CLAIMS

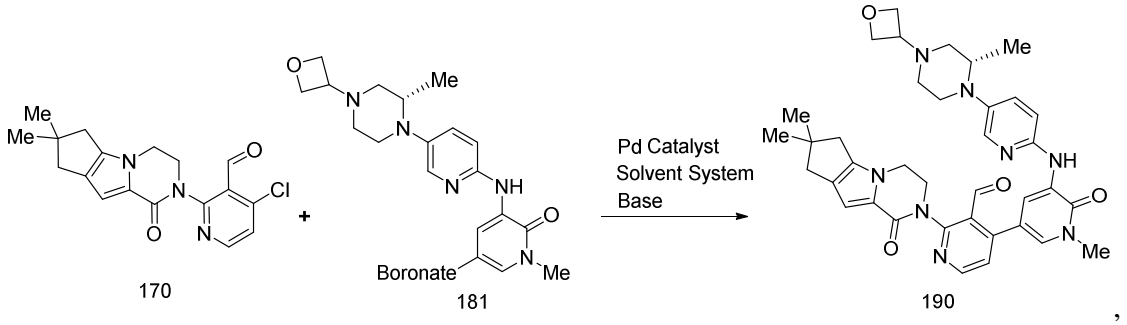
What is claimed is:

1. 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:



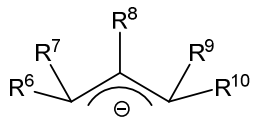
170 181 190

,

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

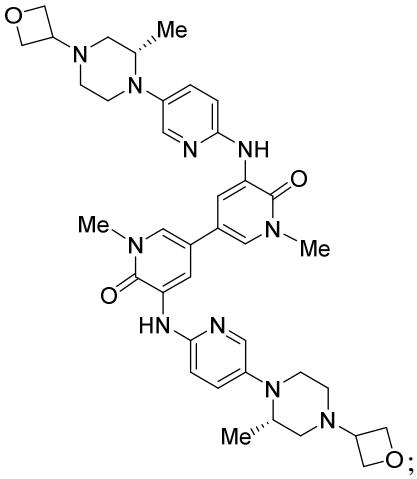


wherein each of R^6 to R^{10} is independently selected from the group consisting of H, optionally substituted C_{1-6} alkyl, optionally substituted C_6 aryl, and optionally substituted heteroaryl; and R^6 and R^{10} may optionally come together to form a fused bicycle comprising an aromatic ring;

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

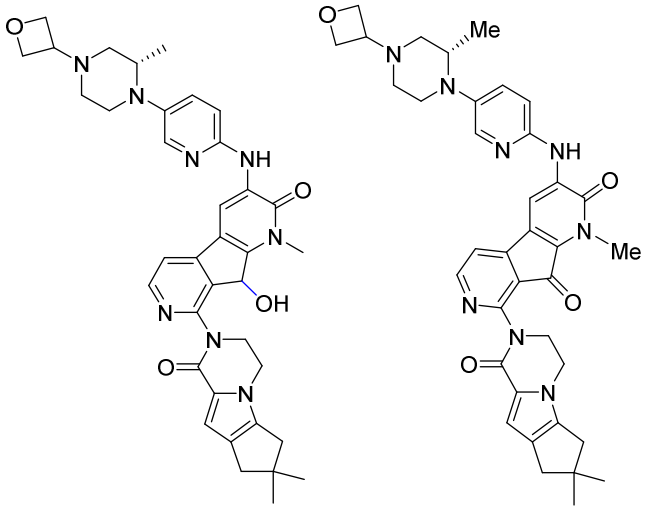
2. The method of claim 1, wherein:

(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 of the structure

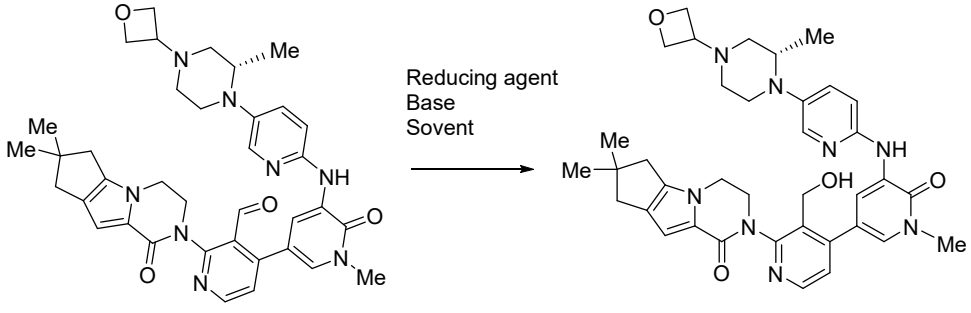


Alcohol Ketone

.

3. The method of claim 1 or 2, further comprising reacting compound 190, or a stereoisomer, geometric isomer, tautomer, or salt thereof, to form compound 200, or a stereoisomer, geometric isomer, tautomer, or salt thereof, the reacting comprising:

(a) contacting compound 190, or the stereoisomer, geometric isomer, tautomer, or salt thereof, with a reducing agent and a base in the presence of a solvent to form compound 200, or the stereoisomer, geometric isomer, tautomer, or salt thereof, according to the following scheme



190 200 ; and

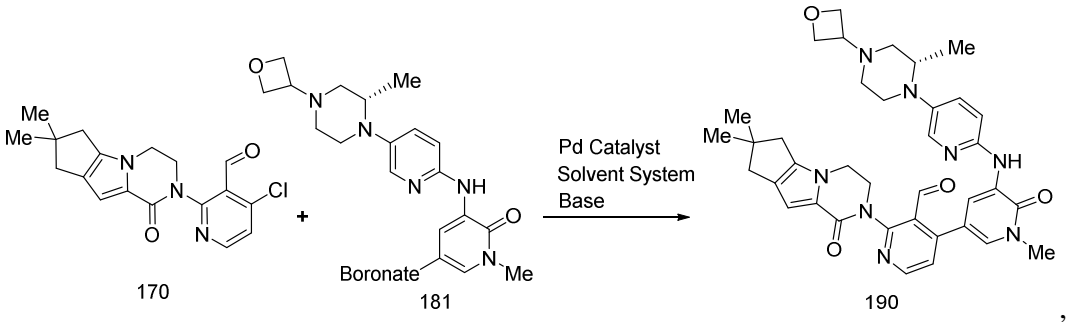
(b) isolating compound 200, or the stereoisomer, geometric isomer, tautomer, or salt thereof,

wherein the yield of compound 200, or a stereoisomer, geometric isomer, tautomer, or salt thereof, based on compound 170 is at least 60%, at least 70%, at least 80%, or at least 85%, and the purity of compound 200, or a stereoisomer, geometric isomer, tautomer, or salt thereof, is at least 99 area% or at least 99.5 area%

4. 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:

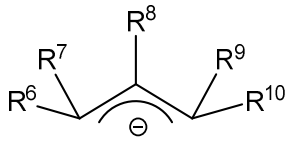


170 181 190 ,

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

wherein:

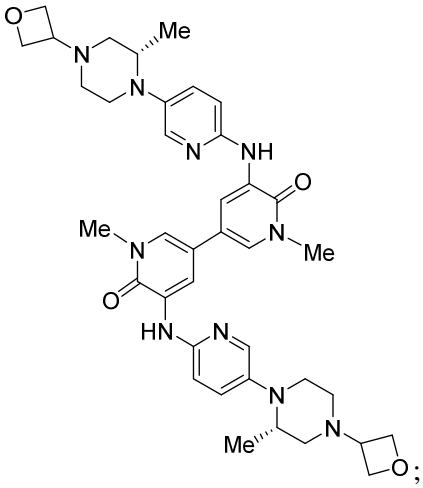
(i) the fragment giving rise to the palladium-carbon bond is an allyl derivative of the formula



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;

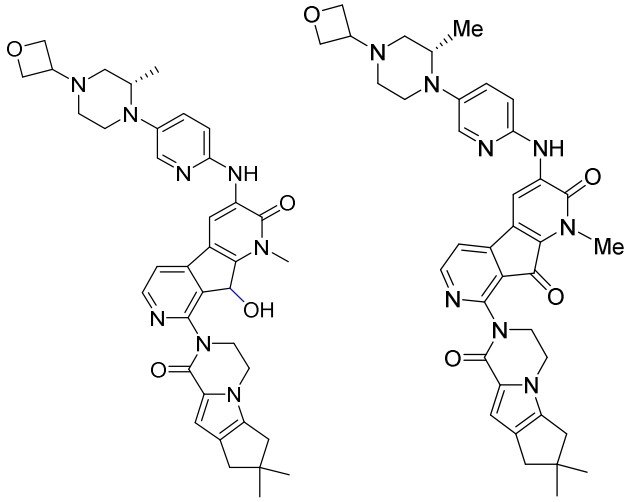
wherein:

(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

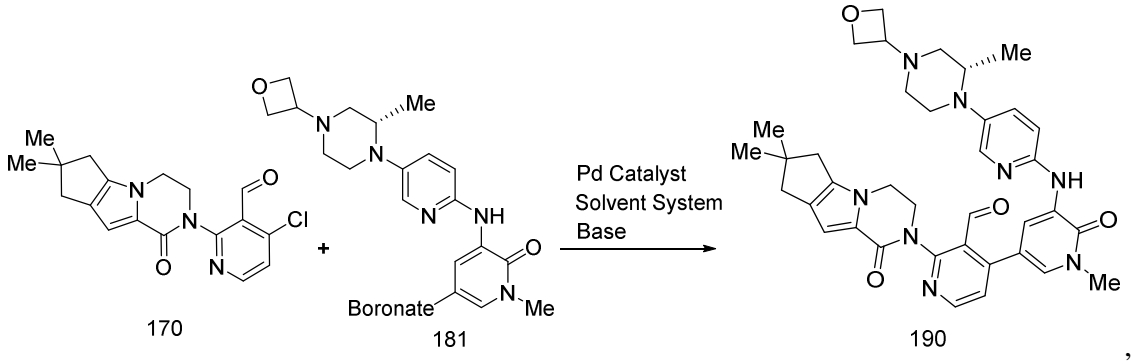


Alcohol Ketone .

5. 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:

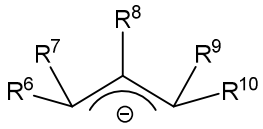


170 181 190 ,

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

wherein:

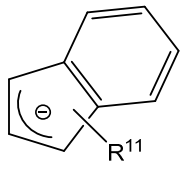
(i) the fragment giving rise to the palladium-carbon bond is an allyl derivative of the formula



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%.

6. The method of any one of claims 1 to 5, wherein the fragment giving rise to the palladium-carbon bond is an indenyl of the formula



, wherein R^{11} is C_{1-10} alkyl.

7. The method of any one of claims 1 to 6, wherein the allyl derivative is selected from:

(a) a derivative wherein each of R^6 to R^{10} is H;

(b) a derivative wherein R^6 is $-CH_3$ and each of R^7 to R^{10} is H;

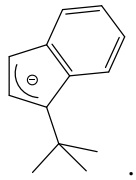
(c) a derivative wherein R^7 is $-CH_3$ and each of R^6 and R^8 to R^{10} is H;

(d) a derivative wherein R^8 is $-CH_3$ and each of R^6, R^7, R^9 and R^{10} is H;

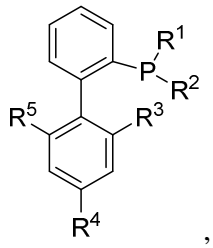
(e) a derivative wherein R^6 is -phenyl and each of R^7 to R^{10} is H;

(f) a derivative wherein R^7 is -phenyl and each of R^6 and R^8 to R^{10} is H; and

(g) a derivative of the structure



8. The method of any one of 1 to 7, wherein phosphine ligand is of the formula

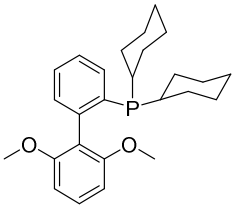


wherein:

R^1 and R^2 are each independently selected from optionally substituted $C_{1\text{-}12}$ alkyl, optionally substituted C_3-C_{20} cycloalkyl, and optionally substituted C_5 or C_6 aryl; and

R^3 to R^5 are each independently selected from H, optionally substituted $C_{1\text{-}6}$ alkyl, alkoxide of the formula -O-$C_{1\text{-}6}$ alkyl, and amine of the formula -N(R^{12})(R^{13}) wherein R^{12} and R^{13} are independently selected from H and $C_{1\text{-}6}$ alkyl.

9. The method of any of claims 1 to 8, wherein the phosphine ligand is SPhos of the following structure



10. The method of any one of claims 1 to 9, wherein the Pd catalyst is selected from:

(a) a cationic palladium species comprising an inorganic or organic counterion X; and

(b) a neutral palladium species comprising a coordinated inorganic or organic ligand X.

11. The method of claim 10, wherein X is selected from a halogen, a carboxylate, a sulfonate, and an inorganic anion.

12. The method of claim 11, wherein:

(a) the carboxylate is selected from $CH_3C(O)O^-$ and $tBuC(O)O^-$;

(b) the sulfonate is selected from $CF_3SO_3^-$, tosylate, besylate, and nosylate; and

(c) the inorganic anion selected from PF_6^-, BF_4^-, $B(C_6F_5)_4^-$, NO_3^-, and SO_4^{2-}.

13. The method of claim 11 or 12, wherein X is $CF_3SO_3^-$.

14. The method of any one of claims 1 to 13, wherein the palladium catalyst comprises a $CF_3SO_3^-$ organic counterion, wherein the phosphine ligand is SPhos, and wherein each of R^6 to R^{10} is H.

15. The method of any one of claims 1 to 14, wherein the solvent system predominantly comprises an aprotic low molecular weight ester solvent and water, wherein the volume ratio of the aprotic low molecular weight ester solvent to water is from about 1:0.1 to about 1:1, and wherein the reaction mixture is heated to from about 60°C to about 80°C.

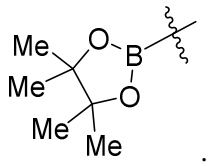
16. The method of any one of claims 1 to 15, wherein the equivalent ratio of compound 181 to compound 170 is greater than 1:1, and the equivalent ratio of the palladium catalyst to compound 170 is from about 0.001:1 to about 0.003:1, or about 0.002:1.

17. The method of any one of claims 1 to 1615, wherein:

(a) the catalyst is [(SPhos)Pd(allyl)] CF_3SO_3;

(b) the solvent system predominantly comprises ethyl acetate and water wherein the volume ratio of ethyl acetate to water is from about 1:0.1 to about 1:1; and

(c) the boronate is 4,4,5,5-tetramethyl-1,3,2-dioxaborolane of the structure:

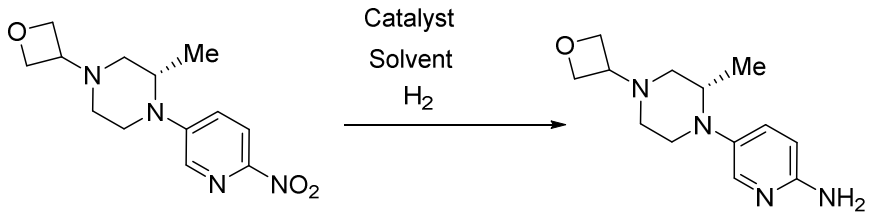


.

18. 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;

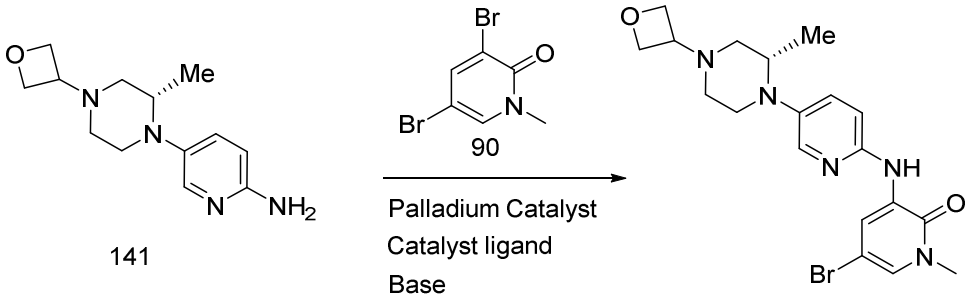
(b) reacting the first reaction mixture to form a first reaction product mixture comprising compound 141 according to the following scheme



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



141 180 ,

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,

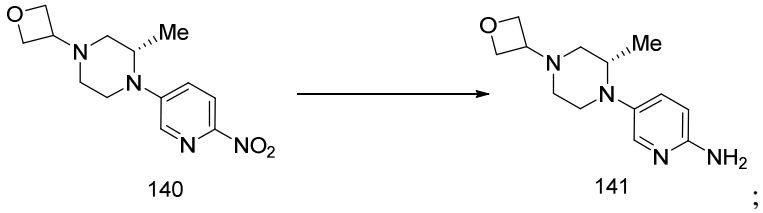
wherein the yield of compound 141 based on compound 140 is at least 90% or at least 95%, and

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%.

19. 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

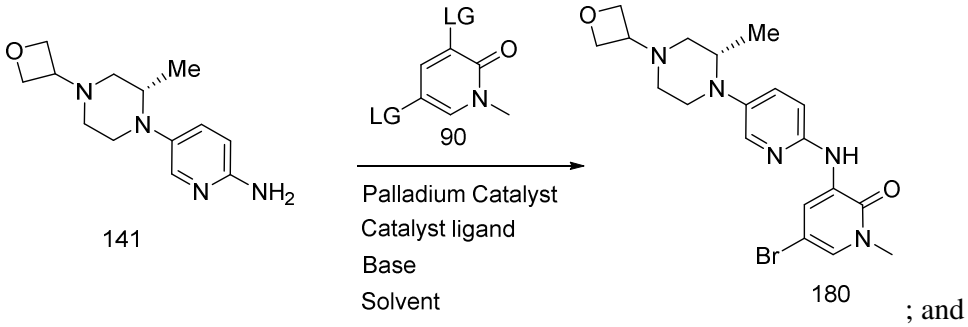
mixture comprising compound 141, wherein the process is a continuous flow process



;

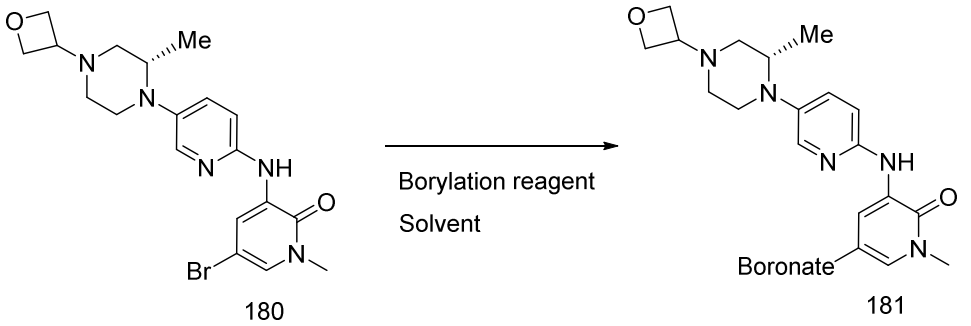
(b) forming a second reaction mixture comprising compound 141, compound 90, a palladium catalyst, a catalyst ligand, a base, and a solvent; and

(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



,

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%.

20. The method of claim 18 or 19, wherein compound 141 is not isolated from the first reaction product mixture prior to formation of the second reaction product mixture.

21. The method of any one of claims 18 to 20, wherein, the first reaction mixture solvent and the second reaction mixture solvent each predominantly comprise a polar aprotic solvent.

22. The method of claim 21, wherein the first reaction mixture solvent predominantly comprises tetrahydrofuran.

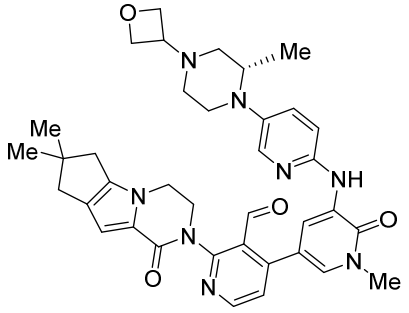
23. The method of any one of claims 18 to 23, wherein the palladium catalyst is $Pd(OAc)_2$ and the catalyst ligand is XantPhos or DPEPhos.

24. The method of any one of claims 18 to 23, wherein the palladium catalyst is $Pd(OAc)_2$, the catalyst ligand is XantPhos, and the base is K_2CO_3; or wherein the palladium catalyst is $Pd(OAc)_2$; the catalyst ligand is DPEPhos, and the base is NaOMe.

25. The method of any one of claims 18 to 23, wherein the first reaction mixture catalyst is Pt/V@C.

26. The method of any one of claims 19 to 23, wherein the first reaction mixture catalyst is Pd/Al_2O_3, Pt/Al_2O_3, Pd/C, or Pt/C.

27. A composition, comprising at least 98.5 w/w% compound 190, or stereoisomer, geometric isomer, tautomer, or salt thereof,

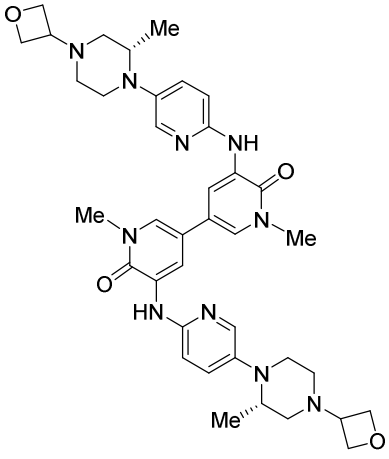


190

,

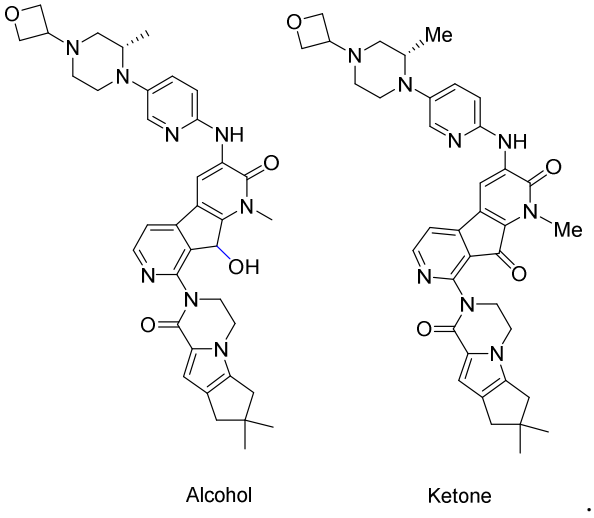
and wherein

(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



.

28. The composition of claim 27, wherein the content of the dimer impurity is less than 0.10 area% based on compound 190.

29. The composition of claim 28, wherein the content of the dimer impurity is less than 0.05 area% based on compound 190.

30. The composition of any one of claims 27 to 29, wherein the combined content of the alcohol and ketone impurities is less than 0.30 area% based on compound 190.

31. The composition of claim 30, wherein the combined content of the alcohol and ketone impurities is less than 0.25 area% based on compound 190.

32. The composition of claim 31, wherein the combined content of the alcohol and ketone impurities is less than 0.20 area% based on compound 190.

33. The composition of any one of claims 27 to 32, comprising at least 99.0 w/w% compound 190, or stereoisomer, geometric isomer, tautomer, or salt thereof.

34. The composition of claim 33, comprising at least 99.5 w/w% compound 190, or stereoisomer, geometric isomer, tautomer, or salt thereof.