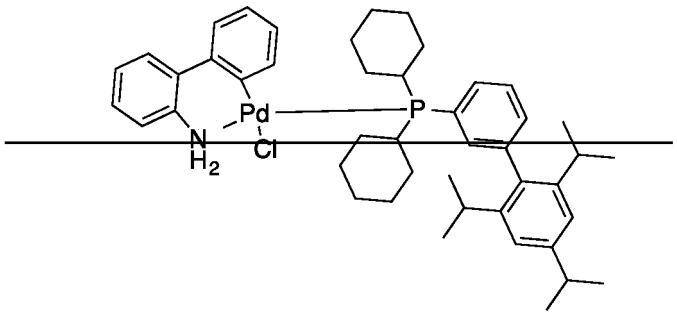
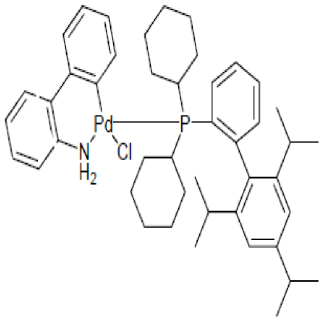
$NHCH_2CH_2OCH_3$, $-NHCOCH_3$, $-NHCOCH_2CH_3$, $-NHCOCH_2OH$, $-NHS(O)_2CH_3$, $-N(CH_3)S(O)_2CH_3$, =O, -OH, $-OCH_3$, $-OCH_2CH_3$, $-OCH(CH_3)_2$, -SH, $-NHC(O)NHCH_3$, $-NHC(O)NHCH_2CH_3$, $-S(O)CH_3$, $-S(O)CH_2CH_3$, $-S(O)_2CH_3$, $-S(O)_2NH_2$, $-S(O)_2NHCH_3$, $-S(O)_2N(CH_3)_2$, and $-CH_2S(O)_2CH_3$. In some aspects, mor is mor-a depicted above.

[78] It is to be understood that every embodiment relating to a specific residue, X^1, X^2, X^3, A, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{10}, R^{15} and mor as disclosed herein may be combined with any other embodiment relating to another residue X^1, X^2, X^3, A, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{10}, R^{15} and mor as disclosed herein.

[79] The catalyst comprising palladium is generally any such catalyst suitable to achieve the yield and purity disclosed herein. In some aspects, the catalyst comprising palladium is selected from chloro(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2-aminoethyl) phenyl)]palladium(II) (e.g., "Xphos PdG1", "Xphos PdG2" and "Xphos PdG3"); 1,1′-bis(diphenylphosphino)ferrocene] dichloropalladium(II) complex with dichloromethane ("$PdCl_2(dppf)•CH_2Cl_2$"); Bis(di-tert-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II) ("$Pd(amphos)Cl_2$"); dichlorobis(di-tert-butylphenylphosphine)palladium(II); Dichlorobis(di-tert-butylphenylphosphine)palladium(II) ("$PdCl_2[(^tBu_2Ph)P]_2$"); $PdCl_2(PPh_3)_2$; Chloro(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II) (Xphos pD G2) of the structure:

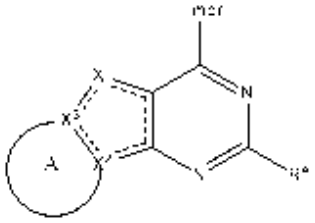




$Pd(t\text{-}Bu)_3$; $Pd(PPh_3)_4$; $Pd(OAc)/PPh_3$; $Cl_2Pd[(Pet_3)]_2$; $Pd(DIPHOS)_2$; $Cl_2Pd(Bipy)$; $[PdCl(Ph_2PCH_2PPh_2)]_2$; $Cl_2Pd[P(o\text{-}tol)_3]_2$; $Pd_2(dba)_3/P(o\text{-}tol)_3$; $Pd_2(dba)/P(furyl)_3$; $Cl_2Pd[P(furyl)_3]_2$; $Cl_2Pd(PmePh_2)_2$; $Cl_2Pd[P(4\text{-}F\text{-}Ph)_3]_2$; $Cl_2Pd[P(C_6F_6)_3]_2$; $Cl_2Pd[P(2\text{-}COOH\text{-}Ph)(Ph)_2]_2$; $Cl_2Pd[P(4\text{-}COOH\text{-}Ph)(Ph)_2]_2$; and encapsulated catalysts Pd EnCat™ 30 (palladium acetate, microencapsulated in a polyuria matrix, comprising 0.4 mmol/g Pd), Pd EnCat™ TPP30 (palladium acetate and triphenylphosphine, microencapsulated in a polyuria matrix, comprising 0.4 mmol/g Pd and 0.3 mmol/g phosphorous), and Pd(II)EnCat™

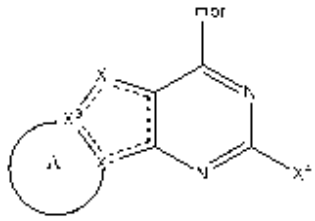
Claims

1. A process for preparing a compound of Formula III,



III

from a compound of Formula II,



II

in a reaction mixture, the process comprising:

(i) forming a reaction mixture comprising the compound of Formula II, organoboron-R^4, ~~the~~ a solvent system comprising at least 5 v/v % water, ~~the~~ a base and ~~the~~ a catalyst;

(ii) reacting the reaction mixture at a temperature of less than 100 °C to form a reaction product mixture comprising the compound of Formula III;

(iii) further comprising adding a polar protic solvent to the reaction product mixture to form an admixture comprising greater than 25 v/v % of the polar protic solvent, and separating the compound of Formula III from the reaction product mixture by solid-liquid separation; and

(iv) isolating the compound of Formula III~~, a stereoisomer, geometric isomer, tautomer, or a pharmaceutically acceptable salt thereof,~~ from the reaction product mixture,

the process further comprising a purification step comprising:

(i) admixing the compound of Formula III with a metal scavenger in a solvent system comprising at least one polar protic solvent;

(ii) heating the admixture to dissolve the compound of Formula III;

(iii) filtering the heated admixture;

(iv) reducing the temperature of the filtrate and admixing seed crystals of the compound of Formula III with the cooled filtrate;

(v) reducing the temperature of the admixture of filtrate and seed crystals to induce crystallization of the purified compound of Formula III; and

(vi) collecting crystals of the purified compound of Formula III,

wherein

the catalyst is selected from the group consisting of Xphos PdG1, Xphos PdG2, Xphos PdG3, and [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane ($PdCl_2(dppf)•CH_2Cl_2$), ~~comprises palladium~~ and the reaction mixture comprises less than 0.05 equivalents of catalyst per equivalent of compound Formula II;

X^1 is S, O, N, NR^6, CR^1, $C(R^1)_2$, or $-C(R^1)_2O-$;

X^2 is C, CR^2 or N;

X^3 is C, CR^3 or N;

X^4 is halogen;

A is a 5, 6, or 7-membered carbocyclyl or heterocyclyl ring fused to X^2 and X^3, optionally substituted with one or more R^5, R^{10} or R^{15} groups;

R^6 is H, C_1-C_{12} alkyl, C_2-C_8 alkeny1, C_2-C_8 alkynyl, -(C_1-C_{12} alkylene)-(C_3-C_{12} carbocyclyl), -(C_1-C_{12} alkylene)(-C_2-C_{20} heterocyclyl), -(C_1-C_{12} alkylene)-C(=O)-(C_2-C_{20} heterocyclyl), (C_1 -C_{12} alkylene)-(C_6-C_{20} aryl), and -(C_1-C_{12} alkylene)-(C_1-C_{20} heteroaryl), where alkyl, alkenyl, alkynyl, alkylene, carbocyclyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one or more groups independently selected from F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, $-C(CH_3)_3$, $-CH_2OH$, $-CH_2CH_2OH$, $-(CH_3)_2OH$, $-CH_2OCH_3$, -CN, $-CO_2H$, $-COCH_3$, $-COC(CH_3)_3$, $-CO_2CH_3$, $-CONH_2$, $-CONHCH_3$, $-CON(CH_3)_2$, $-C(CH_3)_2CONH_2$, -N

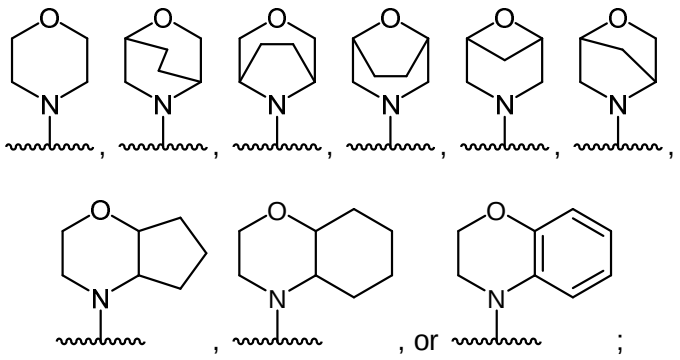
O_2, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -$NHCOCH_3$, -$NHS(O)_2CH_3$, -$N(CH_3)C(CH_3)_2CONH_2$, -$N(CH_3)CH_2CH_2S(O)_2CH_3$, =O, -OH, -$OCH_3$, -$S(O)_2N(CH_3)_2$, -$SCH_3$, -$S(O)_2CH_3$, cyclopropyl, cyclobutyl, oxetanyl, morpholino, or 1,1-dioxo-thiopyran-4-yl;

R^1, R^2, and R^3 are independently selected from H, F, Cl, Br, I, -CH_3, -CH_2CH_3, -$C(CH_3)_3$, -CH_2OH, -CH_2CH_2OH, -$C(CH_3)_2OH$, -CH_2OCH_3, -CN, -CF3, -CO_2H, -$COCH_3$, -$COC(CH_3)_3$, -CO_2CH_3, -$CONH_2$, -$CONHCH_3$, -$CON(CH_3)_2$, -$C(CH_3)_2$, -$CONH_2$, -NO_2, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -$NHCOCH_3$, -$NHS(O)_2CH_3$, -$N(CH_3)C(CH_3)_2CONH_2$, -$N(CH_3)CH_2CH_2S(O)_2CH_3$, =O, -OH, -$OCH_3$, -$S(O)_2N(CH_3)_2$, -$SCH_3$, -$S(O)_2CH_3$, cyclopropyl, cyclobutyl, oxetanyl, morpholino, or 1,1-dioxo-thiopyran-4-yl;

R^4 is ~~selected from~~ C_6-C_{20} aryl~~, C_2-C_{20} heterocyclyl,~~ or C_1-C_{20} heteroaryl, each of which are optionally substituted with one or more groups independently selected from F, Cl, Br, I, -CH_3, -CH_2CH_3, -$CH(CH_3)_2$, -$CH_2CH(CH_3)_2$, -CH_2CH_3, -CH_2CN, -CN, -CF_3, -CH_2OH, -CO_2H, -$CONH_2$, -$CONH(CH_3)$, -$CON(CH_3)_2$, -NO_2, -NH_2, -$NHCH_3$, -$NHCOCH_3$, -OH, -OCH_3, -OCH_2CH_3, -$OCH(CH_3)_2$, -SH, -$NHC(O)NHCH_3$, -$NHC(O)NHCH_2CH_3$, -$NHS(O)_2CH_3$, -$N(CH_3)C(O)OC(CH_3)_3$, -$S(O)_2CH_3$, benzyl, benzyloxy, morpholinyl, morpholinomethyl, or 4-methylpiperazin-1-yl;

each R^5, R^{10} and R^{15} is independently selected from C_1-C_{12} alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, -(C_1-C_{12} alkylene)-(C_3-C_{12} carbocyclyl), -(C_1-C_{12} alkylene)-(C_2-C_{20} heterocyclyl), -(C_1-C_{12} alkylene)-C(O)-(C_2-C_{20} heterocyclyl), -(C_1-C_{12} alkylene)-(C_6-C_{20} aryl), or -(C_1-C_{12} alkylene)-(C_1-C_{20} heteroaryl); or two geminal R^5, R^{10}, or R^{15} groups form a 3, 4, 5, or 6-membered carbocyclyl or heterocyclyl ring, where alkyl, alkenyl, alkynyl, alkylene, carbocyclyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one or more groups independently selected from F, Cl, Br, I, -CH_3, -CH_2CH_3, -$C(CH_3)_3$, -CH_2OH, -CH_2CH_2OH, -$C(CH_3)_2OH$, -CH_2OCH_3, -CN, -CH_2F, -CHF_2, -CF_3, -CO_2H, -$COCH_3$, -$COC(CH_3)_3$, -CO_2CH_3, -$CONH_2$, -$CONHCH_3$, -$CON(CH_3)_2$, -$C(CH_3)_2CONH_2$, -NO_2, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -NH-$COCH_3$, -$NHS(O)_2CH_3$, -$N(CH_3)C(CH_3)_2CONH_2$, -$N(CH_3)CH_2CH_2S(O)_2CH_3$, =O, -OH, -$OCH_3$, -$S(O)_2N(CH_3)_2$, -$SCH_3$, -$S(O)_2CH_3$, cyclopropyl, cyclobutyl, oxetanyl, morpholino, or 1,1-dioxo-thiopyran-4-yl; and

mor is selected from:



wherein mor is optionally substituted with one or more R^7 groups independently selected from F, Cl, Br,
I, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-C(CH_3)_3$, $-CH_2OCH_3$, $-CHF_2$, -CN, $-CF_3$, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2CH_2OH$, $-CH_2C(CH_3)_2OH$, $-CH(CH_3)OH$, $-CH(CH_2CH_3)OH$, $-CH_2CH(OH)CH_3$, $-C(CH_3)_2OH$, $-C(CH_3)_2OCH_3$, $-CH(CH_3)F$, $-C(CH_3)F_2$, $-CH(CH_2CH_3)F$, $-C(CH_2CH_3)_2F$, $-CO_2H$, $-CONH_2$, $-CON(CH_2CH_3)_2$, $-COCH_3$, $-CON(CH_3)_2$, $-NO_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHCH_2CH_3$, $-NHCH(CH_3)_2$, $-NHCH_2CH_2OH$, $-NHCH_2CH_2OCH_3$, $-NHCOCH_3$, $-NHCOCH_2CH_3$, $-NHCOCH_2OH$, $-NHS(O)_2CH_3$, $-N(CH_3)S(O)_2CH_3$,
=O, -OH, $-OCH_3$, $-OCH_2CH_3$, $-OCH(CH_3)_2$, -SH, $-NHC(O)NHCH_3$, $-NHC(O)NHCH_2CH_3$, $-S(O)CH_3$, $-S(O)CH_2CH_3$, $-S(O)_2CH_3$, $-S(O)_2NH_2$, $-S(O)_2NHCH_3$, $-S(O)_2N(CH_3)_2$,
or $-CH_2S(O)_2CH_3$.

2. The process of claim 1, wherein the solvent system further comprises at least one polar aprotic solvent selected from N-methylpyrrolidone, methyl isobutyl ketone, methyl ethyl ketone, tetrahydrofuran, dichloromethane, ethyl acetate, acetone, N,N-dimethylformamide, acetonitrile, or dimethyl sulfoxide.

3. The process of claim 2, wherein the ratio of water to the at least one polar aprotic solvent is about 1:10 v/v to about 5:1 v/v.

4. The process of claim 2 or claim 3, wherein the solvent system comprises water and tetrahydrofuran.

5. The process of claim 2 or claim 3, wherein the solvent system consists essentially of water and the at least one polar aprotic solvent.

6. The process of any one of claims 1 to 5, wherein the organoboron-R^4 is 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-R^4.

7. The process of any one of claims 1 to 6, wherein the base is selected from K_3PO_4, Cs_2CO_3, or KOH.

~~8. The process of any one of claims 1 to 7, wherein the catalyst comprising palladium is selected from chloro(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2-aminoethyl) phenyl)]palladium(II) [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane; Bis(di-tert-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II); dichlorobis(di-tert-butylphenylphosphine)palladium(II); $PdCl_2(PPh_3)_2$; $Pd(t\text{-}Bu)_3$; $Pd(PPh_3)_4$; $Pd(Oac)/PPh_3$; $Cl_2Pd[(Pet_3)]_2$; $Pd(DIPHOS)_2$; $Cl_2Pd(Bipy)$; $[PdCl(Ph_2PCH_2PPh_2)]_2$; $Cl_2Pd[P(o\text{-}tol)_3]_2$; $Pd_2(dba)_3/P(o\text{-}tol)_3$; $Pd_2(dba)/P(furyl)_3$; $Cl_2Pd[P(furyl)_3]_2$; $Cl_2Pd(PmePh_2)_2$; $Cl_2Pd[P(4\text{-}F\text{-}Ph)_3]_2$; $Cl_2Pd[P(C_6F_6)_3]_2$; $Cl_2Pd[P(2\text{-}COOH\text{-}Ph)(Ph)_2]_2$; $Cl_2Pd[P(4\text{-}COOH\text{-}Ph)(Ph)_2]_2$; palladium acetate, microencapsulated in a polyuria matrix, comprising 0.4 mmol/g Pd; palladium acetate and triphenylphosphine, microencapsulated in a polyuria matrix, comprising 0.4 mmol/g Pd and 0.3 mmol/g phosphorous; or palladium acetate and BINAP, microencapsulated in a polyuria matrix, comprising 0.4 mmol/g Pd.~~

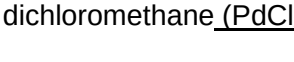
~~9. The process of claim 8, wherein the catalyst comprising palladium is chloro(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2-aminoethyl) phenyl)]palladium(II) or [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane.~~

~~10~~8. The process of any one of claims 1 to ~~9~~7, wherein the equivalent ratio of the catalyst ~~comprising palladium~~ to the compound of Formula II is about 0.003:1 to about 0.05:1.

9. The process of any one of claims 1 to 8, wherein the catalyst is chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (Xphos Pd G2).

10. The process of claim 9, wherein the equivalent ratio of the catalyst to the compound of Formula II is about 0.005:1.

~~11. The process of any one of claims 1 to 7, wherein the catalyst is chloro(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2-aminoethyl) phenyl)]palladium(II) and the equivalent ratio of the catalyst comprising palladium to the compound of Formula II is about 0.004:1 to about 0.015:1.~~

~~12~~11. The process of any one of claims 1 to ~~7~~8, wherein the catalyst is ~~chloro(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2-aminoethyl) phenyl)]palladium(II) or~~ 1,1′-bis(diphenylphosphino)ferrocene] dichloropalladium(II) complex with dichloromethane ().

12. The process of claim 11, ~~and~~ wherein the equivalent ratio of the catalyst ~~comprising palladium~~ to the compound of Formula II is about 0.005:1 to about 0.04:1.

13. The process of any one of claims 1 to 12, wherein the reaction temperature is about 40 °C to about 100 °C.

14. The process of any one of claims 1 to 13, wherein the polar protic solvent is selected from water, methanol, ethanol, isopropanol, n-propanol, or acetic acid.

15. The process of claim 14, wherein the polar protic solvent is water.

16. The process of claim 15, wherein the volume ratio of the solvent system to water added to the reaction product mixture is about 1:5 v/v to about 5:1 v/v.

17. The process of claim 15 or claim 16, further comprising adding seed crystals of the compound of Formula III to the admixture of the reaction product mixture and water.

18. The process of claim 1, wherein in the purification step:

(i) the solvent system comprises water and acetic acid or consists essentially of water and acetic acid wherein the volume ratio of acetic acid to water is about 1:1 to about 10:1;

(ii) the metal scavenger is silica-thiol; and

(iii) the dissolution temperature is about 80 °C to about 100 °C, the seed crystals are combined with the filtrate at a temperature of about 70 °C to about 80 °C, and the crystallization temperature is about 0 °C to about 10 °C.

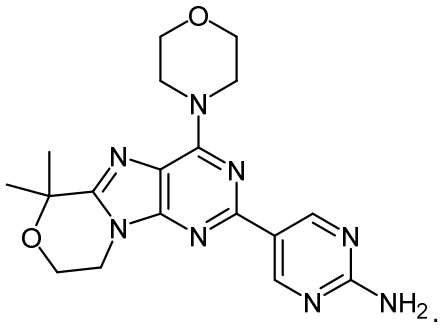
19. The process of claim 18, wherein the volume ratio of acetic acid to water is about 1:1 to about 5:1.

20. The process of claim 18 or claim 19, wherein the volume ratio of acetic acid to water is about 1:1 to about 3:1.

21. The process of any one of claims 18 to 20, wherein the volume ratio of acetic acid to water is about 3:1.

~~19~~22. The process of any one of claims 1 to ~~18~~21, wherein the purity of the compound of ~~formula~~ Formula III is at least 97 ~~%~~ area % as determined by HPLC.

~~20~~23. The process of any one of claims 1 to ~~19~~22, wherein the compound of Formula III is:



~~21. The process of claim 18, wherein the volume ratio of acetic acid to water is about 1:1 to about 5:1.~~

~~22. The process of claim 18, wherein the volume ratio of acetic acid to water is about 1:1 to about 3:1.~~

~~23. The process of claim 18, wherein the volume ratio of acetic acid to water is about 3:1.~~

~~24. The process of claim 1 or claim 18, wherein the catalyst comprising palladium is chloro(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2’-amino-1,1’-biphenyl)]palladium(II).~~

~~25. The process of claim 10, wherein the catalyst comprising palladium is chloro(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2’-amino-1,1’-biphenyl)]palladium(II).~~