CLAIMS

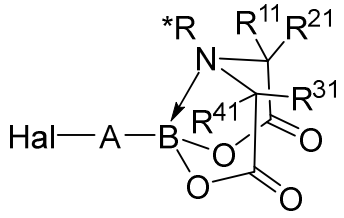
1. A method for iterative carbon-carbon bond formation, comprising a cycle comprising the following steps:

(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

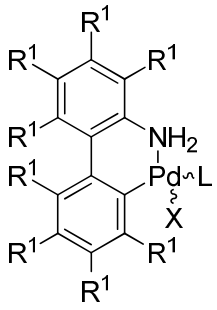
the halogenated reagent is represented by structural formula (I):

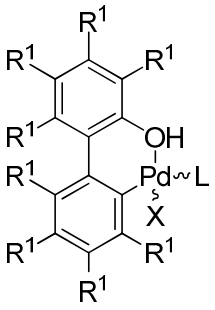


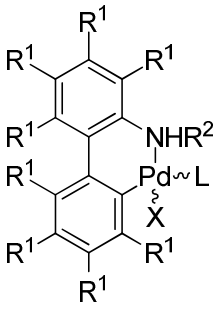
(I);

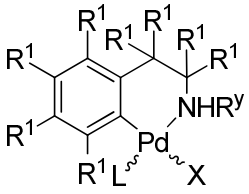
the first boronic ester is a compound of formula $R^5$-B($OR^6$)($OR^7$); and

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



(II),


(III),


(IV),


(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, alkyldiarylphosphine, bis(phosphine), phosphoramide, amine, bis(amine), or N-heterocyclic carbene; and

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

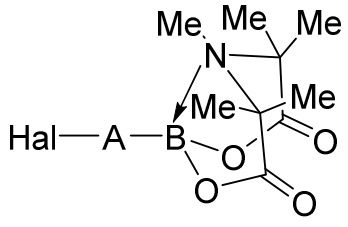
each $R^y$ is independently H, alkyl, haloalkyl, or aryl.

2. The method of claim 1, wherein $R^*$ is methyl; and $R^{11}$, $R^{21}$, $R^{31}$, and $R^{41}$ are each methyl.

3. The method of claim 1 or 2, wherein A is an arylene, a heteroarylene, or an alkenylene.

4. The method of any one of claims 1-3, wherein Hal is Br.

5. The method of any one of claims 1-4, wherein the halogenated reagent is represented by structural formula (Ia):



(Ia).

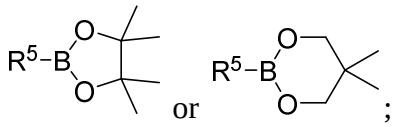
6. The method of any one of claims 1-5, wherein the first silanolate and the second silanolate are each independently selected from the group consisting of lithium trialkyl silanolate, sodium trialkyl silanolate, and potassium trialkyl silanolate.

7. The method of any one of claims 1-6, wherein the first silanolate and the second silanolate are both TMSOK.

8. The method of any one of claims 1-7, wherein $R^6$ and $R^7$ together with oxygen atoms to which they are attached and the boron atom form heterocyclyl.

9. The method of any one of claims 1-8, wherein $R^5$ is aryl, heteroaryl, or vinyl.

10. The method of any one of claims 1-9, wherein the first boronic ester is represented by the following structural formula:

 or ;

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

11. The method of any one of claims 1-10, 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.

12. The method of claim 11, wherein:

i. the first temperature is from about 45 °C to about 65 °C;

ii. the first period of time is about 2 minutes to about 15 minutes, or about 5 minutes to about 10 minutes; and/or

iii. the cross-coupling product is generated in a yield of about 70% to about 100%, or about 85% to about 95%.

13. The method of any one of claims 1-12, 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.

14. The method of claim 13, 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.

15. The method of claim 14, wherein the first solvent comprises methanol; and the second solvent comprises tetrahydrofuran.

16. The method of claim 14 or 15, wherein the sorbent is silica gel.

17. The method of any one of claims 1-16, 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.

18. The method of any one of claims 1-17, wherein the diol is 2,3-dimethyl-2,3-butanediol or 2,2-dimethylpropane-1,3-diol.

19. The method of claim 17 or 18, wherein:

i. the second temperature is about 25 °C;

ii. the second period of time is about 20 minutes to about 90 minutes, or about 60 minutes;

iii. the purified product and the second silanolate are present in a molar ratio from about 1:2 to about 1:5;

iv. the purified product and the diol are present in a molar ratio from about 1:2 to about 1:5; and/or

v. the purified product, the second silanolate, and the diol are present in a molar ratio of about 1:3:3.

20. The method of any one of claims 1-19, 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.

21. The method of claim 20, wherein the halogenated reagent of the first cycle is different from the halogenated reagent of the second cycle.

22. The method of any one of claims 1-21, 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.

23. The method of claim 22, wherein the reaction solvent is tetrahydrofuran.

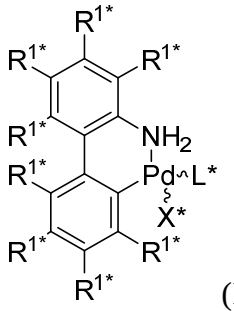
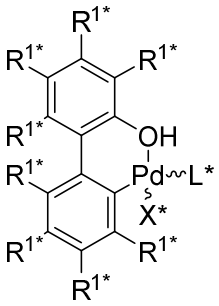
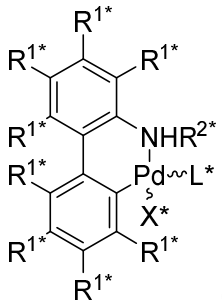
24. The method of any one of claims 1-23, further comprising the following step:

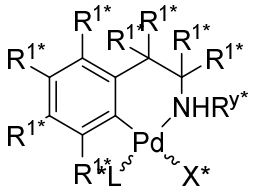
combining the second boronic ester, a third silanolate, a second palladium precatalyst, and a second halogenated reagent under conditions sufficient to produce a second cross-coupling product, wherein

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*):


(II*),

(III*),

(IV*),


(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, alkyldiarylphosphine, bis(phosphine), phosphoramide, 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.

25. An automated synthesizer for iterative carbon-carbon bond formation (e.g., according to the method of any one of claims 1-24), 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.

26. The automated synthesizer of claim 25, wherein:

i. a first boronic ester, a first silanolate, and a halogenated reagent are combined in the reaction module; and/or

ii. a purified product, a second silanolate, and a diol are combined in the deprotection module.

27. The automated synthesizer of claim 25 or 26, 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

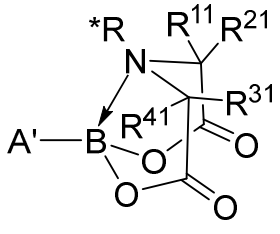
a computer equipped with software;

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.

28. 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):



(II);

wherein

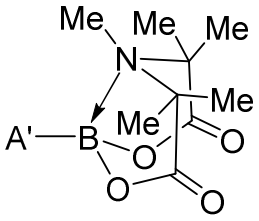
A′ is selected from the group consisting of optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocyclyl, aryl, and heteroaryl; and

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

29. The method of claim 28, wherein $R^*$ is methyl; and wherein $R^{11}$, $R^{21}$, $R^{31}$, and $R^{41}$ are each methyl.

30. The method of claim 28 or 29, wherein A′ is optionally substituted alkyl, cycloalkyl, aryl, heteroaryl, or alkenyl.

31. The method of any one of claims 28-30, wherein the first boronate reagent is represented by structural formula (IIa):



(IIa).

32. The method of any one of claims 28-31, wherein the fourth silanolate is selected from the group consisting of lithium trialkyl silanolate, sodium trialkyl silanolate, and potassium trialkyl silanolate.

33. The method of claim 32, wherein the fourth silanolate is potassium trimethyl silanolate (TMSOK).

34. The method of any one of claims 28-33, 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.

35. The method of claim 34, wherein:

i. the third temperature is about 70 °C;

ii. the third period of time is from about 10 minutes to about 50 minutes;

iii. the first boronate reagent and the fourth silanolate are present in a molar ratio of about 1:1-1:5; and/or

iv. the conversion of the first boronate reagent to the activated boronate reagent is assessed by $^{11}$B NMR.

36. The method of claim 35, wherein the $^{11}$B NMR chemical shift of the activated boronate reagent is shifted upfield as compared to that of the first boronate reagent.

37. The method of claim 35, wherein the $^{11}$B NMR chemical shift of the activated boronate reagent is shifted downfield as compared to that of the first boronate reagent.

38. The method of any one of claims 28-37, 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.

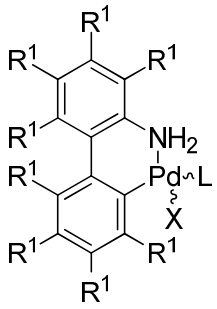
39. The method of claim 38, wherein the second reaction solvent is tetrahydrofuran or toluene.

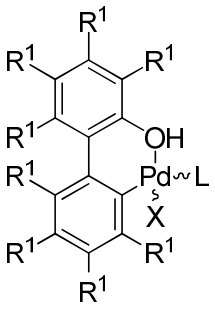
40. The method of any one of claims 28-39, wherein the method further comprises the following step:

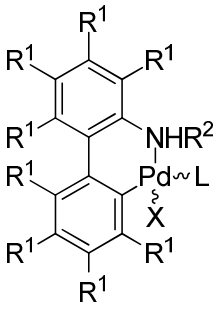
(b) combining the activated boronate reagent, a third halogenated reagent, and a third palladium precatalyst under conditions sufficient to produce a cross-coupling product; wherein

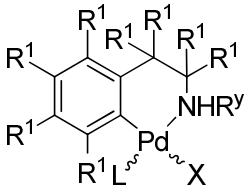
the third halogenated reagent is an alkyl halide, alkenyl halide, alkynyl halide, cycloalkyl halide, cycloalkenyl halide, cycloalkynyl halide, heteroalkyl halide, heteroalkenyl halide, heteroalkynyl halide, heterocyclyl halide, aryl halide, or heteroaryl halide; and

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



(II),


(III),


(IV),


(V),

wherein

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

L is a trialkylphosphine, triarylphosphine, dialkylarylphosphine, alkyldiarylphosphine, bis(phosphine), phosphoramide, 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.

41. The method of claim 40, 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.

42. The method of claim 41, wherein:

i. the fourth temperature is from about 55 °C to about 75 °C; and/or

ii. the fourth period of time is from about 10 minutes to about 120 minutes.

43. The method of any one of claims 40-42, 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.

44. The method of claim 43, wherein the Lewis acid is selected from the group consisting of $AlCl_3$, $BF_3$, $BF_3$•$OEt_2$, $BF_3$•THF, $B(OTMS)_3$, $B(OMe)_3$, and $B(OiPr)_3$.

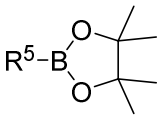
45. The method of claim 44, wherein the Lewis acid is $B(OTMS)_3$.

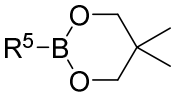
46. The method of any one of claims 28-40, wherein the method further comprises the following step:

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

47. The method of claim 46, wherein the diol is 2,3-dimethyl-2,3-butanediol or 2,2-dimethylpropane-1,3-diol.

48. The method of claim 43, wherein the third boronic ester is represented by the following structural formula:



or


;

wherein $R^5$ is aryl, heteroaryl, or alkenyl.