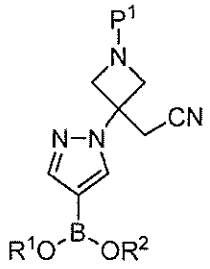
WHAT IS CLAIMED IS:

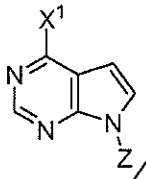
1. A process, comprising:

reacting a compound of Formula III:



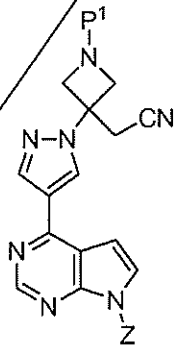
III

with a compound of Formula IV:



IV

under Suzuki coupling conditions to form a compound of Formula II:



II

wherein:

Z is H or a protecting group;

P^1 is a protecting group;

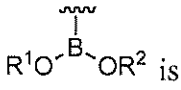
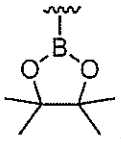
X^1 is halo; and

R^1 and R^2 are each independently H or C_{1-6} alkyl; or

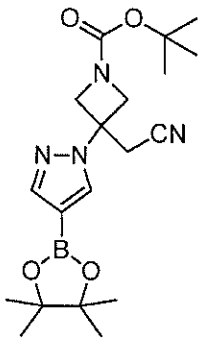
R^1 and R^2, together with the two oxygen atoms to which they are attached and the boron atom to which the oxygen atoms are attached, form a 5- to 6-membered heterocycloalkyl ring, which is optionally substituted with 1, 2, 3, or 4 C_{1-4} alkyl groups.

2. The process according to claim 1, wherein P^1 is benzyloxycarbonyl (Cbz), 2,2,2-trichloroethoxycarbonyl (Troc), 2-(trimethylsilyl)ethoxycarbonyl (Teoc), 2-(4-trifluoromethylphenylsulfonyl)ethoxycarbonyl (Tsc), t-butoxycarbonyl (BOC), 1-adamantyloxycarbonyl (Adoc), 2-adamantylcarbonyl (2-Adoc), 2,4-dimethylpent-3-yloxycarbonyl (Doc), cyclohexyloxycarbonyl (Hoc), 1,1-dimethyl-2,2,2-trichloroethoxycarbonyl (TcBOC), vinyl, 2-chloroethyl, 2-phenylsulfonylethyl, allyl, benzyl, 2-nitrobenzyl, 4-nitrobenzyl, diphenyl-4-pyridylmethyl, N',N'-dimethylhydrazinyl, methoxymethyl, t-butoxymethyl (Bum), benzyloxymethyl (BOM), 2-tetrahydropyranyl (THP), 1,1-diethoxymethyl, (trimethylsilyl)ethoxymethyl (SEM), N-pivaloyloxymethyl (POM) or tert-butoxycarbonyl.

3. The process according to claim 1, wherein P^1 is tert-butoxycarbonyl.

4. The process according to claim 1, wherein  is .

5. The process according to claim 1, wherein the compound of Formula III has Formula IIIa:

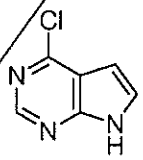


IIIa.

6. The process according to any one of claims 1 to 4, wherein X^1 is chloro.

7. The process according to any one of claims 1 to 4, wherein Z is H.

8. The process according to any one of claims 1 to 4, wherein the compound of Formula IV has Formula IVa:



IVa.

9. The process according to any one of claims 1 to 8, wherein the Suzuki coupling conditions comprise heating a reaction mixture comprising the compound of Formula III, the compound of Formula IV, a Suzuki coupling catalyst, a base and a solvent component.

10. The process according to claim 9, wherein the Suzuki coupling catalyst is $Pd(dppf)_2Cl_2$, [1,1'-bis(dicyclohexylphosphino)ferrocene]dichloropalladium (II), tetrakis(triphenylphosphine)palladium(0), or tetrakis(tri(o-tolyl)phosphine)palladium(0).

11. The process according to claim 9, wherein the Suzuki coupling catalyst is [1,1'-bis(dicyclohexylphosphino)ferrocene]dichloropalladium (II).

12. The process according to any one of claims 9 to 11, wherein the base is sodium carbonate, potassium carbonate, or cesium fluoride.

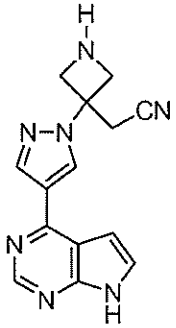
13. The process according to any one of claims 9 to 11, wherein the base is cesium fluoride.

14. The process according to claim 13, wherein the cesium fluoride is present in 3 equivalents or more based on the compound of Formula IV.

15. The process according to any one of claims 9 to 14, wherein the solvent component comprises *tert*-butanol and water.

16. The process according to any one of claims 1 to 15, wherein the compounds of Formula III and IV are present in about a 1:1 molar ratio.

17. The process according to any one of claims 1 to 16, further comprising deprotecting the compound of Formula II to form a compound of Formula V:



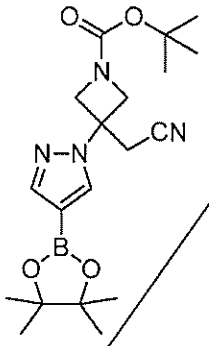
V

or salt thereof.

18. The process according to claim 17, wherein the deprotecting comprises reacting the compound of Formula II with hydrochloric acid in a second solvent component.

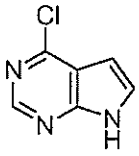
19. The process according to claim 18, wherein hydrochloric acid is present in an amount of 5 to 8 equivalents based on the compound of Formula II.

20. The process according to any one of claims 1 to 16, wherein the process comprises reacting a compound of Formula IIIa:



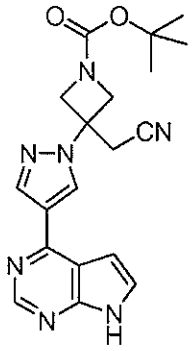
IIIa

with a compound of Formula IVa:



IVa

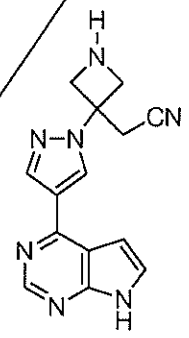
under Suzuki coupling conditions to form a compound of Formula IIa:



IIa

wherein the Suzuki coupling conditions comprise heating a reaction mixture comprising the compound of Formula IIIa, the compound of Formula IVa, [1,1'-bis(dicyclohexylphosphino)ferrocene]dichloropalladium (II), cesium fluoride, and a solvent component, wherein the solvent component comprises water and *tert*-butanol.

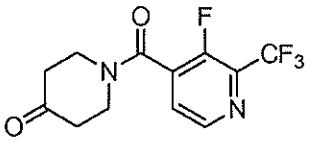
21. The process according to claim 20, further comprising deprotecting the compound of Formula IIa to form a compound of Formula V:



V

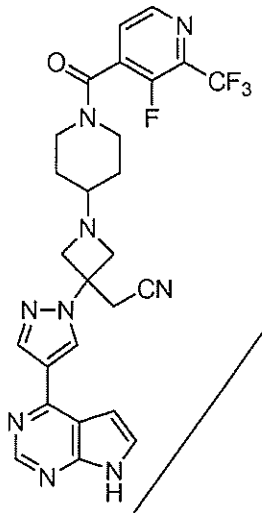
or salt thereof, wherein the deprotecting comprises reacting the compound of Formula IIa with hydrochloric acid in a second solvent component.

22. The process according to any one of claims 17 to 19 and 21, further comprising reacting the compound of Formula V, or salt thereof, with a compound of Formula VI:



VI

in the presence of a reducing agent to form a compound of Formula I:



I

or a salt thereof.

23. The process according to claim 22, wherein the compound of Formula V, or salt thereof, is 2-(3-(4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)azetidin-3-yl)acetonitirile dihydrochloride salt.

24. The process according to claim 22 or 23, wherein said reacting is carried out in the presence of at least two equivalents of a second base.

25. The process according to claim 24, wherein the second base is a tertiary amine.

26. The process according to claim 24, wherein the second base is triethylamine.

27. The process according to any one of claims 22 to 26, wherein the reducing agent is sodium cyanoborohydride or sodium triacetoxyborohydride.

28. The process according to any one of claims 22 to 26, wherein the reducing agent is sodium triacetoxyborohydride.

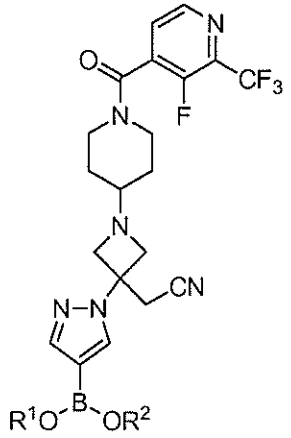
29. The process according to claim 28, wherein greater than 1 equivalent of sodium triacetoxyborohydride is used based on the compound of Formula V, or salt thereof.

30. The process according to any one of claims 22 to 29, wherein greater than 1 equivalent of the compound of Formula VI is used based on the compound of Formula V, or salt thereof.

31. The process according to any one of claims 22 to 30, wherein the reacting is performed in dichloromethane solvent.

32. The process according to any one of claims 22 to 31, further comprising reacting the compound of Formula I with adipic acid to form the adipate salt of the compound of Formula I.

33. A compound of Formula VII:



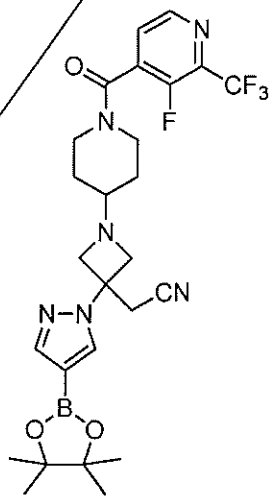
VII

or a salt thereof; wherein:

R^1 and R^2 are each independently H or C_{1-6} alkyl; or

R^1 and R^2, together with the two oxygen atoms to which they are attached and the boron atom to which the oxygen atoms are attached, form a 5- to 6-membered heterocycloalkyl ring, which is optionally substituted with 1, 2, 3, or 4 C_{1-4} alkyl groups.

34. The compound of claim 33, having Formula VIIa:

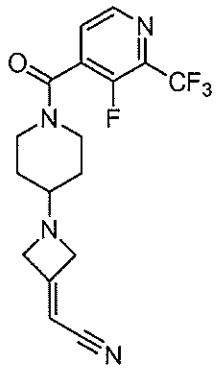


VIIa

or a salt thereof.

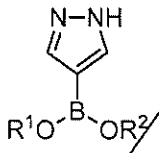
35. A process, comprising:

reacting a compound of Formula VIII:



VIII

with a compound of Formula IX:



IX

in the presence of a coupling agent to form a compound of claim 33; wherein:

R^1 and R^2 are each independently H or C_{1-6} alkyl; or

R^1 and R^2, together with the two oxygen atoms to which they are attached and the boron atom to which the oxygen atoms are attached, form a 5- to 6-membered heterocycloalkyl ring, which is optionally substituted with 1, 2, 3, or 4 C_{1-4} alkyl groups.

36. The process according to claim 35, wherein the coupling agent is 1,8-diazabicyclo[5,4,0]undecene.

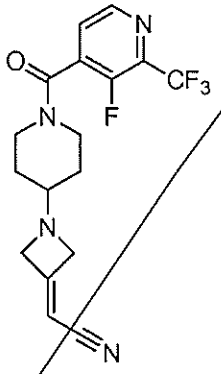
37. The process according to any one of claims 35 to 36, wherein 1.05 to about 1.2 equivalents of coupling agent is used based on the compound of Formula VIII.

38. The process according to any one of claims 35 to 37, wherein the reacting of the compound of Formula VIII with the compound of Formula IX is conducted in a solvent component comprising acetonitrile.

39. The process according to any one of claims 35 to 37, wherein the reacting of the compound of Formula VIII with the compound of Formula IX is conducted in a solvent component comprising acetonitrile at a temperature of about 40 °C to about 60 °C.

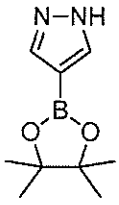
40. The process according to any one of claims 35 to 39, wherein 1 to 1.2 equivalents of the compound of Formula IX are used based on the compound of Formula VIII.

41. The process according to claim 35, wherein the process comprises reacting a compound of Formula VIII:



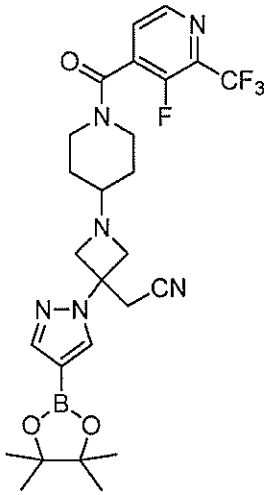
VIII

with a compound of Formula IXa:



IXa

in the presence of a coupling agent to form a compound of Formula VIIa:



VIIa.

42. The process according to claim 41, wherein the coupling agent is 1,8-diazabicyclo[5,4,0]undecene.

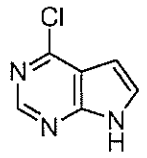
43. The process according to claim 41 or 42, wherein 1.05 to about 1.2 equivalents of coupling agent is used based on the compound of Formula VIII.

44. The process according to any one of claims 41 to 43, wherein the reacting of the compound of Formula VIII with the compound of Formula IXa is conducted in a solvent component comprising acetonitrile.

45. The process according to any one of claims 41 to 43, wherein the reacting of the compound of Formula VIII with the compound of Formula IXa is conducted in a solvent component comprising acetonitrile at a temperature of about 40 °C to about 60 °C.

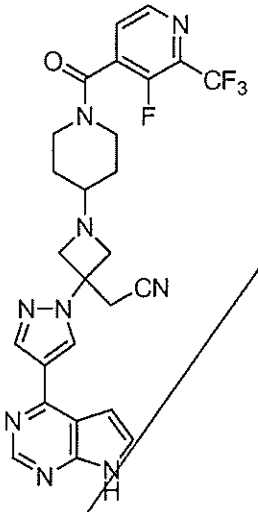
46. The process according to any one of claims 41 to 45, wherein 1 to 1.2 equivalents of the compound of Formula IXa are used based on the compound of Formula VIII.

47. The process according to any one of claims 41 to 46, further comprising reacting the compound of Formula VIIa with a compound of Formula IVa:



IVa

under Suzuki coupling conditions to form a compound of Formula I:



I

wherein the Suzuki coupling conditions comprise heating a reaction mixture comprising the compound of Formula VIIa, the compound of Formula IVa, a Suzuki coupling catalyst, a base and a second solvent component.

48. The process according to claim 47, wherein the catalyst is tetrakis(triphenylphosphine)palladium(0).

49. The process according to claim 47 or claim 48, wherein the base is sodium bicarbonate.

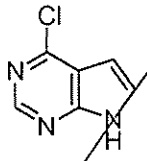
50. The process according to claim 49, wherein the sodium bicarbonate is present in 4 equivalents or more based on the compound of Formula VIIa.

51. The process according to any one of claims 47 to 50, wherein the second solvent component comprises 1,4-dioxane and water.

52. The process according to claim 51, wherein the 1,4-dioxane and water are present in a 1:1 volume ratio.

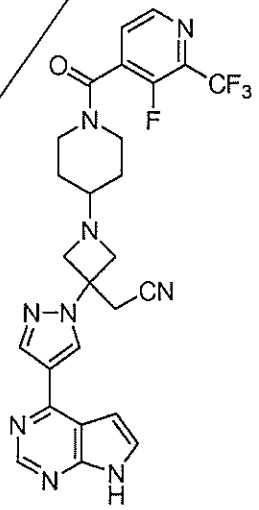
53. The process according to any one of claims 47 to 52, wherein the compounds of Formula VIIa and IVa are present in about a 1:1 molar ratio.

54. The process according to claim 41, further comprising reacting the compound of Formula VIIa with a compound of Formula IVa:



IVa

under Suzuki coupling conditions to form a compound of Formula I:

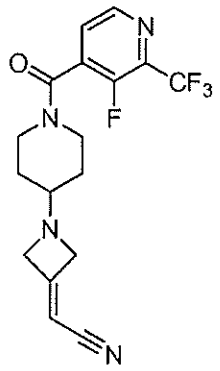


I

wherein the Suzuki coupling conditions comprise heating a reaction mixture comprising the compound of Formula VIIa, the compound of Formula IVa,

tetrakis(triphenylphosphine)palladium(0), sodium bicarbonate, and a second solvent component, wherein the second solvent component comprises water and 1,4-dioxane.

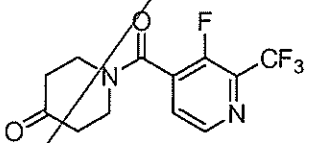
55. A compound of Formula VIII:



VIII

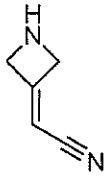
or a salt thereof.

56. A process of preparing a compound of claim 55, or a salt thereof, comprising reacting a compound of Formula VI:



VI

with a compound of Formula X:



X

or a salt thereof, in the presence of a reducing agent.

57. The process according to claim 56, wherein the compound of Formula X, or salt thereof, is 2-(azetidin-3-ylidene)acetonitrile hydrochloride.

58. The process according to claim 56 or claim 57, wherein the reducing agent is sodium cyanoborohydride or sodium triacetoxyborohydride.

59. The process according to claim 56 or claim 57, wherein the reducing agent is sodium triacetoxyborohydride.

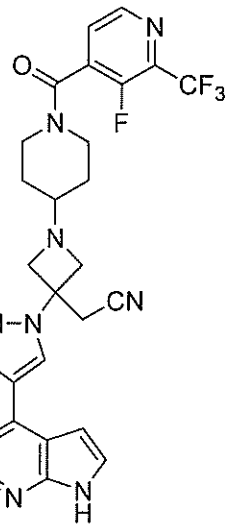
60. The process according to any one of claims 56 to 59, wherein about 1.5 to about 2.5 equivalents of the reducing agent are used based on the compound of Formula X, or salt thereof.

61. The process according to any one of claims 56 to 59, wherein about 2 equivalents of the reducing agent are used based on the compound of Formula X, or salt thereof.

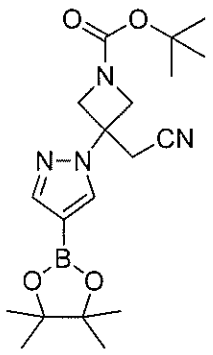
62. The process according to any one of claims 56 to 61, wherein the reacting of the compound of Formula VI and the compound of Formula X, or salt thereof, are conducted in a solvent component comprising dichloromethane.

The Claims defining the invention are as follows:

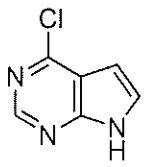
1. A process of preparing a compound of Formula I:



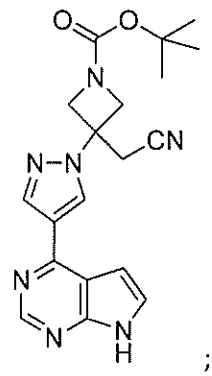
or a salt thereof, comprising: reacting a compound of Formula IIIa:



with a compound of Formula IVa:

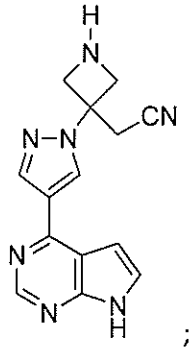


under Suzuki coupling conditions to form a compound of Formula IIa:



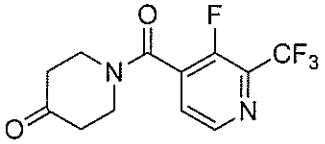
;

deprotecting the compound of Formula IIa by reacting with an inorganic acid to form a compound of Formula V:



;

and reacting the compound of Formula V with a compound of Formula VI:



in the presence of a reducing agent to form a compound of Formula I, or a salt thereof.

2. The process according to Claim 1, wherein the Suzuki coupling conditions comprise heating a reaction mixture comprising the compound of Formula IIIa, the compound of Formula IVa, a Suzuki coupling catalyst, a base and a solvent component.

3. The process according to Claim 2, wherein the Suzuki coupling catalyst is $Pd(dppf)_2Cl_2$, [1,1'-bis(dicyclohexylphosphino)ferrocene]dichloropalladium (II),

tetrakis(triphenylphosphine)palladium(0), or tetrakis(tri(o-tolyl)phosphine)palladium(0).

4. The process according to Claim 2, wherein the Suzuki coupling catalyst is [1,1'-bis(dicyclohexylphosphino)ferrocene]dichloropalladium (II).

5. The process according to Claim 2, wherein the base is sodium carbonate, potassium carbonate, or cesium fluoride.

6. The process according to Claim 2, wherein the base is cesium fluoride.

7. The process according to Claim 6, wherein the cesium fluoride is present in 3 equivalents or more based on the compound of Formula IVa.

8. The process according to Claim 2, wherein the solvent component comprises tert-butanol and water.

9. The process according to Claim 1, wherein the compounds of Formula IIIa and IVa are present in about a 1:1 molar ratio.

10. The process according to Claim 1, wherein the inorganic acid is present in an amount of 5 to 8 equivalents based on the compound of Formula IIa, and wherein the inorganic acid is hydrochloric acid.

11. The process according to Claim 1, wherein the inorganic acid is hydrochloric acid.

12. The process according to Claim 1, wherein said reacting of the compound of Formula V with the compound of Formula VI is carried out in the presence of at least two equivalents of a second base.

13. The process according to Claim 12, wherein the second base is a tertiary amine.

14. The process according to Claim 12, wherein the second base is triethylamine.

15. The process according to Claim 1, wherein the reducing agent is sodium cyanoborohydride or sodium triacetoxyborohydride.

16. The process according to Claim 1, wherein the reducing agent is sodium triacetoxyborohydride.

17. The process according to Claim 16, wherein greater than 1 equivalent of sodium triacetoxyborohydride is used based on the compound of Formula V.

18. The process according to Claim 1, wherein greater than 1 equivalent of the compound of Formula VI is used based on the compound of Formula V.

19. The process according to Claim 1, wherein the reacting of the compound of Formula V with the compound of Formula VI is performed in a halogenated solvent.

20. The process according to Claim 19, wherein the halogenated solvent is dichloromethane.

21. The process according to Claim 1, further comprising reacting the compound of Formula I with adipic acid to form the adipate salt of the compound of Formula I.