used, but the shown chemical structure controls. One such alternative name is (S)-2-(3'-(hydroxymethyl)-1-methyl-5-((5-(2-methyl-4-(oxetan-3-yl)piperazin-1-yl)pyridin-2-yl)amino)-6-oxo-1,6-dihydro-[3,4'-bipyridin]-2' yl)-7,7-dimethyl-2,3,4,6,7,8-hexahydro-1H-cyclopenta[4,5]pyrrolo[1,2 a]pyrazin-1-one. The US 2013/0116235 publication discloses a useful method for preparing 2-{3'-hydroxymethyl-1-methyl-5-[5-((S)-2-methyl-4-oxetan-3-yl-piperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl}-7,7-dimethyl-3,4,7,8-tetrahydro-2H,6H-cyclopenta[4,5]pyrrolo[1,2-a]pyrazin-1-one, but the method requires chromatographic purification and a low yield was achieved.

[0004] A useful process for preparing 2-{3'-hydroxymethyl-1-methyl-5-[5-((S)-2-methyl-4-oxetan-3-yl-piperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl}-7,7-dimethyl-3,4,7,8-tetrahydro-2H,6H-cyclopenta[4,5]pyrrolo[1,2-a]pyrazin-1-one is further known from US 2018/0230155 and from Zhang, H., *et al*., "Development of an Efficient Manufacturing Process for Reversible Bruton's Tyrosine Kinase Inhibitor GDC-0853", *Org. Process Res. Dev*. 2018, 22, 8, 978–990. US 2018/0230155 and the Zhang publication are incorporated herein by reference in its entirety.

[0005] A need exists for improved methods for preparing 2-{3'-hydroxymethyl-1-methyl-5-[5-((S)-2-methyl-4-oxetan-3-yl-piperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl}-7,7-dimethyl-3,4,7,8-tetrahydro-2H,6H-cyclopenta[4,5]pyrrolo[1,2-a]pyrazin-1-one and intermediate compounds therefore. For example, there is a need for improved methods with higher yield, lower presence of byproduct, or combinations thereof.

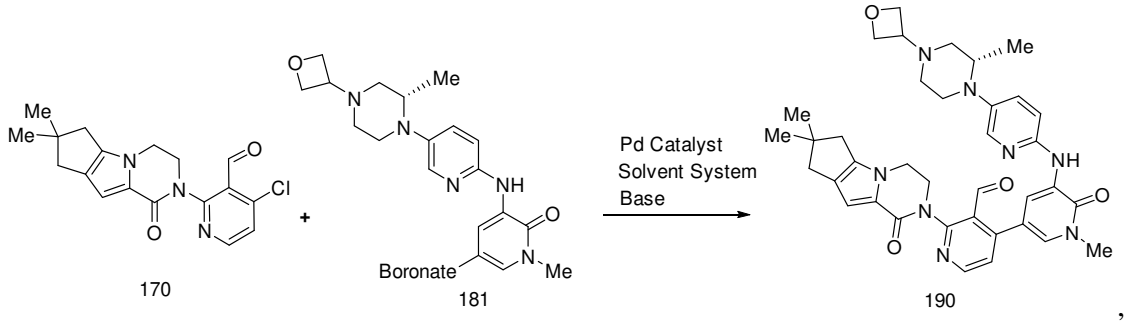
SUMMARY

[0005a] In one aspect, the disclosure provides a method of preparing compound 190, or a stereoisomer, geometric isomer, tautomer, or salt thereof,

the method comprising:

(a) forming a reaction mixture comprising compound 170, compound 181, a palladium catalyst, and a solvent system comprising a base, and wherein the equivalent ratio of the palladium catalyst to compound 170 is from about 0.001:1 to less than 0.005:1; and

(b) reacting the reaction mixture to form a reaction product mixture comprising compound 190 according to the following scheme:

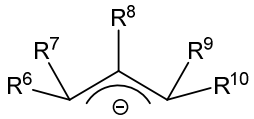


170 181 190 ,

wherein the Pd catalyst comprises a palladium(II) species containing a phosphine ligand and at least one palladium-carbon bond,

wherein:

(i) the fragment giving rise to the palladium-carbon bond is an allyl derivative of the formula



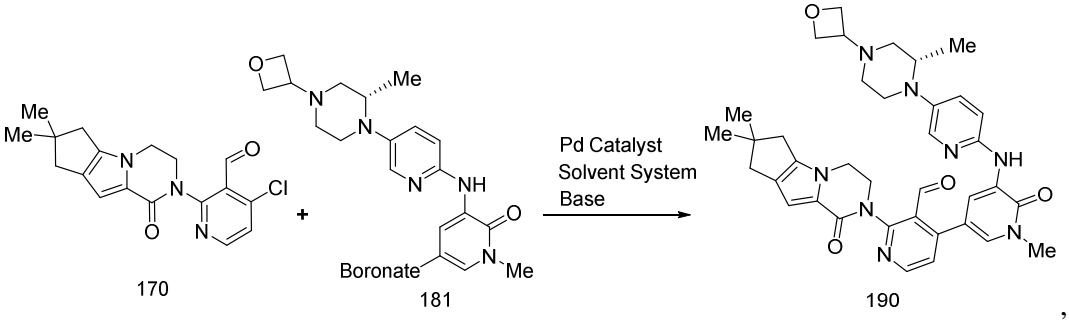
wherein each of R^6 to R^{10} is independently selected from the group consisting of H, optionally substituted C_{1-6} alkyl, optionally substituted C_6 aryl, and optionally substituted heteroaryl; and R^6 and R^{10} may optionally come together to form a fused bicycle comprising an aromatic ring;

wherein the yield of compound 190, or a stereoisomer, geometric isomer, tautomer, or salt thereof, is at least 50% based on compound 170.

[0005b] In one aspect, the disclosure provides a method of reducing byproduct formation in a Suzuki coupling reaction, the method comprising:

(a) forming a reaction mixture comprising compound 170, compound 181, a palladium catalyst, a solvent system, and a base, wherein the equivalent ratio of the palladium catalyst to compound 170 is from about 0.001:1 to less than 0.005:1; and

(b) reacting the reaction mixture to form a reaction product mixture comprising compound 190, or a stereoisomer, geometric isomer, tautomer, or salt thereof, according to the following scheme:

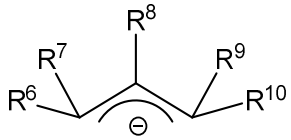


170 181 190 ,

wherein the Pd catalyst comprises a palladium(II) species containing a phosphine ligand and at least one palladium-carbon bond,

wherein:

(i) the fragment giving rise to the palladium-carbon bond is an allyl derivative of the formula

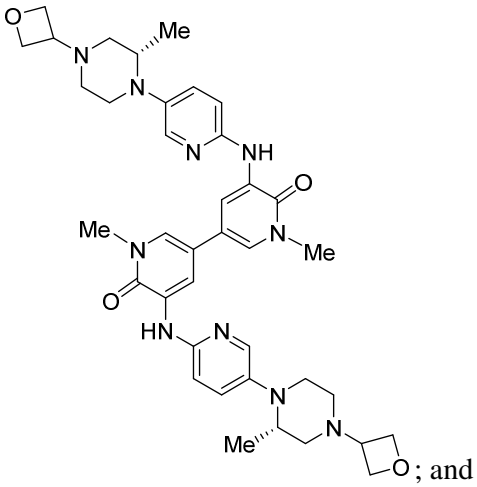


wherein each of R^6 to R^{10} is independently selected from the group consisting of H, optionally substituted C_{1-6} alkyl, optionally substituted C_6

aryl, and optionally substituted heteroaryl; and R^6 and R^{10} may optionally come together to form a fused bicycle comprising an aromatic ring;

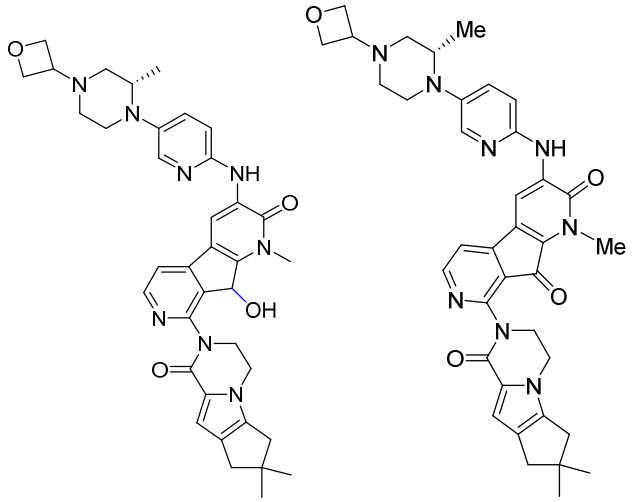
wherein:

(a) the content of a dimer impurity is less than 0.1 area% based on compound 190, or a stereoisomer, geometric isomer, tautomer, or salt thereof, wherein the dimer impurity is of the structure



; and

(b) the combined content of an alcohol and a ketone impurity is less than 0.25 area% based on compound 190, or a stereoisomer, geometric isomer, tautomer, or salt thereof, wherein the alcohol and ketone impurities are is of the structure



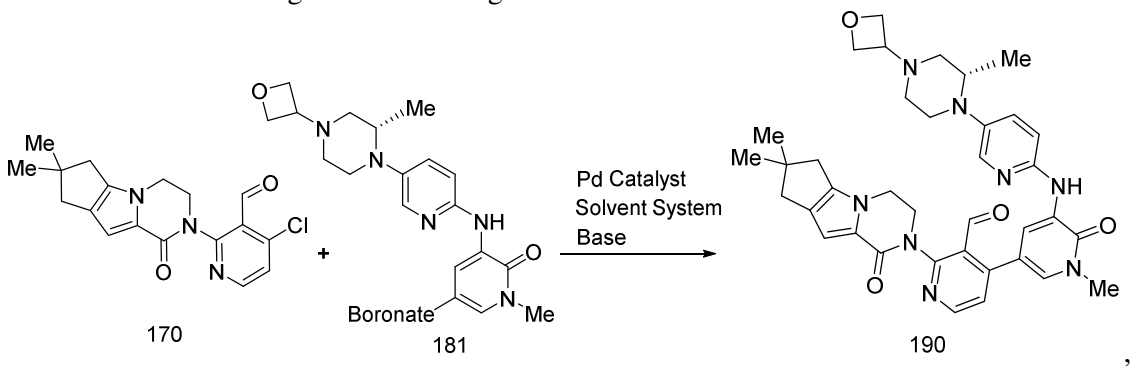
Alcohol Ketone .

[0005c] In one aspect, the disclosure provides a method of improving yield in a Suzuki coupling reaction, the method comprising:

(a) forming a reaction mixture comprising compound 170, compound 181, a palladium catalyst, a solvent system, and a base, wherein the equivalent ratio

of the palladium catalyst to compound 170 is from about 0.001:1 to less than 0.005:1; and

(b) reacting the reaction mixture to form a reaction product mixture comprising compound 190, or a stereoisomer, geometric isomer, tautomer, or salt thereof, according to the following scheme:

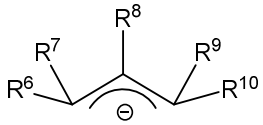


170 181 190 ,

wherein the Pd catalyst comprises a palladium(II) specie containing a phosphine ligand and at least one palladium-carbon bond,

wherein:

(i) the fragment giving rise to the palladium-carbon bond is an allyl derivative of the formula



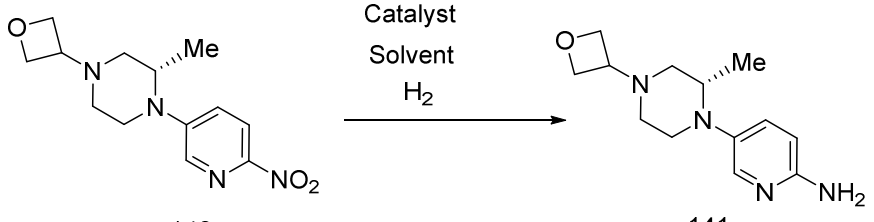
wherein each of R^6 to R^{10} is independently selected from the group consisting of H, optionally substituted C_{1-6} alkyl, optionally substituted C_6 aryl, and optionally substitute heteroaryl; and R^6 and R^{10} may optionally come together to form a fused bicycle comprising an aromatic ring

wherein the yield of compound 190, or a stereoisomer, geometric isomer, tautomer, or salt thereof, based on compound 170 is at least 80% or at least 85%.

[0005d] In one aspect, the disclosure provides a method of preparing compound 180, stereoisomers thereof, geometric isomers thereof, tautomers thereof, and salts thereof, the method comprising:

(a) forming a first reaction mixture comprising compound 140, a catalyst, a solvent, and hydrogen;

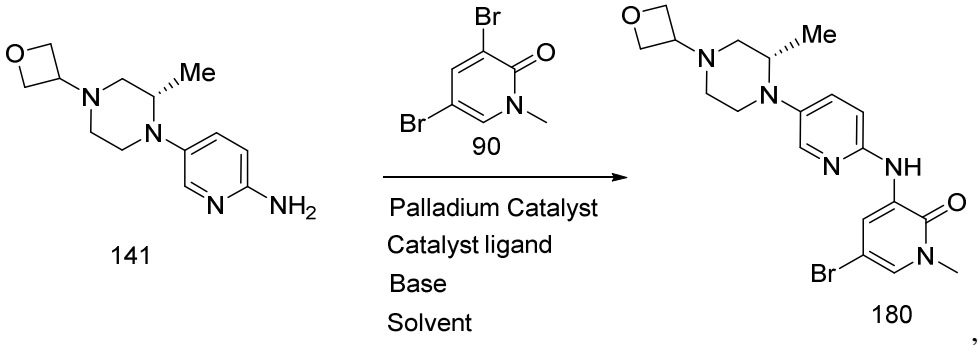
(b) reacting the first reaction mixture to form a first reaction product mixture comprising compound 141 according to the following scheme



140 141 ;

(c) forming a second reaction mixture comprising compound 141, compound 90, a palladium catalyst, a catalyst ligand, a base, and a solvent; and

(d) reacting the second reaction mixture to form a second reaction product mixture comprising compound 180 according to the following scheme



,

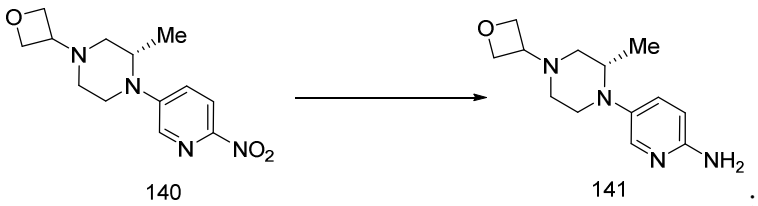
wherein the first reaction mixture catalyst is selected from the group consisting of Ra-Ni, Ra-Co, Pt/V@C, Co@Chitin, Ni-phen@SiO_2, and Ni-phen@TiO_2,

wherein the yield of compound 141 based on compound 140 is at least 90% or at least 95%, and

wherein the yield of compound 180 based on compound 141 is at least 60%, at least 70%, at least 80%, and the purity of compound 180 is at least 95%, at least 98%, or at least 99%.

[0005e] In one aspect, the disclosure provides a method of preparing compound 180 stereoisomers thereof, geometric isomers thereof, tautomers thereof, and salts thereof, the method comprising:

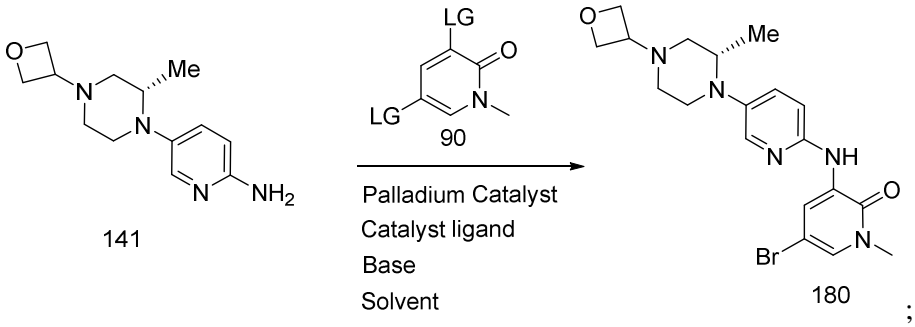
(a) a process of forming a first reaction mixture comprising compound 140 and a solvent comprising organic solvent; and contacting said reaction mixture with a transition metal catalyst in the presence of hydrogen to form a first product mixture comprising compound 141, wherein the process is a continuous flow process



;

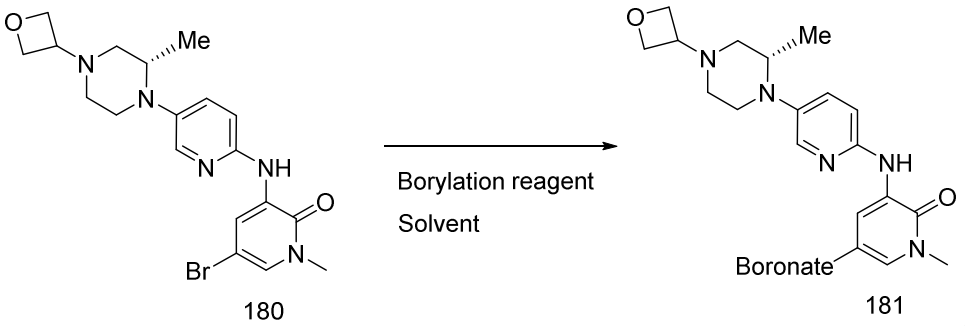
(b) forming a second reaction mixture comprising compound 141, compound 90, a palladium catalyst, a catalyst ligand, a base, and a solvent; and

(c) reacting the second reaction mixture to form a second reaction product mixture comprising compound 180 according to the following scheme where LG is a leaving group



; and

(d) reacting compound 180 with a borylation agent in the presence of a solvent to form compound 181 according to the following scheme

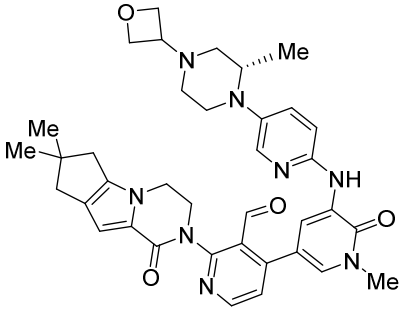


180 181 ,

wherein the yield of compound 141 based on compound 140 is at least 90% or at least 95%, and

wherein the yield of compound 180 based on compound 141 is at least 60%, at least 70%, at least 80%, and the purity of compound 180 is at least 95%, at least 98%, or at least 99%.

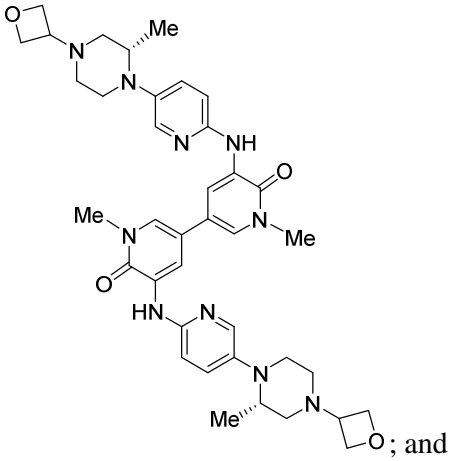
[0005f] In one aspect, the disclosure provides a composition, comprising at least 98.5 w/w% compound 190, or stereoisomer, geometric isomer, tautomer, or salt thereof,



190 ,

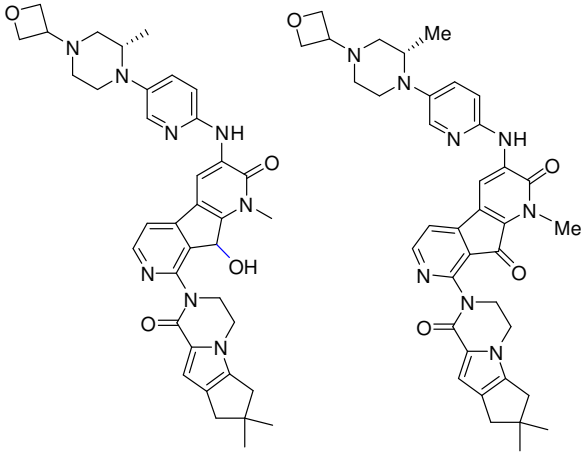
and wherein

(a) the content of a dimer impurity is less than 0.15 area% based on compound 190, wherein the dimer impurity is of the structure



; and

(b) the combined content of an alcohol and a ketone impurity is less than 0.35 area% based on compound 190, wherein the alcohol and ketone impurities are of the structure



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BRIEF DESCRIPTION

[0006] One aspect of the disclosure is directed to a method of preparing compound 190, or a stereoisomer, geometric isomer, tautomer, or salt thereof. The method comprises forming a reaction mixture comprising compound 170, compound 181, a palladium catalyst, a solvent system comprising water and a base, wherein the equivalent ratio of the palladium catalyst to compound 170 is from about 0.001:1 to less than 0.005:1. The reaction mixture is reacted to form a reaction product mixture comprising compound 190 (or a stereoisomer, geometric isomer, tautomer, or salt thereof) according to the following scheme: