

FASTER AUTOMATED ITERATIVE C-C BOND FORMATION

RELATED APPLICATIONS

This application claims the benefit of priority to U.S. Provisional Patent Application
 5 No. 63/533,412, filed August 18, 2023; and U.S. Provisional Patent Application No.
 63/673,311, filed July 19, 2024.

GOVERNMENT SUPPORT

This invention was made with government support under 2019897 awarded by the
 10 National Science Foundation. The government has certain rights in the invention.

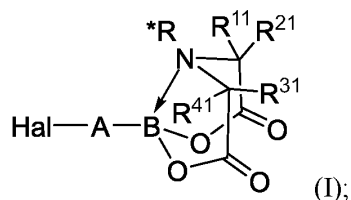
BACKGROUND OF THE INVENTION

Automated iterative small molecule synthesis has the potential to advance and
 democratize the discovery of new medicines, materials, and many other classes of functional
 15 chemical matter. But to date this approach has been limited by a requirement of about one day
 of time per C-C bond-forming step. Accordingly, there is a need for methods shortening the
 time for each C-C bond-forming step.

SUMMARY OF THE INVENTION

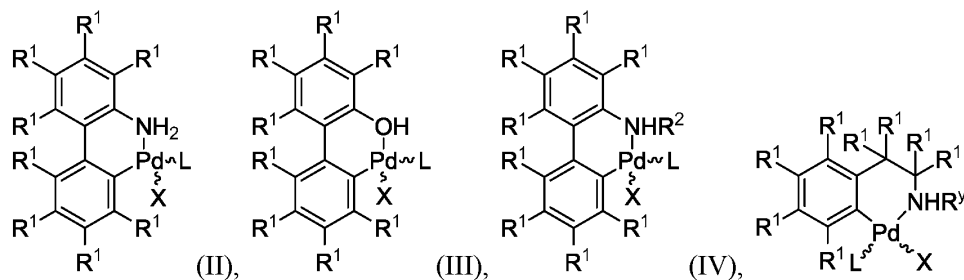
20 In some embodiments, the present disclosure relates to a method for iterative carbon-
 carbon bond formation, comprising a cycle comprising the following steps:

- (a) combining a first boronic ester, a first silanolate, a palladium precatalyst, and a
 halogenated reagent under conditions sufficient to produce a cross-coupling product;
- (b) purifying the cross-coupling product, thereby generating a purified product;
- 25 (c) combining the purified product, a second silanolate, and a diol under
 conditions sufficient to produce a second boronic ester, wherein
 the halogenated reagent is represented by structural formula (I):



the first boronic ester is a compound of formula $R^5-B(OR^6)(OR^7)$; and

the palladium precatalyst is represented by structural formula (II), (III), (IV), or (V):



(V),

wherein

5 Hal is F, Cl, Br, or I;

A is selected from the group consisting of alkylene, alkenylene, alkynylene, cycloalkylene, cycloalkenylene, cycloalkynylene, heteroalkylene, heteroalkenylene, heteroalkynylene, heterocyclylene, arylene, and heteroarylene;

R^* , R^{11} , R^{21} , R^{31} , and R^{41} are each independently alkyl;

10 R^5 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocyclyl, aryl, and heteroaryl;

R^6 and R^7 are each independently alkyl, or

R^6 and R^7 together with oxygen atoms to which they are attached and the boron atom

15 form heterocyclyl; and

X is a non-coordinating anion;

each R^1 is independently H, alkyl, haloalkyl, hydroxy, alkoxy, aryloxy, aryl, or halogen;

L is a trialkylphosphine, triarylphosphine, dialkylarylphosphine, alkyl diarylphosphine, bis(phosphine), phosphoramidate, amine, bis(amine), or N-heterocyclic carbene; and

20 each R^2 is independently alkyl, haloalkyl, or aryl; and

each R^y is independently H, alkyl, haloalkyl, or aryl.

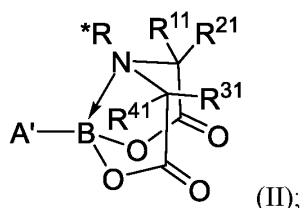
In some embodiments, the present disclosure relates to an automated synthesizer for iterative carbon-carbon bond formation (e.g., according to a method of the disclosure), comprising:

25 a reaction module; a purification module; a deprotection module;
at least one pump which can move liquid from one module to another; and
a computer equipped with software;

wherein all of the modules are under control of the computer; the reaction module is in fluid communication with the purification module; and the purification module is in fluid communication with the deprotection module.

In some embodiments, the present disclosure relates to a method for producing an activated boronate reagent, the method comprising the following step:

(a) combining a first boronate reagent and a fourth silanolate under conditions sufficient to produce an activated boronate reagent; wherein the first boronate reagent is represented by structural formula (I):



wherein

A' is selected from the group consisting of optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocyclyl, aryl, and heteroaryl; and

R*, R¹¹, R²¹, R³¹, and R⁴¹ are each independently alkyl.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1A depicts a comparison of cycle time for one iteration of deprotection, coupling, and purification between automated iterative synthesizers for different classes of molecules.

Figure 1B depicts a synthetic scheme demonstrating iterative cross-coupling cycle reported previously²² based on N-methyliminodiacetic acid (MIDA) boronates and boronic acids.

Figure 1C depicts a synthetic scheme demonstrating iterative cross-coupling cycle according to the present disclosure based on tetramethyl-N-methyliminodiacetic acid (TIDA) boronates and pinacol boronic esters.

Figure 2A depicts a synthetic scheme demonstrating a reaction of MIDA and TIDA boronates with potassium trimethylsilanolate (TMSOK; a/k/a potassium trimethylsiloxide) (2 equiv., monitored by ¹H NMR).

Figure 2B depicts a synthetic scheme demonstrating rapid and homogenous cross-coupling promoted by TMSOK in the presence of a TIDA boronate.

Figure 2C depicts a synthetic scheme and substrate scope for rapid iterative cross-coupling promoted by TMSOK in the presence of a TIDA boronate. Yields are isolated; ^a50 °C; ^b60 °C.

Figure 3A depicts a synthetic scheme demonstrating instability of TIDA boronates to TMSOK at 60 °C.

Figure 3B depicts a synthetic scheme demonstrating stability of TIDA boronates to TMSOK at 60 °C in the presence of boronic esters.

Figure 3C depicts a synthetic scheme demonstrating rapid deprotection of TIDA boronates to pinacol boronic esters at ambient temperature mediated by pinacol and TMSOK.

Figure 3D depicts a synthetic scheme demonstrating deprotection of a dimer TIDA boronate to a pinacol boronic ester and its competence in subsequent iterative Suzuki-Miyaura cross-coupling (SMC).

Figure 4A depicts photographs the next-generation rapid small molecule synthesizer described in the present disclosure.

Figure 4B depicts a synthetic scheme demonstrating that automated cross-coupling followed by automated purification affords high yield and high purity TIDA boronate products.

Figure 4C depicts a synthetic scheme demonstrating that automated deprotection followed by automated coupling affords high conversion to TIDA boronate products.

Figure 4D depicts a synthetic scheme and substrate scope for rapid automated iterative cross-coupling. Yields are isolated.

Figure 5A depicts a synthetic scheme demonstrating that heating TIDA boronates with TMSOK leads to the formation of an unknown boronate species that is highly reactive.

Figure 5B depicts a synthetic scheme demonstrating that the intermediate formed from activating TIDA with TMSOK is a highly reactive cross-coupling partner.

Figure 6 depicts examples of alkyl TIDA coupling with non-TIDA containing substrates.

Figure 7 depicts the coupling of *n*-butyl BTIDA to *m*-bromophenyl BTIDA, which led to the formation of a side product.

Figure 8A depicts a Lewis acid screen for the alkyl BTIDA coupling.

Figure 8B depicts examples of iterative alkyl BTIDA coupling.

Figure 9 depicts a fluorine and boron NMR analysis of the TIDA/TMSOK experiment.

Figure 10 depicts a fluorine NMR analysis of a TIDA boronate in the presence of varying amounts of TMSOK.

Figure 11 depicts a crude fluorine NMR of a TIDA boronate and a mixture of a TIDA boronate and a boronic ester in the presence of TMSOK.

Figure 12 depicts a fluorine NMR of recovered TIDA boronate.

Figure 13 depicts a plot comparing the concentration of TIDA boronate vs. time following treatment with various amounts of TMSOK.

Figure 14 depicts a plot comparing $1/[BTIDA]$ vs. time following treatment with 3 equivalents of TMSOK.

Figure 15 depicts a plot comparing $1/[BTIDA]$ vs. time following treatment with 4.5 equivalents of TMSOK.

Figure 16 depicts a plot comparing $1/[BTIDA]$ vs. time following treatment with 6 equivalents of TMSOK.

Figure 17 depicts a plot comparing $1/[BTIDA]$ vs. time following treatment with 7.5 equivalents of TMSOK.

Figure 18 depicts a plot comparing $1/[BTIDA]$ vs. time following treatment with 9 equivalents of TMSOK.

Figure 19 depicts a plot comparing $k^{0.5}$ vs. $[TMSOK]$.

Figure 20 depicts a plot comparing the concentration of TIDA vs. time in the presence of varying amounts of pinacol.

Figure 21 depicts an NMR of a pinacol boronic ester dimer.

Figure 22 depicts a schematic of a next-generation synthesis machine for faster cross-coupling.

Figure 23 depicts an automated rotary evaporator.

Figure 24 depicts the design of the automated deprotection module.

Figure 25 depicts the design of the automated cross-coupling module.

Figure 26 depicts the design of the automated purification module.

Figure 27 depicts a zoomed-in view of the design of the automated purification module shown in Figure 26.

Figure 28 depicts an NMR demonstrating the results of the automated deprotection of 4-fluorophenyl TIDA boronate.

Figure 29 depicts an NMR analysis of an automated deprotection/cross-coupling sequence.

Figure 30 depicts a zoomed-in view of the NMR analysis of an automated deprotection/cross-coupling sequence shown in Figure 29.

DETAILED DESCRIPTION OF THE INVENTION

The automated synthesis of oligopeptides¹ and oligonucleotides² has transformed science, medicine, and technology,³⁻⁵ and enabled creation of new fields such as proteomics, genomics, and synthetic biology⁶⁻⁹. After decades of optimization, the corresponding automated synthesizers are now general, efficient, and rapid. The resulting broadly available on-demand access to the corresponding biomolecules has shifted the bottleneck of scientific discovery from the synthesis process to the generation and testing of increasingly sophisticated hypotheses^{10,11}. Substantial progress in these same directions has more recently been achieved with the more complex problem of automated oligosaccharide synthesis¹².

All of these approaches leverage the inherent strengths of modular iterative assembly, where prefabricated bifunctional building blocks are assembled under a unified process consisting of repeated deprotection, coupling, and purification steps. This approach trivializes synthesis planning while requiring optimization of only one type of bond-forming chemical reaction. Decades of focused effort to improve and generalize these platforms via advances in both chemistry (e.g., reagents which minimize side reactions like PyBop¹³) and engineering (e.g., flow¹⁴, microwaves¹⁵, thermocycling¹⁶) have yielded synthesizers capable of making even very large target compounds in less than a day¹⁴, a feat requiring cycle times on the order of minutes (**Figure 1A**).

In contrast, small molecules, a class of chemical matter that comprises the majority of known medicines¹⁷, the core components of organic materials with myriad applications, and many other types of functional molecules, are still largely synthesized manually using customized strategies, even when aided by automation.¹⁸ In 2007, a general strategy for small molecule synthesis relying on iterative C-C bond formation via Suzuki-Miyaura cross-coupling (SMC) of bifunctional halo-N-methyliminodiacetic acid (MIDA) boronate building blocks has been reported¹⁹⁻²¹. In 2015, a fully automated small molecule synthesizer employing this strategy has been reported²², and in the years since its capability to automate iterative Csp³-C bond formation has been expanded²³ its utility in materials discovery^{23,24} and its integration with AI-guided closed loop discovery engines has been demonstrated²⁵. In 2022, it was reported that TIDA boronates were significantly more stable than MIDA counterparts, first enabling automated iterative Csp³ bond formation²⁶. Despite these advances, a key limitation of the platform is the long cycle time (more than one day) per C-C bond-forming step, owing principally to the slow and variable kinetics of SMC. This is at least an order of magnitude

slower than analogous state-of-the-art peptide, oligonucleotide, and oligosaccharide synthesizers. The present disclosure describes a significant overhaul to the platform where each step of the iterative cycle has been reimagined and reoptimized for speed, efficiency, and generality. Key advances include the discovery that rapid SMC under homogenous conditions²⁷⁻²⁹, while not tolerated by MIDA boronates, are fully compatible with their more stable TIDA boronate counterparts²⁶, the development of a novel cartridge for rapid catch-and-release purification, and adaptation of AI-generated general reaction conditions for in-situ release cross-coupling of MIDA boronates²⁵ to enable final deprotection step-sparing direct coupling of penultimate TIDA boronate intermediates. Collectively these advances have yielded an order of magnitude rate acceleration per automated C-C bond-forming step (**Figure 1A**).

Results and Discussion

The principal components of an iterative SMC cycle can be broken down into deprotection (D), coupling (C), and purification (P). In the prior design^{22,26} (**Figure 1B**), deprotection occurs via the cleavage of the boron protecting group using aqueous base to furnish a reactive boronic acid which is then rigorously dried using magnesium sulfate followed by molecular sieves (4 hours). Afterwards, the coupling occurs under anhydrous SMC conditions via the slow addition of the freshly prepared boronic acid over 4 hours followed by 12 hours of reaction time with moderate heating (55 °C, 16 hours total). Finally, the purification occurs via harnessing the remarkable capacity of MIDA boronates to undergo catch-and-release on silica gel via ‘catch’ with diethyl ether/methanol then ‘release’ of the boronate product with tetrahydrofuran (4 hours) followed by concentration via argon sparging (6 hours). When deploying this technology in applied contexts, some structure-dependent failures caused by protodeborylation, incomplete conversion, and/or insolubility have been observed. It has been hypothesized that many of these challenges stemmed from the sensitivity of the corresponding boronic acid intermediates, which are unstable species often not amenable to storage or isolation^{30,31}, with the propensity to form insoluble zwitterions^{32,33}, and necessitating slow addition as dilute solutions. To overcome these challenges, more stable intermediates, notably pinacol boronic esters³⁴ and tetramethyl-N-methyliminodiacetic acid (TIDA) boronates²⁶ have been employed. Unexpectedly, a substantially faster and broadly applicable iterative deprotection, coupling, and purification processes, which proceed in absence of water and through stable and isolable intermediates have been discovered (**Figure 1C**).

Rapid and homogenous iterative Suzuki-Miyaura cross-coupling

The first goal was developing rapid and broadly applicable SMC conditions amenable to automation and iteration, as this step represented approximately two-thirds of the total cycle time. For these purposes, reaction conditions which proceeded rapidly while not degrading the TIDA boronate motif were required. SMC using weak, insoluble inorganic bases such as carbonates and phosphates proceeded slowly (hours) but preserved the boronate, while stronger bases such as hydroxides and alkoxides proceeded faster but rapidly degraded the boronate at elevated temperatures ($>40\text{ }^{\circ}\text{C}$).²⁶ Following recent reports by the Denmark group that the soluble base potassium trimethylsilanolate (TMSOK; a/k/a potassium trimethylsiloxide) affords rapid SMC kinetics at mild temperatures²⁷⁻²⁹, the compatibility of MIDA and TIDA boronates with this base were investigated. When subjected to TMSOK at ambient temperature, nearly instantaneous degradation of the MIDA boronate was observed, while the corresponding TIDA boronate appeared unchanged after 12 hours (**Figure 2A**). Remarkably, the model SMC between 4-fluorophenyl neopentyl ester and *m*-bromophenyl TIDA boronate using TMSOK proceeded to full conversion and 95% isolated yield in 5 minutes (**Figure 2B**). These SMC conditions also performed well when applied to a diverse set of aryl, heteroaryl, and vinyl nucleophiles and electrophiles, providing an average isolated yield of 84% across 26 substrates, with all reactions completing within 5-15 minutes (**Figure 2C**). Lewis basic heteroarenes required mild heating ($50\text{-}60\text{ }^{\circ}\text{C}$) but still proceeded to full conversion within 5 minutes. Notably, palladium catalyst-poisoning functional groups such as thioethers³⁵ were well tolerated. Common H-bond donors such as hydroxyl groups and amides coupled effectively. Using pinacol esters in place of neopentyl esters displayed similar performance upon increasing temperature to $60\text{ }^{\circ}\text{C}$ and extending the reaction time to 10 min. Two borylated drugs (Trazodone and Loratadine) were coupled without issue.

Rapid and homogenous TIDA boronate deprotection

The next goal was to develop a mild and rapid deprotection of TIDA boronates to pinacol boronic esters. It has been previously demonstrated this reactivity can be achieved by the action of sodium hydroxide and pinacol²⁶, but this requires moderate heating ($45\text{ }^{\circ}\text{C}$) and long reaction times (6 hours). While these conditions were compatible with simple arenes and Csp³ boronates (which, while less reactive, are also less prone to protodeboronation), when applied to oligoarene structures, protodeboronation was observed. In addition, the conditions used to deprotect polyene MIDA boronates to pinacol boronic esters led to no conversion. Thus, a mild, rapid method to deprotect TIDA boronates to their corresponding pinacol boronic esters was needed. While exploring the reactivity of TMSOK with TIDA boronates, it was surprisingly observed that the base alone could deprotect TIDA boronates at $60\text{ }^{\circ}\text{C}$ in 30

minutes, despite this not occurring during the SMC reaction at the same temperature (**Figure 3A**). It has been hypothesized that the vacant p-orbital of the boronic ester coupling partner during SMC sequesters the silanolate base, preventing degradation of the TIDA boronate. As a control experiment, a mixture of 4-fluorophenyl TIDA boronate, 4-fluorophenyl neopentyl ester, and TMSOK was heated at 60 °C for 30 minutes, resulting in no TIDA degradation products and successful recovery of 89% of the TIDA boronate in >95% purity (**Figure 3B**). It has been found that the combination of pinacol and TMSOK rapidly and cleanly deprotects TIDA boronates to pinacol esters, reaching full conversion within one hour at room temperature (**Figure 3C**). The resulting reaction mixture can be quenched with a variety of reagents (e.g., HCl_(aq), TMSCl, silica gel), however the use of calcium chloride buffered with sodium bicarbonate is preferably employed here as it is well tolerated even by sensitive polyene boronic esters³⁶.

Subsequent experiments revealed that three equivalents of TMSOK and pinacol are required to fully deprotect one equivalent of TIDA boronate. Accordingly, it was hypothesized that the reaction yields one equivalent of TIDA dipotassium salt, two equivalents of trimethylsilanol, residual pinacol, and a TMSOK-bound pinacol boronate. Conveniently, treatment with calcium chloride resolved the reaction solution to clean and monomeric pinacol boronic ester isolated in near-quantitative yield, presumably via removing both diols and silanols (**Figure 3C**). Studies of kinetics using ¹⁹F NMR revealed that this reaction is second order with respect to the silanolate base and zero order with respect to the diol, suggesting some type of interesting dual role for TMSOK in the rate-determining step. While a specific interaction between the TIDA boronate cage and TMSOK prior to deprotection could explain the second-order rate dependence of the base (e.g., binding to the backside of the boronate cage³⁷), such an interaction is not visible on the NMR time scale at ambient temperature (¹H, ¹³C, ¹⁹F, ¹¹B, ²⁹Si). It was found that aryl pinacol boronic esters were unstable to superstoichiometric silanolate base, but that addition of excess pinacol could render them more stable. Thus, 3-5 equivalents of both reagents are used in this work for optimal substrate stability and reaction time. Testing the reactivity of other soluble organic bases (potassium acetate, lithium isopropoxide, potassium phenoxide, potassium triethylsilanolate, and potassium dimethylvinyl silanolate) with TIDA boronates in presence of pinacol revealed that only the silanolates afforded pinacol ester product while the others afforded no reaction, suggesting that this reactivity is unique to this class of bases. TMSOK was utilized for the remainder of the study due to its desirable solubility, reactivity, and broad commercial availability.

Robotic platform for rapid iterative cross-coupling

Optimization of the coupling and deprotection shifted the bottleneck of the process to the automated catch-and-release purification (previously 4 hours), which could be hastened through reengineering. At the same time, the robustness of the procedure could be improved by reducing instances of undesired physical behavior such as clogging, insolubility, and variable mass transfer. To accomplish these goals, the process was redesigned such that precipitation of the TIDA boronate product is afforded directly in the coupling reaction vessel after SMC, with subsequent purification occurring in-line through an extensively prototyped catch-and-release cartridge using vacuum filtration. This design eliminates slow syringe pump transfers and rinses/washes, while decoupling product solubility from the purification process. A rotary evaporator to the system, such that purified TIDA boronates could be eluted using acetone without affecting downstream chemistry. Together, these improvements result in near quantitative isolation of purified and coupled TIDA boronate products in a rapid and fully automated manner (1 hour).

Finally, it was hypothesized that the TIDA boronate could be used as a direct coupling partner in the last step of an automated sequence, saving further time by simultaneously performing the deprotection and coupling steps. To accomplish this in-situ release cross-coupling, it was discovered that the recently reported AI-optimized general reaction conditions employing MIDA boronates²⁵ are also compatible with TIDA boronates, and that the necessary reaction time is short (1 hour). Implementing this chemistry necessitated improving the design of the inert manifold used in previous instruments, such that dry and wet solvents could be simultaneously accommodated. With each elementary step optimized for speed, a next-generation small molecule synthesizer incorporating these advances was built and tested (**Figure 4A**). Translating the chemistry to the automated platform mainly required more dilute concentrations to ensure adequate mixing and high mass transfer between modules, as well as utilizing dichloromethane as a transfer solvent as it uniformly solubilizes TIDA boronates and is compatible with the deprotection and drying procedure. The rapid automated SMC followed by automated purification affords clean TIDA boronates in high purity and yield (**Figure 4B**), and that the rapid automated deprotection affords clean pinacol esters which perform competently in subsequent automated SMC (**Figure 4C**). Finally, to draw a direct comparison to the previous platform,²² three representative oligomers were selected: a natural product derivative, an organic electronic material, and a pharmaceutical, where the automated platform reported here uniformly synthesized these molecules in similar efficiency to the prior report but in significantly less total time (3 hours vs 60 hours previously, **Figure 4D**). Each of these

molecules was synthesized through a faster, fully automated sequence of coupling, purification, and in-situ deprotection-coupling.

In conclusion, a rapid automated iterative cross-coupling platform that utilizes stable TIDA boronate building blocks and isolable pinacol ester intermediates has been developed to achieve an order of magnitude decrease in cycle time compared to the previous state-of-the-art. This is a significant step for automated iterative small molecule synthesis^{17, 26, 38, 39} on its path towards achieving similar efficiency and societal impacts as iterative biomolecule synthesis. The automated process reported here is expected to be amenable to further miniaturization and parallelization due to its rapid kinetics and homogeneity. This technology is having measurable positive impact on ongoing molecular discovery campaigns, particularly those including computer-aided design, which will be reported shortly.

Activation of TIDA boronates

Heating a TIDA boronate in the presence of 3 equivalents of TMSOK leads to a highly reactive intermediate species (**Figure 5A**). This activation protocol may be performed in the presence of a diol (such as pinacol) to achieve efficient deprotection of TIDA boronates. However, if this same hyperactivation protocol is performed in the absence of a diol, the corresponding hyperactive intermediate can serve as a highly reactive cross-coupling partner for both Csp² (**Figure 5B**) and Csp³ (**Figure 6**) boronates.

This method of activation-coupling works with good efficiency for simple aryl and vinyl compounds but is limited to substrates that are not sensitive to protodeboronation (**Figure 5B**). Fortunately, while alkyl borons are significantly less reactive than their Csp² counterparts, they are also less prone to protodeboronation. In addition, using TIDA boronates instead of boronic esters presents several benefits. First, TIDA boronates are column stable and (usually) crystalline solids, thus being significantly easier to weigh out and handle. Second, TIDA boronates are fairly easy to prepare and purify, whether it be by catch-and-release purification or crystallization, thus accessing TIDA boronates is quite trivial.

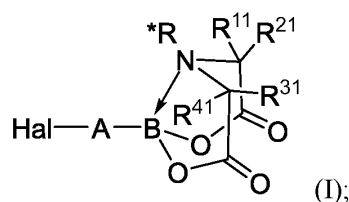
A scope for the Csp³-Csp² coupling of primary alkyl TIDA boronates was first developed (**Figure 6**). When attempting to perform the activate-couple method using *n*-butyl BTIDA, it was found that the coupling proceeded rapidly in toluene using RuPhos-Pd-G4 for non-TIDA containing substrates. In addition, 4-butene-1-BTIDA coupled without issue, which is important because the umpolung coupling would have led to large quantities of β -hydride elimination, which is problematic as the motif is common in PUFAs, further demonstrating the need for both couplings. Importantly, in the case of both an unactivated *trans* and *cis* vinyl halide, the coupling performed with excellent stereospecificity. Furthermore, a 90:10 Z:E

mixture of styrenyl bromide coupled with fairly good stereospecificity despite the propensity for *Z*-styrenyl bromides to undergo *Z* to *E* isomerization.

Unfortunately, when attempting to couple *n*-butyl BTIDA to *m*-Bromophenyl BTIDA, a major side product was observed (**Figure 7**). This side product is derived from deprotection post Csp³-Csp² coupling, followed by Csp²-Csp² coupling. Interestingly, when using SPhos as a ligand, no coupling was observed, but any homocoupling side product were not present in the crude mixture. This suggests that TIDA is stable to the boronate species, but post transmetalation, free TMSOK can deprotect TIDA, leading to formation of a competent coupling partner. Inspired by the Denmark group's heteroaryl-heteroaryl coupling²⁹, it was hypothesized that a Lewis acid could be used to sequester free TMSOK (**Figure 8A**). Attempts to use B(OTMS)₃ in toluene did not lead to any decreased level of homocoupling. B(OMe)₃ led to a mixture of coupling and protodehalogenation. B(OiPr)₃ led to quantitative protodehalogenation in < 1 hour. This suggests that only borates with no β-hydrides next to the oxygen could be used. When reexamining B(OTMS)₃, it was hypothesized that in a nonpolar solvent like toluene, formation of KB(OTMS)₄ was unfavorable. The reaction was performed in THF, which led to a significant improvement in formation of the homocoupled product. With this, *n*-butyl coupled to 5-bromothiophene-2-BTIDA and *m*-bromophenyl BTIDA in good yields (**Figure 8B**).

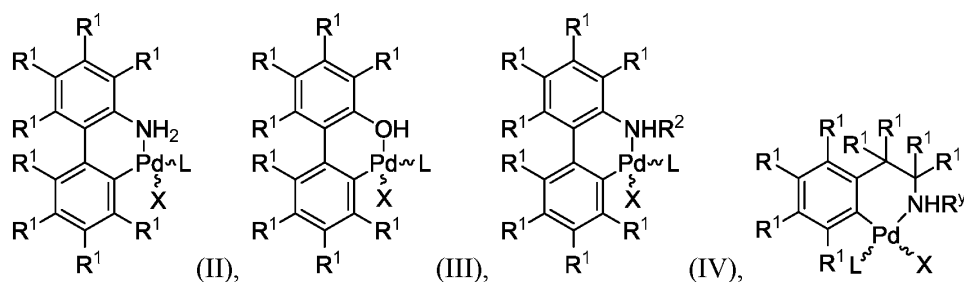
Accordingly, the present disclosure relates to a method for iterative carbon-carbon bond formation, comprising a cycle comprising the following steps:

- (a) combining a first boronic ester, a first silanolate, a palladium (Pd) precatalyst, and a halogenated reagent under conditions sufficient to produce a cross-coupling product;
- (b) purifying the cross-coupling product, thereby generating a purified product;
- (c) combining the purified product, a second silanolate, and a diol under conditions sufficient to produce a second boronic ester, wherein the halogenated reagent is represented by structural formula (I):



the first boronic ester is a compound of formula R⁵-B(OR⁶)(OR⁷); and

the palladium precatalyst is represented by structural formula (II), (III), (IV), or (V):



(V),

wherein

Hal is F, Cl, Br, or I;

5 A is selected from the group consisting of alkylene, alkenylene, alkynylene, cycloalkylene, cycloalkenylene, cycloalkynylene, heteroalkylene, heteroalkenylene, heteroalkynylene, heterocyclylene, arylene, and heteroarylene;

R^* , R^{11} , R^{21} , R^{31} , and R^{41} are each independently alkyl;

10 R^5 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocyclyl, aryl, and heteroaryl;

R^6 and R^7 are each independently alkyl, or

R^6 and R^7 together with oxygen atoms to which they are attached and the boron atom form heterocyclyl; and

15 X is a non-coordinating anion;

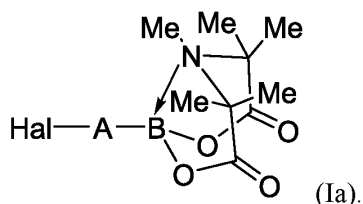
each R^1 is independently H, alkyl, haloalkyl, hydroxy, alkoxy, aryloxy, aryl, or halogen;

L is a trialkylphosphine, triarylphosphine, dialkylarylphosphine, alkyl diarylphosphine, bis(phosphine), phosphoramidate, amine, bis(amine), or N-heterocyclic carbene; and

each R^2 is independently alkyl, haloalkyl, or aryl; and

20 each R^y is independently H, alkyl, haloalkyl, or aryl.

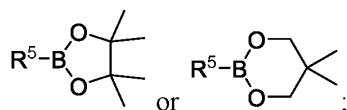
In certain preferred embodiments, R^* is methyl. In some preferred embodiments, R^{11} , R^{21} , R^{31} , and R^{41} are each methyl. In certain embodiments, A is an arylene, a heteroarylene, or an alkenylene. In some embodiments, Hal is Br. In certain embodiments, the halogenated reagent is represented by structural formula (Ia):



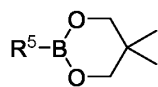
In some embodiments, the first silanolate and the second silanolate are each independently selected from the group consisting of lithium trialkyl silanolate, sodium trialkyl silanolate, and potassium trialkyl silanolate. In certain embodiments, the first silanolate and the second silanolate are each independently selected from the group consisting of lithium trimethyl silanolate, sodium trimethyl silanolate, and potassium trimethyl silanolate (TMSOK). In some embodiments, the first silanolate and the second silanolate are the same. In some preferred embodiments, the first silanolate and the second silanolate are both TMSOK.

In certain embodiments, R^6 and R^7 together with oxygen atoms to which they are attached and the boron atom form heterocyclyl. In some embodiments, R^5 is aryl, heteroaryl, or vinyl.

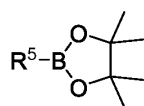
In certain embodiments, the first boronic ester is represented by the following structural formula:



wherein each R^5 is independently aryl, heteroaryl, or alkenyl. In some embodiments, the first boronic ester is represented by the following structural formula:



. In other embodiments, the first boronic ester is represented by the following structural formula:



In certain embodiments, step (a) comprises combining the first boronic ester, the first silanolate, the palladium precatalyst, and the halogenated reagent at a first temperature from about 25 °C to about 70 °C for a first period of time, thereby generating the cross-coupling product. In some embodiments, the first temperature is from about 45 °C to about 65 °C. In some embodiments, the first period of time is about 2 minutes to about 15 minutes, or about 5 minutes to about 10 minutes. In certain embodiments, the cross-coupling product is generated in a yield of about 70% to about 100%, or about 85% to about 95%.

In some embodiments, the methods disclosed herein comprise the following steps: step (a) comprises combining in a vessel the first boronic ester, the first silanolate, the palladium precatalyst, and the halogenated reagent, and

step (b) comprises adding to the vessel a precipitating solvent, thereby generating a precipitated product.

In some embodiments, step (b) further comprises:

- (i) dissolving the precipitated product in a first solvent, thereby forming a first solution;
- 5 (ii) passing the first solution through a sorbent, thereby depositing the precipitated product on the sorbent; and
- (iii) passing a second solvent through the sorbent, thereby eluting a second solution comprising the purified product.

In certain embodiments, the first solvent comprises methanol. In some embodiments, 10 the first solvent comprises methanol and diethyl ether. In some embodiments, the second solvent comprises tetrahydrofuran. In certain embodiments, the sorbent is silica gel.

In some embodiments, step (c) comprises combining the purified product, the second silanolate, and the diol at a second temperature from about 15 °C to about 30 °C for a second period of time.

15 In certain embodiments, the diol is 2,3-dimethyl-2,3-butanediol or 2,2-dimethylpropane-1,3-diol. In some embodiments, the diol is 2,3-dimethyl-2,3-butanediol. In other embodiments, the diol is 2,2-dimethylpropane-1,3-diol.

In certain embodiments, the second temperature is about 25 °C. In some embodiments, the second period of time is about 20 minutes to about 90 minutes, or about 60 minutes. In 20 some embodiments, the purified product and the second silanolate are present in a molar ratio from about 1:2 to about 1:5. In certain embodiments, the purified product and the diol are present in a molar ratio from about 1:2 to about 1:5. In certain embodiments, the purified product, the second silanolate, and the diol are present in a molar ratio of about 1:3:3.

In some embodiments, the method comprises at least a first cycle and a second cycle, 25 wherein:

the second boronic ester of the first cycle is the same as the first boronic ester of the second cycle, and

the halogenated reagent of the first cycle is the same or different from the halogenated reagent of the first cycle.

30 In some embodiments, the halogenated reagent of the first cycle is different from the halogenated reagent of the first cycle. In certain embodiments, the conditions sufficient to produce a cross-coupling product comprise dissolving the first boronic ester, the first silanolate, the palladium precatalyst, and the halogenated reagent in a reaction solvent, thereby generating a homogeneous mixture. In some embodiments, the reaction solvent is tetrahydrofuran.

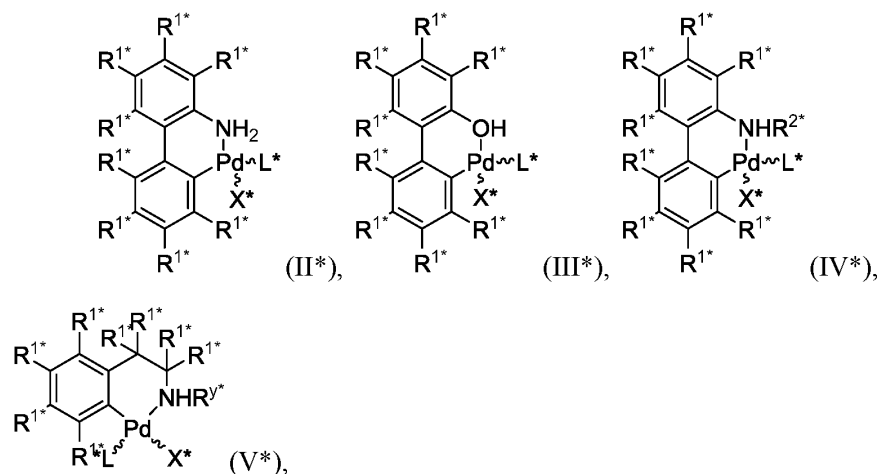
In certain embodiments, the methods disclosed herein further comprise the following step:

- combining the second boronic ester, a third silanolate, a second palladium precatalyst, and a second halogenated reagent under conditions sufficient to produce a second cross-coupling product, wherein

the second boronic ester is a compound of formula $R^5-A-B(OR^{6*})(OR^{7*})$;

- the halogenated reagent is alkyl halide, alkenyl halide, alkynyl halide, cycloalkyl halide, cycloalkenyl halide, cycloalkynyl halide, heteroalkyl halide, heteroalkenyl halide, heteroalkynyl halide, heterocyclyl halide, aryl halide, and heteroaryl halide;

the second palladium precatalyst is represented by structural formula (II*), (III*), (IV*), or (V*):



- wherein

R^{6*} and R^{7*} are each independently alkyl, or

R^{6*} and R^{7*} together with oxygen atoms to which they are attached and the boron atom form heterocyclyl; and

X^* is a non-coordinating anion;

- each R^{1*} is independently H, alkyl, haloalkyl, hydroxy, alkoxy, aryloxy, aryl, or halogen;

L^* is a trialkylphosphine, triarylphosphine, dialkylarylphosphine, alkyl diarylphosphine, bis(phosphine), phosphoramidate, amine, bis(amine), or N-heterocyclic carbene; and

- each R^{2*} is independently alkyl, haloalkyl, or aryl; and

each R^{y*} is independently H, alkyl, haloalkyl, or aryl.

In some aspects, the present disclosure relates to an automated synthesizer for iterative carbon-carbon bond formation (e.g., according to the methods disclosed herein), comprising:

- 5 a reaction module; a purification module; a deprotection module;
at least one pump which can move liquid from one module to another; and
a computer equipped with software;

wherein all of the modules are under control of the computer; the reaction module is in fluid
communication with the purification module; and the purification module is in fluid
10 communication with the deprotection module.

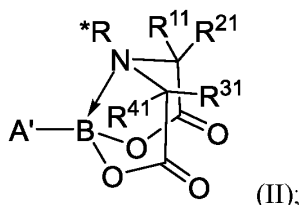
In some embodiments, a first boronic ester, a first silanolate, and a halogenated reagent are combined in the reaction module. In certain embodiments, a purified product, a second silanolate, and a diol are combined in the deprotection module.

In some embodiments, the automated synthesizer disclosed herein comprises:

- 15 a plurality of assemblies of modules;
each assembly of modules comprises a reaction module, a purification module, and a
deprotection module;
at least one pump which can move liquid from one module to another; and
a computer equipped with software;
20 wherein the modules are under the control of the computer; and within each assembly of
modules the reaction module is in fluid communication with the purification module;
and the purification module is in fluid communication with the deprotection module.

In some aspects, the present disclosure relates to a method for producing an activated
25 boronate reagent, the method comprising the following step:

- (a) combining a first boronate reagent and a fourth silanolate under conditions
sufficient to produce an activated boronate reagent; wherein
the first boronate reagent is represented by structural formula (I):

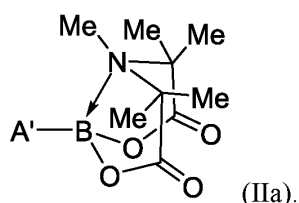


30 wherein

A' is selected from the group consisting of optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocyclyl, aryl, and heteroaryl; and

R^* , R^{11} , R^{21} , R^{31} , and R^{41} are each independently alkyl.

5 In some preferred embodiments, R* is methyl. In certain preferred embodiments, R¹¹, R²¹, R³¹, and R⁴¹ are each methyl. In some embodiments, A' is optionally substituted alkyl, cycloalkyl, aryl, heteroaryl, or alkenyl. In some embodiments, the first boronate reagent is represented by structural formula (IIa):



10 In certain embodiments, the fourth silanolate is selected from the group consisting of lithium trialkyl silanolate, sodium trialkyl silanolate, and potassium trialkyl silanolate. In some embodiments, the fourth silanolate is selected from the group consisting of lithium trimethyl silanolate, sodium trimethyl silanolate, and potassium trimethyl silanolate (TMSOK). In some preferred embodiments, the fourth silanolate is potassium trimethyl silanolate (TMSOK).

15 In certain embodiments, step (a) comprises combining the first boronate reagent and the fourth silanolate at a third temperature from about 25 °C to about 100 °C for a third period of time, thereby generating the activated boronate reagent. In some embodiments, the third temperature is about 70 °C. In certain embodiments, the third period of time is from about 10 minutes to about 50 minutes. In further embodiments, the third period of time is about 30
20 minutes.

In some embodiments, the first boronate reagent and the fourth silanolate are present in a molar ratio of about 1:1-1:5. In certain embodiments, the first boronate reagent and the fourth silanolate are present in a molar ratio of about 1:3.

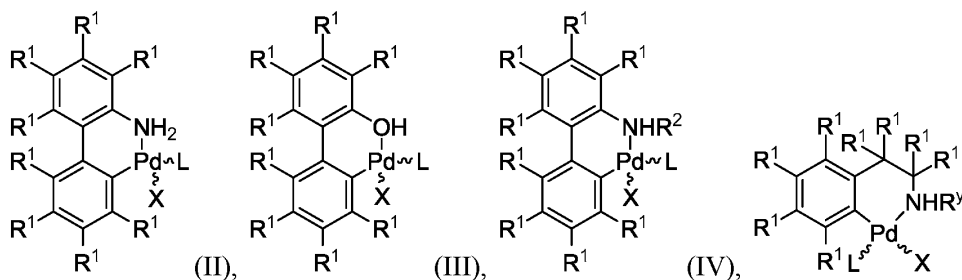
In some embodiments, the conversion of the first boronate reagent to the activated boronate reagent is assessed by ^{11}B NMR. In some preferred embodiments, the ^{11}B NMR chemical shift of the activated boronate reagent is shifted upfield as compared to that of the first boronate reagent. In other preferred embodiments, the ^{11}B NMR chemical shift of the activated boronate reagent is shifted downfield as compared to that of the first boronate reagent.

In certain embodiments, the conditions sufficient to produce an activated boronate reagent comprise dissolving the first boronate reagent and the fourth silanolate in a second reaction solvent, thereby generating a homogeneous mixture. In some embodiments, the second reaction solvent is tetrahydrofuran or toluene.

5 In certain embodiments, the method further comprises the following step:

(b) combining the activated boronate reagent, a third halogenated reagent, and a third palladium precatalyst under conditions sufficient to produce a cross-coupling product; wherein

the third halogenated reagent is an alkyl halide, alkenyl halide, alkynyl halide, cycloalkyl halide, cycloalkenyl halide, cycloalkynyl halide, heteroalkyl halide, heteroalkenyl halide, heteroalkynyl halide, heterocyclyl halide, aryl halide, or heteroaryl halide; and
10 the third palladium precatalyst is represented by structural formula (II), (III), (IV), or (V):



15 (V),

wherein

each R¹ is independently H, alkyl, haloalkyl, hydroxy, alkoxy, aryloxy, aryl, or halogen;

L is a trialkylphosphine, triarylphosphine, dialkylarylphosphine, alkyl diarylphosphine, bis(phosphine), phosphoramidate, amine, bis(amine), or N-heterocyclic carbene; and

20 each R² is independently alkyl, haloalkyl, or aryl; and

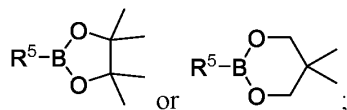
each R^y is independently H, alkyl, haloalkyl, or aryl.

In certain embodiments, step (b) comprises combining the activated boronate reagent, the third palladium precatalyst, and the third halogenated reagent at a fourth temperature from about 25 °C to about 90 °C for a fourth period of time, thereby generating the cross-coupling
25 product. In some embodiments, the fourth temperature is from about 55 °C to about 75 °C. In certain embodiments, the fourth temperature is about 60 °C or about 70 °C. In some embodiments, the fourth period of time is from about 10 minutes to about 120 minutes. In further embodiments, the fourth period of time is about 30 minutes.

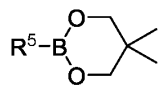
In certain embodiments, step (b) further comprises combining the activated boronate reagent, the third palladium precatalyst, the third halogenated reagent, and a Lewis acid at the fourth temperature from about 25 °C to about 90 °C for the fourth period of time, thereby generating the cross-coupling product. In some embodiments, the Lewis acid is selected from the group consisting of AlCl₃, BF₃, BF₃•OEt₂, BF₃•THF, B(OTMS)₃, B(OMe)₃, and B(OiPr)₃.
 5 In some preferred embodiments, the Lewis acid is B(OTMS)₃.

In certain embodiments, the method further comprises the following step:

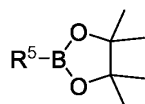
(d) combining the activated boronate reagent and a second diol under conditions sufficient to produce a third boronic ester. In some embodiments, the diol is 2,3-dimethyl-2,3-butanediol or 2,2-dimethylpropane-1,3-diol. In certain embodiments, the diol is 2,3-dimethyl-
 10 2,3-butanediol. In other embodiments, the diol is 2,2-dimethylpropane-1,3-diol. In certain embodiments, the third boronic ester is represented by the following structural formula:



wherein R⁵ is aryl, heteroaryl, or alkenyl. In some embodiments, the third boronic ester is
 15 represented by the following structural formula:



. In other embodiments, the third boronic ester is represented by the following structural formula:



20 Definitions

The articles “a” and “an” are used herein to refer to one or to more than one (i.e., to at least one) of the grammatical object of the article. By way of example, “an element” means one element or more than one element.

The term “heteroatom” is art-recognized and refers to an atom of any element other than carbon or hydrogen. Illustrative heteroatoms include boron, nitrogen, oxygen, phosphorus,
 25 sulfur and selenium, and alternatively oxygen, nitrogen or sulfur.

The term “alkyl” as used herein is a term of art and refers to saturated aliphatic groups, including straight-chain alkyl groups, branched-chain alkyl groups, cycloalkyl groups, alkyl substituted cycloalkyl groups, and (cycloalkyl)alkyl groups. In certain embodiments, a

straight-chain or branched-chain alkyl has about 30 or fewer carbon atoms in its backbone (e.g., C₁-C₃₀ for straight chain, C₃-C₃₀ for branched chain), and alternatively, about 20 or fewer, or 10 or fewer. In certain embodiments, the term “alkyl” refers to a C₁-C₁₀ alkyl group. In certain embodiments, the term “alkyl” refers to a C₁-C₆ alkyl group, for example a C₁-C₆ straight-chain alkyl group. In certain embodiments, the term “alkyl” refers to a C₃-C₁₂ branched-chain alkyl group. In certain embodiments, the term “alkyl” refers to a C₃-C₈ branched-chain alkyl group. Representative examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, and n-hexyl.

The term “cycloalkyl” means mono- or bicyclic saturated carbocyclic rings, each having from 3 to 12 carbon atoms. Certain cycloalkyls have from 5-12 carbon atoms in their ring structure, and may have 6-10 carbons in the ring structure. Preferably, cycloalkyl is (C₃-C₇)cycloalkyl, which represents a monocyclic saturated carbocyclic ring, having from 3 to 7 carbon atoms. Examples of monocyclic cycloalkyls include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl. Bicyclic cycloalkyl ring systems include bridged monocyclic rings and fused bicyclic rings. Bridged monocyclic rings contain a monocyclic cycloalkyl ring where two non-adjacent carbon atoms of the monocyclic ring are linked by an alkylene bridge of between one and three additional carbon atoms (*i.e.*, a bridging group of the form -(CH₂)_w-, where *w* is 1, 2, or 3). Representative examples of bicyclic ring systems include, but are not limited to, bicyclo[3.1.1]heptane, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, bicyclo[3.2.2]nonane, bicyclo[3.3.1]nonane, and bicyclo[4.2.1]nonane. Fused bicyclic cycloalkyl ring systems contain a monocyclic cycloalkyl ring fused to either a phenyl, a monocyclic cycloalkyl, a monocyclic cycloalkenyl, a monocyclic heterocycloalkyl, a monocyclic heterocycloalkenyl, or a monocyclic heteroaryl. The bridged or fused bicyclic cycloalkyl is attached to the parent molecular moiety through any carbon atom contained within the monocyclic cycloalkyl ring. In certain embodiments, the fused bicyclic cycloalkyl is a 5 or 6 membered monocyclic cycloalkyl ring fused to either a phenyl ring, a 5 or 6 membered monocyclic cycloalkyl, a 5 or 6 membered monocyclic cycloalkenyl, a 5 or 6 membered monocyclic heterocycloalkyl, a 5 or 6 membered monocyclic heterocycloalkenyl, or a 5 or 6 membered monocyclic heteroaryl, wherein the fused bicyclic cycloalkyl is optionally substituted.

The term “spirocycloalkyl” as used herein refers to a bicyclic cycloalkyl ring system in which the two rings are linked by a common atom, such as a quaternary carbon atom. The spirocycloalkyl is attached to the parent molecular moiety through any carbon atom contained within the spirocycloalkyl ring system. Suitable spirocycloalkyl groups include, but are not

limited to, spiro[2.2]pentane, spiro[3.3]heptane, spiro[4.4.]nonane, spiro[2.3]hexane, and spiro[3.4]octane.

The term “cycloalkylene” as used herein refers to a divalent cycloalkyl group. In some embodiments, a cycloalkylene may be fused to an arylene or heteroarylene group; i.e., a cycloalkylene may be bonded at two adjacent positions to an arylene or heteroarylene group. In such embodiments, the cycloalkylene is saturated at all atoms except the atoms that are fused to the arylene group.

The term “(cycloalkyl)alkyl” as used herein refers to an alkyl group substituted with one or more cycloalkyl groups. An example of cycloalkylalkyl is cyclohexylmethyl group.

The term “cycloalkenyl” as used herein refers to a cycloalkyl group as defined above that additionally contains at least one carbon-carbon double bond. In certain embodiments, the cycloalkenyl is a mono- or bicyclic carbocyclic ring having at least one carbon-carbon double bond and containing from 3 to 12 carbon atoms. For avoidance of doubt, a cycloalkenyl group is not aromatic.

The term “cycloalkynyl” as used herein refers to a cycloalkyl group as defined above that additionally contains at least one carbon-carbon triple bond. In certain embodiments, the cycloalkynyl is a mono- or bicyclic carbocyclic ring having at least one carbon-carbon triple bond and containing from 3 to 12 carbon atoms. For avoidance of doubt, a cycloalkynyl group is not aromatic.

The term “cycloalkenylene” as used herein refers to a divalent cycloalkenyl group. In some embodiments, a cycloalkenylene may be fused to an arylene or heteroarylene group; i.e., a cycloalkenylene may be bonded at two adjacent positions to an arylene or heteroarylene group. In such embodiments, the cycloalkenylene contains at least one saturated carbon atom and at least one carbon-carbon double bond in addition to the atoms that are fused to the arylene group.

The term “heterocycloalkyl” as used herein refers to a radical of a non-aromatic ring system, including, but not limited to, monocyclic, bicyclic, and tricyclic rings, which can be completely saturated or which can contain one or more units of unsaturation, wherein for the avoidance of doubt, the degree of unsaturation does not result in an aromatic ring system, and having 3 to 12 atoms including at least one heteroatom, such as nitrogen, oxygen, or sulfur. For purposes of exemplification, which should not be construed as limiting the scope of this invention, the following are examples of heterocyclic rings: aziridinyl, aziriny, oxirany, thiirany, thiireny, dioxirany, diaziriny, diazepany, 1,3-dioxany, 1,3-dioxolany, 1,3-dithiolany, 1,3-dithianyl, imidazolidinyl, isothiazolidinyl, isoxazolinyl,

isoxazolidinyl, azetyl, oxetanyl, oxetyl, thietanyl, thietyl, diazetidinyl, dioxetanyl, dioxetenyl, dithietanyl, dithietyl, dioxalanyl, oxazolyl, thiazolyl, triazinyl, isothiazolyl, isoxazolyl, azepines, azetidiny, morpholinyl, oxadiazolinyl, oxadiazolidinyl, oxazolinyl, oxazolidinyl, oxopiperidinyl, oxopyrrolidinyl, piperazinyl, piperidinyl, pyranyl, pyrazolinyl, pyrazolidinyl, 5 pyrrolinyl, pyrrolidinyl, quinuclidinyl, thiomorpholinyl, tetrahydropyranyl, tetrahydrofuranyl, tetrahydrothienyl, thiadiazolinyl, thiadiazolidinyl, thiazolinyl, thiazolidinyl, thiomorpholinyl, 1,1-dioxidothiomorpholinyl (thiomorpholine sulfone), thiopyranyl, trithianyl, and 2-azobicyclo[3.1.0]hexane. A heterocycloalkyl group may be optionally substituted by one or more substituents as described below.

10 The term “spiroheterocycloalkyl” as used herein refers to a bicyclic heterocycloalkyl ring system in which the two rings are linked by a common atom, such as a quaternary carbon atom. The spiroheterocycloalkyl is attached to the parent molecular moiety through any carbon atom contained within the spiroheterocycloalkyl ring system.

The term “heterocycloalkylene” as used herein refers to a divalent heterocycloalkyl group. In some embodiments, a heterocycloalkylene may be fused to an arylene or heteroarylene group; i.e., a heterocycloalkylene may be bonded at two adjacent positions to an arylene or heteroarylene group. In such embodiments, the heterocycloalkylene is saturated at all atoms except the atoms that are fused to the arylene group.

The term “(heterocycloalkyl)alkyl” as used herein refers to an alkyl group substituted 20 with one or more heterocycloalkyl (i.e., heterocyclyl) groups.

The term “heterocycloalkenyl” as used herein refers to a heterocycloalkyl group, as defined above, that additionally contains at least one carbon-carbon double bond. For avoidance of doubt, a heterocycloalkenyl group is not aromatic.

The term “heterocycloalkynyl” as used herein refers to a heterocycloalkyl group, as 25 defined above, that additionally contains at least one carbon-carbon triple bond. For avoidance of doubt, a heterocycloalkynyl group is not aromatic.

The term “heterocycloalkenylene” as used herein refers to a divalent heterocycloalkenyl group. In some embodiments, a heterocycloalkenylene may be fused to an arylene or heteroarylene group; i.e., a heterocycloalkenylene may be bonded at two adjacent 30 positions to an arylene or heteroarylene group. In such embodiments, the heterocycloalkenylene contains at least one carbon-carbon double bond in addition to the atoms that are fused to the arylene group.

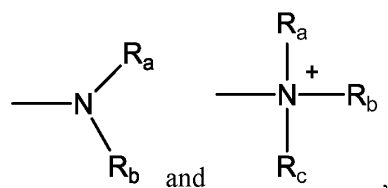
The term “alkenyl” as used herein means a straight or branched chain hydrocarbon radical containing from 2 to 10 carbons and containing at least one carbon-carbon double bond

formed by the removal of two hydrogens. Representative examples of alkenyl include, but are not limited to, ethenyl, 2-propenyl, 2-methyl-2-propenyl, 3-butenyl, 4-pentenyl, 5-hexenyl, 2-heptenyl, 2-methyl-1-heptenyl, and 3-decenyl. The unsaturated bond(s) of the alkenyl group can be located anywhere in the moiety and can have either the (Z) or the (E) configuration about the double bond(s).

The term “alkynyl” as used herein means a straight or branched chain hydrocarbon radical containing from 2 to 10 carbon atoms and containing at least one carbon-carbon triple bond. Representative examples of alkynyl include, but are not limited, to acetylenyl, 1-propynyl, 2-propynyl, 3-butylnyl, 2-pentylnyl, and 1-butylnyl.

The term “alkylene” is art-recognized, and as used herein pertains to a diradical obtained by removing two hydrogen atoms of an alkyl group, as defined above. In one embodiment an alkylene refers to a disubstituted alkane, i.e., an alkane substituted at two positions with substituents such as those described below. That is, in one embodiment, a “substituted alkyl” is an “alkylene”.

The term “amino” is a term of art and as used herein refers to both unsubstituted and substituted amines, e.g., a moiety that may be represented by the general formulas:



wherein R_a , R_b , and R_c each independently represent a hydrogen, $-(\text{CH}_2)_x\text{-R}_d$, $-\text{C}(\text{O})\text{-alkyl}$, $-\text{C}(\text{O})\text{-alkenyl}$, where the alkyl or alkenyl may be optionally substituted, or optionally substituted alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, (cycloalkyl)alkyl, (heterocycloalkyl)alkyl, arylalkyl, heteroarylalkyl, alkoxyalkyl, or haloalkyl, or R_a and R_b , taken together with the N atom to which they are attached form a heterocycle having from 4 to 8 atoms in the ring structure, which may be optionally substituted; R_d represents optionally substituted aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or polycyclyl; and x is zero or an integer in the range of 1 to 8. In certain embodiments, only one of R_a or R_b contains a carbonyl adjacent to the N atom, e.g., R_a , R_b , and the nitrogen together do not form an imide. In other embodiments, R_a and R_b (and optionally R_c) each independently represent hydrogen, optionally substituted alkyl, optionally substituted alkenyl, or $-(\text{CH}_2)_x\text{-R}_d$. In certain embodiments, the term “amino” refers to $-\text{NH}_2$.

In certain embodiments, the term “alkylamino” refers to $-\text{NH}(\text{alkyl})$.

In certain embodiments, the term “dialkylamino” refers to $-N(\text{alkyl})_2$.

The term “amido”, as used herein, means $-NHC(=O)-$, wherein the amido group is bound to the parent molecular moiety through the nitrogen. Examples of amido include alkylamido such as $CH_3C(=O)N(H)-$ and $CH_3CH_2C(=O)N(H)-$.

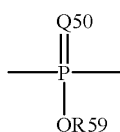
5 The term “acyl” is a term of art and as used herein refers to any group or radical of the form $RC(O)-$ where R is any organic group, e.g., alkyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl. Representative acyl groups include acetyl, benzoyl, and malonyl.

The term “aminoalkyl” as used herein refers to an alkyl group substituted with one or more amino groups. In one embodiment, the term “aminoalkyl” refers to an aminomethyl
10 group, i.e., $-CH_2NH_2$.

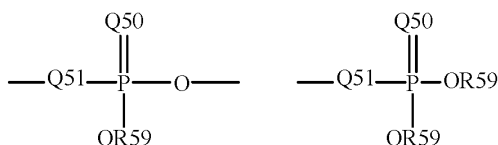
The term “aminoacyl” is a term of art and as used herein refers to an acyl group substituted with one or more amino groups.

The term “thionyl” is a term of art and as used herein refers to any group or radical of the form $RC(S)-$, wherein R is any organic group, e.g., alkyl, aryl, heteroaryl, arylalkyl, and
15 heteroarylalkyl.

The term “phosphoryl” is a term of art and as used herein may in general be represented by the formula:



wherein Q50 represents S or O, and R59 represents hydrogen, optionally substituted (C_1 -
20 C_6)alkyl or optionally substituted aryl; for example, $-P(O)(OMe)-$ or $-P(O)(OH)_2$. When used to substitute, e.g., an alkyl, the phosphoryl group of the phosphorylalkyl may be represented by the general formulas:



wherein Q50 and R59, each independently, are defined above, and Q51 represents O, S or N;
25 for example, $-O-P(O)(OH)OMe$ or $-NH-P(O)(OH)_2$. When Q50 is S, the phosphoryl moiety is a “phosphorothioate.”

The term “aminophosphoryl” as used herein refers to a phosphoryl group substituted with at least one amino group, as defined herein; for example, $-P(O)(OH)NMe_2$.

The term “azide” or “azido”, as used herein, means an $-N_3$ group.

The term “carbonyl” as used herein refers to $-C(=O)-$.

The term “thiocarbonyl” as used herein refers to $-C(=S)-$.

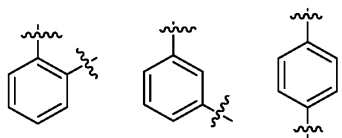
The term “alkylphosphoryl” as used herein refers to a phosphoryl group substituted with at least one alkyl group, as defined herein; for example, $-P(O)(OH)Me$.

5 The term “alkylthio” as used herein refers to $alkyl-S-$. The term “(alkylthio)alkyl” refers to an alkyl group substituted by an alkylthio group.

The term “carboxy”, as used herein, means a $-CO_2H$ group.

The term “aryl” is a term of art and as used herein refers to includes monocyclic, bicyclic and polycyclic aromatic hydrocarbon groups, for example, benzene, naphthalene,
10 anthracene, and pyrene. Typically, an aryl group contains from 6-10 carbon ring atoms (i.e., (C_6-C_{10}) aryl). The aromatic ring may be optionally substituted at one or more ring positions with one or more substituents as described below. The term “aryl” also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings (the rings are “fused rings”) wherein at least one of the rings is an aromatic
15 hydrocarbon, e.g., the other cyclic rings may be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryl, heterocycloalkyls, heterocycloalkenyls, and/or heterocycloalkynyls. In certain embodiments, the term “aryl” refers to a phenyl group.

The term “arylene” as used herein pertains to a diradical obtained by removing two hydrogen atoms of an aryl group, as defined above. Arylene includes, without limitation, 1,2-
20 phenylene, 1,3-phenylene, and 1,4-phenylene, as depicted below:

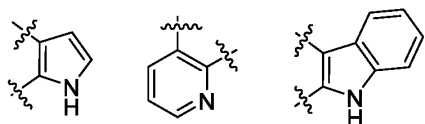


Arylene groups may be optionally substituted at one or more ring positions with one or more substituents, valency permitting, such as the exemplary substituents described below.

The term “heteroaryl” is a term of art and as used herein refers to a monocyclic, bicyclic,
25 and polycyclic aromatic group having 3 to 12 total atoms including one or more heteroatoms such as nitrogen, oxygen, or sulfur in the ring structure. Exemplary heteroaryl groups include azaindolyl, benzo(b)thienyl, benzimidazolyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzothiadiazolyl, benzotriazolyl, benzoxadiazolyl, furanyl, 1,3-dihydro-2H-imidazol-2-one, imidazolyl, imidazopyridinyl, indolyl, indolinyl, indazolyl, isoindolinyl, isoxazolyl,
30 isothiazolyl, isoquinolinyl, oxadiazolyl, oxazolyl, purinyl, pyranyl, pyrazinyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrrolyl, pyrrolo[2,3-d]pyrimidinyl, pyrazolo[3,4-d]pyrimidinyl,

quinolinyl, quinazoliny, triazolyl, thiazolyl, thiophenyl, tetrahydroindolyl, tetrazolyl, thiadiazolyl, thienyl, thiomorpholinyl, triazolyl or tropanyl, and the like. The “heteroaryl” may be optionally substituted at one or more ring positions with one or more substituents as described below. The term “heteroaryl” also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings (the rings are “fused rings”) wherein at least one of the rings is an aromatic group having one or more heteroatoms in the ring structure, e.g., the other cyclic rings may be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, heterocycloalkyls, heterocycloalkenyls, and/or heterocycloalkynyls.

The term “heteroarylene” as used herein pertains to a diradical obtained by removing two hydrogen atoms of a heteroaryl group, as defined above. Heteroarylene includes, without limitation, the divalent heteroarylene groups depicted below:



Heterorylene groups may be optionally substituted at one or more ring positions with one or more substituents, valency permitting, such as the exemplary substituents described below.

The term “aralkyl” or “arylalkyl” is a term of art and as used herein refers to an alkyl group substituted with an aryl group, wherein the moiety is appended to the parent molecule through the alkyl group.

The term “heteroaralkyl” or “heteroarylalkyl” is a term of art and as used herein refers to an alkyl group, as defined herein, substituted with a heteroaryl group, as defined herein, wherein the moiety is appended to the parent molecular moiety through the alkyl group.

The terms “heteroalkyl”, “heteroalkenyl”, and “heteroalkynyl” as used herein refer to an alkyl, alkenyl, or alkynyl group, respectively, having 3 to 12 heavy atoms including at least one heteroatom, such as nitrogen, oxygen, or sulfur. For purposes of exemplification, which should not be construed as limiting the scopes of the terms, the following are examples of a heteroalkyl: 3-methoxypropyl, N-ethylamino-2-ethyl; the following are examples of a heteroalkenyl: 3-allyloxypropenyl, 2-N-ethylaminobutenyl; and the following are examples of a heteroalkynyl: 3-methoxypropynyl, 2-N-propylaminobutynyl.

The term “alkoxy” as used herein refers to an alkyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom. Representative examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, 2-propoxy, butoxy, tert-butoxy, pentyloxy, and hexyloxy.

The term “haloalkoxy” as used herein refers to an alkoxy group, as defined herein, wherein some or all of the hydrogens of the alkyl group are replaced with halogen atoms, as defined herein. Representative examples of haloalkoxy include, but are not limited to, -OCF₃.

The term “alkoxyalkyl” as used herein refers to an alkyl group, as defined herein,
5 substituted by an alkoxy group as defined herein.

The term “alkoxycarbonyl” as used herein means an alkoxy group, as defined herein, appended to the parent molecular moiety through a carbonyl group, represented by -C(=O)-, as defined herein. Representative examples of alkoxycarbonyl include, but are not limited to, methoxycarbonyl, ethoxycarbonyl, and *tert*-butoxycarbonyl.

10 The term “alkylcarbonyl”, as used herein, means an alkyl group, as defined herein, appended to the parent molecular moiety through a carbonyl group, represented by -C(=O)-, as defined herein. Representative examples of alkylcarbonyl include, but are not limited to, acetyl, 1-oxopropyl, 2,2-dimethyl-1-oxopropyl, 1-oxobutyl, and 1-oxopentyl.

The term “arylcarbonyl”, as used herein, means an aryl group, as defined herein,
15 appended to the parent molecular moiety through a carbonyl group, represented by -C(=O)-, as defined herein. Representative examples of arylcarbonyl include, but are not limited to, benzoyl and (2-pyridinyl)carbonyl.

The term “alkylcarbonyloxy” and “arylcarbonyloxy”, as used herein, means an alkylcarbonyl or arylcarbonyl group, as defined herein, appended to the parent molecular
20 moiety through an oxygen atom. Representative examples of alkylcarbonyloxy include, but are not limited to, acetyloxy, ethylcarbonyloxy, and *tert*-butylcarbonyloxy. Representative examples of arylcarbonyloxy include, but are not limited to phenylcarbonyloxy.

The term “alkenoxy” or “alkenoxyl” means an alkenyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom. Representative examples
25 of alkenoxyl include, but are not limited to, 2-propen-1-oxyl (i.e., CH₂=CH-CH₂-O-) and vinyloxy (i.e., CH₂=CH-O-).

The term “aryloxy” as used herein means an aryl group, as defined herein, appended to the parent molecular moiety through an oxygen atom.

The term “heteroaryloxy” as used herein means a heteroaryl group, as defined herein,
30 appended to the parent molecular moiety through an oxygen atom.

The term “carbocyclyl” as used herein means a monocyclic or multicyclic (e.g., bicyclic, tricyclic, etc.) hydrocarbon radical containing from 3 to 12 carbon atoms that is completely saturated or has one or more unsaturated bonds, and for the avoidance of doubt, the degree of unsaturation does not result in an aromatic ring system (e.g., phenyl). Examples of

carbocyclyl groups include 1-cyclopropyl, 1-cyclobutyl, 2-cyclopentyl, 1-cyclopentenyl, 3-cyclohexyl, 1-cyclohexenyl and 2-cyclopentenylmethyl.

The term “cyano” is a term of art and as used herein refers to –CN.

The term “halo” is a term of art and as used herein refers to –F, –Cl, –Br, or –I.

5 The term “haloalkyl” as used herein refers to an alkyl group, as defined herein, wherein some or all of the hydrogens are replaced with halogen atoms, as defined herein. Representative examples of haloalkyl include, but are not limited to, trifluoromethyl and fluoroethyl.

The term “hydroxy” is a term of art and as used herein refers to –OH.

10 The term “hydroxyalkyl”, as used herein, means at least one hydroxy group, as defined herein, is appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of hydroxyalkyl include, but are not limited to, hydroxymethyl, 2-hydroxyethyl, 3-hydroxypropyl, 2,3-dihydroxypentyl, and 2-ethyl-4-hydroxyheptyl.

15 The term “silyl”, as used herein, includes hydrocarbyl derivatives of the silyl (H_3Si –) group (i.e., (hydrocarbyl) $_3\text{Si}$ –), wherein hydrocarbyl groups are univalent groups formed by removing a hydrogen atom from a hydrocarbon, e.g., ethyl, phenyl. The hydrocarbyl groups can be combinations of differing groups which can be varied in order to provide a number of silyl groups, such as trimethylsilyl (TMS), tert-butyldiphenylsilyl (TBDPS), tert-butyl dimethylsilyl (TBS/TBDMS), triisopropylsilyl (TIPS), and [2-(trimethylsilyl)ethoxy]methyl (SEM).

20 The term “silyloxy”, as used herein, means a silyl group, as defined herein, is appended to the parent molecule through an oxygen atom.

Certain compounds contained in compositions of the present invention may exist in particular geometric or stereoisomeric forms. In addition, compounds of the present invention may also be optically active. The present invention contemplates all such compounds, including *cis*- and *trans*-isomers, (*R*)- and (*S*)-enantiomers, diastereoisomers, (*D*)-isomers, (*L*)-isomers, the racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are intended to be included in this invention.

30 If, for instance, a particular enantiomer of compound of the present invention is desired, it may be prepared by asymmetric synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed

with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent recovery of the pure enantiomers.

It will be understood that “substitution” or “substituted with” includes the implicit
5 proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, fragmentation, decomposition, cyclization, elimination, or other reaction.

The term “substituted” is also contemplated to include all permissible substituents of
10 organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and nonaromatic substituents of organic compounds. Illustrative substituents include, for example, those described herein. The permissible substituents may be one or more and the same or different for appropriate organic compounds. For purposes of this invention, the heteroatoms such as nitrogen may have
15 hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. This invention is not intended to be limited in any manner by the permissible substituents of organic compounds.

In certain embodiments, the optional substituents contemplated in this invention include halogen, azide, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl,
20 cycloalkenyl, cycloalkynyl, (cycloalkyl)alkyl, heterocycloalkyl, heterocycloalkenyl, heterocycloalkynyl, (heterocycloalkyl)alkyl, hydroxyl, alkoxy, amino, aminoalkyl, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, carboxylalkyl (e.g., -alkylene-(COOH)), silyl, ether (e.g., -alkylene-O(alkyl)), alkylthio, sulfonyl (e.g., -S(O)₂alkyl), sulfonamido, Boc (-C(O)-O-C(CH₃)₃), ketone (e.g., -CO(alkyl)), aldehyde (-
25 C(O)H), ester (e.g., -COO(alkyl)), haloalkyl, hydroxyalkyl, alkoxyalkyl, haloalkoxy, haloalkoxyalkyl, and cyano.

As used herein, the term “optionally substituted” or “substituted or unsubstituted” when it precedes a list of chemical moieties means that the list of chemical moieties that follow are each substituted or unsubstituted. For example, “substituted or unsubstituted aryl, heteroaryl,
30 and cycloalkyl” or “optionally substituted aryl, heteroaryl, and cycloalkyl” means substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, and substituted or unsubstituted cycloalkyl.

The phrase “protecting group”, as used herein, means temporary substituents which protect a potentially reactive functional group from undesired chemical transformations.

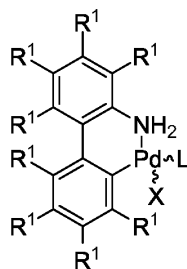
Examples of such protecting groups include esters of carboxylic acids, silyl ethers of alcohols, and acetals and ketals of aldehydes and ketones, respectively. The field of protecting group chemistry has been reviewed (Greene, T.W.; Wuts, P.G.M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley: New York, 1991). Protected forms of the inventive compounds are
 5 included within the scope of this invention.

For purposes of the invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 67th Ed., 1986-87, inside cover.

Other chemistry terms herein are used according to conventional usage in the art, as
 10 exemplified by The McGraw-Hill Dictionary of Chemical Terms (ed. Parker, S., 1985), McGraw-Hill, San Francisco, incorporated herein by reference). Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention pertains.

15 Pd Precatalysts

In certain embodiments, the palladium precatalyst is represented by formula II



II

wherein, independently for each occurrence,

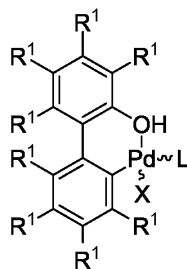
20 X is a non-coordinating anion;

each R¹ is independently H, alkyl, haloalkyl, hydroxy, alkoxy, aryloxy, aryl, or halo;

and

L is a trialkylphosphine, triarylphosphine, dialkylarylphosphine, alkyl diarylphosphine, bis(phosphine), phosphoramidate, amine, bis(amine), or N-heterocyclic carbene.

In certain embodiments, the palladium precatalyst is represented by formula **III**



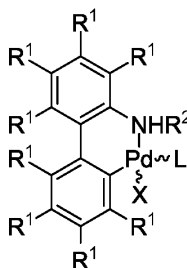
III

wherein, independently for each occurrence,

- 5 X is a non-coordinating anion;
 each R¹ is independently H, alkyl, haloalkyl, hydroxy, alkoxy, aryloxy, aryl, or halo;
 and

L is a trialkylphosphine, triarylphosphine, dialkylarylphosphine, alkyl-diarylphosphine, bis(phosphine), phosphoramidate, amine, bis(amine), or N-heterocyclic carbene.

- 10 In certain embodiments, the palladium precatalyst is represented by formula **IV**

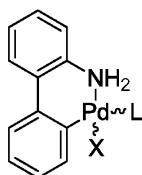


IV

wherein, independently for each occurrence,

- X is a non-coordinating anion;
 15 each R¹ is independently H, alkyl, haloalkyl, hydroxy, alkoxy, aryloxy, aryl, or halo;
 L is a trialkylphosphine, triarylphosphine, dialkylarylphosphine, alkyl-diarylphosphine, bis(phosphine), phosphoramidate, amine, bis(amine), or N-heterocyclic carbene; and
 each R² is independently alkyl, haloalkyl or aryl.

In certain embodiments, the palladium precatalyst is represented by formula **IVa**



IVa

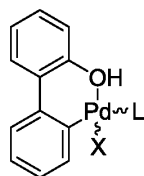
20

wherein, independently for each occurrence,

X is a non-coordinating anion; and

L is a trialkylphosphine, triarylphosphine, dialkylarylphosphine, alkyl diarylphosphine, bis(phosphine), phosphoramidate, amine, bis(amine), or N-heterocyclic carbene.

5 In certain embodiments, the palladium precatalyst is represented by formula **Va**



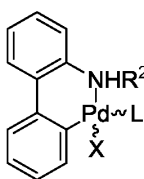
Va

wherein, independently for each occurrence,

X is a non-coordinating anion; and

10 L is a trialkylphosphine, triarylphosphine, dialkylarylphosphine, alkyl diarylphosphine, bis(phosphine), phosphoramidate, amine, bis(amine), or N-heterocyclic carbene.

In certain embodiments, the palladium precatalyst is represented by formula **VI**:



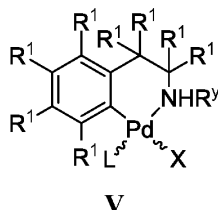
VI

15 wherein, independently for each occurrence,

X is a non-coordinating anion;

L is a trialkylphosphine, triarylphosphine, dialkylarylphosphine, alkyl diarylphosphine, bis(phosphine), phosphoramidate, amine, bis(amine), or N-heterocyclic carbene; and
each R² is independently alkyl, haloalkyl or aryl.

20 In certain embodiments, the palladium precatalyst is represented by formula **V**



V

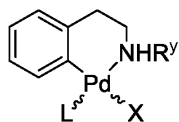
wherein, independently for each occurrence,

X is a non-coordinating anion;

25 each R¹ is independently H, alkyl, haloalkyl, hydroxy, alkoxy, aryloxy, aryl, or halo;

L is a trialkylphosphine, triarylphosphine, dialkylarylphosphine, alkyldiarylphosphine, bis(phosphine), phosphoramidate, amine, bis(amine), or N-heterocyclic carbene; and each R^y is independently H, alkyl, haloalkyl or aryl.

In certain embodiments, the palladium precatalyst is represented by formula **VIII**



VIII

wherein, independently for each occurrence,

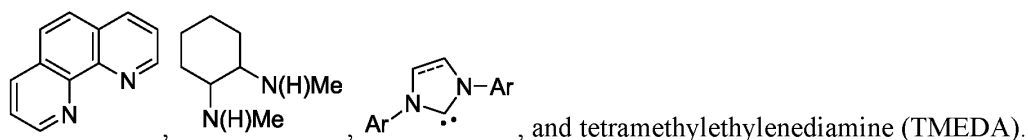
X is a non-coordinating anion;

L is a trialkylphosphine, triarylphosphine, dialkylarylphosphine, alkyldiarylphosphine, bis(phosphine), phosphoramidate, amine, bis(amine), or N-heterocyclic carbene; and each R^y is independently H, alkyl, haloalkyl or aryl.

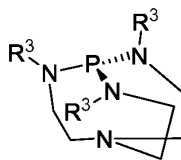
In certain embodiments, the palladium precatalyst is represented by any one of formulae **II**, **III**, **IV**, **V**, **IVa**, **Va**, **VI**, **VII**, or **VIII**, wherein L is a ligand described in U.S. Patent No. 7,858,784, which is hereby incorporated by reference in its entirety.

In certain embodiments, the palladium precatalyst is represented by any one of formulae **II**, **III**, **IV**, **V**, **IVa**, **Va**, **VI**, **VII**, or **VIII**, wherein L is a ligand described in U.S. Patent Application Publication No. 2011/0015401, which is hereby incorporated by reference in its entirety.

In certain embodiments, the palladium precatalyst is represented by any one of formulae **II**, **III**, **IV**, **V**, **IVa**, **Va**, **VI**, **VII**, or **VIII**, wherein L is selected from the group consisting of

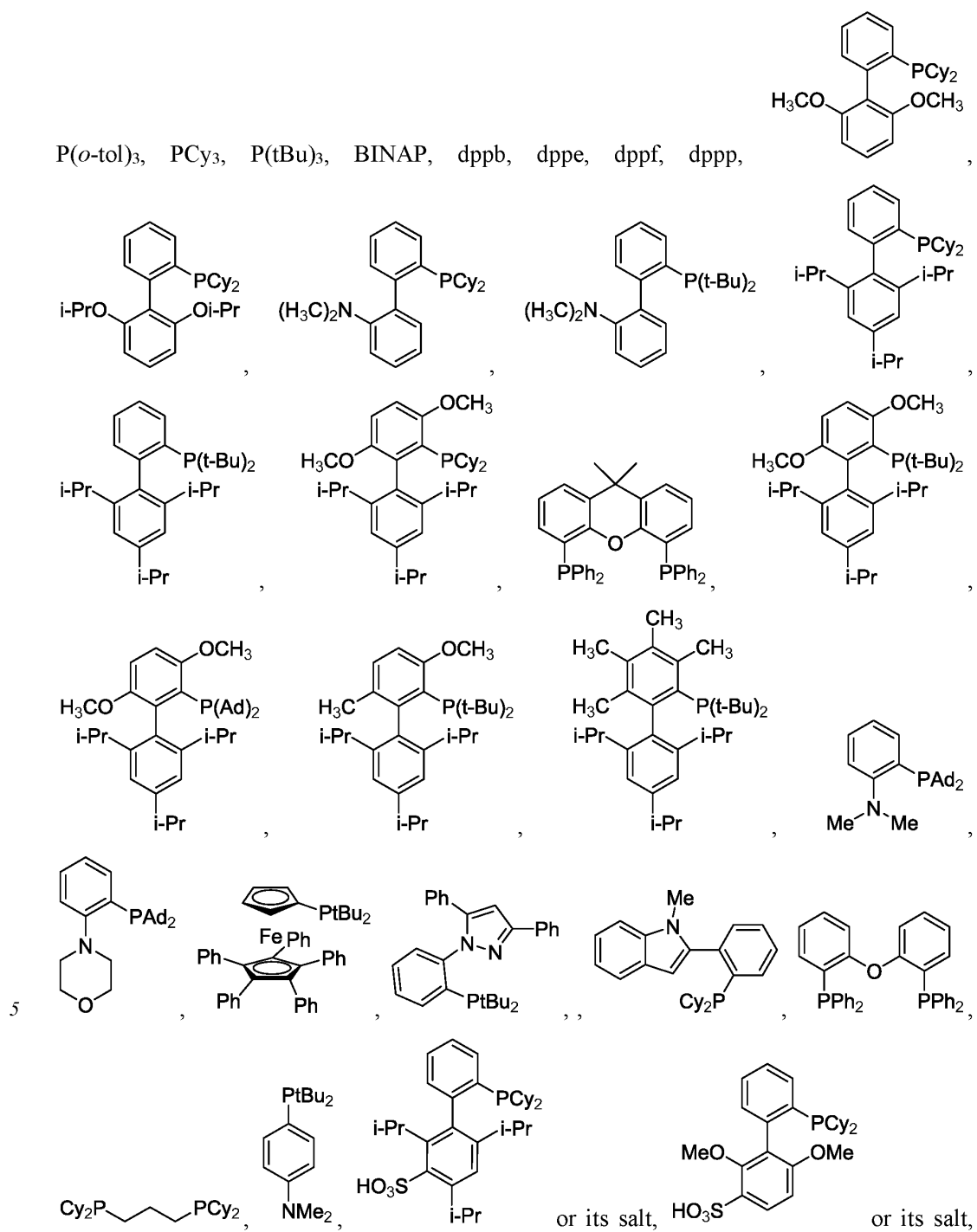


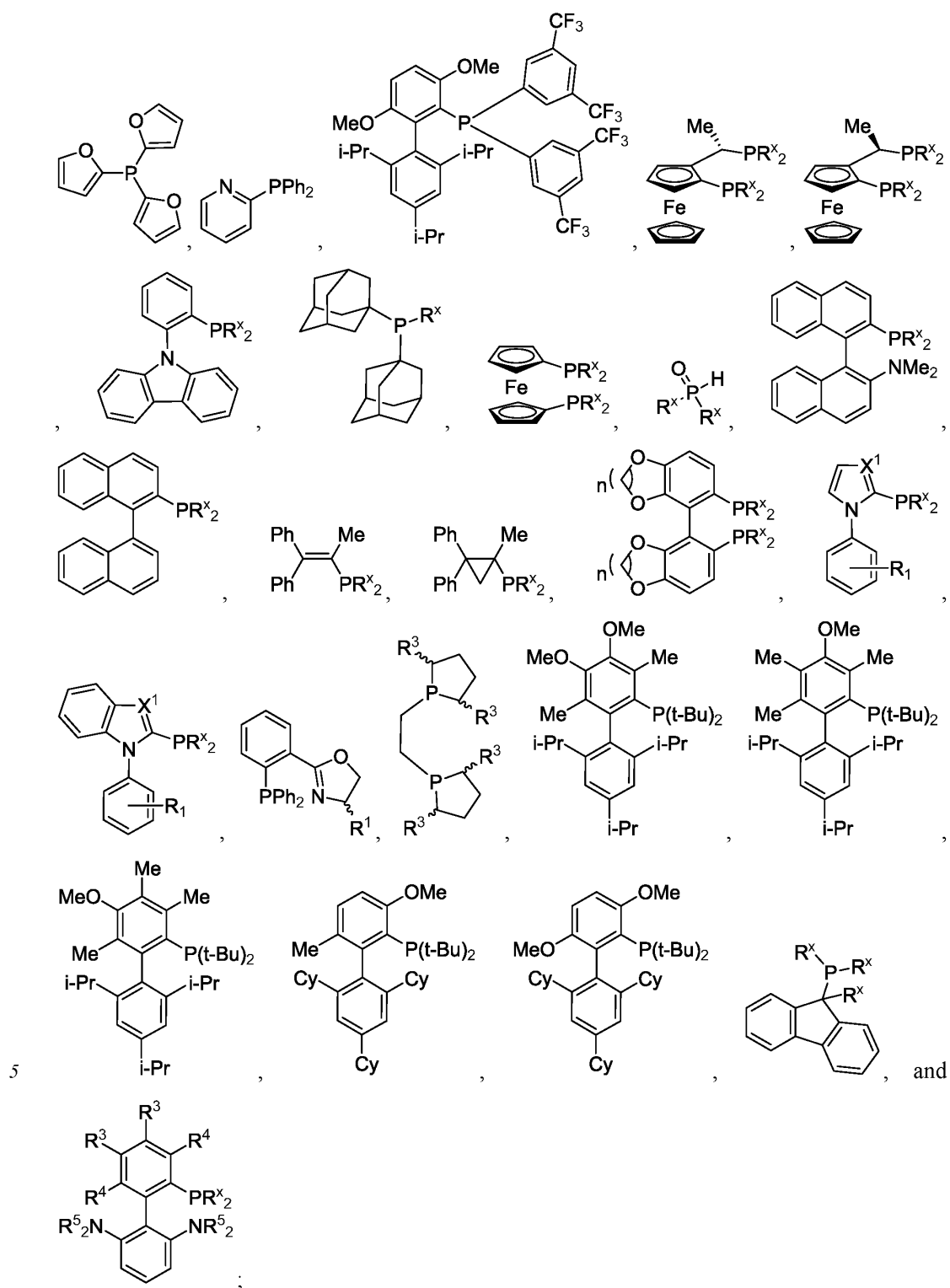
In certain embodiments, the palladium precatalyst is represented by any one of formulae



II, **III**, **IV**, **V**, **IVa**, **Va**, **VI**, **VII**, or **VIII**, wherein L is ; and R³ is H or alkyl.

In certain embodiments, the method uses any one of the aforementioned palladium precatalysts, wherein L is selected from the group consisting of PPh₃, Ph₂P-CH₃, PhP(CH₃)₂,





each R^x is independently alkyl, aralkyl, cycloalkyl, or aryl;

each X^1 is independently CH or N;

each R³ is independently H or alkyl;
 each R⁴ is independently H, alkoxy, or alkyl;
 each R⁵ is independently alkyl or aryl; and
 n is 1, 2, 3, or 4.

5 In certain embodiments, the method uses any one of the aforementioned Pd precatalysts, wherein X is selected from the group consisting of boron tetrafluoride, tetraarylborates (such as B(C₆F₅)₄⁻ and (B[3,5-(CF₃)₂C₆H₃]₄)⁻), hexafluoroantimonate, phosphorus tetrafluoride, phosphorus hexafluoride, alkylsulfonate, haloalkylsulfonate, arylsulfonate, perchlorate, bis(alkylsulfonyl)amide, bis(fluoroalkylsulfonyl)amide,
 10 bis(arylsulfonyl)amide, (fluoroalkylsulfonyl)(fluoroalkylcarbonyl)amide, nitrate, nitrite, sulfate, hydrogensulfate, alkyl sulfate, aryl sulfate, carbonate, bicarbonate, carboxylate, phosphate, hydrogen phosphate, dihydrogen phosphate, phosphinate, and hypochlorite.

In certain embodiments, the method uses any one of the aforementioned Pd precatalysts, wherein X is alkylsulfonate; and the alkyl is substituted alkyl. In certain
 15 embodiments, the method uses any one of the aforementioned Pd precatalysts, wherein X is alkylsulfonate; and the alkyl is unsubstituted alkyl.

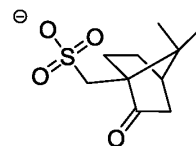
In certain embodiments, the method uses any one of the aforementioned Pd precatalysts, wherein X is alkylsulfonate; and the alkyl is methyl, ethyl, propyl, or butyl. In certain embodiments, the method uses any one of the aforementioned Pd precatalysts, wherein
 20 X is alkylsulfonate; and the alkyl is methyl or ethyl.

In certain embodiments, the method uses any one of the aforementioned Pd precatalysts, wherein X is haloalkylsulfonate. In certain embodiments, the method uses any one of the aforementioned Pd precatalysts, wherein X is fluoroalkylsulfonate.

In certain embodiments, the method uses any one of the aforementioned Pd precatalysts, wherein X is fluoromethylsulfonate. In certain embodiments, the method uses any one of the aforementioned Pd precatalysts, wherein X is trifluoromethylsulfonate.

In certain embodiments, the method uses any one of the aforementioned Pd precatalysts, wherein X is cycloalkylalkylsulfonate. In certain embodiments, the method uses

any one of the aforementioned Pd precatalysts, wherein X is
 30 enantiomer.



or its

In certain embodiments, the invention relates to any one of the aforementioned Pd precatalysts, wherein X is arylsulfonate; and the aryl is substituted aryl. In certain embodiments, the method uses any one of the aforementioned Pd precatalysts, wherein X is arylsulfonate; and the aryl is unsubstituted aryl.

5 In certain embodiments, the method uses any one of the aforementioned Pd precatalysts, wherein X is phenylsulfonate. In certain embodiments, the method uses any one of the aforementioned Pd precatalysts, wherein X is methylphenylsulfonate. In certain embodiments, the method uses any one of the aforementioned Pd precatalysts, wherein X is p-toluenesulfonate.

10 In certain embodiments, the method uses any one of the aforementioned Pd precatalysts, wherein R¹ is H or alkyl. In certain embodiments, the method uses any one of the aforementioned Pd precatalysts, wherein R¹ is H.

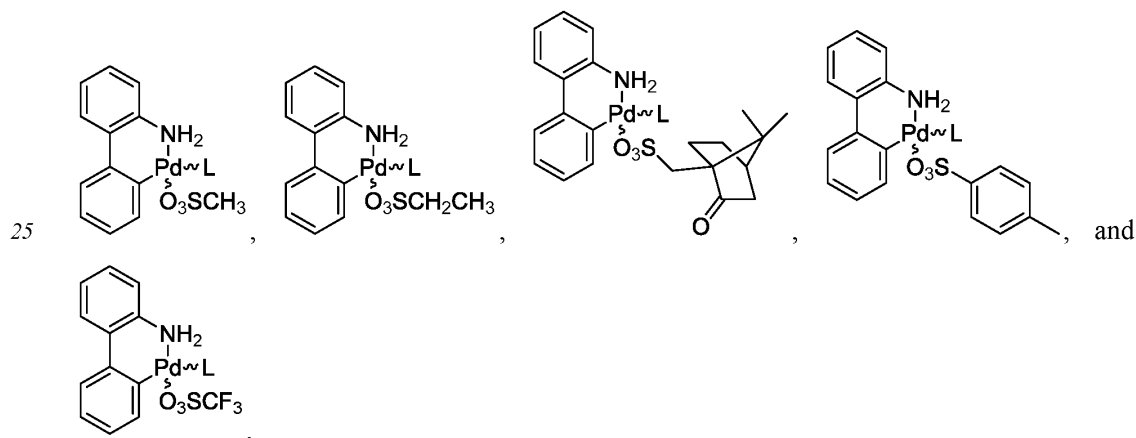
In certain embodiments, the method uses any one of the aforementioned Pd precatalysts, wherein R² is substituted alkyl. In certain embodiments, the method uses any one of the aforementioned Pd precatalysts, wherein R² is unsubstituted alkyl.

15 In certain embodiments, the method uses any one of the aforementioned Pd precatalysts, wherein R² is methyl, ethyl, propyl, or butyl.

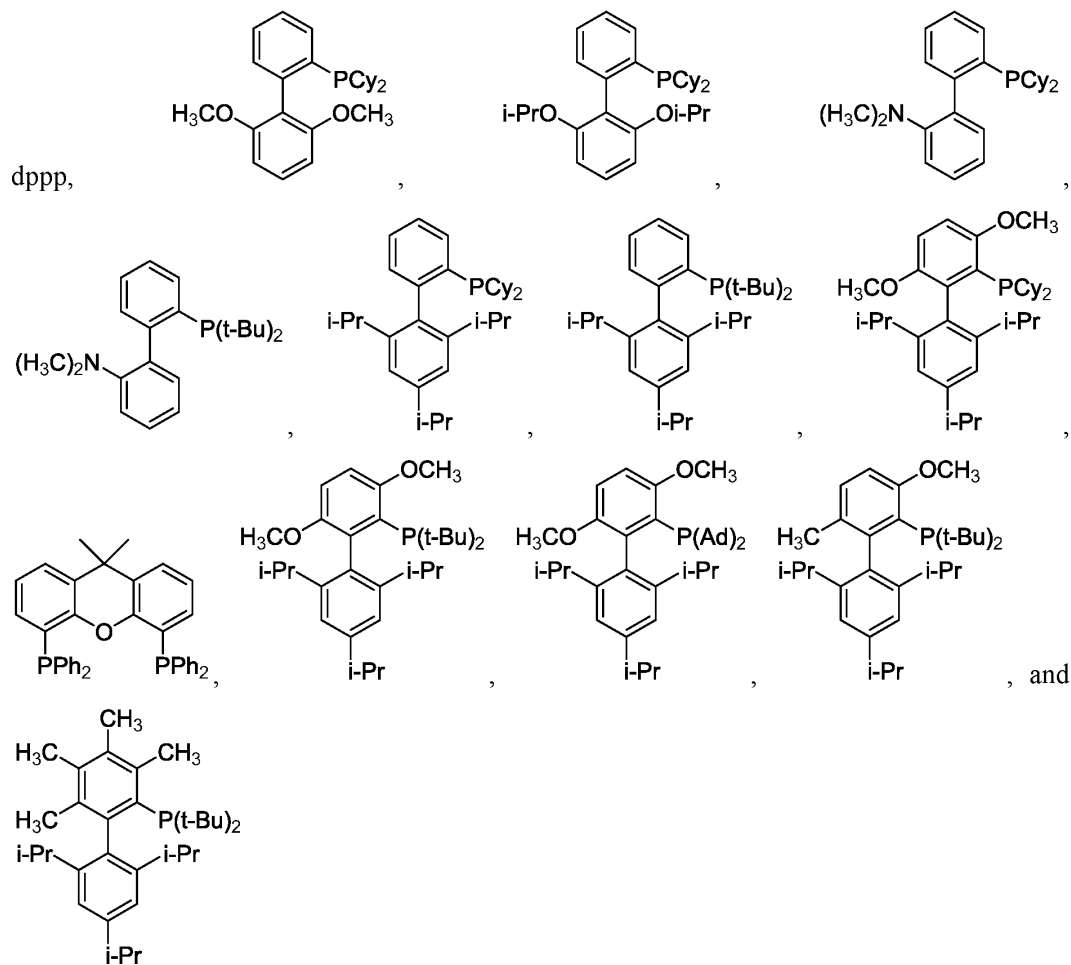
In certain embodiments, the method uses any one of the aforementioned Pd precatalysts, wherein R² is substituted aryl. In certain embodiments, the method uses any one of the aforementioned Pd precatalysts, wherein R² is unsubstituted aryl.

20 In certain embodiments, the method uses any one of the aforementioned Pd precatalysts, wherein R² is phenyl.

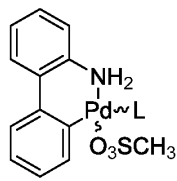
In certain embodiments, the method uses a Pd precatalyst selected from the group consisting of:



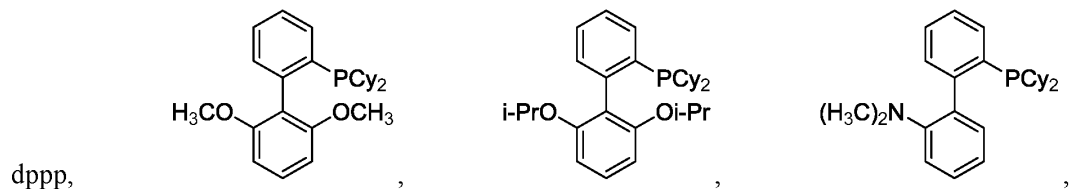
wherein L is selected from the group consisting of PPh₃, P(*o*-tol)₃, PCy₃, P(*t*Bu)₃, BINAP, dppf,

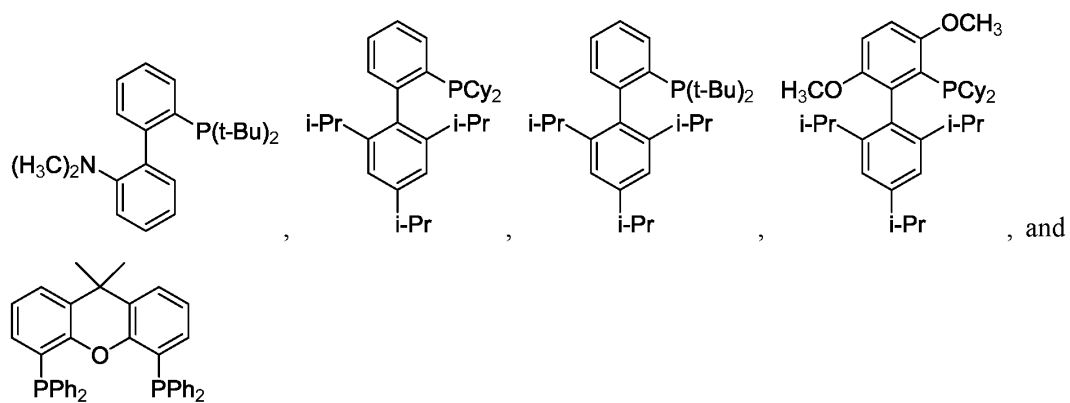


In certain embodiments, the method uses a Pd precatalyst of the following structure:

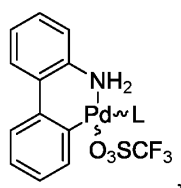


wherein L is selected from the group consisting of PPh₃, P(*o*-tol)₃, PCy₃, P(*t*Bu)₃, BINAP, dppf,

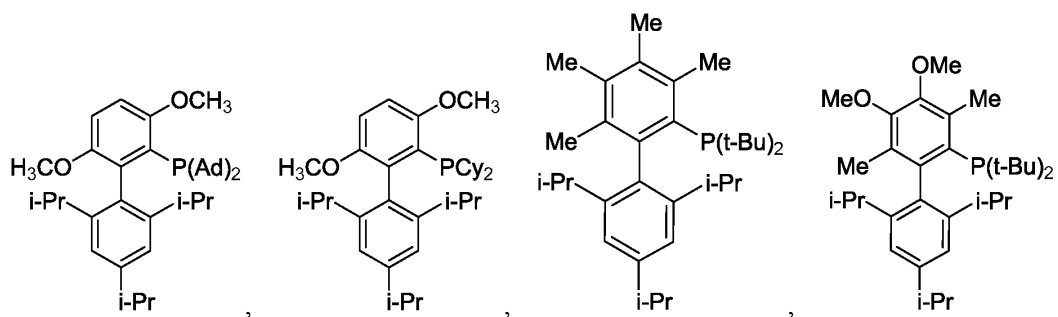
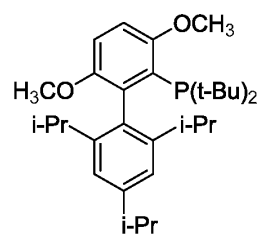


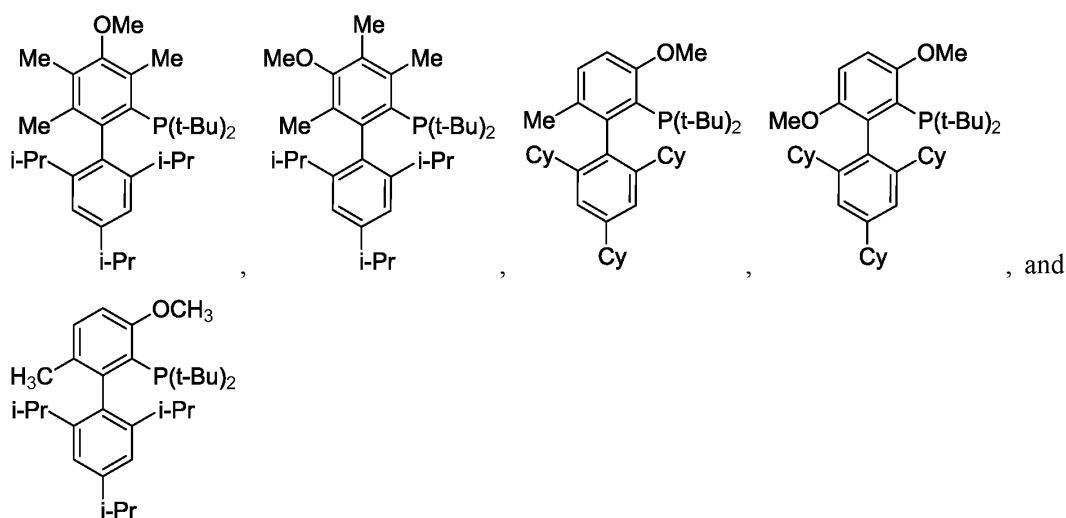


In certain embodiments, the method uses a Pd precatalyst of the following structure:

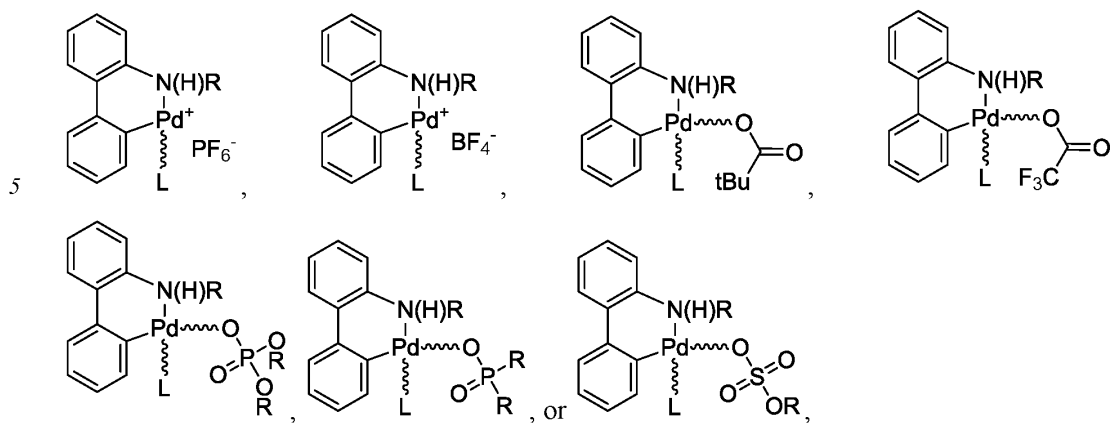


5 wherein L is selected from the group consisting of





In certain embodiments, the method uses a Pd precatalyst of any one of the following structures:

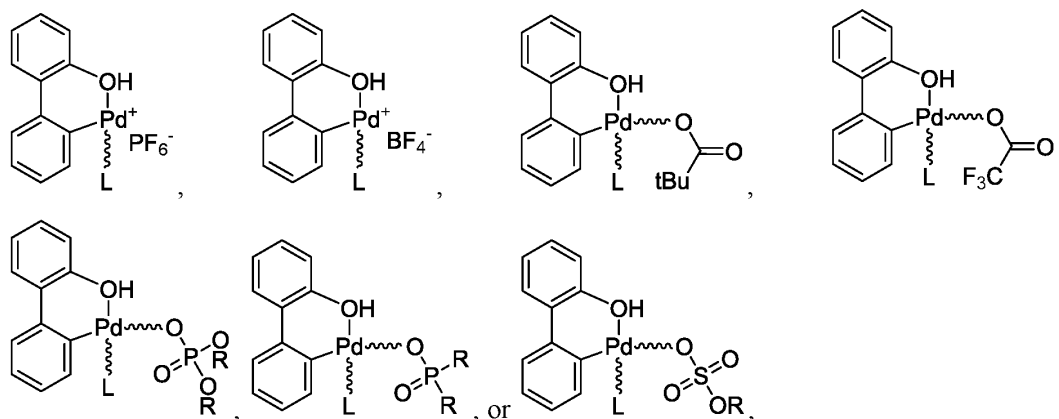


wherein

each R is independently H, alkyl, or aryl; and

L is any one of the aforementioned ligands.

In certain embodiments, the method uses a Pd precatalyst of any one of the following structures:

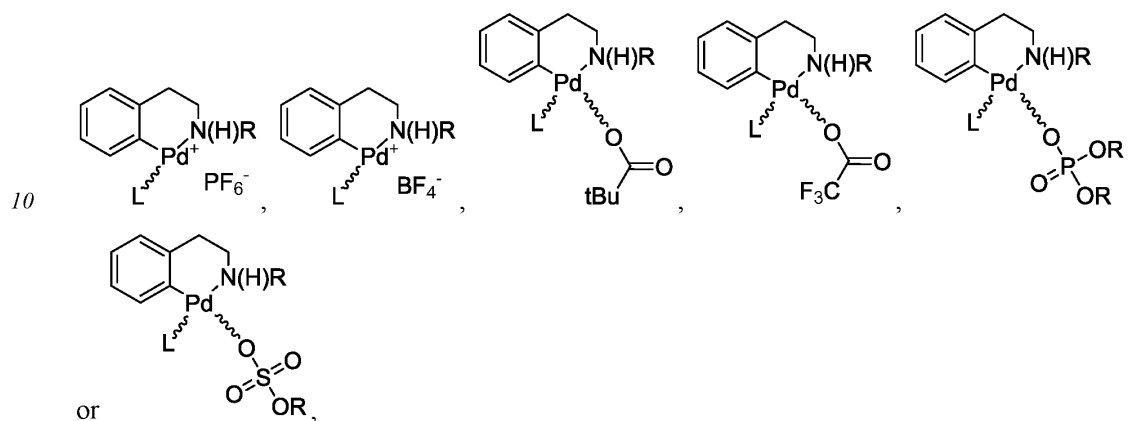


5 wherein

each R is independently H, alkyl, or aryl; and

L is any one of the aforementioned ligands.

In certain embodiments, the method uses a Pd precatalyst of any one of the following structures:



wherein

each R is independently H, alkyl, or aryl; and

L is any one of the aforementioned ligands.

15

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- 2 Caruthers, M. H. Gene Synthesis Machines: DNA Chemistry and Its Uses. *Science* **230**, 281-285 (1985).

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EXAMPLES

The invention now being generally described, it will be more readily understood by
reference to the following examples which are included merely for purposes of illustration of

certain aspects and embodiments of the present invention, and they are not intended to limit the invention.

Example 1: Exemplary Materials and Methods

Reaction mixtures were stirred magnetically. Air- and moisture-sensitive reactions were carried out in flame-dried glassware under nitrogen atmosphere by using standard Schlenk manifold techniques. Fine chemicals were purchased from Acros Organics, Alfa Aesar, Frontier Scientific, Combi-Blocks, or Sigma Aldrich and were used as received unless otherwise mentioned. Anhydrous THF, CH₂Cl₂, toluene, hexane, acetonitrile and Et₂O were dried by passing through a modified Grubbs system of alumina columns, manufactured by Anhydrous Engineering and were transferred under nitrogen via syringe. ¹H Nuclear Magnetic Resonance (NMR) spectra were recorded in CDCl₃ at 400 or 500Mhz on either a Varian Unity 400, Varian Unity 500, Varian Unity Inova 500NB or Bruker 500-MHz spectrometer with broad-band CryoProbe. Chemical shifts (δ_H) are quoted in parts per million (ppm) and referred to the residual protio solvent signals of CHCl₃ (7.27 ppm) or acetone-*d*₆ (2.05 ppm). ¹H NMR coupling constants are reported in hertz and refer to apparent multiplicities. Data are reported as follows: chemical shift, multiplicity (s = singlet, br. s = broad singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sext = sextet, sept = septet, m = multiplet, dd = doublet of doublet, etc.), coupling constant, integration, and assignment. ¹³C NMR spectra were recorded at 126 MHz. Chemical shifts (δ_C) are quoted in ppm and referenced to CHCl₃ (77.0 ppm) or acetone (29.8 ppm). ¹¹B NMR spectra were measured at 161 MHz with complete proton decoupling. ¹⁹F NMR spectra were recorded at 471 MHz. Mass spectra were recorded by by Furong Sun at the University of Illinois School of Chemical Sciences Mass Spectrometry Laboratory using electron impact ionisation (EI), chemical ionisation (CI) or electrospray ionisation (ESI) techniques for high-resolution mass spectra. HRMS EI and CI were performed on a VG Analytical Autospec mass spectrometer at 70 eV. HRMS ESI was performed on either a Bruker Daltonics Apex IV, 7-Tesla FT-ICR or microTOF II.

Synthesis of boronic esters

Boronic acid (1 equiv.) and neopentyl glycol or pinacol (1.05 equiv.) were added to a 7 mL vial equipped with a magnetic stir bar. Anhydrous Et₂O (1 mL) was added followed by MgSO₄ (2 equiv.). The vial was sealed with a screw cap and the mixture was stirred overnight at room temperature. The mixture was diluted with Et₂O (3 mL), solids were allowed to settle, and the solution was drawn up into a 6 mL disposable plastic syringe using a 1" 22G disposable

needle. The needle was removed, replaced with a Whatman syringe filter, and the solution was dispensed into a 40 mL vial. The reaction vial was rinsed with a further portion of Et₂O (5 mL) which was also passed through a syringe filter. The combined filtrate was concentrated *in vacuo*. NaHCO₃ (5 equiv.), CaCl₂ (5 equiv.), anhydrous Et₂O (5 mL) and a magnetic stir bar were added to the residue which was stirred for 1 h at rt. Stirring was stopped, the mixture was allowed to settle, drawn up into a 6 mL disposable syringe and passed through a syringe filter. The filtrate was concentrated *in vacuo* to afford the desired neopentyl ester product. For full experimental details, ¹H NMR and ¹³C NMR spectra see Supplementary Methods.

Synthesis of TIDA boronates

Boronic acid (2 mmol, 1 equiv.) and TIDA (406 mg, 2 mmol, 1 equiv.) were suspended in 2:1 benzene/DMSO (45 mL). A Dean-Stark apparatus fitted with a reflux condenser was attached and the mixture was heated to reflux for 3 h, periodically draining the collection trap a total of 3 times. The reaction mixture was cooled to room temperature, diluted with EtOAc (200 mL), transferred to a separatory funnel, washed with brine (5 x 20 mL), dried over Na₂SO₄, filtered through cotton, and concentrated *in vacuo*. The residue was suspended in acetone (5 mL) and 1:1 hexanes/Et₂O (200 mL) was added causing precipitation of the TIDA boronate product which was collected by vacuum filtration onto a medium porosity fritted funnel. For full experimental details, ¹H NMR and ¹³C NMR spectra see Supplementary Methods.

Cross-coupling of boronic esters with TIDA boronate bifunctionals

In an argon filled glovebox, an oven dried 7 mL vial equipped with a stir bar was charged with halo-TIDA boronate (1 equiv.), neopentyl ester (1.2 equiv.), potassium trimethylsilanolate (1.5 equiv.) and Pd-P(tBu)₃-G3 precatalyst (Sigma Aldrich #804851, CAS 1445086-17-8) (0.10 equiv.). The vial was sealed with a PTFE septum cap, removed from the glovebox and anhydrous THF (1 mL) was added via syringe. *If the neopentyl ester was a liquid it was added at this point via syringe through the PTFE septum cap.* The vial was placed in a pre-equilibrated aluminum heating block at the desired reaction temperature (rt, 50 °C, or 60 °C) and stirred at 500 rpm for 5 minutes. The vial was removed from the heating block and cooled to room temperature and purified.

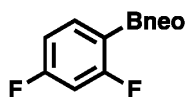
Example 2: Synthesis of Boronic Esters

General Procedure 1 (GP1) Synthesis of Neopentyl Boronic Esters

Boronic acid (1 equiv.) and neopentyl glycol (1.05 equiv.) were added to a 7 mL vial equipped with a magnetic stir bar. Anhydrous Et₂O (1 mL) was added followed by MgSO₄ (2

equiv.). The vial was sealed with a screw cap and the mixture was stirred overnight at room temperature. The mixture was diluted with Et₂O (3 mL), solids were allowed to settle, and the solution was drawn up into a 6 mL disposable plastic syringe using a 1" 22G disposable needle. The needle was removed, replaced with a Whatman syringe filter, and the solution was dispensed into a 40 mL vial. The reaction vial was rinsed with a further portion of Et₂O (5 mL) which was also passed through a syringe filter. The combined filtrate was concentrated *in vacuo*. NaHCO₃ (5 equiv.), CaCl₂ (5 equiv.), anhydrous Et₂O (5 mL) and a magnetic stir bar were added to the residue which was stirred for 1 h at rt. Stirring was stopped, the mixture was allowed to settle, drawn up into a 6 mL disposable syringe and passed through a syringe filter.

The filtrate was concentrated *in vacuo* to afford the desired neopentyl ester product.



(2,4-difluorophenyl)boronic acid neopentyl ester (SI-1)

Prepared according to **GPI** using (2,4-fluorophenyl)boronic acid (158 mg, 1 mmol) in 75% yield (168 mg).

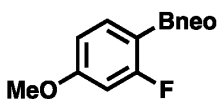
¹H NMR (500 MHz, Chloroform-*d*) δ 1.04 (s, 6H), 3.79 (s, 4H), 6.74 (td, *J* = 9.7, 2.4 Hz, 1H), 6.84 (td, *J* = 8.4, 2.4 Hz, 1H), 7.71 (q, *J* = 7.6 Hz, 1H).

¹³C NMR (126 MHz, Chloroform-*d*) δ 22.0, 32.0, 72.6, 103.8 (dd, *J* = 28.7, 24.1 Hz), 111.0 (dd, *J* = 19.9, 3.6 Hz), 137.6 (dd, *J* = 10.0 Hz), 165.2 (dd, *J* = 251.5, 12.6 Hz), 167.9 (dd, *J* = 252.9, 11.7 Hz).

¹¹B NMR (161 MHz, Chloroform-*d*) δ 25.9.

¹⁹F NMR (471 MHz, Chloroform-*d*) δ -106.71 (p, *J* = 8.8 Hz), -100.63 (td, *J* = 10.2, 7.4 Hz).

HRMS ESI (M+H⁺) C₁₁H₁₃O₂BF₂ calc 226.0977 Found 226.0980.



(2-fluoro-4-methoxyphenyl)boronic acid neopentyl ester (SI-2)

Prepared according to **GPI** using (2-fluoro-4-methoxyphenyl)boronic acid (170 mg, 1 mmol) in 84% yield (200 mg).

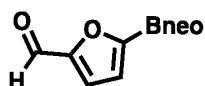
¹H NMR (500 MHz, Chloroform-*d*) δ 1.03 (s, 6H), 3.78 (s, 4H), 3.81 (s, 3H), 6.55 (dd, *J* = 11.7, 2.3 Hz, 1H), 6.67 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.64 (t, *J* = 8.0 Hz, 1H).

¹³C NMR (126 MHz, Chloroform-*d*) δ 22.0, 32.0, 55.6, 72.5, 101.3 (d, *J* = 28.5 Hz), 109.9 (d, *J* = 2.8 Hz), 137.2 (d, *J* = 10.4 Hz), 163.4 (d, *J* = 11.7 Hz), 168.6 (d, *J* = 250.1 Hz).

¹¹B NMR (161 MHz, Chloroform-*d*) δ 26.0.

¹⁹F NMR (471 MHz, Chloroform-*d*) δ -116.17 (dd, *J* = 12.3, 9.3 Hz).

5 **HRMS** ESI (*M*⁺) C₁₂H₁₆O₃BF calc 238.1177 Found 238.1181.



(5-formylfuran2-yl)boronic acid neopentyl glycol ester (SI-3)

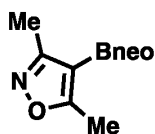
Prepared according to **GP1** using 4-formylfuranboronic acid (1 g, 7.15 mmol, 1 equiv.) and neopentyl glycol (759 mg, 7.29 mmol, 1.02 equiv.) in 92% yield (1.37 g).

¹H NMR (400 MHz, Chloroform-*d*) δ 1.03 (s, 6H), 3.78 (s, 4H), 7.05 (d, *J* = 3.5 Hz, 1H), 7.23 (d, *J* = 3.5 Hz, 1H), 9.78 (s, 1H).

¹³C NMR (126 MHz, Chloroform-*d*) δ 22.0, 32.3, 72.6, 119.1, 122.9, 155.9, 179.2.

¹¹B NMR (161 MHz, Chloroform-*d*) δ 23.1.

15 **HRMS** ESI (*M*⁺) C₁₀H₁₄O₄B calc 209.0985 Found 209.0983.



(3,5-dimethylisoxazol-4-yl)boronic acid neopentyl ester (SI-4)

Prepared according to **GP1** using (3,5-dimethylisoxazol-4-yl)boronic acid (141 mg, 1 mmol) in 84% yield (176 mg).

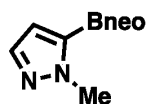
¹H NMR (500 MHz, Chloroform-*d*) δ 1.01 (s, 6H), 2.30 (s, 3H), 2.47 (s, 3H), 3.71 (s, 4H).

¹³C NMR (126 MHz, Chloroform-*d*) δ 12.1, 13.0, 22.0, 32.0, 72.2, 164.0, 177.1.

¹¹B NMR (161 MHz, Chloroform-*d*) δ 25.8.

HRMS ESI (*M*+*H*⁺) C₁₀H₁₇NO₃B calc 210.1301 Found 210.1303.

25



(1-methyl-1H-pyrazol-5-yl)boronic acid neopentyl ester (SI-5)

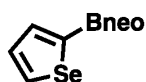
Prepared according to **GP1** using (1-methyl-1H-pyrazol-5-yl)boronic acid (126 mg, 1 mmol) in 80% yield (154 mg).

¹H NMR (500 MHz, Chloroform-*d*) δ 1.00 (s, 6H), 3.70 (s, 4H), 3.90 (s, 3H), 7.56 (s, 1H), 7.70 (s, 1H).

¹³C NMR (126 MHz, Chloroform-*d*) δ 22.1, 32.2, 38.7, 72.2, 136.3, 145.1.

¹¹B NMR (161 MHz, Chloroform-*d*) δ 25.8.

5 **HRMS** ESI ($M+H^+$) $C_9H_{16}N_2O_2B$ calc 195.1305 Found 195.1301.



Selenophen-2-ylboronic acid neopentyl ester (SI-6)

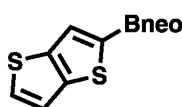
Prepared according to **GP1** using selenophen-2-ylboronic acid (175 mg, 1 mmol) in
10 86% yield (209 mg).

¹H NMR (500 MHz, Chloroform-*d*) δ 1.03 (s, 6H), 3.76 (s, 4H), 7.43 (dd, $J = 5.1, 3.7$ Hz, 1H), 7.87 (d, $J = 3.6$ Hz, 1H), 8.29 (d, $J = 5.2$ Hz, 1H).

¹³C NMR (126 MHz, Chloroform-*d*) δ 22.1, 32.2, 72.6, 131.1, 136.6, 138.0.

¹¹B NMR (161 MHz, Chloroform-*d*) δ 25.7.

15 **HRMS** ESI ($M+H^+$) $C_9H_{13}O_2BSe$ calc 244.0174 Found 244.0176.



Thieno[3,2-*b*]thiophen-2-ylboronic acid neopentyl ester (SI-7)

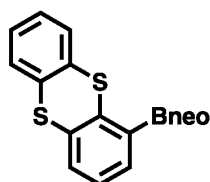
Prepared according to **GP1** using thieno[3,2-*b*]thiophen-2-ylboronic acid (184 mg, 1
20 mmol) in 82% yield (207 mg).

¹H NMR (500 MHz, Chloroform-*d*) δ 1.04 (s, 6H), 3.78 (s, 4H), 7.27 (d, $J = 5.6$ Hz, 1H), 7.45 (d, $J = 5.2$ Hz, 1H), 7.70 (s, 1H).

¹³C NMR (126 MHz, Chloroform-*d*) δ 22.1, 32.3, 72.6, 119.7, 127.6, 129.5, 140.9, 145.0.

¹¹B NMR (161 MHz, Chloroform-*d*) δ 25.1.

25 **HRMS** ESI ($M+H^+$) $C_{11}H_{13}O_2BS_2$ calc 252.0450 Found 252.0453.



Thianthren-1-ylboronic acid neopentyl ester (SI-8)

Prepared according to **GP1** using thianthren-1-ylboronic acid (262 mg, 1 mmol) in 86% yield (286 mg). [2 mL of THF was added during complexation with neopentyl glycol to solubilize the boronic acid].

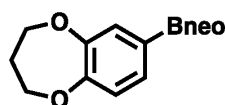
¹H NMR (500 MHz, Chloroform-*d*) δ 1.11 (s, 6H), 3.85 (s, 4H), 7.16 – 7.24 (m, 3H), 7.43 – 7.53 (m, 3H), 7.56 (m, 1H).

¹³C NMR (126 MHz, Chloroform-*d*) δ 22.1, 32.0, 72.7, 126.7, 127.5, 127.6, 128.5, 128.9, 130.7, 133.3, 134.4, 136.3, 136.6, 141.5.

¹¹B NMR (161 MHz, Chloroform-*d*) δ 26.9.

HRMS ESI (M+Na⁺) C₁₇H₁₇O₂BS₂Na calc 351.0661 Found 351.0664.

10



(3,4-dihydro-2H-benzo[b][1,4]dioxepin-7-yl)boronic acid neopentyl ester (SI-9)

Prepared according to **GP1** using (3,4-dihydro-2H-benzo[b][1,4]dioxepin-7-yl)boronic acid (95 mg, 0.49 mmol) in >95% yield (124 mg).

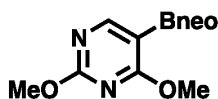
¹H NMR (500 MHz, Chloroform-*d*) δ 1.01 (s, 6H), 2.19 (h, *J* = 5.7 Hz, 2H), 3.74 (s, 4H), 4.21 (dt, *J* = 18.9, 5.6 Hz, 6H), 6.94 (d, *J* = 7.9 Hz, 1H), 7.36 (m, 1H), 7.41 (s, 1H).

¹³C NMR (126 MHz, Chloroform-*d*) δ 21.9, 31.7, 31.9, 70.4, 72.3, 120.8, 127.1, 129.3, 150.5, 153.5.

¹¹B NMR (161 MHz, Chloroform-*d*) δ 26.2.

HRMS ESI (M+H⁺) C₁₄H₁₉O₄B calc 262.1376 Found 262.1377.

20



(2,4-dimethoxypyrimidin-5-yl)boronic acid neopentyl ester (SI-10)

Prepared according to **GP1** using (2,4-dimethoxypyrimidin-5-yl)boronic acid (183 mg, 1 mmol) in 77% yield (195 mg).

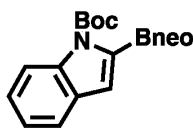
¹H NMR (500 MHz, Chloroform-*d*) δ 1.02 (s, 6H), 3.76 (s, 4H), 4.00 (s, 6H), 8.57 (s, 1H).

¹³C NMR (126 MHz, Chloroform-*d*) δ 22.0, 32.0, 54.3, 54.8, 72.6, 166.7, 167.0, 174.8.

¹¹B NMR (161 MHz, Chloroform-*d*) δ 26.2.

HRMS ESI (M+H⁺) C₁₁H₁₇N₂O₄B calc 253.1360 Found 253.1351.

30



(1-(*tert*-butoxycarbonyl)-1*H*-indol-2-yl)boronic acid neopentyl ester (SI-11)

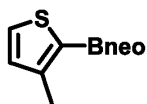
Prepared according to **GP1** using ((1-(*tert*-butoxycarbonyl)-1*H*-indol-2-yl)boronic acid (261 mg, 1 mmol, 1 equiv.) and neopentyl glycol (109 mg, 1.05 mmol 1.05 equiv.) in
 5 85% yield (280 mg).

¹H NMR (500 MHz, Acetone-*d*₆) δ 1.09 (s, 6H), 1.68 (s, 9H), 3.78 (s, 4H), 6.76 (d, *J* = 0.9 Hz, 1H), 7.19 (td, *J* = 7.5, 1.0 Hz, 1H), 7.29 (ddd, *J* = 8.3, 7.1, 1.3 Hz, 1H), 7.56 (dt, *J* = 7.8, 1.0 Hz, 1H), 8.07 (dd, *J* = 8.3, 1.0 Hz, 1H).

¹³C NMR (126 MHz, Acetone-*d*₆) δ 22.2, 28.5, 32.7, 73.1, 84.6, 114.8, 114.9, 115.8, 115.9,
 10 121.8, 123.5, 125.3, 131.9, 137.9, 151.7.

¹¹B NMR (161 MHz, Acetone-*d*₆) δ 30.8.

HRMS EI (*M*⁺) C₁₈H₂₄NO₄B calc 329.1798 Found 329.1806.



(3-methylthiophen-2-yl)boronic acid (SI-12)

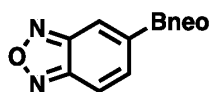
Prepared according to **GP1** using (3-methylthiophen-2-yl)boronic acid (1 g, 7.04 mmol, 1 equiv.) and neopentyl glycol (748.22 mg, 7.12 mmol, 1.02 equiv.) in 46% yield.

¹H NMR (500 MHz, CDCl₃) δ 1.03 (s, 6H), 3.76 (s, 4H), 6.95 (d, *J* = 4.6 Hz, 1H), 7.42 (d, *J* = 4.7 Hz, 1H).

¹³C NMR (126 MHz, CDCl₃) δ 15.9, 21.9, 31.9, 72.3, 130.0, 131.7, 147.5.

20 **¹¹B NMR** (161 MHz, CDCl₃) δ 25.6.

HRMS ESI (*M*⁺) C₁₀H₁₆BO₂S calc 211.0964 Found 211.0964



Benzo[*c*][1,2,5]oxadiazol-5-ylboronic acid neopentyl ester (SI-13)

Prepared according to **GP1** using benzo[*c*][1,2,5]oxadiazol-5-ylboronic acid neopentyl ester (1 mmol) in >95% yield (230 mg) [*THF* was used as the solvent].

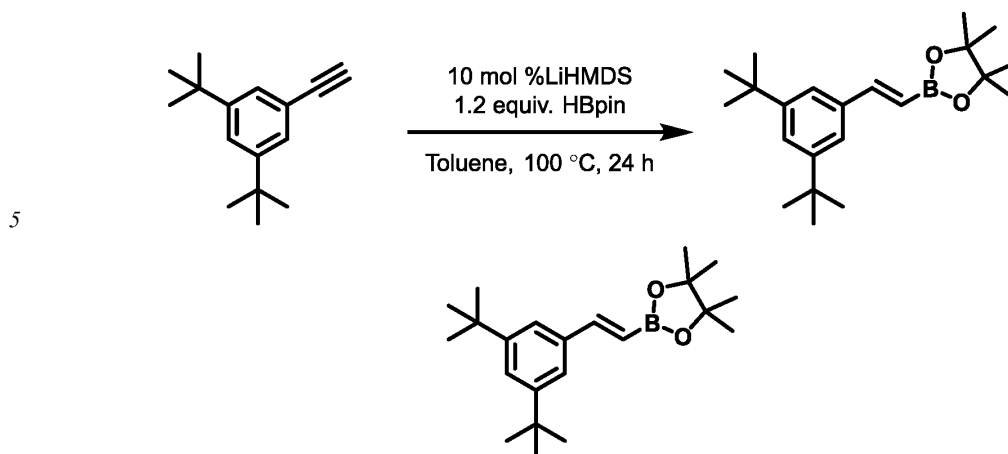
¹H NMR (500 MHz, Chloroform-*d*) δ 1.05 (s, 6H), 3.81 (s, 4H), 7.75 (d, *J* = 1.0 Hz, 2H), 8.32 (s, 1H).

¹³C NMR (126 MHz, Chloroform-*d*) δ 22.0, 32.1, 72.7, 114.9, 123.6, 135.1, 149.4, 149.9.

^{11}B NMR (161 MHz, Chloroform-*d*) δ 25.9.

HRMS ESI (M^+) $\text{C}_{11}\text{H}_{13}\text{BN}_2\text{O}_3$ calc 232.1019 Found 232.1025.

Synthesis of SI-14



(E)-(3,5-di-tert-butylstyryl)boronic acid pinacol ester (SI-14)

In a glovebox, to a flame dried vial charged with a stir bar was added Lithium hexamethyldisilazide (244 mg, 1.46 mmol, 0.1 equiv.) and pinacol borane (2.2 g, 17.5 mmol, 1.2 equiv.). The vial was removed from the glovebox and 1,3-di-tert-butyl-5-ethynylbenzene¹ was subsequently added (3.1251 g, 14.58 mmol) followed by toluene (20 mL). The reaction mixture was stirred for 2 days at 100 °C. The reaction mixture was cooled to room temperature and filtered through a plug of silica eluting with 1:20 Et₂O:Hexane to give the resulting pinacol boronic acid (3.98 g, 80% yield)

15 ^1H NMR (500 MHz, CDCl_3) δ 1.19 – 1.23 (m, 30 h), 6.07 (d, J = 18.4 Hz, 1 H), 7.24 – 7.29 (m, 3H), 7.33 (d, J = 18.4 Hz, 1H)

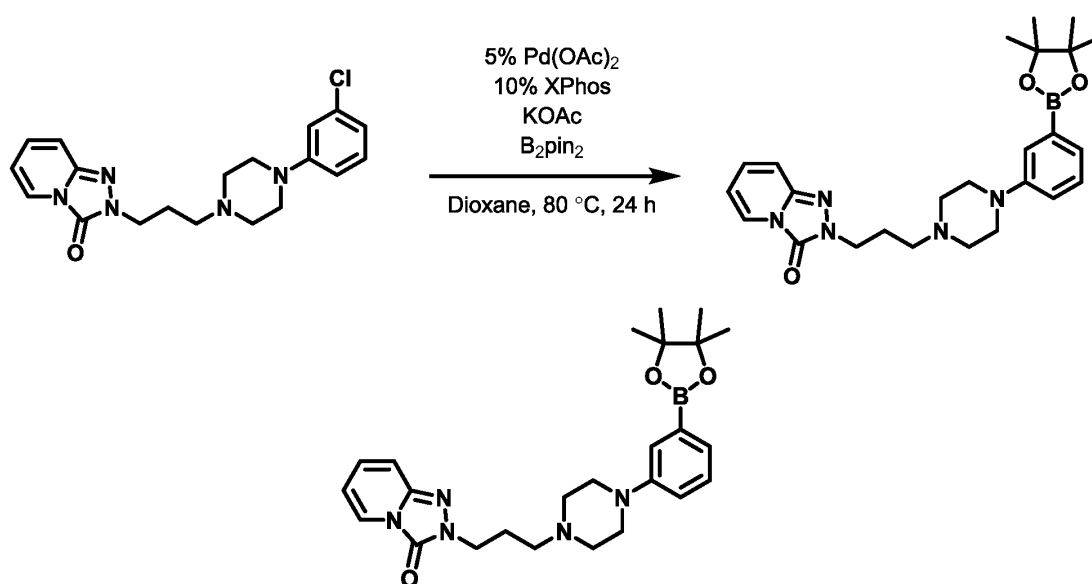
^{13}C NMR (126 MHz, CDCl_3) δ 25.0, 31.5, 35.0, 83.4, 121.6, 123.4, 136.8, 150.8, 151.0.

^{11}B NMR (161 MHz, CDCl_3) δ 30.2.

HRMS EI (M^+) $\text{C}_{22}\text{H}_{35}\text{O}_2\text{B}$ calc 342.27302 Found 342.27320

20

Synthesis of SI-15



(3-(4-(3-(3-oxo-[1,2,4]triazolo[4,3-a]pyridin-2(3H)-yl)propyl)piperazin-1-yl)phenyl)boronic acid pinacol ester (SI-15)

Adapted from Billingsley et al.³ to an oven-dried 40-mL vial equipped with a stir bar was added Pd(OAc)₂ (31.7 mg, 0.14 mmol, 0.05 equiv.), XPhos (134.6 mg, 0.28 mmol, 0.1 equiv.), B₂pin₂ (860.42, 3.39 mmol, 1.2 equiv.), and KOAc (554.2 mg, 5.65 mmol, 2 equiv.). The vial was sealed with a septa cap and removed from the glovebox. A solution of Trazodone (1.05 g, 2.82 mmol, 1 equiv.) in 6 mL dioxane was added to the reaction mixture. The reaction was stirred at 80 °C for 24 h. The reaction was then cooled to room temperature, diluted with ethyl acetate (50 mL), and washed with brine (2 x 50 mL). The brine was then extracted with ethyl acetate (2 x 50 mL), dried with Na₂SO₄, and concentrated *in vacuo*. The crude mixture was purified via silica gel chromatography (1:1 hexane:ethyl acetate) to yield the product as a yellow oil in 84% yield (1.10 g).

¹H NMR (500 MHz, Acetone) δ 1.32 (s, 12H), 2.00 (p, *J* = 6.8 Hz, 2H), 2.46 (t, *J* = 6.7 Hz, 2H), 2.53 – 2.59 (m, 4H), 3.02 – 3.24 (m, 4H), 4.03 (t, *J* = 6.8 Hz, 2H), 6.57 (ddd, *J* = 7.2, 6.1, 1.2 Hz, 1H), 7.04 (ddd, *J* = 8.0, 2.8, 1.4 Hz, 1H), 7.10 – 7.25 (m, 4H), 7.29 (d, *J* = 2.7 Hz, 1H), 7.64 – 7.82 (m, 1H).

¹³C NMR (126 MHz, Acetone) δ 20.5, 24.9, 25.2, 26.7, 44.8, 49.9, 54.0, 56.3, 82.6, 84.4, 111.1, 116.1, 119.7, 122.6, 124.6, 126.4, 129.2, 130.6, 142.1, 149.3, 152.0, 171.9.

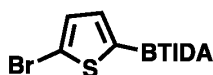
¹¹B NMR (161 MHz, Acetone) δ 31.1.

HRMS ESI (M+H⁺) C₂₅H₃₅BN₅O₃ calc 464.2833 Found 464.2844.

Synthesis of TIDA Boronates

General Procedure 2 (GP2) – Synthesis of TIDA boronates from boronic acids

Boronic acid (2 mmol, 1 equiv.) and TIDA (406 mg, 2 mmol, 1 equiv.) were suspended in 2:1 benzene/DMSO (45 mL). A Dean-Stark apparatus fitted with a reflux condenser was attached and the mixture was heated to reflux for 3 h, periodically draining the collection trap a total of 3 times. The reaction mixture was cooled to room temperature, diluted with EtOAc (200 mL), transferred to a separatory funnel, washed with brine (5 x 20 mL), dried over Na₂SO₄, filtered through cotton, and concentrated *in vacuo*. The residue was suspended in acetone (5 mL) and 1:1 hexanes/Et₂O (200 mL) was added causing precipitation of the TIDA boronate product which was collected by vacuum filtration onto a medium porosity fritted funnel.



(5-bromothiophen-2-yl)boronic acid TIDA ester (SI-16)

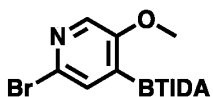
Prepared according to GP2 using (5-Bromothiophen-2-yl)boronic acid (414 mg, 2 mmol, 1 equiv.) in 60% yield (450 mg).

¹H NMR (500 MHz, Chloroform-*d*) δ 1.61 (s, 6H), 1.78 (s, 6H), 2.59 (s, 3H), 7.05 (d, *J* = 3.6 Hz, 1H), 7.08 (d, *J* = 3.7 Hz, 1H).

¹³C NMR (126 MHz, Chloroform-*d*) δ 37.61, 116.84, 131.15, 135.29, 174.07.

¹¹B NMR (161 MHz, Chloroform-*d*) δ 8.38.

HRMS ESI (M+H⁺) C₁₃H₁₈BN₄O₅S⁷⁹Br calc 374.0233 Found 374.0241.



(2-bromo-5-methoxypyridin-4-yl)boronic acid TIDA ester (SI-17)

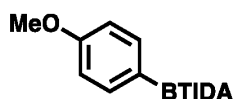
Prepared according to GP2 using (2-Bromo-5-methoxypyridin-4-yl)boronic acid (464 mg, 2 mmol, 1 equiv.) in 27% yield (214 mg).

¹H NMR (500 MHz, Chloroform-*d*) δ 1.59 (s, 6H), 1.77 (s, 6H), 2.62 (s, 3H), 3.89 (s, 3H), 7.60 (s, 1H), 8.02 (s, 1H).

¹³C NMR (126 MHz, Chloroform-*d*) δ 37., 57.3, 133.6, 134.1, 135.1, 158., 174.0.

¹¹B NMR (161 MHz, Chloroform-*d*) δ 8.6.

HRMS ESI (M+H⁺) C₁₅H₂₁BN₂O₅⁷⁹Br calc 399.0727 Found 399.0725.

**(4-methoxyphenyl)boronic acid TIDA ester (SI-18)**

Prepared according to **GP2** using (4-methoxyphenyl)boronic acid (2.00 g, 13.2 mmol, 1 equiv.) and TIDA (2.67 g, 13.2 mmol, 1 equiv.) in 73% yield (3.1 g).

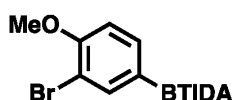
5 **¹H NMR** (500 MHz, Chloroform-*d*) δ 1.54 (s, 6H), 1.78 (s, 6H), 2.46 (s, 3H), 3.81 (s, 3H), 6.88 (d, J = 8.2 Hz, 2H), 7.47 (d, J = 8.2 Hz, 2H).

¹³C NMR (126 MHz, Chloroform-*d*) δ 37.3, 55.1, 113.4, 135.4, 160.5, 174.8.

¹¹B NMR (161 MHz, Chloroform-*d*) δ 9.6.

HRMS ESI ($M+H^+$) $C_{16}H_{23}BNO_5$ calc 320.1669 Found 320.1659.

10

**(3-bromo-4-methoxyphenyl)boronic acid TIDA ester (SI-19)**

SI-1 (319 mg, 1 mmol, 1 equiv.) and NBS (182 mg, 1.02 mmol, 1.02 equiv.) were suspended in acetone (4 mL) and vigorously stirred at room temperature. 1M HCl(aq) (10 mL)
15 was added and the reaction mixture stirred for 30 min at rt. A further portion of NBS (10 mg, ca. 0.1 equiv.) was added and the reaction mixture stirred for 5 min. The reaction mixture was concentrated in vacuo and the residue was triturated with Et₂O (3 x 20 mL) with sonication, keeping the solid. Drying of the resultant solid under vacuum afforded **17** as a white solid (73%, 291 mg).

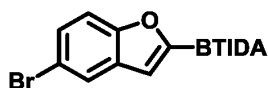
20 **¹H NMR** (500 MHz, Chloroform-*d*) δ 1.55 (s, 6H), 1.79 (s, 6H), 2.49 (s, 3H), 3.90 (s, 3H), 6.88 (d, J = 8.3 Hz, 1H), 7.46 (dd, J = 8.3, 1.9 Hz, 1H), 7.69 (d, J = 1.8 Hz, 1H).

¹³C NMR (126 MHz, Chloroform-*d*) δ 37.4, 56.3, 111.6, 111.9, 134.5, 138.8, 156.0, 174.6.

¹¹B NMR (161 MHz, Chloroform-*d*) δ 9.23.

HRMS ESI ($M+H^+$) $C_{16}H_{22}BNO_5^{79}Br$ calc 398.0774 Found 398.0765.

25

**(5-bromobenzofuran-2-yl)boronic acid TIDA ester (SI-20)**

Prepared according to **GP2** using (5-bromobenzofuran-2-yl)boronic acid (1.03 g, 4.28 mmol, 1 equiv.) and TIDA (869 mg, 4.28 mmol, 1 equiv.) in 79% yield (1.75 g).

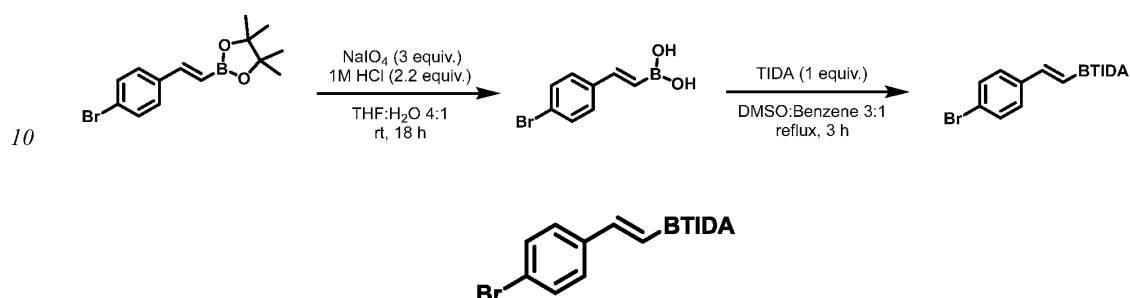
¹H NMR (500 MHz, Chloroform-*d*) δ 1.66 (s, 6H), 1.80 (s, 6H), 2.62 (s, 3H), 7.09 (d, J = 0.9 Hz, 1H), 7.29 – 7.42 (m, 2H), 7.70 (d, J = 1.8 Hz, 1H).

¹³C NMR (126 MHz, Chloroform-*d*) δ 37.1, 40.9, 112.8, 115.6 (d, J = 5.5 Hz), 123.8, 127.5, 129.9, 156.0, 173.9.

5 **¹¹B NMR** (161 MHz, Chloroform-*d*) δ 7.1.

HRMS ESI ($M+H^+$) $C_{17}H_{20}NO_5BrB$ calc 408.0618 found 408.0616

Synthesis of SI-20



(E)-(4-bromostyryl)boronic acid TIDA ester (SI-21)

To a flask charged with a stir bar, the (E)-(4-bromostyryl)boronic acid pinacol ester² (1.9 g, 6.12 mmol, 1 equiv.) and sodium periodate (3.9g, 18.37 mmol, 3 equiv.) were added and dissolved in a 4:1 mixture of THF:H₂O (24 mL) and stirred. After 10 minutes, 1.0 M aqueous HCl was added dropwise (2.78 mL, 2.78 mmol, 2.2 equiv.), and the solution was stirred at room temperature for 18 hours. The reaction mixture was diluted with 100 mL of water and washed with Et₂O (3 x 100 mL) and dried with Na₂SO₄. 20 mL DMSO was added to the ether solution of boronic acid and the ether was concentrated by rotary evaporation to afford an 0.3 M solution of the boronic acid in DMSO. To the boronic acid solution was added 60 mL of Benzene and tetramethyl N-methyliminodiacetic acid (1.25 g, 6.13 mmol, 1 equiv.). The flask was fitted with a Dean Starke trap and reflux condenser filled with benzene, and the solution was heated to reflux with stirring for 3 hours. The reaction mixture was cooled to room temperature, diluted in 100 mL of ethyl acetate, transferred to a separatory funnel, washed with brine (3 x 100 mL), and dried with Na₂SO₄. The solvent was evaporated under reduced pressure and the solid was triturated with Et₂O and filtered to give (**18**) as a white solid (1.32 g, 55% yield over 2 steps)

15

20

25

¹H NMR (500 MHz, CDCl₃) δ 1.62 (s, 6H), 1.77 (s, 6H), 2.57 (s, 3H), 6.18 (d, J = 18.1 Hz, 1H), 7.01 (d, J = 18.0 Hz, 1H), 7.30 (d, J = 8.5 Hz, 2H), 7.45 (d, J = 8.5 Hz, 2H).

30

^{13}C NMR (126 MHz, CDCl_3) δ 36.8, 122.3, 128.3, 131.8, 136.8, 142.5, 174.4.

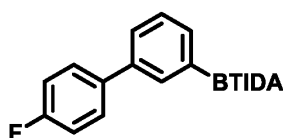
^{11}B NMR (161 MHz, CDCl_3) δ 9.2.

HRMS ESI ($\text{M}+\text{H}^+$) $\text{C}_{17}\text{H}_{22}\text{NO}_4^{79}\text{BrB}$ calc 394.0825 Found 394.0824

5 Example 3: Cross-coupling Reactions with TIDA Boronates

General Procedure 3 (GP3) Rapid Cross-Coupling

In an argon filled glovebox, an oven dried 7 mL vial equipped with a stir bar was charged with halo-TIDA boronate (1 equiv.), neopentyl ester (1.2 equiv.), potassium trimethylsilanolate (1.5 equiv.) and Pd-P(tBu)₃-G3 precatalyst (Sigma Aldrich #804851, CAS 1445086-17-8) (0.10 equiv.). The vial was sealed with a PTFE septum cap, removed from the glovebox and anhydrous THF (1 mL) was added via syringe. *If the neopentyl ester was a liquid it was added at this point via syringe through the PTFE septum cap.* The vial was placed in a pre-equilibrated aluminum heating block at the desired reaction temperature (rt, 50 °C, or 60 °C) and stirred at 500 rpm for 5 minutes. The vial was removed from the heating block and cooled to room temperature and purified as specified.



(4'-fluoro-[1,1'-biphenyl]-3-yl)boronic acid TIDA ester (1)

Prepared according to **GP3** at rt, (3-bromophenyl)boronic acid TIDA ester⁴ (73.6 mg, 0.2 mmol, 1 equiv.) and (4-fluorophenyl)boronic acid neopentyl ester (49.9 mg, 0.24 mmol, 1.2 equiv.) in 94% yield (76.4 mg). The reaction was purified by transferring to a 40 mL vial using Ethyl Acetate (20 mL) and washing with 1 M NaOH_{aq} (2 x 10 mL) and sat. $\text{NH}_4\text{Cl}_{\text{aq}}$ (10 mL). The reaction mixture was dried with Na_2SO_4 , filtered, and concentrated *in vacuo*. Additional impurities were purged *via* trituration with Et_2O (5-10 mL).

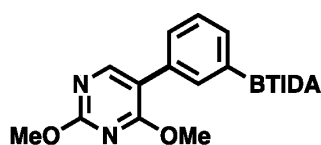
^1H NMR (500 MHz, Chloroform-*d*) δ 1.57 (s, 6H), 1.81 (s, 6H), 2.53 (s, 3H), 7.12 (t, J = 8.7 Hz, 2H), 7.42 (t, J = 7.6 Hz, 1H), 7.50 – 7.57 (m, 4H), 7.70 (d, J = 1.7 Hz, 1H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 37.6, 115.7 (d, J = 21.3 Hz), 128.3 (d, J = 33.0 Hz), 128.9 (d, J = 7.9 Hz), 132.9 (d, J = 54.7 Hz), 137.5 (d, J = 3.3 Hz), 139.8, 162.6 (d, J = 246.3 Hz), 174.8.

^{19}F NMR (471 MHz, Chloroform-*d*) δ -115.78 (m).

^{11}B NMR (161 MHz, Chloroform-*d*) δ 9.4.

HRMS ESI ($\text{M}+\text{H}^+$) $\text{C}_{21}\text{H}_{24}\text{BNO}_4\text{F}$ calc 384.1782 Found 384.1781



(3-(2,4-dimethoxypyrimidin-5-yl)phenyl)boronic acid TIDA ester (2)

Prepared according to **GP3** at 50 °C, (3-bromophenyl)boronic acid TIDA ester (73.6 mg, 0.2 mmol, 1 equiv.) and **SI-10** (60.5 mg, 0.24 mmol, 1.2 equiv.) in 92% yield (78.6 mg).

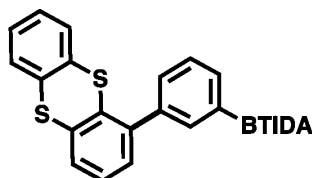
5 The reaction was purified by transferring to a 40 mL vial using Ethyl Acetate (20 mL) and washing with 1 M NaOH_{aq} (2 x 10 mL) and sat. NH₄Cl_{aq} (10 mL). The reaction mixture was dried with Na₂SO₄, filtered, and concentrated *in vacuo*. Additional impurities were purged *via* trituration with Et₂O (5-10 mL).

¹H NMR (500 MHz, Acetone-*d*₆) δ 1.59 (s, 6H), 1.80 (s, 6H), 2.77 (s, 3H), 3.96 (s, 3H), 3.97
10 (s, 3H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.53 (dt, *J* = 7.7, 1.5 Hz, 1H), 7.57 (dt, *J* = 7.4, 1.4 Hz, 1H), 7.73 (s, 1H), 8.30 (s, 1H).

¹³C NMR (126 MHz, Acetone-*d*₆) δ 38.2, 54.4, 55.1, 117.2, 128.6, 130.3, 133.6, 134.1, 135.6, 158.7, 165.7, 169.1, 175.7.

¹¹B NMR (161 MHz, Acetone-*d*₆) δ 9.1.

15 **HRMS** ESI (M+H⁺) C₂₁H₂₇BN₃O₆ calc 428.1993 Found 428.2005.



(3-(thianthren-1-yl)phenyl)boronic acid TIDA ester (3)

Prepared according to **GP3** at rt, (3-bromophenyl)boronic acid TIDA ester (73.6 mg, 0.2 mmol, 1 equiv.) and **SI-8** (78.8 mg, 0.24 mmol, 1.2 equiv.) in >95% yield (96 mg). The reaction was purified by transferring to a 40 mL vial using Ethyl Acetate (20 mL) and washing with 1 M NaOH_{aq} (2 x 10 mL) and sat. NH₄Cl_{aq} (10 mL). The reaction mixture was dried with Na₂SO₄, filtered, and concentrated *in vacuo*. Additional impurities were purged *via* trituration with Et₂O (5-10 mL).

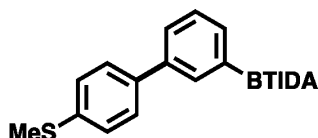
25 **¹H NMR** (500 MHz, Chloroform-*d*) δ 1.61 (s, 6H), 1.82 (s, 6H), 2.62 (s, 3H), 7.17 (t, *J* = 7.4 Hz, 1H), 7.21 – 7.25 (m, 2H), 7.27 – 7.33 (m, 2H), 7.40 (d, *J* = 7.5 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 1H), 7.51 (t, *J* = 8.6 Hz, 2H), 7.59 (s, 1H), 7.65 (d, *J* = 7.4 Hz, 1H).

¹³C NMR (126 MHz, Chloroform-*d*) δ 37.7, 127.3, 127.7, 127.9, 128.0, 128.4, 128.8, 128.9, 129.5, 130.2, 133.5, 135.0, 135.2, 135.4, 135.9, 136.6, 139.8, 142.7, 174.7.

¹¹B NMR (161 MHz, Chloroform-*d*) δ 9.4.

HRMS ESI (M+H⁺) C₂₇H₂₇BNO₄S₂ calc 504.1475 Found 504.1478.

5



(4'-(methylthio)-[1,1'-biphenyl]-3-yl)boronic acid TIDA ester (4)

Prepared according to **GP3** at rt, (3-bromophenyl)boronic acid TIDA ester (73.6 mg, 0.2 mmol, 1 equiv.) and (4-(methylthio)phenyl)boronic acid neopentyl ester (56.7 mg, 0.24 mmol, 1.2 equiv.) in 82% yield (67.6 mg). The reaction was purified by transferring to a 40 mL vial using Ethyl Acetate (20 mL) and washing with 1 M NaOH_{aq} (2 x 10 mL) and sat. NH₄Cl_{aq} (10 mL). The reaction mixture was dried with Na₂SO₄, filtered, and concentrated *in vacuo*. Additional impurities were purged *via* trituration with Et₂O (5-10 mL).

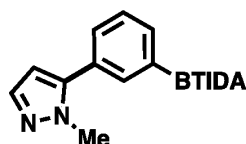
¹H NMR (500 MHz, Chloroform-*d*) δ 1.56 (s, 6H), 1.81 (s, 6H), 2.52 (s, 6H), 7.32 (d, *J* = 8.2 Hz, 2H), 7.41 (t, *J* = 7.5 Hz, 1H), 7.52 – 7.57 (m, 4H), 7.73 (d, *J* = 1.5 Hz, 1H).

¹³C NMR (126 MHz, Chloroform-*d*) δ 16.1, 37.6, 127.1, 127.7, 128.0, 128.4, 132.5, 133.0, 137.8, 138.2, 140.1, 174.8.

¹¹B NMR (161 MHz, Chloroform-*d*) δ 9.4.

HRMS ESI (M+H⁺) C₂₂H₂₇BNO₄S calc 412.1754 Found 412.1753.

20



(3-(1-methyl-1H-pyrazol-5-yl)phenyl)boronic acid TIDA ester (5)

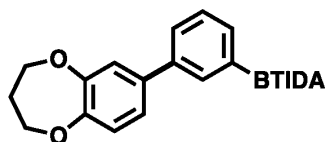
Prepared according to **GP3** at 50 °C, (3-bromophenyl)boronic acid TIDA ester (73.6 mg, 0.2 mmol, 1 equiv.) and **SI-5** (46.6 mg, 0.24 mmol, 1.2 equiv.) in 86% yield (63.5 mg). The reaction was purified by transferring to a 40 mL vial using Ethyl Acetate (20 mL) and washing with 1 M NaOH_{aq} (2 x 10 mL) and sat. NH₄Cl_{aq} (10 mL). The reaction mixture was dried with Na₂SO₄, filtered, and concentrated *in vacuo*. Additional impurities were purged *via* trituration with Et₂O (5-10 mL).

¹H NMR (500 MHz, Chloroform-*d*) δ 1.57 (s, 6H), 1.81 (s, 6H), 2.52 (s, 3H), 3.95 (s, 3H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.44 (dd, *J* = 7.8 Hz, 2H), 7.63 (d, *J* = 4.8 Hz, 2H), 7.74 (s, 1H).

¹³C NMR (126 MHz, Chloroform-*d*) δ 37.6, 39.2, 123.4, 126.7, 127.3, 128.5, 131.2, 132.2, 136.8, 174.8.

5 **¹¹B NMR** (161 MHz, Chloroform-*d*) δ 9.5.

HRMS ESI ($M+H^+$) $C_{19}H_{25}BN_3O_4$ calc 370.1938 Found 370.1942.



(3-(3,4-dihydro-2H-benzo[b][1,4]dioxepin-7-yl)phenyl)boronic acid TIDA ester (6)

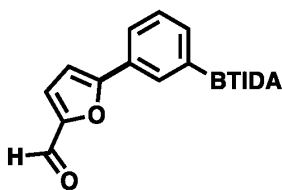
Prepared according to **GP3** at rt, (3-bromophenyl)boronic acid TIDA ester (73.6 mg, 0.2 mmol, 1 equiv.) and **SI-9** (62.9 mg, 0.24 mmol, 1.2 equiv.) in 94% yield (82.4 mg). The reaction was purified by transferring to a 40 mL vial using Ethyl Acetate (20 mL) and washing with 1 M NaOH_{aq} (2 x 10 mL) and sat. NH₄Cl_{aq} (10 mL). The reaction mixture was dried with Na₂SO₄, filtered, and concentrated *in vacuo*. Additional impurities were purged *via* trituration with Et₂O (5-10 mL).

15 **¹H NMR** (500 MHz, Chloroform-*d*) δ 1.56 (s, 6H), 1.81 (s, 6H), 2.22 (p, *J* = 5.6 Hz, 2H), 2.52 (s, 3H), 4.25 (q, *J* = 6.0 Hz, 4H), 7.03 (d, *J* = 8.2 Hz, 1H), 7.14 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.20 (d, *J* = 2.2 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.52 (t, *J* = 7.3 Hz, 2H), 7.70 (s, 1H).

¹³C NMR (126 MHz, Chloroform-*d*) δ 32.0, 37.6, 70.8, 120.4, 122.0, 122.2, 128.0, 128.4, 132.5, 132.9, 136.8, 139.8, 150.8, 151.4, 174.8.

20 **¹¹B NMR** (161 MHz, Chloroform-*d*) δ 9.5.

HRMS ESI ($M+H^+$) $C_{24}H_{29}BNO_6$ calc 438.2088 Found 438.2081.



(3-(5-formylfuran-2-yl)phenyl)boronic acid TIDA ester (7)

25 Prepared according to **GP3** at rt, (3-bromophenyl)boronic acid TIDA ester (73.6 mg, 0.2 mmol, 1 equiv.) and **SI-3** (49.9 mg, 0.24 mmol, 1.2 equiv.) in 88% yield (66.5 mg). The reaction was purified by transferring to a 40 mL vial using Ethyl Acetate (20 mL) and washing with 1 M NaOH_{aq} (2 x 10 mL) and sat. NH₄Cl_{aq} (10 mL). The reaction mixture was dried with

Na₂SO₄, filtered, and concentrated *in vacuo*. Additional impurities were purged *via* trituration with Et₂O (5-10 mL).

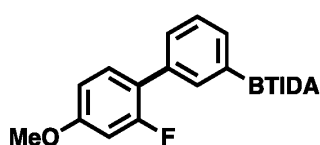
¹H NMR (500 MHz, Chloroform-*d*) δ 1.57 (s, 6H), 1.81 (s, 6H), 2.55 (s, 3H), 6.87 (d, *J* = 3.7 Hz, 1H), 7.32 (d, *J* = 3.7 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.61 (d, *J* = 7.5 Hz, 1H), 7.84 (d, *J* = 7.7 Hz, 1H), 7.94 (s, 1H), 9.67 (s, 1H).

¹³C NMR (126 MHz, Chloroform-*d*) δ 37.5, 108.1, 126.5, 128.7, 128.8, 130.7, 135.4, 152.3, 159.7, 174.6, 177.5.

¹¹B NMR (161 MHz, Chloroform-*d*) δ 9.2.

HRMS ESI (M+H⁺) C₂₀H₂₃BNO₆ calc 384.1618 Found 384.1617.

10



(2'-fluoro-4'-methoxy-[1,1'-biphenyl]-3-yl)boronic acid TIDA ester (8)

Prepared according to **GP3** at rt, (3-bromophenyl)boronic acid TIDA ester (73.6 mg, 0.24 mmol, 1 equiv.) and **SI-2** (57.1 mg, 0.24 mmol, 1.2 equiv.) in 89% yield (74.0 mg). The reaction was purified by transferring to a 40 mL vial using Ethyl Acetate (20 mL) and washing with 1 M NaOH_{aq} (2 x 10 mL) and sat. NH₄Cl_{aq} (10 mL). The reaction mixture was dried with Na₂SO₄, filtered, and concentrated *in vacuo*. Additional impurities were purged *via* trituration with Et₂O (5-10 mL).

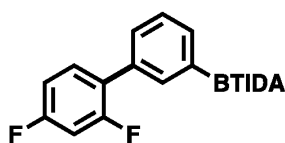
¹H NMR (500 MHz, Chloroform-*d*) δ 1.57 (s, 6H), 1.80 (s, 6H), 2.53 (s, 3H), 3.84 (s, 3H), 6.69 (dd, *J* = 12.4, 2.5 Hz, 1H), 6.77 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.34 (t, *J* = 8.8 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.49 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.54 (dd, *J* = 7.4, 1.3 Hz, 1H), 7.66 (d, *J* = 2.0 Hz, 1H).

¹³C NMR (126 MHz, Chloroform-*d*) δ 37.6, 55.8, 102.2 (d, *J* = 26.6 Hz), 110.3 (d, *J* = 3.0 Hz), 121.7 (d, *J* = 13.7 Hz), 128.1, 129.9 (d, *J* = 2.6 Hz), 131.3 (d, *J* = 5.3 Hz), 132.9, 134.7 (d, *J* = 2.5 Hz), 135.2, 159.4, 160.4 (d, *J* = 11.1 Hz), 161.4, 174.8.

¹¹B NMR (161 MHz, Chloroform-*d*) δ 9.4.

¹⁹F NMR (471 MHz, Chloroform-*d*) δ -116.17 (dd, *J* = 12.3, 9.3 Hz).

HRMS ESI (M+H⁺) C₂₂H₂₆BNO₅F calc 414.1888 Found 414.1886.



(2',4'-difluoro-[1,1'-biphenyl]-3-yl)boronic acid TIDA ester (9)

Prepared according to **GP3** at rt, (3-bromophenyl)boronic acid TIDA ester (73.6 mg, 0.2 mmol, 1 equiv.) and **SI-1** (54.2 mg, 0.24 mmol, 1.2 equiv.) in >95% yield (76.2 mg). The reaction was purified by transferring to a 40 mL vial using Ethyl Acetate (20 mL) and washing with 1 M NaOH_{aq} (2 x 10 mL) and sat. NH₄Cl_{aq} (10 mL). The reaction mixture was dried with Na₂SO₄, filtered, and concentrated *in vacuo*. Additional impurities were purged *via* trituration with Et₂O (5-10 mL).

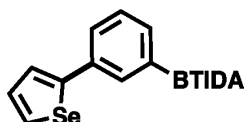
¹H NMR (500 MHz, Chloroform-*d*) δ 1.57 (s, 6H), 1.81 (s, 6H), 2.53 (s, 3H), 6.89 (ddd, *J* = 11.1, 8.8, 2.6 Hz, 1H), 6.95 (td, *J* = 8.3, 2.5 Hz, 1H), 7.36 – 7.45 (m, 2H), 7.48 (d, *J* = 7.7 Hz, 1H), 7.58 (d, *J* = 7.3 Hz, 1H), 7.65 (s, 1H).

¹³C NMR (126 MHz, Chloroform-*d*) δ 37.6, 104.4 (dd, *J* = 26.7, 25.4 Hz), 111.8 (dd, *J* = 21.0, 3.8 Hz), 125.6 (dd, *J* = 13.8, 3.8 Hz), 128.2, 129.9 (d, *J* = 2.4 Hz), 131.7 (dd, *J* = 9.4, 4.9 Hz), 133.5, 134.5, 134.7 (d, *J* = 2.6 Hz), 159.8 (dd, *J* = 249.4, 11.8 Hz), 162.4 (dd, *J* = 248.9, 11.8 Hz), 174.8.

¹¹B NMR (161 MHz, Chloroform-*d*) δ 9.4.

¹⁹F NMR (471 MHz, Chloroform-*d*) δ -114.09 (q, *J* = 8.9 Hz), -111.43 (p, *J* = 7.6 Hz).

HRMS ESI (M+H⁺) C₂₁H₂₃BNO₄F₂ calc 402.1688 Found 402.1687.



(3-(selenophen-2-yl)phenyl)boronic acid TIDA ester (10)

Prepared according to **GP3** at rt, (3-bromophenyl)boronic acid TIDA ester (73.6 mg, 0.2 mmol, 1 equiv.) and **SI-6** (58.3 mg, 1.2 mmol, 0.24 equiv.) in 79% yield (66.1 mg). The reaction was purified by transferring to a 40 mL vial using Ethyl Acetate (20 mL) and washing with 1 M NaOH_{aq} (2 x 10 mL) and sat. NH₄Cl_{aq} (10 mL). The reaction mixture was dried with Na₂SO₄, filtered, and concentrated *in vacuo*. Additional impurities were purged *via* trituration with Et₂O (5-10 mL).

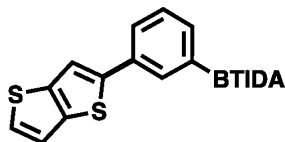
¹H NMR (500 MHz, Chloroform-*d*) δ 1.57 (s, 6H), 1.81 (s, 6H), 2.52 (s, 3H), 7.31 (dd, *J* = 5.5, 3.8 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.46 (d, *J* = 3.8 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.72 (s, 1H), 7.94 (d, *J* = 5.5 Hz, 1H).

¹³C NMR (126 MHz, Chloroform-*d*) δ 37.6, 125.5, 127.7, 128.6, 130.2, 130.7, 131.8, 133.4, 136.0, 151.0, 174.7.

¹¹B NMR (161 MHz, Chloroform-*d*) δ 9.3.

HRMS ESI (M+H⁺) C₁₉H₂₃BNO₄Se calc 420.0885 Found 420.0886.

5



(3-(thieno[3,2-b]thiophen-2-yl)phenyl)boronic acid TIDA ester (11)

Prepared according to **GP3** at rt, (3-bromophenyl)boronic acid TIDA ester (73.6 mg, 0.2 mmol, 1 equiv.) and **SI-7** (60.5 mg, 0.24 mmol, 1.2 equiv.) in 92% yield (78.7 mg). The reaction was purified by transferring to a 40 mL vial using Ethyl Acetate (20 mL) and washing with 1 M NaOH_{aq} (2 x 10 mL) and sat. NH₄Cl_{aq} (10 mL). The reaction mixture was dried with Na₂SO₄, filtered, and concentrated *in vacuo*. Additional impurities were purged *via* trituration with Et₂O (5-10 mL).

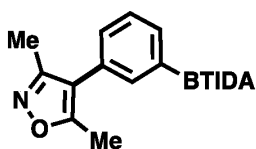
¹H NMR (500 MHz, Chloroform-*d*) δ 1.58 (s, 6H), 1.82 (s, 6H), 2.53 (s, 3H), 7.23 – 7.26 (m, 1H), 7.36 (d, *J* = 5.2 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.50 – 7.53 (m, 2H), 7.62 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.80 (s, 1H).

¹³C NMR (126 MHz, Chloroform-*d*) δ 37.6, 115.6, 119.7, 127.0, 127.1, 128.6, 131.4, 133.6, 134.5, 138.6, 140.2, 146.5, 174.7.

¹¹B NMR (161 MHz, Chloroform-*d*) δ 9.3.

HRMS ESI (M+H⁺) C₂₁H₂₃BNO₄S₂ calc 428.1162 Found 428.1165.

20



(3-(3,5-dimethylisoxazol-4-yl)phenyl)boronic acid TIDA ester (12)

Prepared according to **GP3** at 50 °C, (3-bromophenyl)boronic acid TIDA ester (73.6 mg, 0.2 mmol, 1 equiv.) and **SI-4** (50.2 mg, 0.24 mmol, 1.2 equiv.) in 89% yield (68.5 mg). The reaction was purified by transferring to a 40 mL vial using Ethyl Acetate (20 mL) and washing with 1 M NaOH_{aq} (2 x 10 mL) and sat. NH₄Cl_{aq} (10 mL). The reaction mixture was dried with Na₂SO₄, filtered, and concentrated *in vacuo*. Additional impurities were purged *via* trituration with Et₂O (5-10 mL).

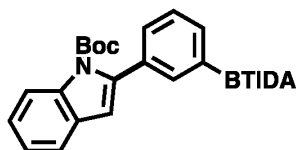
25

¹H NMR (500 MHz, Chloroform-*d*) δ 1.57 (s, 6H), 1.81 (s, 6H), 2.25 (s, 3H), 2.39 (s, 3H), 2.54 (s, 3H), 7.20 – 7.27 (m, 1H), 7.39 – 7.47 (m, 2H), 7.55 (d, *J* = 7.5 Hz, 1H).

¹³C NMR (126 MHz, Chloroform-*d*) δ 11.1, 11.8, 37.5, 116.8, 128.4, 130.1, 133.3, 134.7, 158.7, 165.3, 174.6.

5 **¹¹B NMR** (161 MHz, Chloroform-*d*) δ 9.3.

HRMS ESI ($M+H^+$) $C_{20}H_{26}BN_2O_5$ calc 385.1935 Found 385.1935.



(3-(1-(tert-butoxycarbonyl)-1H-indol-2-yl)phenyl)boronic acid TIDA ester (13)

10 Prepared according to **GP3** at 50 °C, (3-bromophenyl)boronic acid TIDA ester (73.6 mg, 0.2 mmol, 1 equiv.) and **SI-11** (92 mg, 0.28 mmol, 1.4 equiv.) in 77% yield (77.7 mg). The reaction was purified by transferring to a 40 mL vial using Ethyl Acetate (20 mL) and washing with 1 M NaOH_{aq} (2 x 10 mL) and sat. NH₄Cl_{aq} (10 mL). The reaction mixture was dried with Na₂SO₄, filtered, and concentrated *in vacuo*. Additional impurities were purged *via*

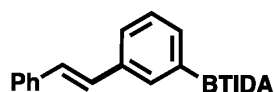
15 trituration with Et₂O (5-10 mL).

¹H NMR (500 MHz, Chloroform-*d*) δ 1.34 (s, 9H), 1.56 (s, 6H), 1.80 (s, 6H), 2.53 (s, 3H), 6.54 (s, 1H), 7.24 (m, 1H), 7.33 (m, 1H), 7.39 (t, *J* = 7.4 Hz, 1H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.55 (dd, *J* = 10.6, 7.7 Hz, 2H), 7.61 (d, *J* = 1.7 Hz, 1H), 8.21 (d, *J* = 8.4 Hz, 1H).

¹³C NMR (126 MHz, Chloroform-*d*) δ 27.6, 37.4, 83.6, 110.1, 115.4, 120.4, 122.9, 124.3, 127.3, 129.2, 129.5, 133.1, 134.3, 134.4, 137.4, 140.7, 150.2, 174.6.

20 **¹¹B NMR** (161 MHz, Chloroform-*d*) δ 9.4.

HRMS ESI ($M+H^+$) $C_{28}H_{34}BN_2O_6$ calc 505.2510 Found 505.2505.



25 **(E)-(3-styrylphenyl)boronic acid TIDA ester (14)**

Prepared according to **GP3** at rt, (3-bromophenyl)boronic acid TIDA ester (73.6 mg, 0.2 mmol, 1 equiv.) and (*E*)-styrylboronic acid neopentyl ester (51.9 mg, 0.24 mmol, 1.2 equiv.) in 95% yield (99.1 mg). The reaction was purified by transferring to a 40 mL vial using Ethyl Acetate (20 mL) and washing with 1 M NaOH_{aq} (2 x 10 mL) and sat. NH₄Cl_{aq} (10 mL). The

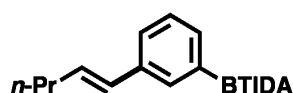
reaction mixture was dried with Na₂SO₄, filtered, and concentrated *in vacuo*. Additional impurities were purged *via* trituration with Et₂O (5-10 mL).

¹H NMR (500 MHz, Acetone-*d*₆) δ 1.58 (s, 6H), 1.80 (s, 6H), 2.75 (s, 3H), 7.21 – 7.31 (m, 3H), 7.36 (t, *J* = 7.6 Hz, 3H), 7.51 (m, 1H), 7.57 – 7.67 (m, 3H), 7.80 (s, 1H).

5 ¹³C NMR (126 MHz, Acetone-*d*₆) δ 38.2, 127.5, 127.7, 128.5, 128.9, 129.4, 129.7, 130.1, 133.7, 134.4, 137.6, 138.7, 175.7.

¹¹B NMR (161 MHz, Acetone-*d*₆) δ 9.1.

HRMS ESI (M+H⁺) C₂₃H₂₇BNO₄ calc 392.2033 Found 392.2034.



10 **(E)-(3-(pent-1-en-1-yl)phenyl)boronic acid TIDA ester (15)**

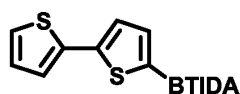
Prepared according to **GP3** at rt, (3-bromophenyl)boronic acid TIDA ester (73.6 mg, 0.2 mmol, 1 equiv.) and (*E*)-pent-1-en-1-ylboronic acid neopentyl ester (43.7 mg, 0.24 mmol, 1.2 equiv.) in 84% yield (60.0 mg). The reaction was purified by transferring to a 40 mL vial using Ethyl Acetate (20 mL) and washing with 1 M NaOH_{aq} (2 x 10 mL) and sat. NH₄Cl_{aq} (10 mL). The reaction mixture was dried with Na₂SO₄, filtered, and concentrated *in vacuo*. Additional impurities were purged *via* trituration with Et₂O (5-10 mL).

¹H NMR (500 MHz, Chloroform-*d*) δ 0.95 (t, *J* = 7.4 Hz, 3H), 1.44 – 1.59 (m, 8H), 1.80 (s, 6H), 2.14 – 2.25 (m, 2H), 2.49 (s, 3H), 6.22 (dt, *J* = 15.8, 6.9 Hz, 1H), 6.38 (d, *J* = 15.8 Hz, 1H), 7.28 (d, *J* = 7.6 Hz, 1H), 7.35 – 7.41 (m, 2H), 7.49 (s, 1H).

20 ¹³C NMR (126 MHz, Chloroform-*d*) δ 13.9, 22.6, 35.3, 37.6, 126.7, 128.1, 130.1, 131.2, 131.9, 132.6, 137.4, 174.9.

¹¹B NMR (161 MHz, Chloroform-*d*) δ 9.5.

HRMS ESI (M+H⁺) C₂₀H₂₈BNO₄ calc 358.2182 Found 358.2184.



25 **[2,2'-bithiophen]-5-ylboronic acid TIDA ester (16)**

Prepared according to **GP3** at rt, **SI-15** (74.8 mg, 0.2 mmol, 1 equiv.) and (2-thiophene boronic acid neopentyl ester (47.1 mg, 0.24 mmol, 1.2 equiv.) in 83% yield (62.6 mg). The reaction was purified by transferring to a 40 mL vial using Ethyl Acetate (20 mL) and washing with 1 M NaOH_{aq} (2 x 10 mL) and sat. NH₄Cl_{aq} (10 mL). The reaction mixture was dried with

30 with 1 M NaOH_{aq} (2 x 10 mL) and sat. NH₄Cl_{aq} (10 mL). The reaction mixture was dried with

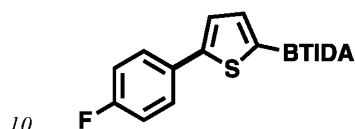
Na₂SO₄, filtered, and concentrated *in vacuo*. Additional impurities were purged *via* trituration with Et₂O (5-10 mL).

¹H NMR (500 MHz, CDCl₃) δ 1.6 (s, 6H), 1.8 (s, 6H), 2.6 (s, 3H), 7.0 (dd, *J* = 5.1, 3.6 Hz, 1H), 7.2 (d, *J* = 3.5 Hz, 2H), 7.2 – 7.2 (m, 2H).

5 ¹³C NMR (126 MHz, CDCl₃) δ 37.6, 123.8, 123.9, 124.4, 124.6, 124.6, 127.8, 127.9, 135.5, 137.3, 142.1, 174.2.

¹¹B NMR (161 MHz, CDCl₃) δ 8.6.

HRMS ESI (M+H⁺) C₁₇H₂₀BNO₄S₂ calc 377.0927 Found 377.0931



(5-(4-fluorophenyl)thiophen-2-yl)boronic acid TIDA ester (17)

Prepared according to **GP3** at rt, **SI-15** (74.8 mg, 0.2 mmol, 1 equiv.) and (4-fluorophenyl)boronic acid neopentyl ester (49.9 mg, 0.24 mmol, 1.2 equiv.) in 83% yield (62.3 mg). The reaction was purified by transferring to a 40 mL vial using Ethyl Acetate (20 mL) and washing with 1 M NaOH_{aq} (2 x 10 mL) and sat. NH₄Cl_{aq} (10 mL). The reaction mixture was dried with Na₂SO₄, filtered, and concentrated *in vacuo*. Additional impurities were purged *via* trituration with Et₂O (5-10 mL).

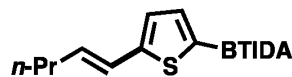
20 ¹H NMR (500 MHz, Chloroform-*d*) δ 1.65 (s, 6H), 1.80 (s, 6H), 2.64 (s, 3H), 7.06 (t, *J* = 8.7 Hz, 2H), 7.24 (d, *J* = 3.5 Hz, 1H), 7.29 (d, *J* = 3.6 Hz, 1H), 7.56 (ddt, *J* = 8.3, 5.1, 2.5 Hz, 2H).

¹³C NMR (126 MHz, Chloroform-*d*) δ 37.7, 115.9, 116.1, 124.2, 127.6, 127.7, 130.7, 136.0, 148.2, 174.3.

¹¹B NMR (161 MHz, Chloroform-*d*) δ 8.5.

¹⁹F NMR (471 MHz, Chloroform-*d*) δ -118.5 (m).

25 **HRMS** ESI (M+H⁺) C₁₉H₂₂NO₄FSB calc 390.1347 Found 390.1335.



(E)-(5-(pent-1-en-1-yl)thiophen-2-yl)boronic acid TIDA ester (18)

30 Prepared according to **GP3** at rt, **SI-15** (74.8 mg, 0.2 mmol, 1 equiv.) and (*E*)-pent-1-en-1-ylboronic acid neopentyl ester (43.7 mg, 0.24 mmol, 1.2 equiv.) in 69% yield (50.1 mg). The reaction was purified by transferring to a 40 mL vial using Ethyl Acetate (20 mL) and

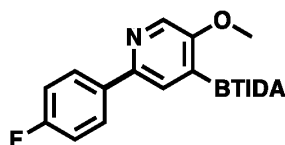
washing with 1 M NaOH_{aq} (2 x 10 mL) and sat. NH₄Cl_{aq} (10 mL). The reaction mixture was dried with Na₂SO₄, filtered, and concentrated *in vacuo*. Additional impurities were purged *via* trituration with Et₂O (5-10 mL).

¹H NMR (500 MHz, Chloroform-*d*) δ 0.94 (t, *J* = 7.4 Hz, 3H), 1.47 (h, *J* = 7.5 Hz, 2H), 1.62 (s, 6H), 1.78 (s, 6H), 2.15 (qd, *J* = 7.2, 1.4 Hz, 2H), 2.60 (s, 3H), 6.09 (dt, *J* = 15.5, 7.0 Hz, 1H), 6.50 (m, 1H), 6.86 (d, *J* = 3.4 Hz, 1H), 7.15 (d, *J* = 3.5 Hz, 1H).

¹³C NMR (126 MHz, Chloroform-*d*) δ 13.8, 22.6, 35.1, 37.7, 123.2, 125.3, 132.0, 135.2, 148.1, 174.4.

¹¹B NMR (161 MHz, Chloroform-*d*) δ 8.6.

HRMS ESI (M+H⁺) C₁₈H₂₆BNO₄S calc 364.1754 Found 364.1770.



(2-(4-fluorophenyl)-5-methoxypyridin-4-yl)boronic acid TIDA ester (19)

Prepared according to **GP3** at 60 °C, **SI-16** (79.8 mg, 0.2 mmol, 1 equiv.) and (4-fluorophenyl)boronic acid neopentyl ester (49.9 mg, 0.24 mmol, 1.2 equiv.) in 92% yield (71.9 mg). The reaction was purified by transferring to a 40 mL vial using Ethyl Acetate (20 mL) and washing with 1 M NaOH_{aq} (2 x 10 mL) and sat. NH₄Cl_{aq} (10 mL). The reaction mixture was dried with Na₂SO₄, filtered, and concentrated *in vacuo*. Additional impurities were purged *via* trituration with Et₂O (5-10 mL).

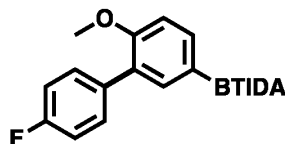
¹H NMR (500 MHz, Acetone-*d*₆) δ 1.59 (s, 6H), 1.79 (s, 6H), 2.84 (s, 3H), 3.95 (s, 3H), 7.21 (t, *J* = 8.8 Hz, 2H), 7.89 (s, 1H), 8.06 (dd, *J* = 8.7, 5.6 Hz, 2H), 8.40 (s, 1H).

¹³C NMR (126 MHz, Acetone-*d*₆) δ 38.0, 57.1, 116.3 (d, *J* = 21.6 Hz), 126.3, 129.2 (d, *J* = 8.2 Hz), 135.5, 137.0 (d, *J* = 3.2 Hz), 149.5, 159.6, 164.0 (d, *J* = 245.3 Hz), 175.3.

¹¹B NMR (161 MHz, Acetone-*d*₆) δ 8.7.

¹⁹F NMR (471 MHz, Acetone-*d*₆) δ -116.51 (ddd, *J* = 14.7, 9.3, 5.3 Hz).

HRMS ESI (M+H⁺) C₂₁H₂₅N₂O₅FB calc 415.1841 Found 415.1848.



(4'-fluoro-6-methoxy-[1,1'-biphenyl]-3-yl)boronic acid TIDA ester (20)

Prepared according to **GP3** at 60 °C. **SI-18** (79.6 mg, 0.2 mmol, 1 equiv.) and (4-fluorophenyl)boronic acid neopentyl ester (49.9 mg, 0.12 mmol, 1.2 equiv.) in 74% yield (64.0 mg). The reaction was purified by transferring to a 40 mL vial using Ethyl Acetate (20 mL) and washing with 1 M NaOH_{aq} (2 x 10 mL) and sat. NH₄Cl_{aq} (10 mL). The reaction mixture was

dried with Na₂SO₄, filtered, and concentrated *in vacuo*. Additional impurities were purged *via* trituration with Et₂O (5-10 mL).

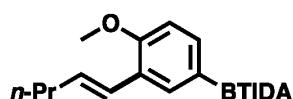
¹H NMR (500 MHz, Chloroform-*d*) δ 1.57 (s, 6H), 1.80 (s, 6H), 2.51 (s, 3H), 3.82 (s, 3H), 6.96 (d, *J* = 8.3 Hz, 1H), 7.08 (t, *J* = 8.6 Hz, 2H), 7.40 – 7.48 (m, 3H), 7.52 (dd, *J* = 8.3, 1.9 Hz, 1H).

¹³C NMR (126 MHz, Chloroform-*d*) δ 37.5, 55.6, 110.8, 115.0 (d, *J* = 21.2 Hz), 129.2, 131.3 (d, *J* = 7.9 Hz), 134.5 (d, *J* = 3.4 Hz), 135.0, 136.5, 157.5, 162.1 (d, *J* = 246.0 Hz), 174.9.

¹¹B NMR (161 MHz, Chloroform-*d*) δ 9.3.

¹⁹F NMR (471 MHz, Chloroform-*d*) δ -115.8 (ddd, *J* = 14.0, 8.8, 5.3 Hz).

HRMS ESI (M+H⁺) C₂₂H₂₅BFNO₅ calc 414.1888 Found 414.1885.



(E)-(4-methoxy-3-(pent-1-en-1-yl)phenyl)boronic acid TIDA ester (21)

Prepared according to **GP3** at 60 °C. **SI-18** (79.6 mg, 0.2 mmol, 1 equiv.) and (*E*)-pent-1-en-1-ylboronic acid neopentyl ester (43.7 mg, 0.24 mmol, 1.2 equiv.) in 86% yield (66.7 mg).

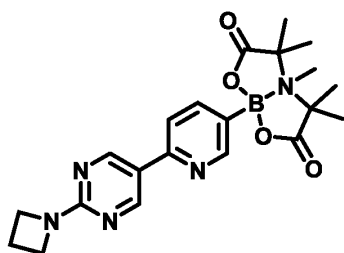
The reaction was purified by transferring to a 40 mL vial using Ethyl Acetate (20 mL) and washing with 1 M NaOH_{aq} (2 x 10 mL) and sat. NH₄Cl_{aq} (10 mL). The reaction mixture was dried with Na₂SO₄, filtered, and concentrated *in vacuo*. Additional impurities were purged *via* trituration with Et₂O (5-10 mL).

¹H NMR (500 MHz, Chloroform-*d*) δ 0.88 (t, *J* = 7.3 Hz, 3H), 1.37 – 1.63 (m, 8H), 1.72 (s, 6H), 2.12 (q, *J* = 7.2 Hz, 3H), 2.41 (s, 3H), 3.77 (s, 3H), 6.14 (dt, *J* = 15.8, 6.9 Hz, 1H), 6.59 (d, *J* = 15.9 Hz, 1H), 6.76 (d, *J* = 8.3 Hz, 1H), 7.30 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.47 (d, *J* = 1.8 Hz, 1H).

¹³C NMR (126 MHz, Chloroform-*d*) δ 14.0, 22.8, 35.8, 37.5, 55.5, 110.3, 124.6, 126.5, 132.2, 132.4, 134.0, 157.5, 175.0.

¹¹B NMR (161 MHz, Chloroform-*d*) δ 9.4.

HRMS ESI (M+H⁺) C₂₁H₃₁BNO₅ calc 388.2295 Found 388.2296.



(6-(2-(azetidin-1-yl)pyrimidin-5-yl)pyridin-3-yl)boronic acid TIDA ester (22)

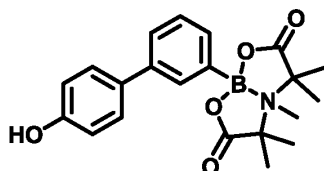
Prepared according to **GP3** at 60 °C. (6-bromopyridin-3-yl)boronic acid TIDA ester (73.8 mg, 0.2 mmol, 1 equiv.) and (2-(azetidin-1-yl)pyrimidin-5-yl)boronic acid neopentyl ester (74.1 mg, 0.24 mmol, 1.2 equiv.) in 57% yield (48.5 mg). The reaction was purified by diluting with hexane (30 mL) and filtering the mixture through a silica plug. The plug was then eluted with copious amounts of 98.5:1.5 Et₂O:MeOH and EtOAc to remove all impurities. Acetone was then eluted through the silica plug and concentrated in vacuo. Additional impurities were triturated away with Et₂O.

¹H NMR (500 MHz, CDCl₃) δ 1.56 (s, 6H), 1.82 (s, 7H), 2.44 (p, *J* = 7.6 Hz, 2H), 2.54 (s, 3H), 4.02 – 4.48 (m, 4H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.95 (dd, *J* = 8.2, 2.0 Hz, 1H), 8.78 (dd, *J* = 2.0, 0.9 Hz, 1H), 8.97 (s, 2H).

¹³C NMR (126 MHz, CDCl₃) δ 16.4, 37.3, 50.5, 174.0.

¹¹B NMR (161 MHz, CDCl₃) δ 8.8.

HRMS ESI (*M*+*H*⁺) C₂₁H₂₇BN₅O₄ calc 424.2156 Found 424.2165.



(4'-hydroxy-[1,1'-biphenyl]-3-yl)boronic acid TIDA ester (23)

Prepared according to **GP3** at rt. (3-bromophenyl)boronic acid TIDA ester (73.8 mg, 0.2 mmol, 1 equiv.) and (4-hydroxyphenyl)boronic acid neopentyl ester (49.5 mg, 0.24 mmol, 1.2 equiv.) in 73% yield (55.7 mg). The reaction was purified by diluting with hexane (30 mL) and filtering the mixture through a silica plug. The plug was then eluted with copious amounts of 98.5:1.5 Et₂O:MeOH to remove all impurities. Acetone was then eluted through the silica plug and concentrated in vacuo. Additional impurities were triturated away with Et₂O.

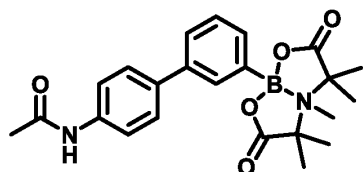
¹H NMR (500 MHz, Acetone) δ 1.59 (s, 6H), 1.80 (s, 6H), 2.77 (s, 3H), 6.91 (d, J = 8.6 Hz, 2H), 7.39 (t, J = 7.5 Hz, 1H), 7.45 – 7.52 (m, 3H), 7.56 (dt, J = 7.6, 1.6 Hz, 1H), 7.78 (d, J = 1.8 Hz, 1H), 8.40 (s, 1H).

¹³C NMR (126 MHz, Acetone) δ 38.0, 116.5, 127.7, 128.8, 129.0, 132.8, 133.0, 133.6,

5 140.9, 157.9, 175.6.

¹¹B NMR (161 MHz, Acetone) δ 9.3.

HRMS ESI (M+H⁺) C₂₁H₂₅BN₂O₅ calc 382.1826 Found 382.1820.



(4'-acetamido-[1,1'-biphenyl]-3-yl)boronic acid TIDA ester (24)

10 Prepared according to **GP3** at 50 °C. (3-bromophenyl)boronic acid TIDA ester (73.8 mg, 0.2 mmol, 1 equiv.) and (4-acetamidophenyl)boronic acid neopentyl ester (59.3 mg, 0.24 mmol, 1.2 equiv.) in 77% yield (58.6 mg). The reaction was purified by diluting with hexane (30 mL) and filtering the mixture through a silica plug. The plug was then eluted with copious amounts of 98.5:1.5 Et₂O:MeOH to remove all impurities. Acetone was then eluted through

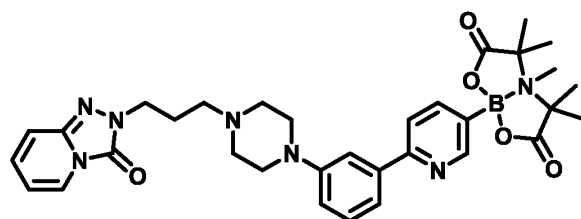
15 the silica plug and concentrated in vacuo. Additional impurities were triturated away with Et₂O. **¹H NMR (500 MHz, Acetone)** δ 1.48 (s, 6H), 1.69 (s, 6H), 2.65 – 2.68 (m, 6H), 7.31 (t, J = 7.6 Hz, 1H), 7.43 (dt, J = 7.5, 1.3 Hz, 1H), 7.46 – 7.49 (m, 2H), 7.50 (dt, J = 8.0, 1.5 Hz, 1H), 7.60 – 7.65 (m, 2H), 7.72 (t, J = 1.7 Hz, 1H), 9.10 (s, 1H).

¹³C NMR (126 MHz, Acetone) δ 24.3, 26.2, 38.0, 55.0, 68.1, 120.2, 127.9, 128.0, 128.9,

20 133.0, 133.5, 136.9, 139.9, 140.6, 168.8, 175.6.

¹¹B NMR (161 MHz, Acetone) δ 9.2.

HRMS ESI (M+H⁺) C₂₃H₂₈BN₂O₅ calc 423.2091 Found 423.2091.



(6-(3-(4-(3-(3-oxo-[1,2,4]triazolo[4,3-a]pyridin-2(3H)-yl)propyl)piperazin-1-yl)phenyl)pyridin-3-yl)boronic acid TIDA ester (25)

25 Prepared according to **GP3** at 60 °C and stirred for 10 minutes. (6-bromopyridin-3-yl)boronic acid TIDA ester (36.9 mg, 0.1 mmol, 1 equiv.) and **(SI-15)** (69.5 mg, 0.15 mmol,

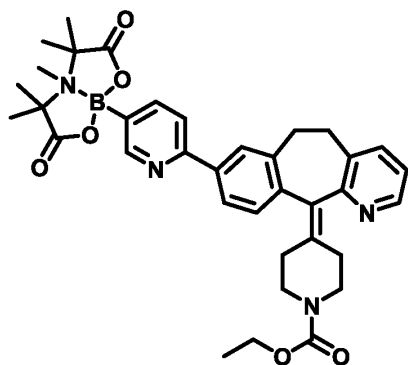
1.5 equiv.) in 83% yield (52.2 mg). The reaction was purified by diluting with hexane (30 mL) and filtering the mixture through a silica plug. The plug was then eluted with copious amounts of 98.5:1.5 Et₂O:MeOH and EtOAc to remove all impurities. Acetone was then eluted through the silica plug and concentrated in vacuo. Additional impurities were triturated away with Et₂O.

5 **¹H NMR (500 MHz, Acetone)** δ 1.60 (t, J = 6.4 Hz, 6H), 1.81 (s, 6H), 2.01 (p, J = 6.8, 5.7 Hz, 2H), 2.47 (t, J = 6.6 Hz, 2H), 2.56 – 2.61 (m, 4H), 2.80 (s, 3H), 3.19 (dd, J = 6.2, 3.8 Hz, 4H), 4.04 (t, J = 6.8 Hz, 2H), 6.57 (ddd, J = 7.2, 6.0, 1.3 Hz, 1H), 7.00 (dd, J = 8.2, 2.5 Hz, 1H), 7.10 – 7.20 (m, 2H), 7.32 (t, J = 8.0 Hz, 1H), 7.52 – 7.59 (m, 1H), 7.72 – 7.77 (m, 2H), 7.88 (d, J = 7.9 Hz, 1H), 7.97 (dd, J = 8.0, 2.1 Hz, 1H), 8.79 (d, J = 2.0 Hz, 1H).

10 **¹³C NMR (126 MHz, Acetone)** δ 25.2, 26.7, 37.8, 44.8, 49.8, 54.0, 56.3, 109.6, 111.1, 114.9, 116.1, 117.4, 118.5, 119.6, 120.0, 120.9, 124.6, 126.5, 130.0, 130.7, 140.8, 142.1, 143.2, 149.3, 152.9, 155.5, 158.2, 175.3.

¹¹B NMR (161 MHz, Acetone) δ 9.1.

HRMS ESI (M+H⁺) C₃₃H₄₁BN₇O₅ calc 626.3262 Found 626.3271.



15

(6-(11-(1-(ethoxycarbonyl)piperidin-4-ylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-8-yl)pyridin-3-yl)boronic acid TIDA ester (26)

Prepared according to **GP3** at 60 °C and stirred for 10 minutes. (6-bromopyridin-3-yl)boronic acid TIDA ester (36.9 mg, 0.1 mmol, 1 equiv.) and (11-(1-(ethoxycarbonyl)piperidin-4-ylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-8-yl)boronic acid pinacol ester⁵ (69.5 mg, 0.15 mmol, 1.5 equiv.) in 71% yield (45.0 mg). The reaction was purified by diluting with hexane (30 mL) and filtering the mixture through a silica plug. The plug was then eluted with copious amounts of 98.5:1.5 Et₂O:MeOH and EtOAc to remove all impurities. Acetone was then eluted through the silica plug and concentrated in vacuo. Additional impurities were triturated away with Et₂O.

25

¹H NMR (500 MHz, Acetone) δ 1.16 – 1.26 (m, 3H), 1.54 – 1.66 (m, 6H), 1.80 (d, J = 5.4 Hz, 6H), 2.31 (dddd, J = 30.1, 13.8, 6.3, 4.0 Hz, 2H), 2.39 – 2.51 (m, 2H), 2.79 (s, 3H), 2.95

(dddd, $J = 20.3, 15.8, 8.7, 4.7$ Hz, 2H), 3.33 (dd, $J = 21.6, 9.5$ Hz, 2H), 3.40 – 3.58 (m, 2H), 3.64 – 3.74 (m, 2H), 4.09 (q, $J = 7.1$ Hz, 2H), 7.17 (dd, $J = 7.7, 4.7$ Hz, 1H), 7.26 (d, $J = 8.0$ Hz, 1H), 7.57 (ddd, $J = 8.0, 4.1, 1.3$ Hz, 1H), 7.88 (dd, $J = 8.1, 1.0$ Hz, 1H), 7.97 (ddd, $J = 12.9, 8.0, 2.0$ Hz, 2H), 8.03 (d, $J = 1.9$ Hz, 1H), 8.38 (dd, $J = 4.8, 1.7$ Hz, 1H), 8.72 – 8.89 (m, 1H).

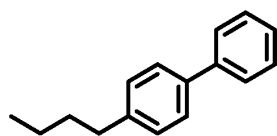
^{13}C NMR (126 MHz, Acetone) δ 14.3, 15.0, 23.3, 32.3, 32.7, 37.7, 37.8, 45.7, 45.8, 61.5, 119.8, 123.0, 125.0, 128.2, 128.4, 130.4, 133.8, 134.7, 136.0, 137.4, 138.1, 139.1, 139.3, 141.3, 143.3, 145.3, 147.3, 155.6, 155.8, 157.4, 158.5, 175.3.

^{11}B NMR (161 MHz, Acetone) δ 8.9.

HRMS ESI ($\text{M}+\text{H}^+$) $\text{C}_{36}\text{H}_{42}\text{BN}_4\text{O}_6$ calc 637.3197 Found 637.3202.

Example 4: General Procedure 3 (GP3) Cross-Coupling of primary alkyl TIDA boronates with non-TIDA containing aryl and vinyl halides

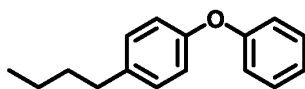
In an argon filled glovebox, an oven dried 7 mL vial equipped with a stir bar was charged with alkyl TIDA boronate (2.00 equiv.) and TMSOK (6.5 equiv.). In a separate oven dried 7 mL vial equipped with a stir bar was charged with aryl or vinyl halide (1.00 equiv.) and Pd-RuPhos-G4 (10 mol%). Both vials were sealed with a PTFE septum cap and removed from the glovebox. Anhydrous toluene (0.1 M relative to halide) was added to the TIDA and TMSOK vial and the vial was placed in a pre-equilibrated aluminum block and heated at 70 °C for 30 minutes. After stirring for 30 minutes, the TIDA-TMSOK Toluene solution was added directly to the vial containing the aryl or vinyl halide and Pd-RuPhos-G4 and the reaction was stirred at 70 °C for 20 minutes (aryl halide) or 90 minutes (vinyl halide). Upon completion of the reaction, the reaction was cooled to room temperature, dry loaded onto celite, and purified via column chromatography.



4-butyl-1,1'-biphenyl

Prepared using GP3 with 4-iodo-1-phenylbenzene (28 mg, 0.1 mmol), *n*-butylboronic acid TIDA ester (54 mg, 0.2 mmol), TMSOK (78.3 mg, 0.61 mmol), and Pd-RuPhos-G4 (8.5 mg, 0.01 mmol). The product was purified via column chromatography (hexanes) to obtain the product (19.2 mg, 91% yield). NMR was consistent with literature values.

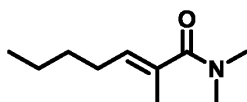
¹H NMR (499 MHz, CDCl₃) δ 0.95 (td, *J* = 7.3, 1.2 Hz, 3H), 1.39 (h, *J* = 7.5 Hz, 2H), 1.64 (tt, *J* = 8.6, 6.8 Hz, 2H), 2.54 – 2.94 (m, 2H), 7.25 (d, *J* = 6.0 Hz, 2H), 7.32 (td, *J* = 7.3, 1.3 Hz, 1H), 7.43 (td, *J* = 7.7, 1.3 Hz, 2H), 7.47 – 7.55 (m, 2H), 7.55 – 7.61 (m, 2H).



1-butyl-4-phenoxybenzene

Prepared using **GP3** with 1-bromo-4-phenoxybenzene (25 mg, 0.1 mmol), *n*-butylboronic acid TIDA ester (54 mg, 0.2 mmol), TMSOK (78.3 mg, 0.61 mmol), and Pd-RuPhos-G4 (8.5 mg, 0.01 mmol). The product was purified via column chromatography (hexanes) to obtain the product (20.5 mg, 91% yield). NMR was consistent with literature values.

¹H NMR (499 MHz, CDCl₃) δ 0.95 (t, *J* = 7.4 Hz, 3H), 1.38 (dq, *J* = 14.6, 7.4 Hz, 2H), 1.58 – 1.71 (m, 2H), 2.32 – 3.22 (m, 2H), 6.93 – 6.97 (m, 2H), 6.98 – 7.05 (m, 2H), 7.09 (tt, *J* = 7.4, 1.2 Hz, 1H), 7.13 – 7.19 (m, 2H), 7.31 – 7.38 (m, 2H).

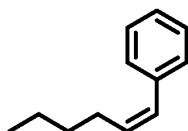


(E)-N,N,2-trimethylhept-2-enamide

Prepared using **GP3** with (E)-3-bromo-N,N,2-trimethylacrylamide (15.7 mg, 0.082 mmol), *n*-butylboronic acid TIDA ester (44 mg, 0.16 mmol), TMSOK (64 mg, 0.61 mmol), and Pd-RuPhos-G4 (7.0 mg, 0.0082 mmol). The product was purified via column chromatography (hexanes -> ethyl acetate) to obtain the product (7.9 mg, 57% yield).

¹H NMR (500 MHz, CDCl₃) δ 0.91 (t, *J* = 7.1 Hz, 3H), 1.29 – 1.41 (m, 4H), 1.82 (d, *J* = 1.6 Hz, 3H), 2.10 (q, *J* = 7.1 Hz, 2H), 2.98 (s, 6H), 5.53 (tt, *J* = 7.3, 1.6 Hz, 1H).

¹³C NMR (126 MHz, CDCl₃) δ 14.1, 14.3, 22.6, 27.4, 29.8, 31.2, 131.5 (d, *J* = 30.7 Hz), 174.1.

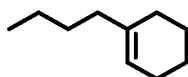


(Z)-hex-1-en-1-ylbenzene

Prepared using **GP3** with styrenylbromide (18.3 mg, 0.1 mmol), *n*-butylboronic acid TIDA ester (54 mg, 0.2 mmol), TMSOK (78.3 mg, 0.61 mmol), and Pd-RuPhos-G4 (8.5 mg,

0.01 mmol). The product was purified via column chromatography (hexanes) to obtain the product (7.0 mg, 44% yield, 86:14 Z:E).

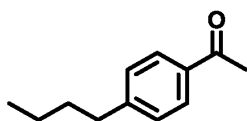
¹H NMR (499 MHz, CDCl₃) δ 0.90 (t, *J* = 7.3 Hz, 3H), 1.29 – 1.49 (m, 4H), 2.33 (qd, *J* = 7.3, 1.9 Hz, 2H), 5.67 (dt, *J* = 11.6, 7.3 Hz, 1H), 6.34 – 6.47 (m, 1H), 7.19 – 7.24 (m, 1H), 7.27 – 7.30 (m, 2H), 7.33 (dd, *J* = 8.5, 6.6 Hz, 2H).



1-butylcyclohex-1-ene

Prepared using **GP3** with bromocyclohexene (16.1 mg, 0.1 mmol), *n*-butylboronic acid TIDA ester (54 mg, 0.2 mmol), TMSOK (78.3 mg, 0.61 mmol), and Pd-RuPhos-G4 (8.5 mg, 0.01 mmol). The product was purified via column chromatography (hexanes) to obtain the product (10.0 mg, 72% yield).

¹H NMR (500 MHz, CDCl₃) δ 0.89 (t, *J* = 7.2 Hz, 3H), 1.16 – 1.47 (m, 4H), 1.50 – 1.75 (m, 4H), 1.91 (q, *J* = 6.5, 5.1 Hz, 4H), 1.97 (ddt, *J* = 6.1, 4.1, 2.0 Hz, 2H), 5.38 (tt, *J* = 3.7, 1.7 Hz, 1H).



1-(4-butylphenyl)ethan-1-one

Prepared using **GP3** with 4-bromoacetophenone (19.9 mg, 0.1 mmol), *n*-butylboronic acid TIDA ester (54 mg, 0.2 mmol), TMSOK (78.3 mg, 0.61 mmol), and Pd-RuPhos-G4 (8.5 mg, 0.01 mmol). The product was purified via column chromatography (hexanes → 90:10 ethyl acetate:hexane) to obtain the product (9.5 mg, 54% yield). NMR was consistent with literature values.

¹H NMR (499 MHz, CDCl₃) δ 0.93 (t, *J* = 7.4 Hz, 3H), 1.29 – 1.45 (m, 2H), 1.58 – 1.69 (m, 2H), 2.58 (s, 3H), 2.63 – 2.76 (m, 2H), 7.25 – 7.31 (m, 2H), 7.84 – 7.92 (m, 2H).



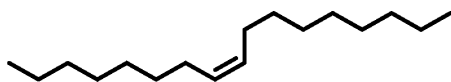
(E)-pentadec-7-ene

Prepared using **GP3** with (E)-1-bromonon-1-ene (20.5 mg, 0.1 mmol), *n*-heptylboronic acid TIDA ester (62 mg, 0.2 mmol), TMSOK (78.3 mg, 0.61 mmol), and Pd-RuPhos-G4 (8.5

mg, 0.01 mmol). The product was purified via column chromatography (hexanes) to obtain the product (14.4 mg, 64% yield).

¹H NMR (499 MHz, CDCl₃) δ 0.88 (t, *J* = 6.8 Hz, 6H), 1.13 – 1.46 (m, 18H), 1.76 – 2.24 (m, 4H), 5.39 (td, *J* = 3.7, 1.8 Hz, 2H).

5



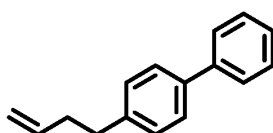
(Z)-heptadec-8-ene

Prepared using **GP3** with (Z)-1-bromodec-1-ene (22 mg, 0.1 mmol), *n*-heptylboronic acid TIDA ester (62 mg, 0.2 mmol), TMSOK (78.3 mg, 0.61 mmol), and Pd-RuPhos-G4 (8.5 mg, 0.01 mmol). The product was purified via column chromatography (hexanes) to obtain the product (22.4 mg, >95% yield).

10

¹H NMR (500 MHz, CDCl₃) δ 0.88 (t, *J* = 6.7 Hz, 6H), 1.30 (dq, *J* = 22.2, 6.8 Hz, 22H), 2.01 (q, *J* = 6.5 Hz, 4H), 5.35 (t, *J* = 4.9 Hz, 2H).

15



4-(but-3-en-1-yl)-1,1'-biphenyl

Prepared using **GP3** with biphenylbromide (22 mg, 0.1 mmol), but-3-en-1-ylboronic acid TIDA ester (53 mg, 0.2 mmol), TMSOK (78.3 mg, 0.61 mmol), and Pd-RuPhos-G4 (8.5 mg, 0.01 mmol). The product was purified via column chromatography (hexanes) to obtain the product (15.6 mg, 75% yield).

20

¹H NMR (500 MHz, CDCl₃) δ 2.42 (tdt, *J* = 7.9, 6.6, 1.4 Hz, 2H), 2.76 (dd, *J* = 9.0, 6.7 Hz, 2H), 4.87 – 5.52 (m, 2H), 5.90 (ddt, *J* = 16.9, 10.2, 6.5 Hz, 1H), 7.27 (d, *J* = 7.0 Hz, 2H), 7.30 – 7.35 (m, 1H), 7.43 (t, *J* = 7.7 Hz, 2H), 7.52 (d, *J* = 8.1 Hz, 2H), 7.55 – 7.62 (m, 2H).

25

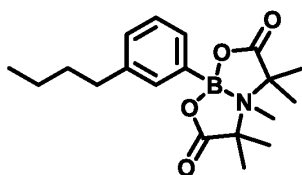
¹³C NMR (126 MHz, CDCl₃) δ 35.1, 35.6, 115.2, 127.1, 127.2, 128.9, 129.0, 138.2, 138.9, 141.1, 141.2.

Example 5: General Procedure 4 (GP4) Cross-Coupling of primary alkyl TIDA boronates with TIDA containing aryl halides

In an argon filled glovebox, an oven dried 7 mL vial equipped with a stir bar was charged with alkyl TIDA boronate (2.00 equiv.) and TMSOK (6.5 equiv.). In a separate oven dried 7 mL vial equipped with a stir bar was charged with aryl or vinyl halide (1.00 equiv.) and

30

Pd-RuPhos-G4 (10 mol%). Both vials were sealed with a PTFE septum cap and removed from the glovebox. B(OTMS)₃ (6 equiv.) was added to the vial containing TIDA and catalyst and anhydrous THF (0.1 M relative to halide) was added to the TIDA and TMSOK vial. The TIDA-TMSOK vial was placed in a pre-equilibrated aluminum block and heated at 70 °C for 30 minutes. After stirring for 30 minutes, the TIDA-TMSOK THF solution was added directly to the vial containing the aryl halide, B(OTMS)₃, and Pd-RuPhos-G4 and the reaction was stirred at 70 °C for 24 hours. Upon completion of the reaction, the reaction was cooled to room temperature, dry loaded onto celite, and purified via column chromatography.

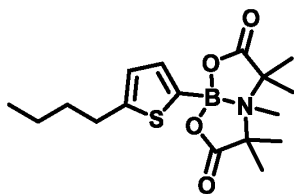


10

(3-butylphenyl)boronic acid TIDA ester

Prepared using **GP4** with 3-bromophenylboronic acid TIDA ester (36.8 mg, 0.1 mmol), *n*-butylboronic acid TIDA ester (54 mg, 0.2 mmol), TMSOK (78.3 mg, 0.61 mmol), B(OTMS)₃ (0.1 mL, 0.3 mmol) and Pd-RuPhos-G4 (8.5 mg, 0.01 mmol). The product was purified via column chromatography (hexanes → ethyl acetate) to obtain the product (26.6 mg, 77% yield). ¹H NMR (499 MHz, CDCl₃) δ 0.91 (t, *J* = 7.3 Hz, 3H), 1.33 (q, *J* = 7.4 Hz, 2H), 1.55 (d, *J* = 9.7 Hz, 8H), 1.80 (s, 6H), 2.48 (s, 3H), 2.55 – 2.62 (m, 2H), 7.17 (d, *J* = 7.6 Hz, 1H), 7.25 (d, *J* = 11.2 Hz, 1H), 7.36 (s, 2H).

15



20

(5-butylthiophen-2-yl)boronic acid TIDA ester

Prepared using **GP4** with 5-bromothiophene-2-boronic acid TIDA ester (37.4 mg, 0.1 mmol), *n*-butylboronic acid TIDA ester (54 mg, 0.2 mmol), TMSOK (78.3 mg, 0.61 mmol), B(OTMS)₃ (0.1 mL, 0.3 mmol) and Pd-RuPhos-G4 (8.5 mg, 0.01 mmol). The product was purified via column chromatography (hexanes → ethyl acetate) to obtain the product (28.8 mg, 82% yield).

25

¹H NMR (500 MHz, CDCl₃) δ 0.92 (t, *J* = 7.4 Hz, 3H), 1.33 – 1.42 (m, 2H), 1.60 – 1.71 (m, 8H), 1.77 (s, 6H), 2.59 (d, *J* = 2.2 Hz, 3H), 2.75 – 2.88 (m, 2H), 6.77 (dd, *J* = 3.3, 1.0 Hz, 1H), 7.13 (d, *J* = 3.4 Hz, 1H).

¹³C NMR (126 MHz, CDCl₃) δ 14.0, 22.4, 29.9, 33.9, 37.7, 125.3, 134.9, 151.3, 174.5.

5 **¹¹B NMR** (161 MHz, CDCl₃) δ 8.7.

Example 6: Exemplary Automated Procedures

Automated Coupling Procedure

To a 40 mL I-Chem vial was loaded TIDA bifunctional, boronic ester, TMSOK, and
10 Pd-P(tBu)₃-G3. The vial was placed in the coupling module aluminum heating block set to 45 °C. An automated Schlenk-line procedure³ was performed followed by addition of 4 mL THF via main pump. The reaction was heated and stirred for the given reaction time.

Automated Purification Procedure

To the crude reaction mixture was added heptanes (30 mL) via the auxiliary pump to
15 precipitate the TIDA boronate. To minimize over pressurization, mild vacuum was applied during the solvent addition step by the rotary evaporator. The heptane was then purged through the filter and purification cartridge via a diaphragm vacuum pump (5 minutes). A 98.5:1.5 MTBE:MeOH (30 mL) solution was then added to the reaction vial and purged through the filter and purification cartridge (5 minutes). Acetone was then reverse eluted (3x15 mL) and
20 concentrated via automated rotary evaporation (5 minutes), followed by an air plug (15 mL) to ensure complete elution of acetone, and automated rotary evaporation (10 minutes). Finally, to ensure complete removal of acetone, 5 mL of DCM was added via main pump and concentrated via automated rotary evaporation (5 minutes). To the reaction vial was then added DCM (3x5 mL). The DCM solution of purified TIDA boronate was then filtered through celite to remove
25 any remaining salt impurities into either a tared isolation vial (for structural analysis) or a deprotection cartridge (for further automated iterative synthesis).

Automated Deprotection Procedure 1

To the reaction cartridge containing 1 equiv. TIDA boronate is added 5 mL DCM. The DCM TIDA boronate solution is transferred to the deprotection cartridge containing 5 equiv.
30 TMSOK and 5 equiv. Pinacol. This sequence is repeated 2 more times and the reaction is stirred for 1 hour. Upon completion of the reaction, the solution is transferred to the drying cartridge. The deprotection cartridge is rinsed with an additional 5 mL of DCM and transferred to the drying cartridge. The 2nd filter cartridge is then rinsed with 5 mL DCM followed by an air plug to ensure complete transfer. The reaction is then stirred in the drying cartridge for 30 minutes

and transferred back to the coupling module into a reaction cartridge connected to the automated rotary evaporator. The drying cartridge is rinsed with 5 mL DCM and transferred to the reaction cartridge. The cartridge is then concentrated for 5 minutes at 45 °C to yield the boronic ester.

5 **Automated Deprotection Procedure 2**

Following **Automated Purification Procedure**, DCM is concentrated off via automated rotary evaporation. To the TIDA boronate is added 5 mL toluene followed by manual addition of 5 equiv. TMSOK and 5 equiv. Pinacol. The reaction is stirred for 1 hour and 30 minutes. Upon completion of the reaction, the solution is transferred to the drying
10 cartridge. The deprotection cartridge is rinsed with an additional 5 mL of toluene and transferred to the drying cartridge. The 2nd filter cartridge is then rinsed with 5 mL toluene followed by an air plug to ensure complete transfer. The reaction is then stirred in the drying cartridge for 30 minutes and transferred back to the coupling module into a reaction cartridge connected to the automated rotary evaporator. The drying cartridge is rinsed with 5 mL toluene
15 and transferred to the reaction cartridge. The cartridge is then concentrated for 20 minutes at 60 °C to yield the boronic ester.

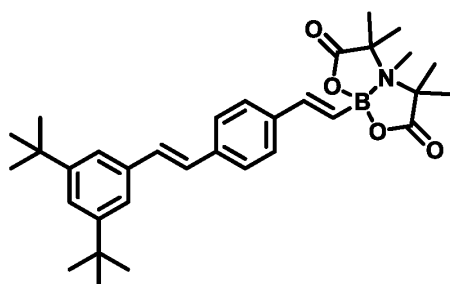
Automated Deprotection-Coupling Procedure

Following the **Automated Deprotection Procedure**, dry and degassed THF is added to dissolve the concentrated boronic ester. The THF solution of boronic ester is then transferred
20 to a vial containing halide, TMSOK, and Pd-P(tBu)₃-G3. The reaction is then stirred at the desired time and temperature.

Automated in Situ Deprotection-Coupling Procedure

Following the **Automated Purification Procedure**, TIDA boronate, halide, Pd XPhos G4, and Na₂CO₃ are dissolved in 4 mL degassed 5:1 dioxane:water. is added to dissolve the
25 concentrated boronic ester. The THF solution of boronic ester is then transferred to a vial containing halide, TMSOK, and Pd-P(tBu)₃-G3. The reaction is then heated to the desired temperature and stirred for the desired time.

Example 7: Automated Synthesis of Exemplary Dimers



((E)-4-((E)-3,5-di-tert-butylstyryl)styryl)boronic acid TIDA ester (29)

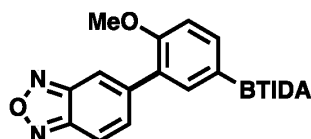
29 was synthesized following **Automated Coupling Procedure** with **SI-21** (118.2 mg, 0.3 mmol, 1 equiv.), **SI-14** (154 mg, 0.45 mmol, 1.5 equiv.), TMSOK (65.4 mg, 0.51 mmol, 1.7 equiv.), and Pd-P(tBu)₃-G3 (17.6 mg, 0.03 mmol, 0.1 equiv.). The reaction was stirred at 45 °C for 10 minutes and purified via **Automated Purification Procedure**. The product was obtained in 63% yield (99.7 mg).

¹H NMR (500 MHz, CDCl₃) δ 1.36 (s, 18H), 1.64 (s, 6H), 1.77 (s, 6H), 2.59 (s, 3H), 6.19 (d, *J* = 18.0 Hz, 1H), 7.07 (d, *J* = 17.1 Hz, 2H), 7.16 (d, *J* = 16.3 Hz, 1H), 7.36 (q, *J* = 1.7 Hz, 3H), 7.44 (d, *J* = 8.1 Hz, 2H), 7.50 (d, *J* = 8.2 Hz, 2H).

¹³C NMR (126 MHz, CDCl₃) δ 31.6, 35.0, 36.9, 121.0, 122.4, 126.8, 127.2, 127.6, 130.2, 136.5, 137.0, 137.8, 143.5, 151.2, 174.6.

¹¹B NMR (161 MHz, CDCl₃) δ 9.5.

HRMS ESI (M⁺) C₃₃H₄₄BNO₄ calc 599.3363 Found 599.3372



(3-(benzo[c][1,2,5]oxadiazol-5-yl)-4-methoxyphenyl)boronic acid TIDA ester (30)

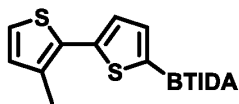
30 was synthesized following **Automated Coupling Procedure** with **SI-19** (119.4 mg, 0.3 mmol, 1 equiv.), **SI-13** (104.4 mg, 0.45 mmol, 1.5 equiv.), TMSOK (65.4 mg, 0.51 mmol, 1.7 equiv.), and Pd-P(tBu)₃-G3 (17.6 mg, 0.03 mmol, 0.1 equiv.). The reaction was stirred at 60 °C for 20 minutes and purified via **Automated Purification Procedure**. The product was obtained in 90% yield (118.1 mg).

¹H NMR (500 MHz, Acetone-*d*₆) δ 1.59 (s, 6H), 1.79 (s, 6H), 2.81 (s, 3H), 3.91 (s, 3H), 7.19 (d, *J* = 8.8 Hz, 1H), 7.61 – 7.72 (m, 2H), 7.78 (dd, *J* = 9.3, 1.4 Hz, 1H), 7.86 – 7.99 (m, 2H).

¹³C NMR (126 MHz, Acetone-*d*₆) δ 38.1, 56.1, 111.9, 115.4, 115.6, 128.4, 136.9, 137.2, 137.5, 144.4, 149.4, 150.7, 158.5, 175.7.

¹¹B NMR (161 MHz, Acetone-*d*₆) δ 9.1.

HRMS ESI (M+H⁺) C₂₂H₂₄BN₃O₆ calc 438.1836 Found 438.1835.



5 **(3'-methyl-[2,2'-bithiophen]-5-yl)boronic acid TIDA ester (31)**

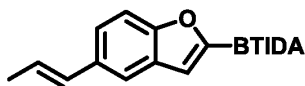
44 was synthesized following **Automated Coupling Procedure** with **SI-16** (74.8 mg, 0.2 mmol, 1 equiv.), **SI-12** (63.3, 0.3 mmol, 1.5 equiv.), TMSOK (43.6 mg, 0.34 mmol, 1.7 equiv.), and Pd-P(tBu)₃-G3 (11.7 mg, 0.03 mmol, 0.1 equiv.). The reaction was stirred at 45 °C for 10 minutes and purified via **Automated Purification Procedure**. The product was obtained
10 in 90% yield (70.4 mg).

¹H NMR (500 MHz, CDCl₃) δ 1.64 (s, 6H), 1.79 (s, 6H), 2.39 (s, 3H), 2.64 (s, 3H), 6.87 (d, *J* = 5.1 Hz, 1H), 7.13 (dd, *J* = 7.3, 4.3 Hz, 2H), 7.24 – 7.29 (m, 1H).

¹³C NMR (126 MHz, CDCl₃) δ 15.7, 37.7, 123.4, 126.3, 131.2, 131.7, 134.2, 135.3, 141.7, 174.4.

15 ¹¹B NMR (161 MHz, CDCl₃) δ 8.7.

HRMS ESI (M+H⁺) C₁₈H₂₂BNO₄ calc 391.1083 Found 391.1091.



20 **(E)-(5-(prop-1-en-1-yl)benzofuran-2-yl)boronic acid TIDA ester (32)**

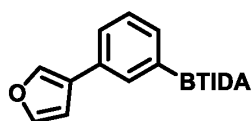
45 was synthesized following **Automated Coupling Procedure** with **SI-19** (204.03 mg, 0.5 mmol, 1 equiv.), (E)-prop-1-en-1-ylboronic acid¹⁰ (64.4 mg, 0.75 mmol, 1.5 equiv.), TMSOK (109 mg, 0.85 mmol, 1.7 equiv.), and Pd-P(tBu)₃-G3 (29.3 mg, 0.05 mmol, 0.1 equiv.). The reaction was stirred at 60 °C for 20 minutes and purified via **Automated Purification Procedure**. The product was obtained in 66% yield (122 mg).

25 ¹H NMR (500 MHz, CDCl₃) δ 1.66 (s, 6H), 1.80 (s, 6H), 1.89 (dd, *J* = 6.6, 1.7 Hz, 3H), 2.62 (s, 3H), 6.19 (dq, *J* = 15.7, 6.6 Hz, 1H), 6.48 (dd, *J* = 15.7, 1.9 Hz, 1H), 7.10 (d, *J* = 0.9 Hz, 1H), 7.29 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.35 – 7.44 (m, 1H), 7.49 (d, *J* = 1.8 Hz, 1H).

¹³C NMR (126 MHz, CDCl₃) δ 18.5, 25.6, 37.3, 68.0, 111.4, 116.5, 118.4, 122.9, 124.6, 128.3, 131.0, 133.0, 156.7, 174.2.

30 ¹¹B NMR (161 MHz, CDCl₃) δ 7.3.

HRMS ESI (M+H⁺) C₂₀H₂₅BNO₅ calc 438.1836 Found 438.1835.



(3-(furan-3-yl)phenyl)boronic acid TIDA ester (33)

33 was synthesized following **Automated Coupling Procedure** with **SI-19** (73.6 mg, 0.2 mmol, 1 equiv.), furan-3-ylboronic acid neopentyl ester (54.0 mg, 0.3 mmol, 1.5 equiv.),
 5 TMSOK (43.6 mg, 0.34 mmol, 1.7 equiv.), and Pd-P(tBu)₃-G3 (11.4 mg, 0.02 mmol, 0.1 equiv.). The reaction was stirred at 45 °C for 10 minutes and purified via **Automated Purification Procedure**. The product was obtained in 75% yield (55.8 mg).

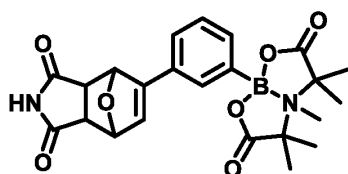
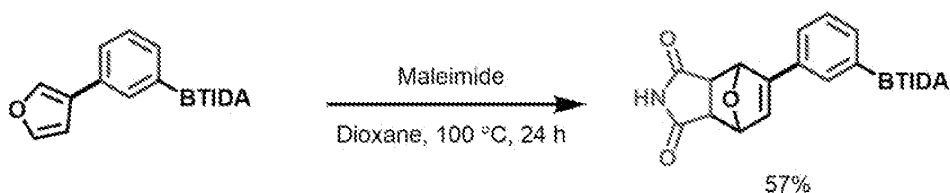
¹H NMR (500 MHz, CDCl₃) δ 1.57 (s, 6H), 1.81 (s, 6H), 2.52 (s, 3H), 6.70 (dd, *J* = 2.0, 0.9 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.44 – 7.52 (m, 3H), 7.65 (t, *J* = 1.7 Hz, 1H), 7.73 (t, *J* = 1.2
 10 Hz, 1H).

¹³C NMR (126 MHz, CDCl₃) δ 37.6, 109.1, 126.6, 127.1, 128.4, 131.4, 132.0, 132.9, 138.7, 143.8, 174.8.

¹¹B NMR (161 MHz, CDCl₃) δ 9.6.

HRMS ESI (M+H)⁺ C₁₉H₂₃BNO₅ calc 356.1669 Found 356.1665.

Diels-Alder Reaction with 33



5-(3-(TIDA ester)phenyl)-3a,4,7,7a-tetrahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione (SI-22)

An oven dried 7-mL vial equipped with a stir bar was charged with maleimide (65.6 mg, 0.68 mmol, 3 eq.), **33** (80 mg, 0.23 mmol, 1 eq.), and anhydrous dioxane (3 mL) was added via syringe. The vial was placed on a pre-equilibrated heating block at 100 °C and stirred at 450 rpm for 20h. After the reaction period, the vial was cooled to room temperature and concentrated in vacuo. The crude mixture was dissolved in CH₂Cl₂ and loaded onto a silica gel
 25 column and washed with hexanes (30 mL) and Et₂O (30 mL). The product was then eluted

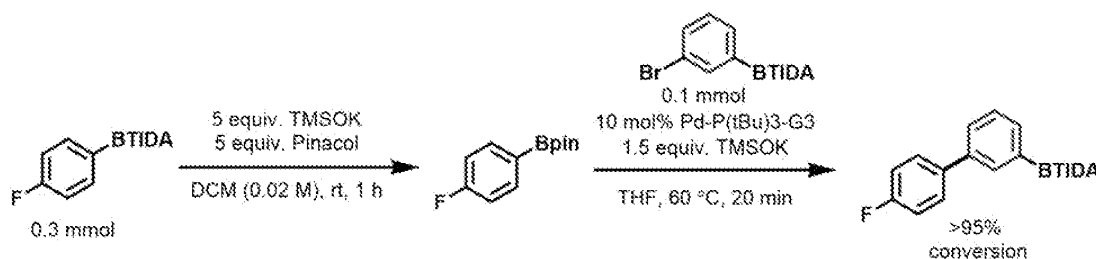
through the silica column with acetone (5 mL). The solution was concentrated in vacuo to yield **34** as a yellow solid in 52% yield (53.8 mg).

¹H NMR (500 MHz, Acetone) δ 1.56 (s, 6H), 1.79 (s, 6H), 2.76 (s, 3H), 3.01 (d, J = 6.5 Hz, 1H), 3.11 (d, J = 6.5 Hz, 1H), 5.28 (d, J = 1.8 Hz, 1H), 5.64 (s, 1H), 6.86 (d, J = 1.9 Hz, 1H),
 5 7.41 (t, J = 7.6 Hz, 1H), 7.51 (dt, J = 7.7, 1.5 Hz, 1H), 7.56 (dt, J = 7.4, 1.4 Hz, 1H), 7.79 (t, J = 1.6 Hz, 1H), 10.02 (s, 1H).

¹³C NMR (126 MHz, Acetone) δ 30.6, 37.9, 49.7, 51.4, 82.3, 83.4, 127.1, 129.0, 129.9, 131.5, 132.1, 135.1, 150.3, 177.6, 177.7.

¹¹B NMR (161 MHz, Acetone) δ 9.1.

10 **HRMS ESI (M+Na⁺)** C₂₃H₂₅BN₂O₇Na calc 475.1653 Found 475.1650.



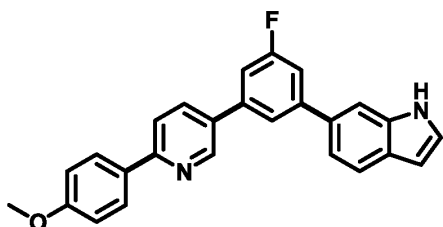
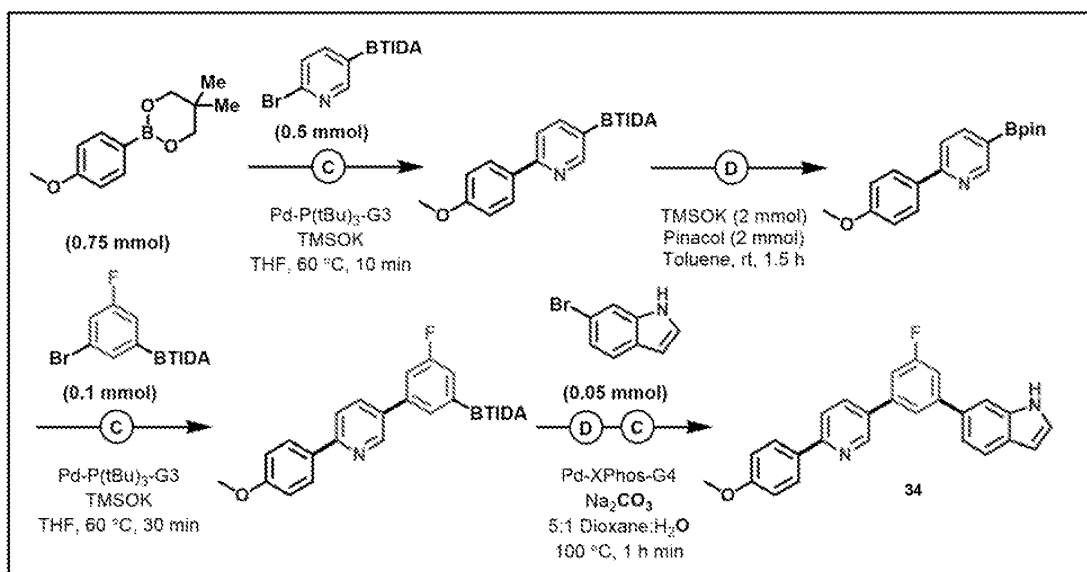
Automated Deprotection of 4-Fluorophenyl TIDA Boronate

4-fluorophenyl TIDA boronate (61.4 mg, 0.2 mmol, 1 equiv.) was deprotected via
 15 **Automated Deprotection Procedure** using TMSOK (128.3 mg, 1 mmol, 5 equiv.), Pinacol (118.2 mg, 1 mmol, 5 equiv.) to deprotect and CaCl₂ (444 mg, 4 mmol, 20 equiv.) and NaHCO₃ (336 mg, 4 mmol, 20 equiv.) to yield 4-fluorophenyl pinacol boronic ester in >95% conversion and >99% purity.

Automated Deprotection-Coupling to Synthesis 14

20 **14** was synthesized via **Automated Deprotection-Coupling Procedure**. Deprotection was performed using 4-fluorophenyl boronic acid TIDA ester (92.1 mg, 0.3 mmol, 3 equiv.), TMSOK (192.5, 15 equiv., 1.5 mmol), Pinacol (177 mg, 15 equiv., 1.5 mmol), CaCl₂ (666 mg, 6 mmol, 60 equiv.), NaHCO₃ (504 mg, 6 mmol, 60 equiv.). Coupling was performed 3-bromophenyl boronic acid TIDA ester (36.8 mg, 0.1 mmol, 1 equiv.), TMSOK (21.8 mg, 0.17
 25 mmol, 1.7 equiv.), and Pd-P(tBu)₃-G3 (5.82 mg, 0.01 mmol, 0.1 equiv.). The reaction was stirred at 60 °C for 20 minutes. H-NMR analysis revealed the reaction was >95% converted.

Example 8: Automated Synthesis of Exemplary Tetramers



6-(3-fluoro-5-(6-(4-methoxyphenyl)pyridin-3-yl)phenyl)-1H-indole (34)

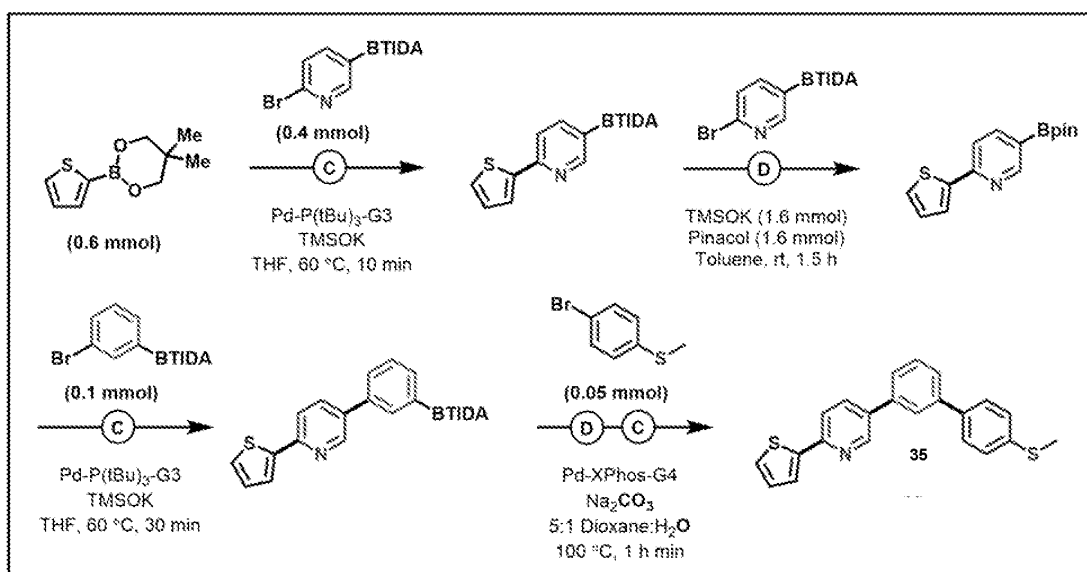
Synthesized via sequence of Automated Coupling Procedure Automated
 5 Purification Procedure, Automated Deprotection Procedure 2, Automated Deprotection-
 Coupling Procedure, Automated Purification Procedure, and Automated in-situ
 Deprotection-Coupling Procedure. Automated Coupling Procedure was performed with
 (6-bromopyridin-3-yl)boronic acid TIDA ester (184.5 mg, 0.5 mmol), 4-methoxyphenyl
 boronic acid neopentyl ester (165.1 mg, 0.75 mmol), TMSOK (109.0 mg, 0.85 mmol), and Pd-
 10 P(tBu)₃-G3 (28.6 mg, 0.05 mmol). Automated Deprotection Procedure 2 was performed with
 TMSOK (256.6 mg, 2 mmol) and pinacol (236 mg, 2 mmol). Automated Deprotection-
 Coupling Procedure was performed with (3-bromo-5-fluorophenyl)boronic acid TIDA ester
 (38.6 mg, 0.1 mmol), TMSOK (21.8 mg, 0.17 mmol), and Pd-P(tBu)₃-G3 (5.7 mg, 0.01 mmol).
 Automated in-situ Deprotection-Coupling Procedure was performed with 5-bromo-1H-
 15 indole (9.8 mg, 0.05 mmol), Pd-XPhos-G4 (4.3 mg, 0.005 mmol), and Na₂CO₃ (39.8 mg, 0.375
 mmol). The product was purified via column chromatography (hexanes → 50% EtOAc in
 hexanes) to yield the product in 59% yield (11.2 mg).

¹H NMR (500 MHz, CDCl₃) δ 3.89 (s, 4H), 6.65 (t, *J* = 2.8 Hz, 1H), 6.99 – 7.08 (m, 2H), 7.29 (dd, *J* = 3.2, 2.4 Hz, 1H), 7.38 (ddd, *J* = 9.9, 2.4, 1.5 Hz, 1H), 7.48 – 7.53 (m, 2H), 7.68 (t, *J* = 1.6 Hz, 1H), 7.78 (dd, *J* = 8.3, 0.8 Hz, 1H), 7.89 – 7.94 (m, 1H), 7.98 (dd, *J* = 8.2, 2.4 Hz, 1H), 7.99 – 8.06 (m, 2H), 8.25 (s, 1H), 8.95 (dd, *J* = 2.5, 0.8 Hz, 1H).

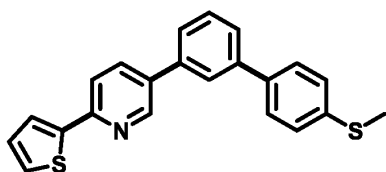
¹³C NMR (126 MHz, CDCl₃) δ 55.5, 103.4, 111.6, 111.8, 113.7 (d, *J* = 22.0 Hz), 114.4, 119.6, 119.8, 121.8, 125.3, 128.3, 128.6, 131.6, 132.0, 133.5, 135.3, 135.8, 140.3, 145.8, 148.1, 156.5, 160.8, 162.8, 164.7.

¹⁹F NMR (471 MHz, CDCl₃) δ -112.90 (t, *J* = 9.6 Hz).

HRMS ESI (M+H⁺) C₂₆H₂₀N₂OF calc 395.1560 Found 395.1558.



10



5-(4'-(methylthio)-[1,1'-biphenyl]-3-yl)-2-(thiophen-2-yl)pyridine (35)

Synthesized via sequence of Automated Coupling Procedure Automated Purification Procedure, Automated Deprotection Procedure 2, Automated Deprotection-Coupling Procedure, Automated Purification Procedure, and Automated in-situ Deprotection-Coupling Procedure. Automated Coupling Procedure was performed with (6-bromopyridin-3-yl)boronic acid TIDA ester (147.6 mg, 0.4 mmol), thiophene-2-boronic acid neopentyl ester (117.6 mg, 0.6 mmol), TMSOK (87.2 mg, 0.68 mmol), and Pd-P(tBu)₃-G3 (22.9 mg, 0.04 mmol). Automated Deprotection Procedure 2 was performed with

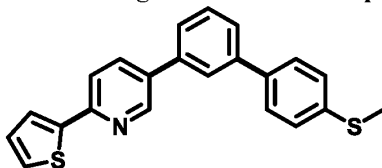
TMSOK (205.3 mg, 1.6 mmol) and pinacol (189 mg, 1.6 mmol). **Automated Deprotection-Coupling Procedure** was performed with 3-bromophenylboronic acid TIDA ester (36.8 mg, 0.1 mmol), TMSOK (21.8 mg, 0.17 mmol), and Pd-P(tBu)₃-G3 (5.7 mg, 0.01 mmol). **Automated in-situ Deprotection-Coupling Procedure** was performed with 4-bromothioanisole (10.1 mg, 0.05 mmol), Pd-XPhos-G4 (4.3 mg, 0.005 mmol), and Na₂CO₃ (39.8 mg, 0.375 mmol). The product was purified via column chromatography (hexanes -> 30% EtOAc in hexanes) to yield the product in 33% yield (6.0 mg).

¹H NMR (500 MHz, CDCl₃) δ 2.54 (s, 3H), 7.15 (dd, *J* = 5.1, 3.6 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.43 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.52 – 7.68 (m, 6H), 7.70 – 7.81 (m, 2H), 7.94 (dd, *J* = 8.4, 2.3 Hz, 1H), 8.86 (d, *J* = 2.3 Hz, 1H).

¹³C NMR (126 MHz, CDCl₃) δ 29.9, 125.6, 125.9, 126.7, 127.1, 127.7, 127.9, 128.3, 129.8, 134.8, 135.3, 137.7, 138.3, 141.7, 148.2.

HRMS ESI (M+H⁺) C₂₂H₁₈NS₂ calc 360.0881 Found 360.0878.

Table 1: Automated timing breakdown of steps for tetramers



Automated Step	Time
Coupling 1	10 min
Purification	60 min
Concentration	20 min
Deprotection	90 min
Deprotection Drying	30 min
Deprotect Concentration	30 min
Coupling 2	30 min
Purification 2	60 min
Concentration 2	20 min
In situ coupling	60 min
Pump and Valve Moves	70 min
Total Time	480 min

Detailed Experimental Procedure for Tetramers

Coupling 1: Halide, Catalyst, TMSOK, and TIDA bifunctional are loaded into a reaction cartridge. Following 10 automated Schlenk cycles, syringe pump 1 adds THF to the reaction cartridge. The reaction cartridge is stirred at 60 °C for **10 minutes**.

Purification 1: Immediately following the first coupling, the auxiliary pump adds 30 mL of hexane. The hexane is then purged via vacuum filtration through the purification cartridge for **5 minutes**. The auxiliary pump then adds 98.5:1.5 Et₂O:MeOH to the reaction mixture and the solution is purged via vacuum filtration through the purification cartridge for **5 minutes**. This is repeated one more time. Finally, the auxiliary pump reverses elutes 10 mL acetone through the purification cartridge. The acetone is concentrated off via automated rotary evaporation for **5 minutes**. This process is repeated 3 times. Finally, the auxiliary pump pushes 15 mL of argon through the purification cartridge and rotary evaporation is performed for **10 minutes**. Syringe pump 1 then adds 5 mL DCM to the reaction cartridge and rotary evaporation is performed for **5 minutes**. Syringe pump 1 then adds 7 mL DCM to the reaction cartridge and filters it through celite into an isolation cartridge. This process is repeated 3 times. Total time for vacuum filtration amounts to **45 minutes** plus around **15 minutes** for valve and syringe pump moves equals a **60 minute** purification time.

Concentration 1: The isolation cartridge undergoes automated rotary evaporation for **20 minutes** following **Purification 1** to ensure complete removal of DCM.

Deprotection: After **Concentration 1**, TMSOK and Pinacol are added to the isolation cartridge and 5 mL of dry toluene is added via syringe pump 1. The reaction is then stirred for **90 minutes**.

Deprotection drying: Following **Deprotection**, 5 mL of toluene is added to syringe pump 1. The solution is then filtered through celite into the drying cartridge containing CaCl₂ and NaHCO₃. This process is repeated twice. The celite is then rinsed with toluene and the drying cartridge is stirred for **30 minutes**. Upon completion of stirring, the solution is syringe filtered into isolation cartridge 2. 5 mL of toluene is then added to the drying cartridge, which is then syringe filtered into isolation cartridge 2.

Deprotect concentration: Following **Deprotection drying**, isolation cartridge 2 then undergoes automated rotary evaporation for **30 minutes**.

Coupling 2: Halide, catalyst, and TMSOK are loaded into reaction cartridge 2. Following 10 schlenk cycles, THF is added to isolation cartridge 2 to dissolve the corresponding pinacol boronic ester. The solution is then added to reaction cartridge 2. Reaction cartridge 2 is then stirred for **30 minutes** at 60 °C.

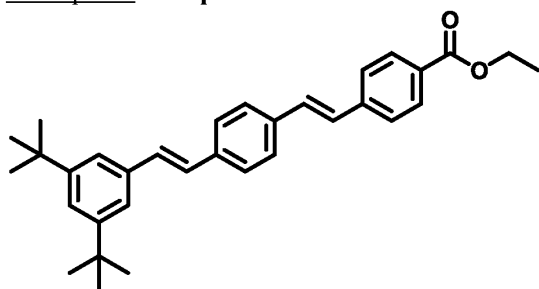
Purification 2: **Purification 2** follows the same procedure as **Purification 1** except is performed on reaction cartridge 2 and filtered into isolation cartridge 3.

Concentration 2: Isolation Cartridge 3 undergoes automated rotary evaporation for **20 minutes** following **Purification 2** to ensure complete removal of DCM.

In situ coupling: Following **Concentration 2**, Syringe pump 1 adds dioxane to isolation cartridge 3 to dissolve the trimer TIDA boronate. The solution is then transferred to reaction cartridge 4, containing halide, catalyst, and Na₂CO₃. This process is repeated twice. Finally, an aqueous pump adds H₂O to the reaction mixture, and the reaction mixture is stirred at 100 °C for **60 minutes**.

Valve and pump movements: Valve and pump movements during **Coupling 1**, **Deprotection**, **Deprotection drying**, **Coupling 2**, and **In situ coupling** account for up to **70 minutes** of total time.

Example 9: Comparison to Previous Platform



Ethyl 4-((E)-4-((E)-3,5-di-tert-butylstyryl)styryl)benzoate (36)

Synthesized via **Automated in Situ Deprotection-Coupling Procedure** using ethyl 4-bromobenzoate (22.9 mg, 0.1 mmol, 1 equiv.), **29** (79.4 mg, 0.15 mmol, 1.5 equiv.), Pd-XPhos-G4 (8.6 mg, 0.01 mmol, 0.1 equiv.), and Na₂CO₃ (79.5 mg, 0.75 mmol, 7.5 equiv.) and stirred at 100 °C for 1 hour. The reaction was cooled to room temperature and purified via chromatography using a 28g Biotage Sfar KP-Amino D biotage column (100% hexanes to 10% ethyl acetate in hexanes) to afford **36** in 47% yield (21.9 mg).

¹H NMR (499 MHz, CDCl₃) δ 1.37 (d, *J* = 1.0 Hz, 18H), 1.41 (t, *J* = 7.2, 1.0 Hz, 3H), 4.39 (q, *J* = 7.5, 7.1 Hz, 2H), 7.09 – 7.25 (m, 4H), 7.35 – 7.41 (m, 3H), 7.51 – 7.68 (m, 6H), 8.04 (d, *J* = 8.0 Hz, 2H).

¹³C NMR (126 MHz, CDCl₃) δ 14.5, 31.6, 35.0, 61.1, 121.1, 122.4, 126.4, 127.0, 127.3, 127.4, 127.6, 129.4, 130.2, 130.3, 130.9, 136.0, 136.5, 137.8, 141.9, 151.2, 166.6.

HRMS ESI (M+H⁺) C₃₃H₃₉O₂ calc 467.2950 Found 467.2943

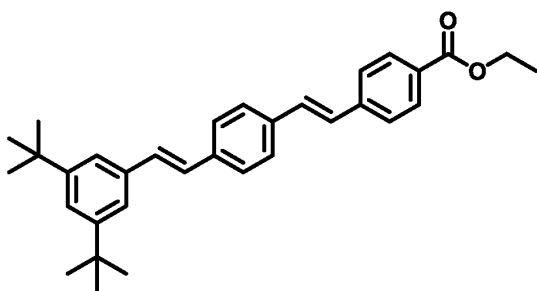
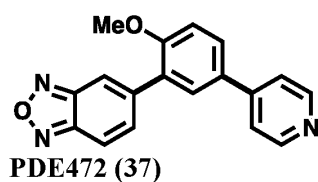


Table 2: Comparison of ^{13}C NMR shift data for 36

Reported J. Li <i>et al Science</i> 2015 (125 MHz, $\text{CDCl}_3\text{-d}$)	This Study (126 MHz, $\text{CDCl}_3\text{-d}$)
166.5	166.6 (+0.1)
151.2	151.2
141.9	141.9
137.8	137.8
136.5	136.5
136.0	136.0
130.9	130.9
130.2	130.3 (+0.1)
130.1	130.2 (+0.1)
129.3	129.4 (+0.1)
127.5	127.6 (+0.1)
127.4	127.4
127.3	127.3
127.0	127.0
126.4	126.4
122.4	122.4
121.0	121.1 (+0.1)
61.0	61.1 (+0.1)
35.0	35.0
31.6	31.6
14.5	14.5

5



Synthesized via **Automated in Situ Deprotection-Coupling Procedure** using ethyl 4-bromopyridine hydrochloric acid (19.5 mg, 0.1 mmol, 1 equiv.), **30** (90.9 mg, 0.15 mmol, 1.5 equiv.), Pd-XPhos-G4 (8.6 mg, 0.01 mmol, 0.1 equiv.), and Na₂CO₃ (69.6 mg, 0.85 mmol, 8.5 equiv.) and stirred at 100 °C for 1 hour. The reaction was cooled to room temperature and purified via chromatography using a 25 g Biotage Sfar Silica HC D column (100% hexanes to

¹H NMR (500 MHz, Acetone-*d*₆) δ 3.98 (s, 3H), 7.36 (d, *J* = 8.6 Hz, 1H), 7.71 – 7.77 (m, 2H), 7.87 (dd, *J* = 9.3, 1.4 Hz, 1H), 7.93 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.94 – 8.01 (m, 2H), 8.13 (t, *J* = 1.3 Hz, 1H), 8.60 – 8.63 (m, 2H).

¹³C NMR (126 MHz, Acetone-*d*₆) δ 56.6, 113.5, 115.8, 116.0, 121.9, 129.8, 130.0, 130.2, 131.7, 136.6, 143.6, 147.8, 149.5, 150.7, 151.4, 158.8.

¹H NMR (500 MHz, DMSO-*d*₆) δ 3.90 (s, 3H), 7.35 (d, *J* = 8.5 Hz, 1H), 7.78 – 7.82 (m, 2H), 7.84 (dd, *J* = 9.4, 1.3 Hz, 1H), 7.93 – 7.97 (m, 2H), 8.07 (dd, *J* = 9.4, 0.9 Hz, 1H), 8.22 (t, *J* = 1.4 Hz, 1H), 8.47 – 8.78 (m, 2H).

¹³C NMR (126 MHz, DMSO-*d*₆) δ 56.1, 112.7, 114.9, 120.9, 128.1, 129.0, 129.1, 129.7, 135.8, 142.2, 146.1, 148.1, 149.3, 150.1, 157.3.

HRMS ESI (M+H⁺) C₁₈H₁₄N₃O₂ calc 304.1086 Found 304.1093.

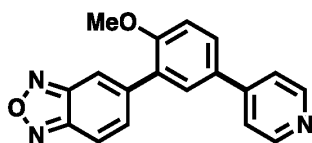
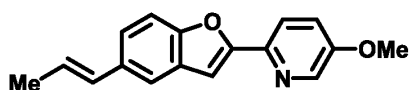


Table 3: Comparison of ¹³C NMR shift data for PDE472 (37)

Reported J. Li <i>et al</i> <i>Science</i> 2015 (125 MHz, DMSO- <i>d</i> ₆)	This Study (126 MHz, DMSO- <i>d</i> ₆)
157.3	157.3
150.1	150.1
149.3	149.3
148.1	148.1
146.1	146.1
142.2	142.2
135.8	135.8
129.8	129.7 (-0.1)
129.1	129.1
129.0	129.0

128.2	128.1 (-0.1)
120.9	120.9
114.9	114.9
112.7	112.7
56.1	56.1



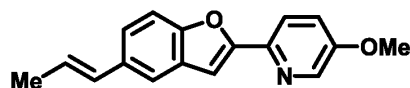
(E)-5-methoxy-2-(5-(prop-1-en-1-yl)benzofuran-2-yl)pyridine (38)

5 Synthesized via **Automated in Situ Deprotection-Coupling Procedure** using 2-bromo-5-methoxypyridine (12.7 mg, 0.0673 mmol, 1 equiv.), **31** (74.6 mg, 0.202 mmol, 3 equiv.), Pd-XPhos-G4 (8.6 mg, 0.01 mmol, 0.1 equiv.), and Na₂CO₃ (160.5 mg, 1.51 mmol, 22.5 equiv.) and stirred at 100 °C for 1 hour. The reaction was cooled to room temperature and purified via chromatography using a 25 g Biotage Sfar Silica HC D column (100% hexanes to
10 20% ethyl acetate in hexanes) to afford **38** in 47% yield (8.4 mg).

¹H NMR (500 MHz, Acetone) δ 1.87 (dd, *J* = 6.5, 1.8 Hz, 3H), 3.95 (s, 3H), 6.29 (dq, *J* = 15.7, 6.5 Hz, 1H), 6.53 (dd, *J* = 15.8, 1.8 Hz, 1H), 7.31 (d, *J* = 0.9 Hz, 1H), 7.39 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.46 – 7.51 (m, 2H), 7.63 (d, *J* = 1.8 Hz, 1H), 7.89 (d, *J* = 8.7 Hz, 1H), 8.37 (d, *J* = 2.9 Hz, 1H).

15 **¹³C NMR** (126 MHz, Acetone) δ 18.6, 56.2, 103.6, 111.9, 119.3, 120.9, 121.2, 123.8, 125.1, 130.4, 132.0, 134.5, 139.2, 142.5, 155.2, 156.6, 157.0,

HRMS ESI (M+H⁺) C₁₇H₁₆NO₂ calc 266.1181 Found 266.1188.



20

Table 4: Comparison of ¹³C NMR shift data for 37

Reported J. Li <i>et al</i> Science 2015 (125 MHz, Acetone- <i>d</i> ₆)	This Study (126 MHz, Acetone- <i>d</i> ₆)
157.0	157.0
156.6	156.6
155.2	155.2
142.5	142.5
139.2	139.2

134.5	134.5
132.0	132.0
130.4	130.4
125.1	125.1
123.7	123.8 (+0.1)
121.2	121.2
120.9	120.9
119.3	119.3
111.9	111.9
103.6	103.6
56.2	56.2
18.6	18.6

Example 10: Timing comparison between models

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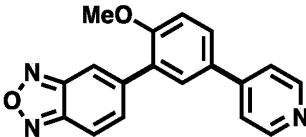
Table 5: Automated timing breakdown

Automated Step	J. Li <i>et al Science</i> 2015 ⁵	This work
Deprotection	60 min	60 min
Deprotection drying	180 min	30 min
Coupling	960 min	Up to 30 min
Purification	240 min	60 min
Concentration	360 min	5 ^a – 30 ^b min
In situ Deprotect/Couple	n/a	60

^aFollowing deprotection. ^bFollowing purification.

10

Table 6: Automated timing breakdown of steps for trimers



Automated Step	Time
Coupling 1	10 min
Purification	60 min
Concentration	20 min
Slow Release Coupling	60 min
Pump and Valve Moves	30 min
Total Time	180 min

Enabling Citations in Experimental Section

15

- 1 Stoll, R. S. *et al.* Photoswitchable Catalysts: Correlating Structure and
Conformational Dynamics with Reactivity by a Combined Experimental and
Computational Approach. *Journal of the American Chemical Society* **131**, 357-367
(2009).
- 5 2 Liu, J. *et al.* Hexamethyldisilazane Lithium (LiHMDS)-Promoted Hydroboration of
Alkynes and Alkenes with Pinacolborane. *The Journal of Organic Chemistry* **87**,
3442-3452 (2022).
- 3 Billingsley, K. L. *et al.* Palladium-Catalyzed Borylation of Aryl Chlorides: Scope,
Applications, and Computational Studies. *Angewandte Chemie International Edition*
10 **46**, 5359-5363 (2007).
- 4 Blair, D. J. *et al.* Automated iterative Csp³-C bond formation. *Nature* **604**, 92-97
(2022).
- 5 Gong, L. Ni-Catalyzed Suzuki-Miyaura Cross-Coupling of α -Oxo-vinylsulfones To
Prepare C-aryl Glycals and Acyclic Vinyl Ethers. *Journal of the American Chemical*
15 *Society* **141**(19), 7680-7686 (2019).
- 6 Woerly, E. M., Roy, J. & Burke, M. D. Synthesis of most polyene natural product
motifs using just 12 building blocks and one coupling reaction. *Nature Chemistry* **6**,
484-491 (2014).
- 7 Li, J. *et al.* Synthesis of many different types of organic small molecules using one
20 automated process. *Science* **347**, 1221-1226 (2015).
- 8 Li, S. *et al.* Using automated synthesis to understand the role of side chains on
molecular charge transport. *Nature Communications* **13**, 2102 (2022).
- 9 Angello, N. H. *et al.* Closed-loop optimization of general reaction conditions for
heteroaryl Suzuki-Miyaura coupling. *Science* **378**, 399-405 (2022).
- 25 10 Gillis, E. P. & Burke, M. D. A Simple and Modular Strategy for Small Molecule
Synthesis: Iterative Suzuki-Miyaura Coupling of B-Protected Haloboronic Acid
Building Blocks. *Journal of the American Chemical Society* **129**, 6716-6717 (2007).

INCORPORATION BY REFERENCE

All patents and published patent applications mentioned in the description above are incorporated by reference herein in their entirety.

5

EQUIVALENTS

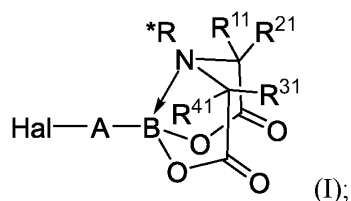
Having described the present invention in some detail by way of illustration and example for purposes of clarity of understanding, it will be obvious to one of ordinary skill in the art that the same can be performed by modifying or changing the invention within a wide and equivalent range of conditions, formulations and other parameters without affecting the scope of the invention or any specific embodiment thereof, and that such modifications or
10 changes are intended to be encompassed within the scope of the appended claims.

CLAIMS

We claim:

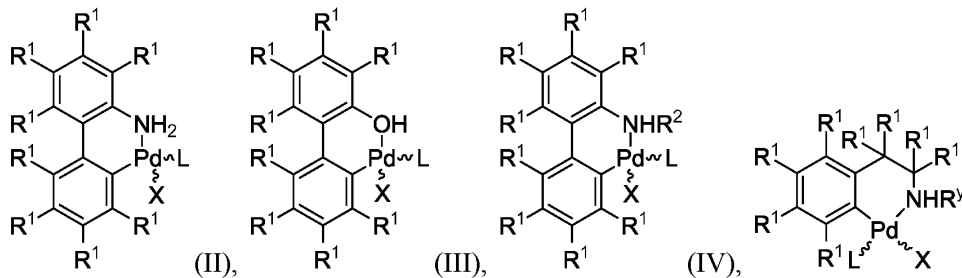
1. A method for iterative carbon-carbon bond formation, comprising a cycle comprising the following steps:

- (a) combining a first boronic ester, a first silanolate, a palladium (Pd) precatalyst, and a halogenated reagent under conditions sufficient to produce a cross-coupling product;
- (b) purifying the cross-coupling product, thereby generating a purified product;
- (c) combining the purified product, a second silanolate, and a diol under conditions sufficient to produce a second boronic ester, wherein the halogenated reagent is represented by structural formula (I):



the first boronic ester is a compound of formula $R^5-B(OR^6)(OR^7)$; and

the palladium precatalyst is represented by structural formula (II), (III), (IV), or (V):



(V),

wherein

Hal is F, Cl, Br, or I;

A is selected from the group consisting of alkylene, alkenylene, alkynylene, cycloalkylene, cycloalkenylene, cycloalkynylene, heteroalkylene, heteroalkenylene, heteroalkynylene, heterocyclylene, arylene, and heteroarylene;

R^* , R^{11} , R^{21} , R^{31} , and R^{41} are each independently alkyl;

R^5 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocyclyl, aryl, and heteroaryl;

R^6 and R^7 are each independently alkyl, or

R^6 and R^7 together with oxygen atoms to which they are attached and the boron atom form heterocyclyl; and

X is a non-coordinating anion;

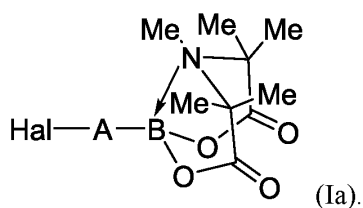
each R^1 is independently H, alkyl, haloalkyl, hydroxy, alkoxy, aryloxy, aryl, or halogen;

L is a trialkylphosphine, triarylphosphine, dialkylarylphosphine, alkyl diarylphosphine, bis(phosphine), phosphoramidate, amine, bis(amine), or N-heterocyclic carbene; and

each R^2 is independently alkyl, haloalkyl, or aryl; and

each R^y is independently H, alkyl, haloalkyl, or aryl.

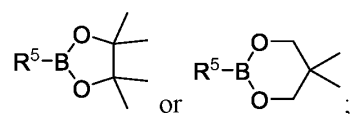
2. The method of claim 1, wherein R^* is methyl.
3. The method of claim 1 or 2, wherein R^{11} , R^{21} , R^{31} , and R^{41} are each methyl.
4. The method of any one of claims 1-3, wherein A is an arylene, a heteroarylene, or an alkenylene.
5. The method of any one of claims 1-4, wherein Hal is Br.
6. The method of any one of claims 1-5, wherein the halogenated reagent is represented by structural formula (Ia):



7. The method of any one of claims 1-6, wherein the first silanolate and the second silanolate are each independently selected from the group consisting of lithium trialkyl silanolate, sodium trialkyl silanolate, and potassium trialkyl silanolate.

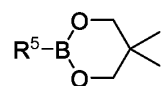
8. The method of any one of claims 1-7, wherein the first silanolate and the second silanolate are each independently selected from the group consisting of lithium trimethyl silanolate, sodium trimethyl silanolate, and potassium trimethyl silanolate (TMSOK).
9. The method of any one of claims 1-8, wherein the first silanolate and the second silanolate are the same.
10. The method of any one of claims 1-9, wherein the first silanolate and the second silanolate are both TMSOK.
11. The method of any one of claims 1-10, wherein R^6 and R^7 together with oxygen atoms to which they are attached and the boron atom form heterocyclyl.
12. The method of any one of claims 1-11, wherein R^5 is aryl, heteroaryl, or vinyl.

13. The method of any one of claims 1-12, wherein the first boronic ester is represented by the following structural formula:

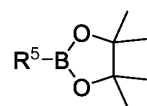


wherein each R^5 is independently aryl, heteroaryl, or alkenyl.

14. The method of claim 13, wherein the first boronic ester is represented by the following structural formula:



15. The method of claim 13, wherein the first boronic ester is represented by the following structural formula:



16. The method of any one of claims 1-15, wherein step (a) comprises combining the first boronic ester, the first silanolate, the palladium precatalyst, and the halogenated reagent at a first temperature from about 25 °C to about 70 °C for a first period of time, thereby generating the cross-coupling product.
17. The method of claim 16, wherein the first temperature is from about 45 °C to about 65 °C.
18. The method of claim 16 or 17, wherein the first period of time is about 2 minutes to about 15 minutes, or about 5 minutes to about 10 minutes.
19. The method of any one of claims 16-18, wherein the cross-coupling product is generated in a yield of about 70% to about 100%, or about 85% to about 95%.
20. The method of any one of claims 1-19, wherein:
step (a) comprises combining in a vessel the first boronic ester, the first silanolate, the palladium precatalyst, and the halogenated reagent, and
step (b) comprises adding to the vessel a precipitating solvent, thereby generating a precipitated product.
21. The method of claim 20, wherein step (b) further comprises:
(i) dissolving the precipitated product in a first solvent, thereby forming a first solution;
(ii) passing the first solution through a sorbent, thereby depositing the precipitated product on the sorbent; and
(iii) passing a second solvent through the sorbent, thereby eluting a second solution comprising the purified product.
22. The method of claim 21, wherein the first solvent comprises methanol.
23. The method of claim 21 or 22, wherein the first solvent comprises methanol and diethyl ether.
24. The method of any one of claims 21-23, wherein the second solvent comprises tetrahydrofuran.

25. The method of any one of claims 21-24, wherein the sorbent is silica gel.
26. The method of any one of claims 1-25, wherein step (c) comprises combining the purified product, the second silanolate, and the diol at a second temperature from about 15 °C to about 30 °C for a second period of time.
27. The method of any one of claims 1-26, wherein the diol is 2,3-dimethyl-2,3-butanediol or 2,2-dimethylpropane-1,3-diol.
28. The method of claim 27, wherein the diol is 2,3-dimethyl-2,3-butanediol.
29. The method of claim 27, wherein the diol is 2,2-dimethylpropane-1,3-diol.
30. The method of any one of claims 26-29, wherein the second temperature is about 25 °C.
31. The method of any one of claims 26-30, wherein the second period of time is about 20 minutes to about 90 minutes, or about 60 minutes.
32. The method of any one of claims 26-31, wherein the purified product and the second silanolate are present in a molar ratio from about 1:2 to about 1:5.
33. The method of any one of claims 26-32, wherein the purified product and the diol are present in a molar ratio from about 1:2 to about 1:5.
34. The method of any one of claims 26-33, wherein the purified product, the second silanolate, and the diol are present in a molar ratio of about 1:3:3.
35. The method of any one of claims 1-34, wherein the method comprises at least a first cycle and a second cycle, and wherein:
the second boronic ester of the first cycle is the same as the first boronic ester of the second cycle, and

the halogenated reagent of the first cycle is the same or different from the halogenated reagent of the first cycle.

36. The method of claim 35, wherein the halogenated reagent of the first cycle is different from the halogenated reagent of the first cycle.

37. The method of any one of claims 1-36, wherein the conditions sufficient to produce a cross-coupling product comprise dissolving the first boronic ester, the first silanolate, the palladium precatalyst, and the halogenated reagent in a reaction solvent, thereby generating a homogeneous mixture.

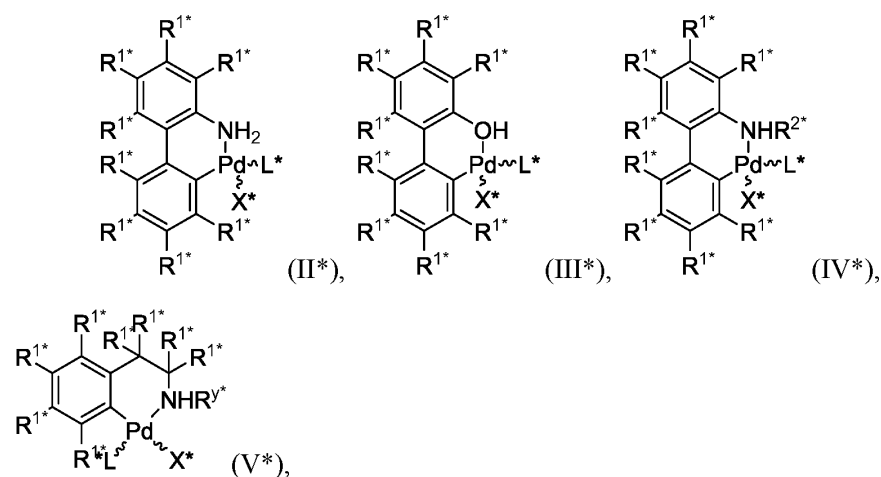
38. The method of claim 37, wherein the reaction solvent is tetrahydrofuran.

39. The method of any one of claims 1-38, further comprising the following step:
combining the second boronic ester, a third silanolate, a second palladium precatalyst, and a second halogenated reagent under conditions sufficient to produce a second cross-coupling product, wherein

the second boronic ester is a compound of formula $R^5-A-B(OR^{6*})(OR^{7*})$;

the halogenated reagent is alkyl halide, alkenyl halide, alkynyl halide, cycloalkyl halide, cycloalkenyl halide, cycloalkynyl halide, heteroalkyl halide, heteroalkenyl halide, heteroalkynyl halide, heterocyclyl halide, aryl halide, and heteroaryl halide;

the second palladium precatalyst is represented by structural formula (II*), (III*), (IV*), or (V*):



wherein

R^{6*} and R^{7*} are each independently alkyl, or

R^{6*} and R^{7*} together with oxygen atoms to which they are attached and the boron atom form heterocyclyl; and

X^{*} is a non-coordinating anion;

each R^{1*} is independently H, alkyl, haloalkyl, hydroxy, alkoxy, aryloxy, aryl, or halogen;

L^{*} is a trialkylphosphine, triarylphosphine, dialkylarylphosphine, alkyl diarylphosphine, bis(phosphine), phosphoramidate, amine, bis(amine), or N-heterocyclic carbene; and

each R^{2*} is independently alkyl, haloalkyl, or aryl; and

each R^{3*} is independently H, alkyl, haloalkyl, or aryl.

40. An automated synthesizer for iterative carbon-carbon bond formation (e.g., according to the method of any one of claims 1-39), comprising:

a reaction module; a purification module; a deprotection module;

at least one pump which can move liquid from one module to another; and

a computer equipped with software;

wherein all of the modules are under control of the computer; the reaction module is in fluid communication with the purification module; and the purification module is in fluid communication with the deprotection module.

41. The automated synthesizer of claim 40, wherein a first boronic ester, a first silanolate, and a halogenated reagent are combined in the reaction module.

42. The automated synthesizer of claim 40 or 41, wherein a purified product, a second silanolate, and a diol are combined in the deprotection module.

43. The automated synthesizer of any one of claims 40-42, comprising:

a plurality of assemblies of modules;

each assembly of modules comprises a reaction module, a purification module, and a deprotection module;

at least one pump which can move liquid from one module to another; and

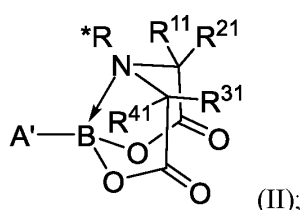
a computer equipped with software;

wherein the modules are under the control of the computer; and within each assembly of modules the reaction module is in fluid communication with the purification module; and the purification module is in fluid communication with the deprotection module.

44. A method for producing an activated boronate reagent, the method comprising the following step:

(a) combining a first boronate reagent and a fourth silanolate under conditions sufficient to produce an activated boronate reagent; wherein

the first boronate reagent is represented by structural formula (I):



wherein

A' is selected from the group consisting of optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocyclyl, aryl, and heteroaryl; and

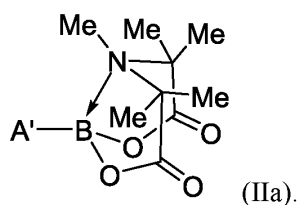
R*, R¹¹, R²¹, R³¹, and R⁴¹ are each independently alkyl.

45. The method of claim 44, wherein R* is methyl.

46. The method of claim 44 or 45, wherein R¹¹, R²¹, R³¹, and R⁴¹ are each methyl.

47. The method of any one of claims 44-46, wherein A' is optionally substituted alkyl, cycloalkyl, aryl, heteroaryl, or alkenyl.

48. The method of any one of claims 44-47, wherein the first boronate reagent is represented by structural formula (IIa):



49. The method of any one of claims 44-48, wherein the fourth silanolate is selected from the group consisting of lithium trialkyl silanolate, sodium trialkyl silanolate, and potassium trialkyl silanolate.

50. The method of any one of claims 44-49, wherein the fourth silanolate is selected from the group consisting of lithium trimethyl silanolate, sodium trimethyl silanolate, and potassium trimethyl silanolate (TMSOK).

51. The method of claim 50, wherein the fourth silanolate is potassium trimethyl silanolate (TMSOK).

52. The method of any one of claims 44-51, wherein step (a) comprises combining the first boronate reagent and the fourth silanolate at a third temperature from about 25 °C to about 100 °C for a third period of time, thereby generating the activated boronate reagent.

53. The method of claim 52, wherein the third temperature is about 70 °C.

54. The method of claim 52 or 53, wherein the third period of time is from about 10 minutes to about 50 minutes.

55. The method of claim 54, wherein the third period of time is about 30 minutes.

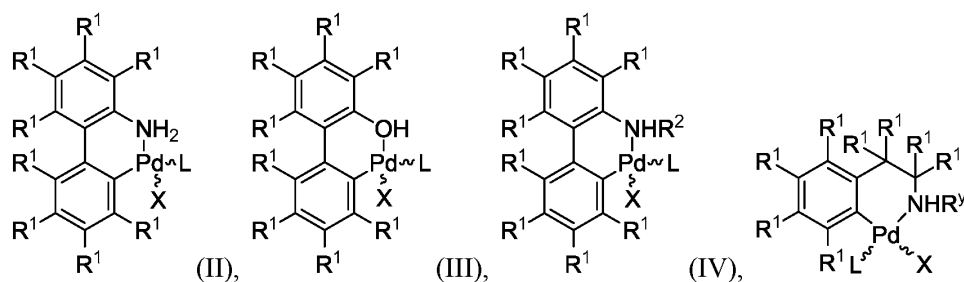
56. The method of any one of claims 44-55, wherein the first boronate reagent and the fourth silanolate are present in a molar ratio of about 1:1-1:5.

57. The method of claim 56, wherein the first boronate reagent and the fourth silanolate are present in a molar ratio of about 1:3.

58. The method of any one of claims 44-57, wherein the conversion of the first boronate reagent to the activated boronate reagent is assessed by ^{11}B NMR.

59. The method of claim 58, wherein the ^{11}B NMR chemical shift of the activated boronate reagent is shifted upfield as compared to that of the first boronate reagent.

60. The method of claim 58, wherein the ^{11}B NMR chemical shift of the activated boronate reagent is shifted downfield as compared to that of the first boronate reagent.
61. The method of any one of claims 44-60, wherein the conditions sufficient to produce an activated boronate reagent comprise dissolving the first boronate reagent and the fourth silanolate in a second reaction solvent, thereby generating a homogeneous mixture.
62. The method of claim 61, wherein the second reaction solvent is tetrahydrofuran or toluene.
63. The method of any one of claims 44-62, wherein the method further comprises the following step:
- (b) combining the activated boronate reagent, a third halogenated reagent, and a third palladium precatalyst under conditions sufficient to produce a cross-coupling product; wherein
- the third halogenated reagent is an alkyl halide, alkenyl halide, alkynyl halide, cycloalkyl halide, cycloalkenyl halide, cycloalkynyl halide, heteroalkyl halide, heteroalkenyl halide, heteroalkynyl halide, heterocyclyl halide, aryl halide, or heteroaryl halide; and
- the third palladium precatalyst is represented by structural formula (II), (III), (IV), or (V):



- (V),
- wherein
- each R^1 is independently H, alkyl, haloalkyl, hydroxy, alkoxy, aryloxy, aryl, or halogen;
- L is a trialkylphosphine, triarylphosphine, dialkylarylphosphine, alkyl diarylphosphine, bis(phosphine), phosphoramidate, amine, bis(amine), or N-heterocyclic carbene; and
- each R^2 is independently alkyl, haloalkyl, or aryl; and
- each R^y is independently H, alkyl, haloalkyl, or aryl.

64. The method of claim 63, wherein step (b) comprises combining the activated boronate reagent, the third palladium precatalyst, and the third halogenated reagent at a fourth temperature from about 25 °C to about 90 °C for a fourth period of time, thereby generating the cross-coupling product.

65. The method of claim 64, wherein the fourth temperature is from about 55 °C to about 75 °C.

66. The method of claim 64, wherein the fourth temperature is about 60 °C or about 70 °C.

67. The method of any one of claims 64-66, wherein the fourth period of time is from about 10 minutes to about 120 minutes.

68. The method of claim 67, wherein the fourth period of time is about 30 minutes.

69. The method of any one of claims 64-68, wherein step (b) further comprises combining the activated boronate reagent, the third palladium precatalyst, the third halogenated reagent, and a Lewis acid at the fourth temperature from about 25 °C to about 90 °C for the fourth period of time, thereby generating the cross-coupling product.

70. The method of claim 69, wherein the Lewis acid is selected from the group consisting of AlCl_3 , BF_3 , $\text{BF}_3 \cdot \text{OEt}_2$, $\text{BF}_3 \cdot \text{THF}$, $\text{B}(\text{OTMS})_3$, $\text{B}(\text{OMe})_3$, and $\text{B}(\text{OiPr})_3$.

71. The method of claim 70, wherein the Lewis acid is $\text{B}(\text{OTMS})_3$.

72. The method of any one of claims 44-63, wherein the method further comprises the following step:

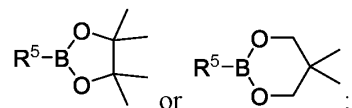
(d) combining the activated boronate reagent and a second diol under conditions sufficient to produce a third boronic ester.

73. The method of claim 72, wherein the diol is 2,3-dimethyl-2,3-butanediol or 2,2-dimethylpropane-1,3-diol.

74. The method of claim 73, wherein the diol is 2,3-dimethyl-2,3-butanediol.

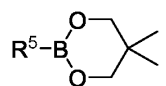
75. The method of claim 73, wherein the diol is 2,2-dimethylpropane-1,3-diol.

76. The method of claim 69, wherein the third boronic ester is represented by the following structural formula:



wherein R^5 is aryl, heteroaryl, or alkenyl.

77. The method of claim 70, wherein the third boronic ester is represented by the following structural formula:



78. The method of claim 70, wherein the third boronic ester is represented by the following structural formula:

