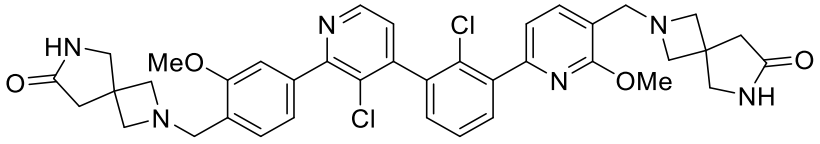
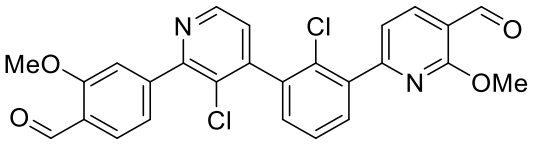
CLAIMS

1. A method of preparing 2-((6-(2-chloro-3-(3-chloro-2-(3-methoxy-4-((7-oxo-2,6-diazaspiro[3.4]octan-2-yl)methyl)phenyl)pyridin-4-yl)phenyl)-2-methoxypyridin-3-yl)methyl)-2,6-diazaspiro[3.4]octan-7-one (**K**), or a salt or solvate thereof:



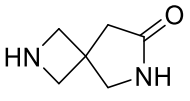
(**K**),

the method comprising reacting 6-(2-chloro-3-(3-chloro-2-(4-formyl-3-methoxyphenyl)pyridin-4-yl)phenyl)-2-methoxynicotinaldehyde (**I**):



(**I**),

and 2,6-diazaspiro[3.4]octan-7-one (**J**):



(**J**),

in the presence of a reducing agent and a base, so as to generate a first reaction system comprising (**K**).

2. The method of claim 1, wherein at least one of the following applies:

(a) the reducing agent is $NaBH(OAc)_3$;

(b) the base comprises NaOMe or *i*-$PrNEt_2$;

(c) (**J**) is selected from the group consisting of 2,6-diazaspiro[3.4]octan-7-one hydrochloride, 2,6-diazaspiro[3.4]octan-7-one hydrobromide, 2,6-diazaspiro[3.4]octan-7-one trifluoroacetate, 2,6-diazaspiro[3.4]octan-7-one mesylate, and 2,6-diazaspiro[3.4]octan-7-one tosylate; and

(d) the reaction of (**I**) and (**J**) occurs in the presence of a solvent, optionally wherein the solvent comprises at least one of a mixture comprising dichloromethane (DCM) and methanol (MeOH), a mixture comprising 2-methyltetrahydrofuran (MeTHF) and MeOH, tetrahydrofuran (THF), dimethylformamide (DMF), and dimethylacetamide (DMAc), or any mixtures thereof.

3. The method of claim 1 or 2, wherein purification of (**K**) comprises:

(a) adding water to the first reaction system comprising (**K**) to generate a biphasic solution;

(b) separating the biphasic solution to provide a first aqueous phase and a first organic phase;

(c) adding an organic solvent to the first aqueous phase to provide a second biphasic solution;

(d) basifying the second biphasic solution to pH 8-11 to provide a basified biphasic solution; and

(e) separating the basified biphasic solution to provide a second aqueous phase and a second organic phase comprising (**K**).

4. The method of any one of claims 1-3, wherein purification of (**K**) comprises steps (1-a) to (1-d) or steps (2-a) to (2-e):

(1-a) providing crude (**K**) in a solvent comprising 2-propanol to afford a dilute crude solution of (**K**),

wherein the dilute crude solution of (**K**) has a concentration of about 110 g/L to about 140 g/L;

(1-b) at least partially evaporating the dilute crude solution of (**K**) to provide a concentrated crude solution of (**K**),

wherein the concentrated crude solution of (**K**) has a concentration of about 220 g/L to about 280 g/L;

(1-c) cooling the concentrated crude solution of (**K**) to a temperature of about 20 °C provide a purified (**K**) slurry; and

(1-d) filtering the purified slurry of (**K**) to provide (**K**);

or

(2-a) providing crude (**K**) in a solvent comprising MeOH to afford a crude solution of (**K**),

wherein the crude solution of (**K**) has a concentration of about 200 g/L to about 300 g/L;

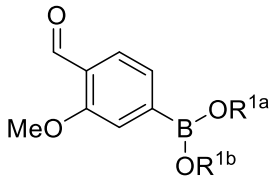
(2-b) heating the crude solution of (**K**) to a temperature of about 50 °C to provide a hot crude solution of (**K**);

(2-c) cooling the hot crude solution of (**K**) to a temperature of about 20 °C provide a cooled (**K**) slurry;

(2-d) adding a solvent comprising methyl *tert*-butyl ether (MTBE) to the cooled (**K**) slurry to provide a purified (**K**) slurry; and

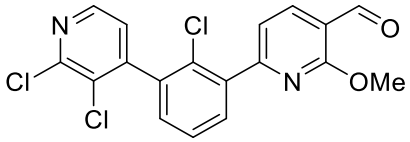
(2-e) filtering the purified (**K**) slurry to provide (**K**).

5. The method of any one of claims 1-4, wherein (**I**) is prepared by reacting 2-methoxy-4-(B(OR^{1a})(OR^{1b}))-benzaldehyde (**H**):



(**H**),

and 6-(2-chloro-3-(2,3-dichloropyridin-4-yl)phenyl)-2-methoxynicotinaldehyde (**F**):



(**F**),

in the presence of a palladium catalyst and a base;

wherein each R^{1a} and R^{1b} are each independently selected from the group consisting of C_1-C_6 alkyl and C_3-C_8 cycloalkyl,

or R^{1a} and R^{1b} may combine with the atoms to which they are bound to form a C_2-C_3 heterocycloalkyl.

6. The method of claim 5, wherein at least one of the following applies:

(a) the palladium catalyst comprises $Pd(PPh_3)_4$;

(b) the palladium catalyst is present in an amount ranging from about 0.1 mol% to about 5 mol%;

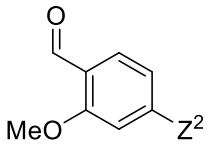
(c) the base comprises K_2CO_3;

(d) the reaction of (**H**) and (**F**) occurs in the presence of a solvent, optionally wherein the solvent comprises at least one of 2-methyltetrahydrofuran (MeTHF), dimethylformamide (DMF), and water;

(e) the reaction of (**H**) and (**F**) occurs at a temperature of about 65 °C to about 70 °C; and

(f) purification of (**I**) comprises adding a N-acetyl cysteine to the reaction of (**H**) and (**F**).

7. The method of claim 5 or 6, wherein (**H**) is prepared by reacting 4-Z^2-2-methoxybenzaldehyde (**G**):



(**G**),

wherein Z^2 is selected from the group consisting of Cl, Br, and I;

and a borylating reagent in the presence of a palladium catalyst and a base.

8. The method of claim 7, wherein at least one of the following applies:

(a) the borylating reagent comprises bis(pinacolato)diboron;

(b) the palladium catalyst comprises Pd(dppf)Cl_2;

(c) the base comprises KOAc;

(d) the reaction of (**G**) and the borylating reagent occurs in the presence of a solvent, optionally wherein the solvent comprises dimethylformamide (DMF) or toluene;

(e) the reaction of (**G**) and the borylating reagent occurs at a temperature of about 80 °C to about 90 °C; and

(f) purification of (**H**) comprises at least one of (i) steps (3-a) to (3-b) and (ii) steps (4-a) to (4-d):

(3-a) adding N-acetyl cysteine to the reaction of (**G**) and the borylating reagent; and

(3-b) adding activated carbon to the reaction of (**G**) and the borylating reagent; and

(4-a) providing crude (**H**) in a solvent comprising 2-propanol to afford a dilute crude solution of (**H**),

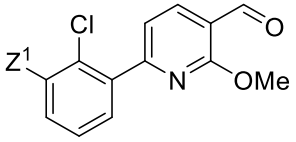
wherein the dilute crude solution of (**H**) has a concentration of about 390 g/L to about 430 g/L;

(4-b) at least partially evaporating the dilute crude solution of (**H**) to provide a concentrated crude solution of (**H**), wherein the at least partial evaporation optionally comprises heating the dilute crude solution of (**H**) to a temperature of about 50 °C, and further optionally maintaining the temperature for a period of about 1.5 h;

(4-c) cooling the concentrated crude solution of (**H**) to a temperature of about 6 °C, provide a purified (**H**) slurry, wherein the cooling optionally occurs over a period of about 3 h; and

(4-d) filtering the purified (**H**) slurry to provide (**H**).

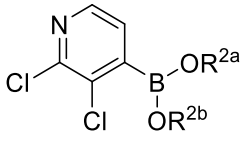
9. The method of claim 5 or 6, wherein (**F**) is prepared by reacting 6-(3-Z^1-2-chlorophenyl)-2-methoxynicotinaldehyde (**D**):



(**D**),

wherein Z^1 is selected from the group consisting of Br and I;

and 2,3-dichloro-4-(B(OR^{2a})(OR^{2b}))-pyridine (**E**):



(**E**),

in the presence of a palladium catalyst and a base;

wherein each R^{2a} and R^{2b} are each independently selected from the group consisting of H, C_1-C_6 alkyl, and C_3-C_8 cycloalkyl,

or R^{2a} and R^{2b} may combine with the atoms to which they are bound to form a C_2-C_3 heterocycloalkyl.

10. The method of claim 9, wherein at least one of the following applies:

(a) R^{2a} and R^{2b} are each independently H;

(b) the palladium catalyst comprises $Pd(amphos)Cl_2$;

(c) the palladium catalyst is present in an amount ranging from about 0.1 mol% to about 5 mol%;

(d) the base comprises K_2HPO_4;

(e) the reaction of (**D**) and (**E**) comprises addition of (**E**) to a reaction vessel comprising (**D**), wherein (**E**) is optionally added to the vessel comprising (**D**) over a period of about 3.5 h;

(f) the reaction of (**D**) and (**E**) occurs in the presence of a solvent, optionally wherein the solvent comprises 2-methyltetrahydrofuran (MeTHF), dimethylacetamide (DMAc), and/or water;

(g) the reaction of (**D**) and (**E**) occurs at a temperature of about 65 °C to about 70 °C;

(h) purification of (**F**) comprises adding a N-acetyl cysteine to the reaction of (**D**) and (**E**); and

(i) purification of (**F**) comprises:

(5-a) providing crude (**F**) in a solvent comprising 2-propanol to afford a dilute crude solution of (**F**),

wherein the dilute crude solution of (**F**) has a concentration of about 100 g/L to about 150 g/L;

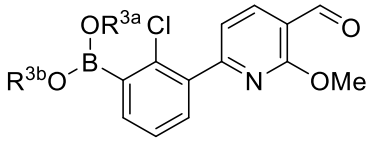
(5-b) at least partially evaporating the dilute crude solution of (**F**) to provide a concentrated crude solution of (**F**), wherein the at least partial evaporation optionally comprises heating the dilute crude solution of (**F**) to a temperature of about 40 °C to about 55 °C, and further optionally maintaining the temperature for a period of about 1 h;

(5-c) cooling the concentrated crude solution of (**F**) to a temperature of about 20 °C to about 25 °C, to provide a crude (**F**) slurry, wherein the cooling optionally occurs over a period of about 3 h; and

(5-d) filtering the crude (**F**) slurry to provide (**F**), wherein the filtering optionally further comprises washing with a solvent comprising 2-

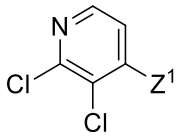
propanol.

11. The method of claim 5 or 6, wherein (**F**) is prepared by reacting 6-(2-chloro-3-(B(OR^{3a})(OR^{3b}))phenyl)-2-methoxynicotinaldehyde (**D'**):



(**D'**),

and 2,3-dichloro-4-Z^1-pyridine (**E'**):



(**E'**),

wherein Z^1 is selected from the group consisting of Br an I;

in the presence of a palladium catalyst and a base;

wherein each R^{3a} and R^{3b} are each independently selected from the group consisting of C_1-C_6 alkyl and C_3-C_8 cycloalkyl,

or R^{3a} and R^{3b} may combine with the atoms to which they are bound to form a C_2-C_3 heterocycloalkyl.

12. The method of claim 11, wherein at least one of the following applies:

(a) (**D'**) is 6-(2-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-2-methoxynicotinaldehyde;

(b) the palladium catalyst comprises $Pd(dppf)Cl_2$;

(c) the palladium catalyst is present in an amount ranging from about 0.1 mol% to about 5 mol%.;

(d) the base comprises K_2CO_3;

(e) the reaction of (**D'**) and (**E'**) occurs in the presence of a solvent, optionally wherein the solvent comprises 2-methyltetrahydrofuran (MeTHF) and water;

(f) the reaction of (**D'**) and (**E'**) occurs at a temperature of about 55 °C;

(g) purification of (**F**) comprises adding N-acetyl cysteine to the reaction of (**D'**) and (**E'**) or (6-a) to (6-d):

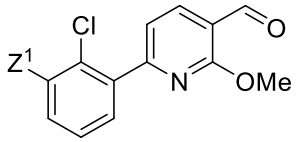
(6-a) providing crude (**F**) in 2-propanol to afford a dilute crude solution of (**F**), wherein the dilute crude solution of (**F**) has a concentration of about 100 g/L to about 140 g/L;

(6-b) at least partially evaporating the dilute crude solution of (**F**) to provide a concentrated crude solution of (**F**), wherein the at least partial evaporation optionally comprises heating the dilute crude solution of (**F**) to a temperature of about 50 °C to about 55 °C, and further optionally maintaining the temperature for a period of about 1 h;

(6-c) cooling the concentrated crude solution of (**F**) to a temperature of about 20 °C to about 25 °C, to provide a purified (**F**) slurry; and

(6-d) filtering the purified (**F**) slurry to provide (**F**).

13. The method of any one of claims 9-12, wherein (**D'**) is prepared by reacting (**D**):



(**D**),

wherein Z^1 is selected from the group consisting of Br and I;

and a borylating reagent in the presence of a palladium catalyst and a base.

14. The method of claim 13, wherein at least one of the following applies:

(a) the borylating reagent comprises bis(pinacolato)diboron;

(b) the palladium catalyst comprises $Pd(dppf)Cl_2$;

(c) the palladium catalyst is present in an amount ranging from about 0.1 mol% to about 7 mol%.;

(d) wherein the base comprises KOAc;

(e) the reaction of (**D**) and the borylating reagent occurs in the presence of a solvent, optionally wherein the solvent comprises dimethylformamide (DMF) and/or toluene;

(f) the reaction of (**D**) and the borylating reagent occurs at temperature of about 90 °C to about 100 °C;

(g) purification of (**D'**) comprises at least one of (i) steps (7-a) to (7-b) and (ii) steps (8-a) to (8-c):

(7-a) adding a N-acetyl cysteine to the reaction of (**D**) and the borylating reagent; and

(7-b) adding activated carbon to the reaction of (**D**) and the borylating reagent; and

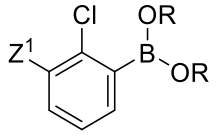
(8-a) providing crude (**D'**) in a solvent comprising 2-propanol to afford a crude solution of (**D'**),

wherein the crude solution of (**D'**) has a concentration of about 140 g/L to about 180 g/L;

(8-b) cooling the crude solution of (**D'**) to a temperature of about 0 °C to about 5 °C, to provide a purified (**D'**) slurry; and

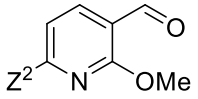
(8-c) filtering the purified (**D'**) slurry to provide (**D'**).

15. The method of any one of claims 9-10 and 13-14, wherein (**D**) is prepared by reacting 1-(B(OR^{4a})(OR^{4b}))-2-chloro-3-Z^1-benzene (**B**):



(**B**),

and 6-Z^2-2-methoxynicotinaldehyde (**C**):



(**C**),

in the presence of a palladium catalyst and a base;

wherein Z^1 is selected from the group consisting of Br and I;

wherein Z^2 is selected from the group consisting of Cl, Br, and I;

wherein each R^{4a} and R^{4b} are each independently selected from the group consisting of C_1-C_6 alkyl and C_3-C_8 cycloalkyl,

or R^{4a} and R^{4b} may combine with the atoms to which they are bound to form a C_2-C_3 heterocycloalkyl.

16. The method of claim 15, wherein at least one of the following applies:

(a) (**B**) is 2-(3-bromo-2-chlorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane;

(b) the palladium catalyst comprises $Pd(PPh_3)_4$;

(c) the base comprises K_2CO_3;

(d) the reaction of (**B**) and (**C**) occurs in the presence of a solvent, optionally wherein the solvent comprises 2-methyltetrahydrofuran (MeTHF) and/or water;

(e) the reaction of (**B**) and (**C**) occurs at a temperature of about 50 °C to about 60 °C;

(f) purification of (**D**) comprises adding N-acetyl cysteine to the reaction of (**B**) and (**C**) or steps (9-a) to (9-d):

(9-a) providing crude (**D**) in solvent comprising 2-propanol to afford a dilute crude solution of (**D**),

wherein the dilute crude solution of (**D**) has a concentration of about 160 g/L to about 220 g/L;

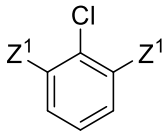
(9-b) at least partially evaporating the dilute crude solution of (**D**) to provide a concentrated crude solution of (**D**), wherein the at least partial evaporation optionally comprises heating the dilute crude solution of (**D**) to a temperature of about 50 °C to about 55 °C, and further optionally maintaining the temperature for a period of about 1 h;

(9-c) cooling the concentrated crude solution of (**D**) to a temperature of about 20 °C to about 25 °C, to provide a purified (**D**) slurry; and

(9-d) filtering the purified (**D**) slurry to provide (**D**).

17. The method of claim 15 or 16, wherein (**B**) is prepared by:

(a) reacting 1-Z^1-2-chloro-3-Z^1-benzene (**A**):



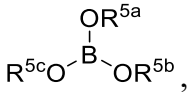
(**A**),

wherein each occurrence of Z^1 is independently selected from the group consisting of Br and I;

and an organomagnesium halide to form an arylmagnesium intermediate; and

(b) reacting the arylmagnesium intermediate with a borate.

18. The method of claim 17, wherein the borate is:



wherein each R^{5a}, R^{5b}, and R^{5c} are each independently selected from the group consisting of C_1-C_6 alkyl and C_3-C_8 cycloalkyl,

or any two selected from the group consisting of R^{5a}, R^{5b}, and R^{5c} may combine with the atoms to which they are bound to form a C_2-C_3 heterocycloalkyl.

19. The method of claim 17 or 18, wherein at least one of the following applies:

(a) the borate comprises 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane;

(b) the organomagnesium halide comprises *i*-PrMgCl, wherein the *i*-PrMgCl is optionally a solution comprising *i*-PrMgCl complexed with LiCl (*i.e.*, an *i*-PrMgCl•LiCl solution);

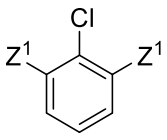
(c) the reaction of (**A**) and the organomagnesium halide occurs in a solvent, optionally wherein the solvent comprises 2-methyltetrahydrofuran (MeTHF);

(d) the reaction of (**A**) and the organomagnesium halide occurs at a temperature of about -25 °C to about -15 °C; and

(e) the reaction of the arylmagnesium intermediate and the borate occurs at a temperature of about -18 °C to about -15 °C, wherein the reaction is optionally subsequently warmed to a temperature of about 2 °C.

20. The method of any one of claims 9-10 and 13-14, wherein (**D**) is prepared by:

(a) providing 1-Z^1-2-chloro-3-Z^1-benzene (**A**):



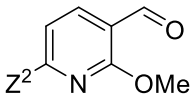
(**A**),

wherein each occurrence of Z^1 is independently selected from the group consisting of Br and I;

and an organomagnesium halide to form an arylmagnesium intermediate;

(b) reacting the arylmagnesium intermediate with a borate to provide a boronic ester intermediate; and

(c) reacting the boronic ester intermediate and 6-Z^2-2-methoxynicotinaldehyde (**C**):



(**C**),

wherein Z^2 is selected from the group consisting of Cl, Br, and I;

in the presence of a palladium catalyst and a base.

21. The method of claim 20, wherein at least one of the following applies:

(a) the organomagnesium halide comprises *i*-PrMgCl, wherein the *i*-PrMgCl is optionally a solution comprising *i*-PrMgCl complexed with LiCl (*i.e.*, an *i*-PrMgCl•LiCl solution);

(b) the reaction of (**A**) and the organomagnesium halide occurs in a solvent, optionally wherein the solvent comprises 2-methyltetrahydrofuran (MeTHF);

(c) the reaction of (**A**) and the organomagnesium halide occurs at a temperature of about -25 °C to about -15 °C; and

(d) the reaction of the arylmagnesium intermediate and the borate occurs at a temperature of about -18 °C to about -15 °C, wherein the reaction is optionally subsequently warmed to a temperature of about 2 °C;

(e) the borate comprises 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane;

(f) the palladium catalyst comprises $Pd(PPh_3)_4$;

(g) the palladium catalyst is present in an amount ranging from about 0.1 mol% to about 5 mol%;

(h) the base comprises K_2CO_3;

(i) the reaction of the boronic ester intermediate and (**C**) occurs in the presence of a solvent, optionally wherein the solvent comprises 2-methyltetrahydrofuran (MeTHF) and/or water;

(j) the reaction of the boronic ester intermediate and (**C**) occurs at a temperature of about 50 °C to about 60 °C; and

(k) purification of (**D**) comprises adding N-acetyl cysteine to the reaction of (**C**) and the boronic ester intermediate or steps (10-a) to (10-d):

(10-a) providing crude (**D**) in a solvent comprising 2-propanol to afford a dilute crude solution of (**D**),

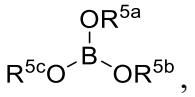
wherein the dilute crude solution of (**D**) has a concentration of about 160 g/L to about 220 g/L;

(10-b) at least partially evaporating the dilute crude solution of (**D**) to provide a concentrated crude solution of (**D**), wherein the at least partial evaporation optionally comprises heating the dilute crude solution of (**D**) to a temperature of about 50 °C to about 55 °C, and further optionally maintaining the temperature for a period of about 1 h;

(10-c) cooling the concentrated crude solution of (**D**) to a temperature of about 20 °C to about 25 °C, to provide a purified (**D**) slurry; and

(10-d) filtering the purified (**D**) slurry to provide (**D**).

22. The method of claim 20 or 21, wherein the borate is:



wherein each R^{5a}, R^{5b}, and R^{5c} are each independently selected from the group consisting of C_1-C_6 alkyl and C_3-C_8 cycloalkyl,

or any two selected from the group consisting of R^{5a}, R^{5b}, and R^{5c} may combine with the atoms to which they are bound to form a C_2-C_3 heterocycloalkyl.