removed via rotary evaporation and the compound was placed on the high vacuum, producing a crystalline, white solid (242.8 mg, 100% yield) as a mix of diastereomers. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 3.14 (app dt, 2H), 2.31 (app d, 3H), 1.58 (app ddq, 4H), 0.83 (app td, 6H). *Note: This spectrum is that of the 1:1 mixture of diastereomers—all peaks appear to split as "doublets" but it's really just the two diastereomers resolving.*



This compound was synthesized in a manner analogous to benzyl 2-bromobutyrate using 3.96 mL (25 mmol, 1 eq) of 2-bromohexanoyl bromide. A clear oil (6.884 g, 97% yield) was isolated. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.38 (m, 5H), 5.21 (s, 2H), 4.25 (dd, J = 7.8, 7.0 Hz, 1H), 2.02 (m, 2H), 1.35 (m, 4H), 0.89 (app t, J = 7.0 Hz, 3H).

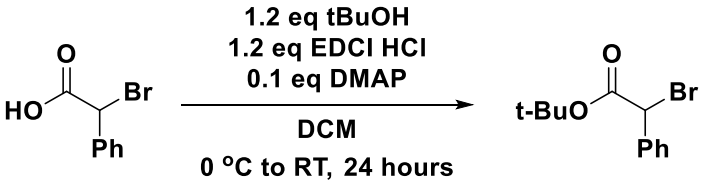


A 20 mL vial with stir bar was charged with potassium carbonate (2.067 g, 14.8 mmol, 5.86 eq) and methylamine hydrochloride salt (203.6 mg, 3.02 mmol, 1 eq). The vial was capped and purged with nitrogen for 10 minutes. Acetonitrile (3.5 mL) and the 2-bromobenzyl ester (2.007 g, 7.01 mmol, 2.3 eq) were added subsequently with stirring via syringe. The nitrogen inlet was removed and the vial was sealed with Teflon tape. The reaction was heated at 82 ºC in a heat block for 8 days. The mixture was filtered over a pad of Celite and washed with ethyl acetate (3 x 35 mL). The solvent was removed via rotary evaporation, producing a pale, yellow oil (1.43 g crude). A gradient silica column was run with 7.5-10% ethyl acetate in hexanes. A clear oil was isolated (709.4 mg, 52% yield) as a mixture of diastereomers. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.34 (m, 10H), 5.04 (app ddd, 4H), 3.40 (app dt, 2H), 2.51 (app d, 3H), 1.71 (m, 4H), 1.26 (m, 8H), 1.84 (td, 6H). *Note: This spectrum is that of the 1:1 mixture of diastereomers—all peaks appear to split as "doublets" but it's really just the two diastereomers resolving.*

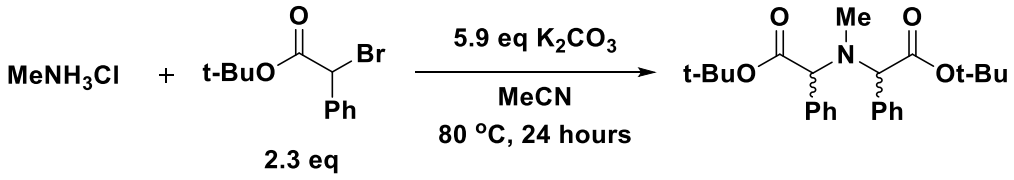


This compound was synthesized in a manner analogous to diethylMIDA using 666.4 mg (1.52 mmol, 1.0 eq) of dibutylMIDA benzyl ester. 388.2 mg (99% yield) of a white crystalline solid was obtained as a mixture of diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.20 (app dt, 2H), 2.32 (app d, 3H), 1.55 (m, 4H), 1.24 (m, 8H), 0.84 (t, 6H). *Note: This spectrum is that of*

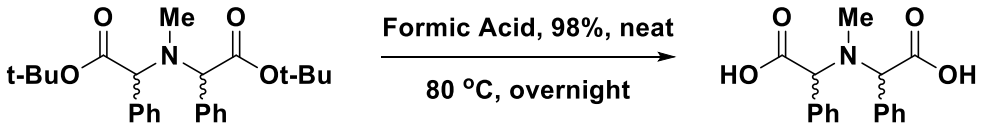
the 1:1 mixture of diastereomers—all peaks appear to split as "doublets" but it's really just the two diastereomers resolving.



A 250 mL Schlenk flask was charged with a stir bar, the 2-bromo acid (6.45 g, 30 mmol, 1 eq), and DMAP (366.5 mg, 3.0 mmol, 0.1 eq). The flask was sealed with a rubber septum and vac/filled three times with nitrogen gas. DCM (110 mL) was added via syringe, producing a yellow, clear solution. Tert-butanol (3.5 mL, 36 mmol, 1.2 eq) was added via syringe and the flask was cooled to 0 ºC in an ice bath for 15 minutes. The septum was removed and EDCI·HCl (6.90 g, 36 mmol, 1.2 eq) was added. DCM (10 mL) was used to wash flask, and the septum was replaced. The water bath was removed, and the reaction was stirred for 24 hours at room temperature. The reaction was quenched with the addition of water (50 mL). The mixture was transferred to a separatory funnel, and the aqueous layer was extracted with ethyl acetate (3 x 50 mL). The organics were washed with brine (50 mL), dried with $MgSO_4$, filtered over a pad of Celite, and solvent was removed via rotary evaporation. Column chromatography (2.5-5% EtOAc/hexanes) gave 1.734 g (21% yield) of a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (dd, 2H), 7.36 (m, 3H), 5.25 (s, 1H), 1.44 (s, 9H).

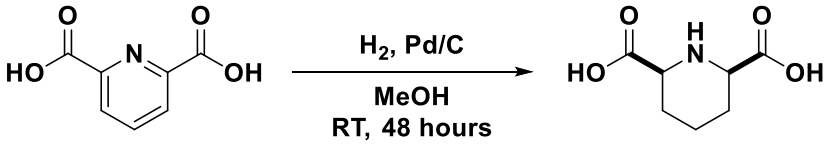


A 20 mL vial with stir bar was charged with potassium carbonate (3.96 g, 28.66 mmol, 5.86 eq) and methylamine hydrochloride salt (338 mg, 4.89 mmol, 1 eq). The vial was capped and purged with nitrogen for 10 minutes. Acetonitrile (5.6 mL) and the 2-bromo-t-butyl ester (3.04 g, 11.25 mmol, 2.3 eq) were added subsequently with stirring via syringe. The nitrogen inlet was removed and the vial was sealed with Teflon tape. The reaction was heated at 80 ºC in a heat block for 24 hours. The mixture was filtered over a pad of Celite and washed with ethyl acetate (3 x 35 mL). The solvent was removed via rotary evaporation, producing a pale, yellow oil. A silica column was run and the product was isolated (1.29 g, 64% yield) as a mixture of diastereomers. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.48 (app dd, 4H), 7.32 (m, 6H), 4.49 (app d, 2H), 3.29 (app d, 3H), 1.44 (app d, 18H). *Note: This spectrum is that of the 1:1 mixture of diastereomers—all peaks appear to split as "doublets" but it's really just the two diastereomers resolving.*

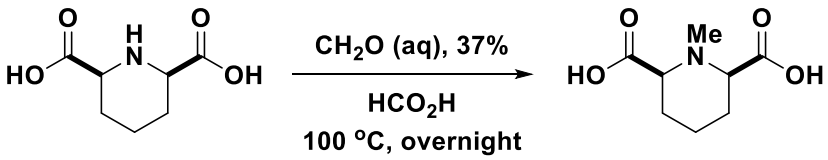


A 20 mL vial was charged with a stir bar, the DPMIDA di-t-butyl ester (1.29 g, 3.12 mmol, 1 eq), and formic acid (3.1 mL, 82.6 mmol, 26 eq). The vial was capped and stirred at 80 ºC overnight. The reaction mixture was cooled, and transferred to a 100 mL RBF. The formic acid was removed via rotary evaporation, producing a light brown solid. Methanol (around 4 mL) was added to the solid, creating a suspension. The suspension was sonicated, and five

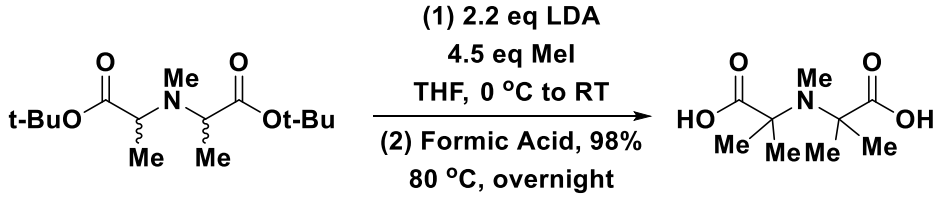
volumes of acetone (20 mL) were added dropwise to the stirring suspension over 15 minutes. The mixture was vacuum filtered over filter paper. The resulting solid was transferred to a 20 mL vial and placed on high vacuum for one hour. The diacid was isolated as a white crystalline solid (515.7 mg, 55% yield), and as a single diastereomer. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 7.40 (m, 8H), 7.33 (m, 2H), 4.51 (s, 2H), 3.33 (s, 18H), 2.03 (s, 3H).



2,6-Pyridinedicarboxylic acid (1.50 g, 9.00 mmol) was placed into a 100 mL recovery flask along with MeOH (28 mL). The mixture was then degassed by bubbling nitrogen through it with stirring for 10 minutes. Pd/C (150 mg, 10 wt%, wet, Degussa type) was then added in a single portion before sealing the flask with a rubber septum and Teflon tape. Hydrogen gas was then bubbled through the solution with stirring for ~10 minutes (1 balloon) before being placed under an atmosphere of hydrogen (3 balloons simultaneously) and stirred for a total of 48 hours. The mixture was then degassed by bubbling nitrogen through it as before (10 minutes) before filtering over Celite and washing with MeOH (500 mL). Solvent was removed under vacuum and the resulting solid was recrystallized from water to give 851.4 mg (55% yield) of flaky off-white crystals. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 3.43 (dd, 2H), 2.03 (m, 2H), 1.79 (m, 1H), 1.49 (m, 3H).



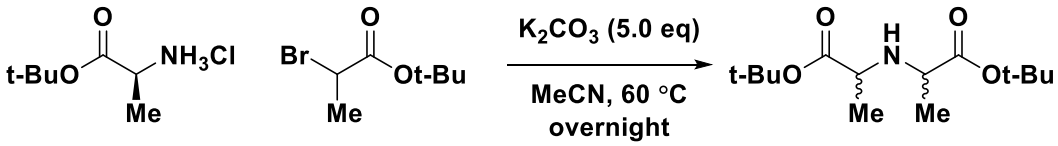
Cis-2,6-piperidinedicarboxylic acid (173 mg, 1.0 mmol) , formalin (5.0 mL) and formic acid (75 µL, 2.0 mmol) were placed in a 20 mL vial under ambient atmosphere. This vial was sealed and placed in a 100 °C heat block and allowed to stir overnight. The reaction was then cooled to room temperature and rinsed into an Erlenmeyer flask with water (5 mL). Acetone (50 mL) was added with stirring, causing a slight amount of precipitation. Diethyl ether (50 mL) was then added with stirring, causing more significant precipitation. The solid was then collected by vacuum filtration and dried under high vacuum overnight, yielding 52.1 mg (28% yield) of a white crystalline solid. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 2.79 (dd, 2H), 2.18 (s, 3H), 1.81 (dd, 2H), 1.74 (m, 1H), 1.49 (qd, 2H), 1.33 (qt, 1H).



To a solution of DIPA (3.22 mL, 23.0 mmol, 2.2 eq) in THF (26 mL) under nitrogen at -78 ºC was added *n*-BuLi (14.35 mL, 1.6 M in hexanes, 22.96 mmol, 2.2 eq) dropwise over 5 minutes. The reaction was placed in an ice bath and stirred at 0 ºC for 25 minutes, giving a light yellow homogenous solution. Substrate was added as a solution in THF (26 mL) over ~15 minutes. After stirring at 0 °C for 30 minutes, methyl iodide (2.92 mL, 47.0 mmol, 4.5 eq) was added dropwise over 5 minutes. The ice bath was then removed and the reaction was warmed to room temperature. Precipitate formed and TLC (10% EtOAc/hexanes, $KMnO_4$) showed

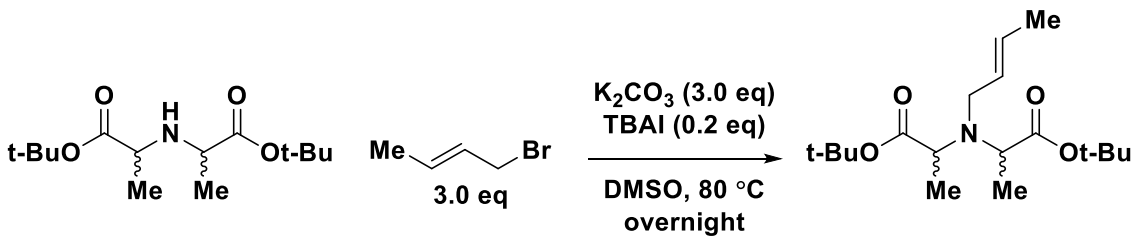
complete conversion. The reaction was then quenched with NH_4Cl solution (25 mL), extracted with EtOAc (3 x 50 mL), dried over sodium sulfate, filtered, and concentrated under vacuum to a yellow oil with some solids suspended in it. This was taken on to the next step without further purification.

To the crude intermediate from the above reaction was added 10.5 mL 98% formic acid while transferring to a capped 40 mL vial. The homogenous solution was stirred at 80 °C overnight. The reaction was then concentrated under vacuum to a brown solid. This solid was dissolved in ~18 mL water with heating, and this solution was then washed once with 20 mL DCM. Residual DCM in the aqueous layer was blown off under a nitrogen stream. In an Erlenmeyer flask, 100 mL of acetone was added to this solution to induce crystallization. After 30 minutes stirring in an ice bath, the solids were collected by filtration and dried under high vacuum to give a white solid (1.48 g, 70% yield) over two steps. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 2.37 (s, 3H), 1.34 (s, 12H).



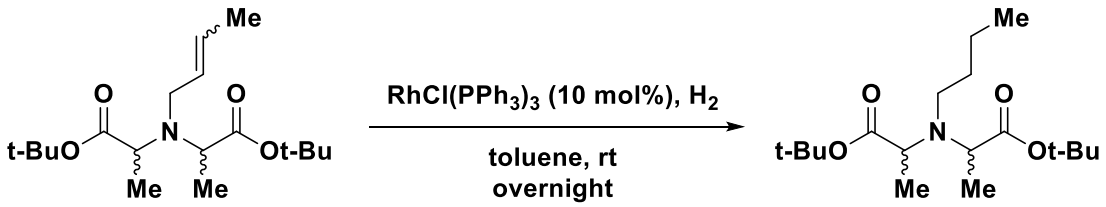
Potassium carbonate (28.53 g, 206.4 mmol, 5.0 eq) and tert butyl alanine ester hydrochloride (7.50 g, 41.3 mmol, 1.0 eq) were placed into a 500 mL round bottom flask, followed by MeCN (200 mL) and tert butyl 2-bromopropionate (10.36 g, 49.5 mmol, 1.2 eq). A reflux condenser was placed was placed on top of the flask and the reaction was purged with nitrogen for five minutes before being sealed with a septum pierced with a nitrogen inlet needle. The flask was then placed in a 60 °C oil bath and stirred overnight. The next day, the reaction was cooled and filtered through Celite, rinsing copiously with EtOAc (2x100 mL). The crude

mixture was then loaded onto Celite via rotovap and placed atop a silica gel column equilibrated with 5% EtOAc/hexanes. Purified by gradient column (5 to 10 to 15% EtOAc/hexanes, 9 cm width by 10 cm height column) to yield 8.31 grams of a colorless oil. ^{1}H-NMR (500 MHz, $CDCl_3$): 3.24 (app dq, 2H), 2.19 (br s, 1H), 1.44 (app d, 18H), 1.25 (app dd, 6H). *Note: This spectrum is that of the 1:1 mixture of diastereomers—all peaks appear to split as "doublets" but it's really just the two diastereomers resolving.*

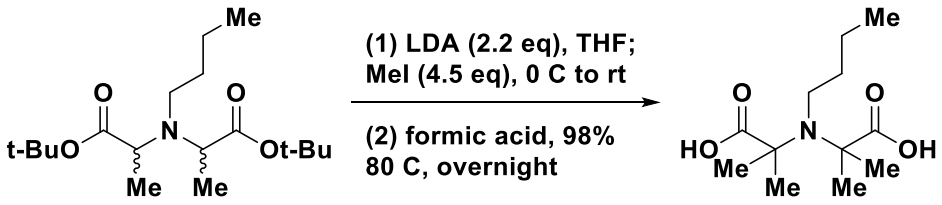


A 200 mL round bottom flask was charged with potassium carbonate (2.07 g, 15.0 mmol, 3.0 eq) and tetrabutylammonium iodide (369.4 mg, 1.00 mmol, 0.2 mmol). The flask was then fit with a rubber septum and vacuum/N_2 filled (3x). DMSO (50 mL) was then added via syringe, followed by the amine (1.37 g, 5.00 mmol, 1.0 eq, added via syringe). After stirring briefly, crotyl bromide (2.03 g, 15.0 mmol, 3.0 eq) was added dropwise via syringe before placing the flask in an 80 °C oil bath and stirring overnight. The next day, the reaction was cooled and poured into a separatory funnel containing water (100 mL) and EtOAc (100 mL). After shaking and separation, the aqueous layer was extracted with EtOAc (2x100 mL). The combined organic layers were washed with water (2x50 mL) to remove DMSO, followed by brine (50 mL). The organic layer was then dried over $MgSO_4$, filtered, and concentrated to a viscous pale yellow oil. Column chromatography (10 to 20% EtOAc/hexanes) gave the product as a complex mixture of diastereomers and *E/Z* isomers (due to impure crotyl bromide). 1.02 g, 62% yield. ^{1}H-NMR (500 MHz, $CDCl_3$): 5.62-5.54 (app m, 1H), 5.43-5.35 (app m, 1H), 3.59-3.53 (app m, 2H), 3.48-3.33

(app m, 2H), 1.68 (app dp, 3H), 1.45-1.44 (app m, 18H), 1.26-1.22 (app m, 6H). *Note: This mixture is inconsequential for our purposes as the double bond will be hydrogenated and the stereocenters will later be made non-stereogenic.*



Wilkinson's catalyst (197.8 mg, 0.214 mmol, 10 mol%) was massed into a 40 mL vial under ambient atmosphere (this batch of catalyst had been stored under air). The vial was then vaccum/N_2 filled (3x) before adding the substrate (700 mg, 2.14 mmol, 1.0 eq) as a solution in toluene (20 mL). Hydrogen gas was then bubbled through the solution via balloon (1 balloons worth, ~10 minutes, through a 20 gauge needle). The vial was then placed under a hydrogen atmosphere (balloon). Reaction was stirred for five days (for convenience). The solution and vial were then purged with nitrogen for 10 minutes before filtering the solution through Celite, washing with acetone. The solution was then concentrated and the resulting oil was purified by column chromatography (5 to 10% EtOAc/hexanes) to give 368 mg (52% yield) of a colorless oil. ^{1}H-NMR (500 MHz, $CDCl_3$): 3.52 (app dq, 2H), 2.77 (app ddd, 2H), 1.44 (app s, 18H), 1.37 (app m, 2H), 1.28 (app m, 2H), 1.23 (app dd, 6H), 0.88 (app s, 3H). *Note: This spectrum is that of the 1:1 mixture of diastereomers—all peaks appear to split as "doublets" but it's really just the two diastereomers resolving.*

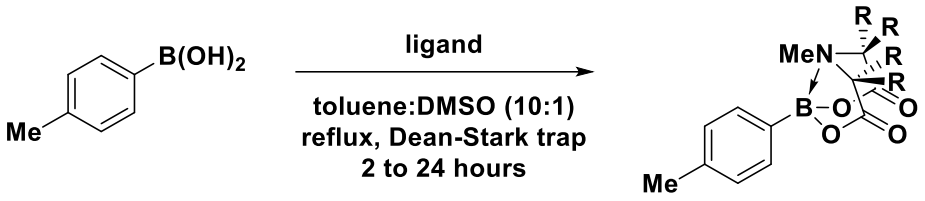


A flame dried 50 mL Schlenk flask was charged with THF (5.0 mL) and freshly distilled diisopropylamine (445 µL, 3.20 mmol). The flask was then cooled in a ice-water bath for 10 minutes before adding *n*BuLi (1.6 M in hexanes, 1.98 mL, 3.17 mmol) dropwise via syringe. After stirring for 5 minutes in the ice-water bath, the diester substrate (347.6 mg, 1.05 mmol) was added dropwise via syringe as a solution in THF (5.0 mL) over the course of ~10 minutes. The reaction was then allowed to stir in the ice-water bath for 30 minutes, taking on a pale yellow color. Methyl iodide, neat (395 µL, 6.33 mmol) was then added dropwise via syringe over the course of ~ 5 minutes. The reaction was then stirred in the ice-water bath for 2 hours before removing the bath and allowing it to stir and warm to room temperature. After stirring another hour, TLC indicated complete conversion (10% EtOAc/hexanes). The reaction was then quenched by addition of 1:1 water:sat. NH_4Cl (10 mL). The mixture was then added to a separatory funnel containing EtOAc (10 mL) and water (5 mL). After shaking and separating, the aqueous layer was extracted with EtOAc (3x10 mL). The combined organic layers were then dried with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated to give a deep orange oil. Crude ^{1}H NMR indicated the desired product as the primary component (~>90%). This material was used in the next step without further purification.

The crude orange oil from the previous step was transferred to a 7 mL vial using formic acid (2x1.0 mL). The vial was then sealed and placed in a 80 °C heat block and allowed to stir overnight. The next day, the mixture was transferred to a 50 mL recovery flask using DCM (2x1.5 mL) and was concentrated via rotovap (50 °C water bath, ~1 hour) to a deep brown

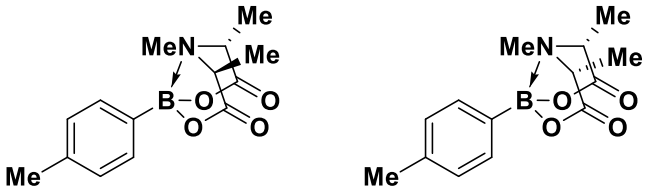
chunky solid. The flask was then placed on high vac for 3 hours to remove residual formic acid. The brown solid was then taken up in a minimum of water with warming via heat gun (~4.0 mL). The solution was then cooled to room temperature (some precipitate formed) before being washed with DCM (4.0 mL), removing much of the brown color. The aqueous layer was then placed on the rotovap to remove residual DCM, before adding 25 mL acetone with vigorous stirring, causing precipitation of the product. The mixture was capped and stirred in an ice bath for 30 minutes before filtered and washing the solid with acetone (2x10 mL). The solid was collected and placed on high vac overnight, giving 154 mg of a white solid (60% yield over two steps). ^{1}H-NMR (500 MHz, DMSO-d_6): 2.75 (app m, 2H), 1.52 (app m, 2H), 1.35 (s, 12H), 1.19 (app m, 2H), 0.86 (t, J = 7.3 Hz, 3H).

Boronate Synthesis

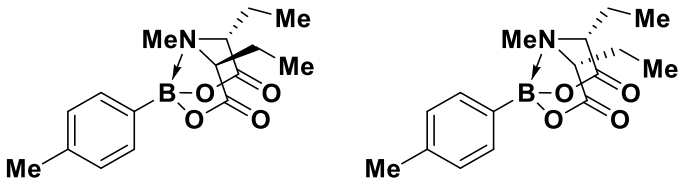


General Procedure for the Synthesis of *p*-tolyl MIDA Boronate Derivatives. Under ambient atmosphere, a recovery flask containing a stir bar was charged with *p*-tolylboronic acid and ligand. To this was added a given volume 10:1 solvent mixture of toluene and DMSO before fitting the flask with a Dean-Stark trap (prefilled with toluene) and condenser. This flask was then stirred in a 110-120 °C oil bath with azeotropic removal of water until TLC indicated consumption of starting material. The reaction mixture was then cooled and poured into a separatory funnel containing containing water (five times the reaction volume) and EtOAc (five times the reaction volume). After shaking and phase separation, the aqueous layer was extracted twice with EtOAc (five times the reaction volume). The combined organic layers were then

washed sequentially with water, 1:1 water:brine, and brine (five times the reaction volume each), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting solid was then purified by column chromatography, crystallization, or a combination thereof. In the cases where diastereomers were possible, the two isomers were separated by column chromatography.

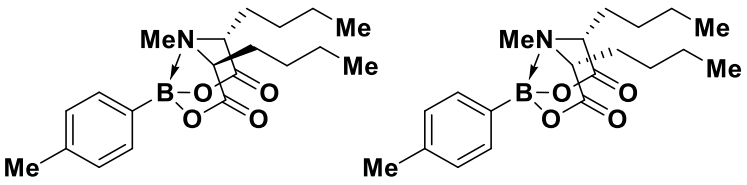


The general procedure was followed using dimethylMIDA (200 mg, 1.14 mmol, 1.0 eq), *p*-tolylboronic acid (1.2 eq), and 12 mL 10:1 toluene:DMSO. The resulting mixture of product diastereomers was purified by two rounds of column chromatography (10% to 20% to 30% acetone/hexanes) to give 95.7 mg (30% yield) of the out-out and 107.3 mg (34% yield) of the in-out diastereomers respectively. ^{1}H-NMR (500 MHz, acetone-d_6): [out-out diastereomer] δ 7.42 (d, *J* = 7.9 Hz, 2H), 7.18 (d, *J* = 7.7 Hz, 2H), 4.18 (q, *J* = 7.3 Hz, 2H), 2.46 (s, 3H), 2.32 (s, 3H), 1.49 (d, *J* = 7.3 Hz, 6H). [in-out diastereomer] δ 7.40 (d, *J* = 7.9 Hz, 2H), 7.18 (d, *J* = 7.8 Hz, 2H), 4.25 (q, *J* = 7.1 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 1H), 2.47 (s, 3H), 2.32 (s, 3H), 1.60 (d, *J* = 7.0 Hz, 3H), 1.56 (d, *J* = 7.1 Hz, 3H).

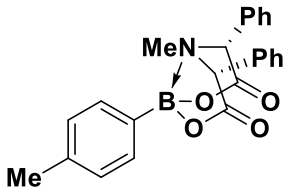


The general procedure was followed using diethylMIDA (210.6 mg, 1.04 mmol, 1.0 eq), *p*-tolylboronic acid (211.3 mg, 1.55 mmol, 1.5 eq), and 10 mL of a 95:5 toluene:DMSO solvent mixture. Column chromatography (0 to 2% MeOH/DCM) gave 95.8 mg (30% yield) of the out-

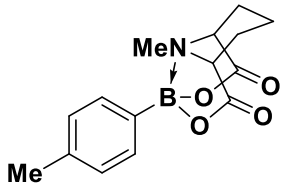
out and 123.4 mg (40% yield) of the in-out diastereomers respectively. ^{1}H-NMR (500 MHz, DMSO-d_6): [out-out diastereomer] δ 7.41 (d, *J* = 7.9 Hz, 2H), 7.17 (d, *J* = 7.7 Hz, 2H), 3.90 (dd, *J* = 9.9, 5.5 Hz, 2H), 2.49 (s, 3H), 2.32 (s, 3H), 1.99 (m, 2H), 1.84 (m, 2H) 1.21 (t, *J* = 7.4 Hz, 6H). [in-out diastereomer] δ 7.39 (d, *J* = 7.8 Hz, 2H), 7.17 (d, *J* = 7.4 Hz, 2H), 3.91 (dd, *J* = 7.3, 6.0 Hz, 1H), 3.83 (dd, *J* = 9.5, 4.3 Hz), 2.50 (s, 3H), 2.32 (s, 3H), 2.13-2.00 (m, 2H), 2.01-1.92 (m, 2H), 1.33 (t, *J* = 7.4 Hz, 3H), 1.30 (t, *J* = 7.4 Hz, 3H).



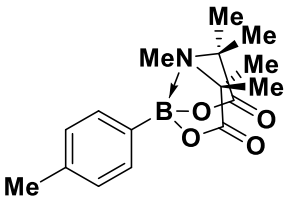
The general procedure was followed using dibutylMIDA (354.1 mg, 1.37 mmol, 1.0 eq), *p*-tolylboronic acid (278.4 mg, 2.05 mmol, 1.5 eq), and 13 mL of a 95:5 toluene:DMSO solvent mixture. Column chromatography (0 to 2% MeOH/DCM) gave 109.5 mg (22% yield) of the out-out and 265.1 mg (54% yield) of the in-out diastereomers respectively. ^{1}H-NMR (500 MHz, DMSO-d_6): [out-out diastereomer] δ 7.48 (d, *J* = 7.8 Hz, 2H), 7.29 (d, *J* = 7.4 Hz, 2H), 3.87 (dd, *J* = 9.2, 6.2 Hz, 2H), 2.44 (s, 3H), 2.42 (s, 3H), 1.84 (m, 6H), 1.48 (m, 6H), 1.02 (t, *J* = 7.3 Hz, 6H). [in-out diastereomer] δ 7.40 (d, *J* = 7.8 Hz, 2H), 7.17 (d, *J* = 7.2 Hz, 2H), 3.96 (dd, 1H), 3.86 (dd, 1H), 2.53 (s, 3H), 2.32 (s, 3H), 1.98 (m, 6H), 1.60 (m, 2H), 1.43 (m, 4H), 0.95 (t, *J* = 7.4 Hz, 3H), 0.93 (t, *J* = 7.4 Hz, 3H).



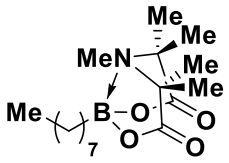
The general procedure was followed using diphenylMIDA (515.7 mg, 1.72 mmol, 1 eq), *p*-tolylboronic acid (349.6 mg, 2.58 mmol, 1.5 eq), and 16.4 mL of a 95:5 toluene:DMSO solvent mixture. Column chromatography (0 to 2% MeOH/DCM) gave the in-out diastereomer (285.6 mg, 42% yield) as a white crystalline solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.70 (d, 2H), 7.60 (m, 1H), 7.52 (m, 4H), 7.23 (m, 3H), 7.04 (m, 2H), 6.37 (d, 2H), 5.75 (s, 1H), 5.64 (s, 1H), 2.35 (s, 3H), 2.16 (s, 3H).



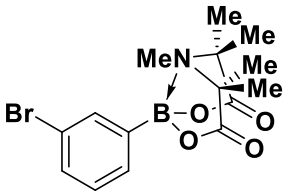
The general procedure was followed using SchMIDA (49.6 mg, 0.26 mmol, 1.2 eq), *p*-tolylboronic acid (30.0 mg, 0.22 mmol, 1.0 eq), and 11 mL of a 10:1 toluene:DMSO solvent mixture. Column chromatography (30 to 40 to 50% acetone/hexanes) gave 41.2 mg (65% yield) of a white crystalline solid. ^{1}H-NMR (500 MHz, acetone-d_6): δ 7.49 (d, 2H), 7.32 (d, 2H), 3.89 (t, 2H), 2.58 (s, 3H), 2.45 (s, 3H), 2.17 (m, 4H), 1.86 (m, 2H).



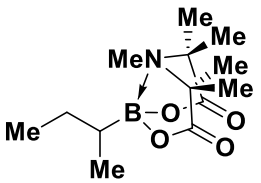
The general procedure was followed using TIDA (89.4 mg, 0.443 mmol, 1.1 eq), *p*-tolylboronic acid (54.4 mg, 0.403 mmol, 1.0 eq), and 4 mL of a 95:5 toluene:DMSO solvent mixture. Column chromatography (20 to 40% acetone/hexanes) gave 67.5 mg (55% yield) of a white crystalline solid. ^{1}H-NMR (500 MHz, acetone-d_6): δ 7.45 (d, 2H), 7.16 (d, 2H), 2.67 (s, 3H), 2.31 (s, 3H), 1.77 (s, 6H), 1.54 (s, 6H).



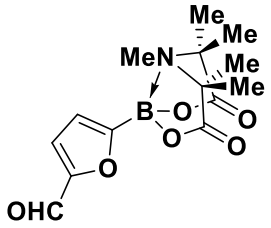
The general procedure was followed using TIDA (402.4 mg, 1.98 mmol, 1.1 eq), octylboronic acid (284.5 mg, 1.8 mmol, 1.0 eq), and 19.8 mL of a 10:1 toluene:DMSO solvent mixture. Trituation of the crude product with 1:1 diethyl ether:hexanes (3x5 mL) gave 478.1 mg (82% yield) of a white solid. ^{1}H-NMR (500 MHz, acetone-d6): δ 2.72 (s, 3H), 1.70 (s, 6H), 1.60 (s, 6H), 1.42 (br m, 2H), 1.30 (br m, 10H), 0.88 (t, *J* = 6.9 Hz, 3H), 0.63 (m, 2H). Slow evaporation from THF in a 7 mL vial covered with a kimwipe gave crystals suitable for single crystal x-ray analysis.



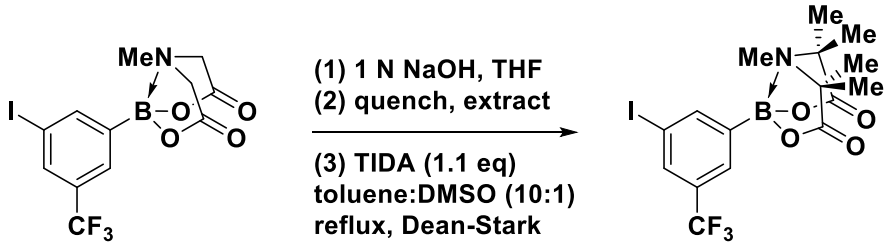
The general procedure was followed using TIDA (335.3 mg, 1.65 mmol, 1.1 eq), *m*-bromophenylboronic acid (301.2 mg, 1.5 mmol, 1.0 eq), and 16.5 mL of a 10:1 toluene:DMSO solvent mixture. Trituration with 1:1 diethyl ether:hexanes (3x5 mL) gave 302.3 mg (55% yield) of a white solid. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.68 (s, 1H), 7.49 (app dd, 2H), 7.22 (t, *J* = 7.7 Hz, 1H), 2.50 (s, 3H), 1.79 (br s, 6H), 1.54 (br s, 6H).



The general procedure was followed using TIDA (335.3 mg, 1.65 mmol, 1.1 eq), *rac-sec*-butylboronic acid (152.9 mg, 1.5 mmol, 1.0 eq), and 15 mL of a 10:1 toluene:DMSO solvent mixture. Trituration with 1:1 diethyl ether:hexanes (3x5 mL) gave 183.5 mg (45% yield) of a white solid. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.60 (s, 3H), 1.72 (d, *J* = 21.2 Hz, 6H), 1.61 (d, *J* = 8.9 Hz, 6H), 1.54 (m, 1H), 1.29 (ddt, *J* = 16.0, 14.1, 7.4 Hz, 1H), 0.93 (app t, 6H), 0.77 (br m, 1H).



The general procedure was followed using TIDA (335.3 mg, 1.65 mmol, 1.1 eq), 5-formyl-2-furylboronic acid (209.9 mg, 1.50 mmol, 1.0 eq), and 15 mL of a 10:1 toluene:DMSO solvent mixture. Trituration with 1:1 diethyl ether:hexanes (3x5 mL) gave 170.2 mg of an off-white solid of ~85% purity (31% yield) by proton NMR. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 9.67 (s, 1H), 7.22 (d, *J* = 3.5 Hz, 1H), 6.94 (d, *J* = 3.5 Hz, 1H), 2.62 (s, 3H), 1.79 (br s, 6H), 1.62 (s, 6H).



Under ambient atmosphere, a 40 mL vial was charged with 3-iodo-5-(trifluoromethyl)phenyl MIDA boronate (500 mg, 1.17 mmol, 1.0 eq) and a stir bar. To this was added THF (7.5 mL), followed by aqueous NaOH (1 N, 3.5 mL, 3.5 mmol, 3.0 eq). The vial was capped and stirred vigorously for 15 minutes. TLC (20% acetone/hexanes) showed complete

conversion, so the reaction was quenched via the addition of sat. NH_4Cl (10 mL). The crude mixture was then partitioned between EtOAc (20 mL) and water (20 mL). The aqueous layer was then extracted with EtOAc (3x20 mL). The combined organics were then washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated. The resulting wet solid was azeotroped with toluene (2x20 mL) until a minimum volume of toluene remained with solids suspended within it (~3 mL). To this crude solution of boronic acid in a 50 mL recovery flask was added toluene (15 mL) and DMSO (1.5 mL), followed by TIDA (261.3 mg, 1.29 mmol, 1.1 eq). The flask was then fit with a Dean-Stark trap (prefilled with toluene) and a condenser. The flask was then refluxed with azeotropic removal of water for 3 hours. TLC (20% acetone/hexanes) showed complete conversion. The reaction was then worked up as in the general procedure and the resulting solid was triturated with 1:1 diethyl ether:hexanes (3x5 mL) to give 482.0 mg (85% yield) of a white solid. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.07 (s, 1H), 7.95 (s, 1H), 7.75 (s, 1H), 2.50 (s, 3H), 1.81 (br s, 6H), 1.55 (br s, 6H).

Hydrolysis Assay

The following assay was developed based upon conditions previously reported by Knapp et al.[21]

To each of twelve 1 mL conical vials equipped with stirring vanes was added 100 µL (0.08 M, 0.008 mmol) of a THF-d_8 solution of the indicated boronate, followed by 20 µL (3.0 M, 0.06 mmol, 7.5 eq) of a D_2O solution of K_3PO_4. Each vial was then capped, shaken briefly to mix, and then stirred in a 60 °C heat block at 800 RPM. At the indicated times, two vials were removed from the heat block, cooled briefly under a stream of air, and then had 680 µL DMSO-d_6 containing 1,4-dimethoxybenzene (~0.008 M) as an internal standard added. The vials were then again briefly capped, shaken to mix, and the solutions were then immediately transferred to

NMR tubes and spectra were taken (16 scans, d1 = 10 s). Time points were taken at 0, 0.5, 1, 1.5, 2.0, 4.0, and 6.0 hours. The solutions for the 0 time points were made directly in the NMR tubes, shaken, and then had spectra obtained. The percentage boronate remaining was determined by average the integration of the aryl protons (which fully resolved from the corresponding aryl protons on the parent boronic acid) across the two runs, except in the case of octyl TIDA boronate, for which the terminal methyl group of the octyl chain was used.

In all cases, each time point represents the average of *n*=2 experiments, except in the case of the *N*-Cy and *N*-iPr MIDA, for which *n*=1.

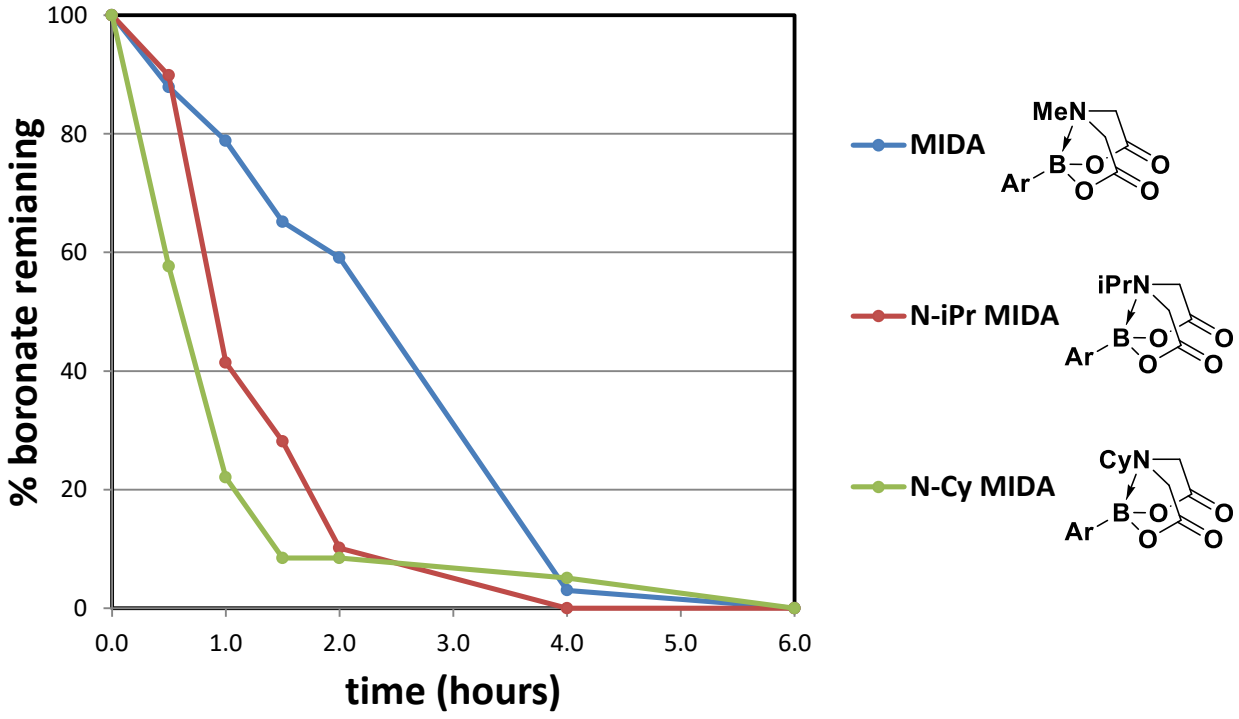


Figure 3.11. Hydrolysis behavior of MIDA derivatives modified at nitrogen

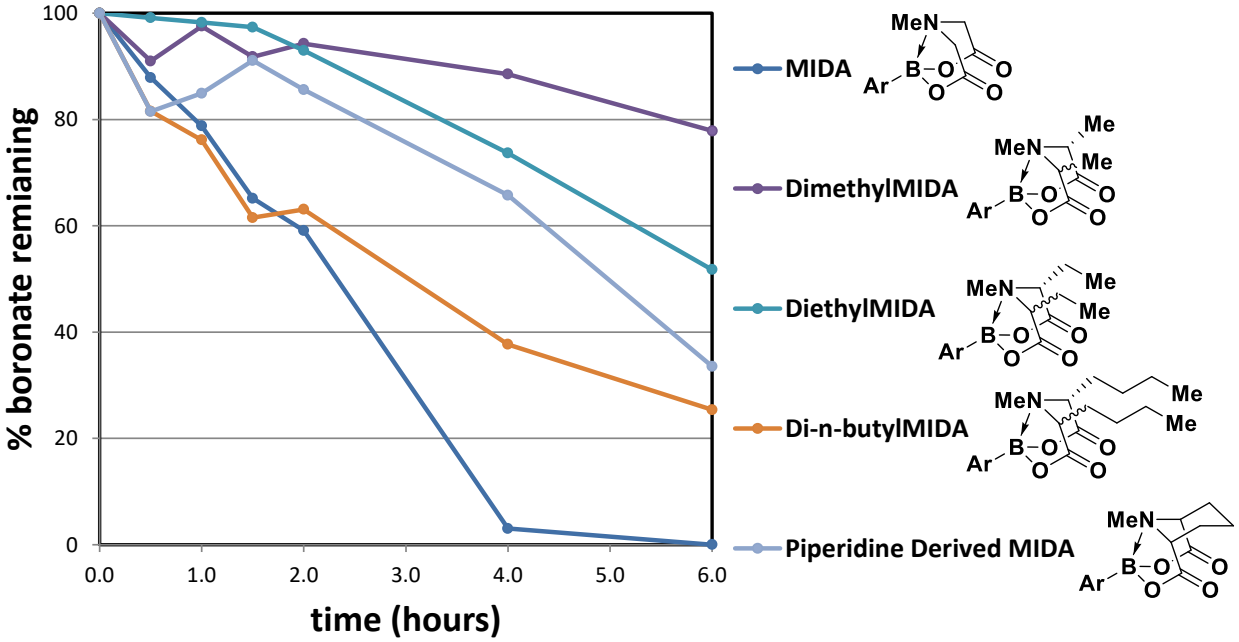


Figure 3.12. Hydrolysis behavior of MIDA derivatives modified at the backbone methylenes

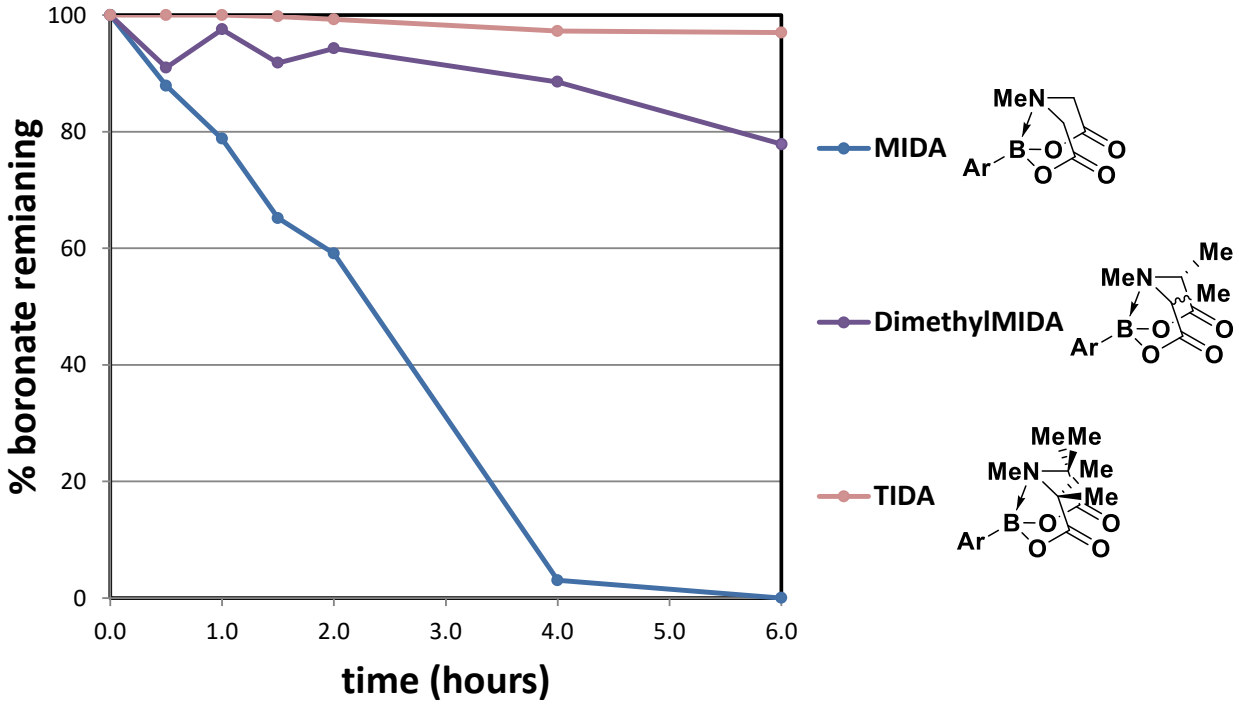


Figure 3.13. Hydrolysis behavior of MIDA, DimethylMIDA, and TetramethylMIDA (TIDA)

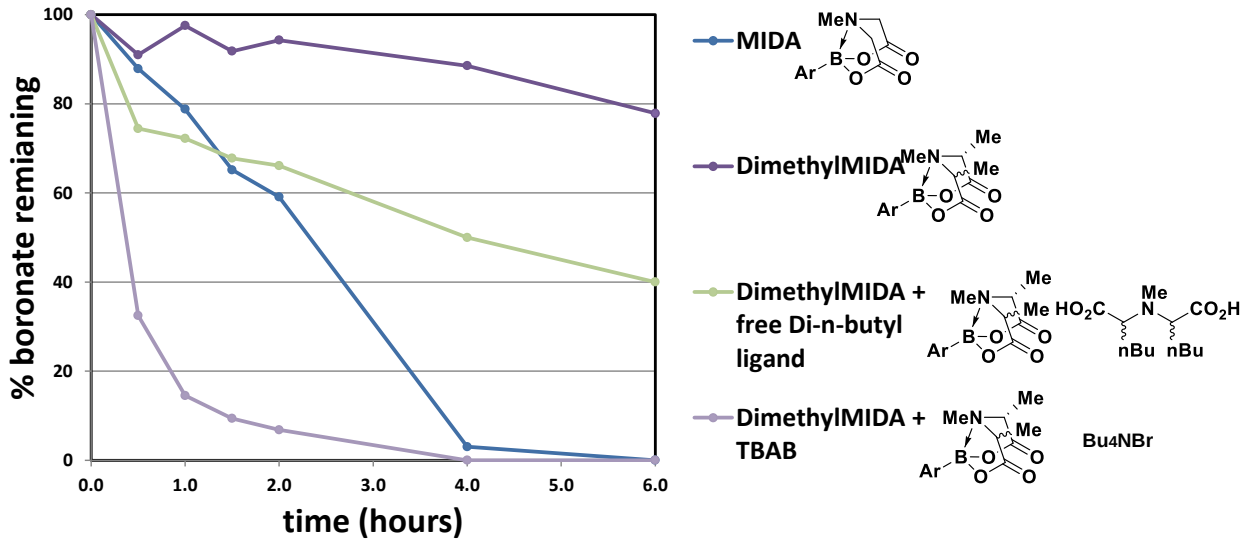
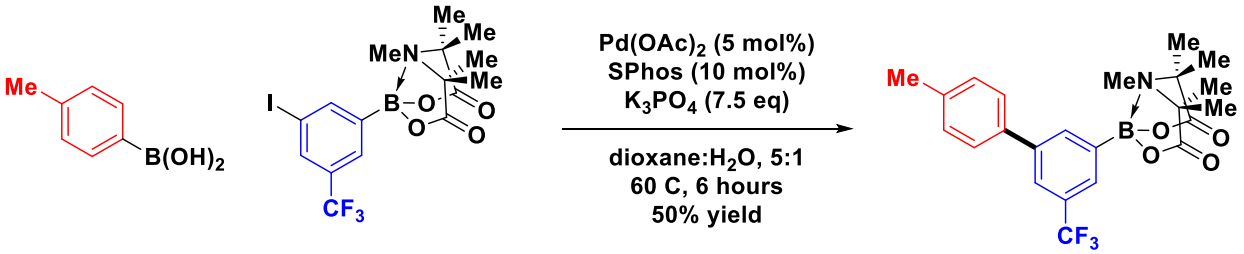


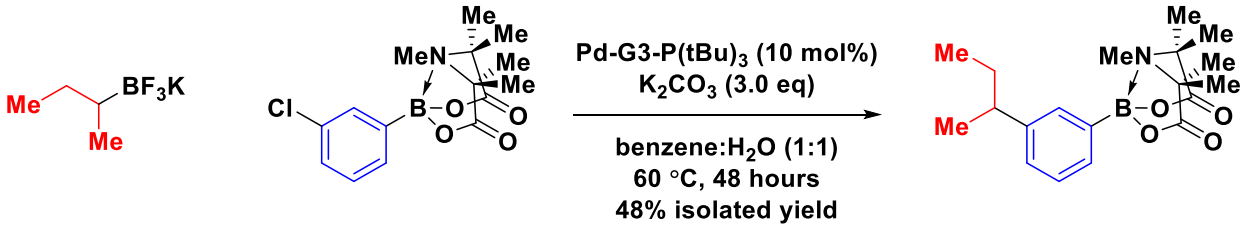
Figure 3.14. Evidence for phase transfer effects in the hydrolysis of MIDA boronates and derivatives

Coupling Reactions



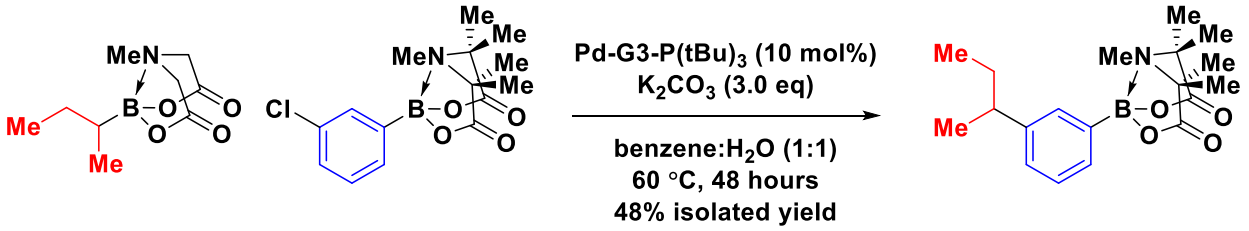
Under ambient atmosphere, $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 5 mol%), SPhos (20.5 mg, 0.05 mmol, 10 mol%), 3-iodo-5-(trifluoromethyl)phenyl TIDA boronate (241.5 mg, 0.5 mmol, 1.0 eq), and *p*-tolylboronic acid (81.6 mg, 0.6 mmol, 1.2 eq) were charged into a 40 mL vial containing a stir bar. The vial was then sealed with a PTFE-lined septum screw cap and wrapped with Teflon tape. The vial was then placed under vacuum and back filled nitrogen three times before adding dioxane (7.25 mL). The mixture was then stirred at room temperature for 10 minutes, giving a deep red homogenous solution. Aqueous K_3PO_4 (1.25 mL, 3.0 M, 3.75 mmol, 7.5 eq) was then added via syringe and the vial was placed in a 60 °C heat block and allowed to

stir for 6 hours. At this point, TLC (20% acetone/hexanes, $KMnO_4$) appeared to indicate no conversion; however it was later determined that the starting material and product co-elute. The reaction mixture was partitioned between EtOAc (30 mL) and water (30 mL). The aqueous layer was extracted with EtOAc (3x30 mL). The combined organics were then washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Crude ^{1}H NMR showed product as the main component of the resulting solid. The solid was then adsorbed onto Celite from an acetone solution and then placed atop a silica gel column equilibrated with 20% acetone/hexanes. Column chromatography (20% to 30% to 40% acetone/hexanes) gave 110.7 mg (50% yield) of a white solid. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.92 (s, 1H), 7.80 (s, 1H), 7.74 (s, 1H), 7.48 (d, *J* = 8.1 Hz, 2H), 7.27 (d, 2H, overlaps with solvent), 2.53 (s, 3H), 2.41 (s, 3H), 1.83 (br s, 6H), 1.57 (br s, 6H).



On the benchtop, *meta* chlorophenylTIDA boronate (64.7 mg, 0.20 mmol, 1.0 eq), potassium 2-butyltrifluoroborate (49.2 mg, 0.30 mmol, 1.5 eq), potassium carbonate (82.9 mg, 0.60 mmol, 3.0 eq), and $P(tBu)_3$ third generation Buchwald precatalyst (11.4 mg, 0.02 mmol, 10 mol%) were weighed into a 7 mL vial. The vial was sealed with a septum cap and vacuum/N_2 filled (3x). Benzene (400 µL) and water (400 µL) were then added via syringe. The nitrogen inlet needle was then removed and the septum was covered with electrical tape before placing the vial in a 60 °C heat block and stirring for 48 hours. The reaction was then cooled and transferred to a separatory funnel containing EtOAc (10 mL) and sat. NH_4Cl (10 mL). After shaking and

separation, the aqueous layer was extracted with EtOAc (2x10 mL). The combined organic layers were dried with brine (10 mL), $MgSO_4$, filtered, and concentrated to give a yellow solid. This solid was loaded onto Celite and purified by column chromatography (20 to 30 to 40% acetone/hexanes) to give 33.2 mg (48% yield) of a white solid. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.38-7.33 (m, 2H), 7.29-7.24 (m, 1H, overlaps with solvent), 7.19-7.15 (m, 1H), 2.57 (app br q, *J* = 7.0 Hz, 1H), 2.47 (s, 3H), 1.79 (br s, 6H), 1.62-1.50 (m, 8H), 1.21 (d, *J* = 6.9 Hz, 3H), 0.78 (t, *J* = 7.3 Hz, 3H).



On the benchtop, *meta* chlorophenylTIDA boronate (64.7 mg, 0.20 mmol, 1.0 eq), 2-butylMIDA boronate (63.9 mg, 0.30 mmol, 1.5 eq), potassium carbonate (82.9 mg, 0.60 mmol, 3.0 eq), and $P(tBu)_3$ third generation Buchwald precatalyst (11.4 mg, 0.02 mmol, 10 mol%) were weighed into a 7 mL vial. The vial was sealed with a septum cap and vacuum/N_2 filled (3x). Benzene (400 µL) and water (400 µL) were then added via syringe. The nitrogen inlet needle was then removed and the septum was covered with electrical tape before placing the vial in a 60 °C heat block and stirring for 48 hours. The reaction was then cooled and transferred to a separatory funnel containing EtOAc (10 mL) and sat. NH_4Cl (10 mL). After shaking and separation, the aqueous layer was extracted with EtOAc (2x10 mL). The combined organic layers were dried with brine (10 mL), $MgSO_4$, filtered, and concentrated to give a yellow solid. This solid was loaded onto Celite and purified by column chromatography (20 to 30 to 40% acetone/hexanes) to give 17.5 mg (25% yield) of a white solid. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.38-7.33 (m, 2H), 7.29-7.24 (m, 1H, overlaps with solvent), 7.19-7.15 (m, 1H), 2.57 (app br q, *J*

= 7.0 Hz, 1H), 2.47 (s, 3H), 1.79 (br s, 6H), 1.62-1.50 (m, 8H), 1.21 (d, *J* = 6.9 Hz, 3H), 0.78 (t, *J* = 7.3 Hz, 3H).

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