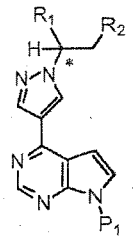
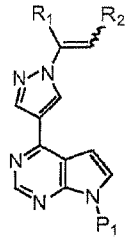
~~What is claimed is:~~ Claims:

~~1. A process of preparing a composition comprising a compound of Formula I:~~



I

comprising reacting a compound of Formula II:



II

with hydrogen gas in the presence of a hydrogenation catalyst;

wherein:

* indicates a chiral carbon;

R_1 is selected from C_{3-7} cycloalkyl, C_{1-6} alkyl, and C_{1-6} fluoroalkyl;

R_2 is selected from $-C(=O)-NH_2$, $-C(=O)O-R_3$, and cyano;

R_3 is selected from C_{1-4} alkyl or C_{1-4} fluoroalkyl; and

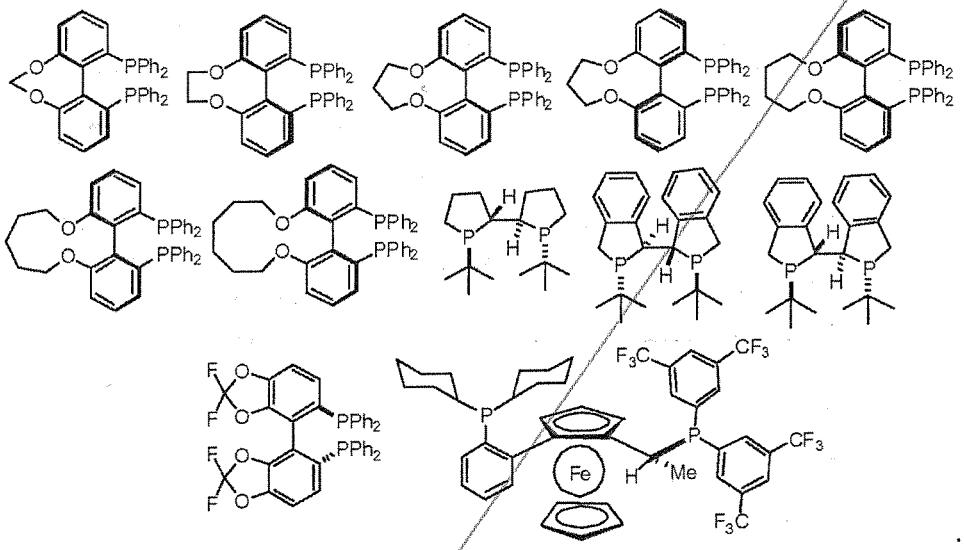
P_1 is a protecting group.

2. A process according to claim 1, wherein said composition comprises an enantiomeric excess of a (R)- or (S)-enantiomer of the compound of Formula I; and said hydrogenation catalyst is a ruthenium or rhodium catalyst having L_1; wherein L_1 is a chiral phosphine ligand.

3. A process according to claim 2, wherein said enantiomeric excess is equal to or ~~greater than about 90%.~~

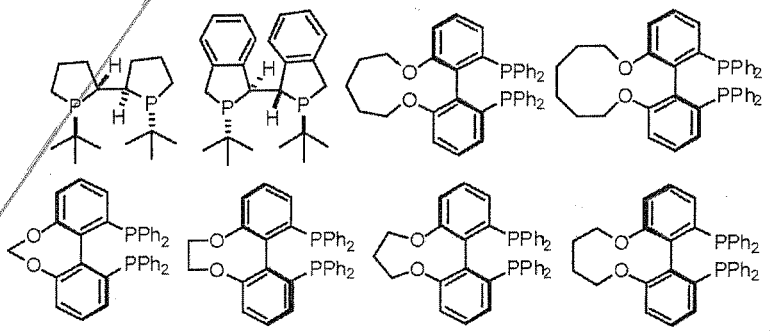
4. A process according to claim 2, wherein said enantiomeric excess is equal to or greater than about 99%.

5 A process according to claim 2, wherein said chiral phosphine ligand is selected from one of the following:



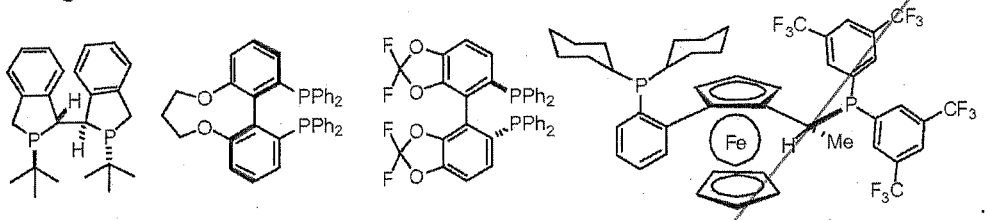
6. A process according to claim 2, wherein said composition comprises an enantiomeric excess of the (*S*)-enantiomer of the compound of Formula I.

7. A process according to claim 6, wherein L_1 is selected from one of the following ligands:

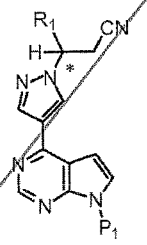


8. A process according to claim 2, wherein said composition comprises an enantiomeric excess of the (*R*)-enantiomer of the compound of Formula I.

9. A process according to claim 8, wherein L_1 is selected from one of the following ligands:



10. A process according to any one of claims 2 to 9, wherein said product is a compound of Formula Ia:



Ia

wherein:

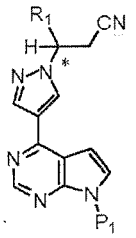
* indicates a chiral carbon;

R_1 is selected from C_{3-7} cycloalkyl, C_{1-6} alkyl, and C_{1-6} fluoroalkyl; and

P_1 is a protecting group.

11. A process according to any one of claims 2 to 9, wherein R_2 is -C(=O)-NH_2.

12. A process according to claim 11, further comprising reacting said compound of Formula I under dehydrating conditions to form a compound of Formula Ia:



Ia

wherein:

* indicates a chiral carbon;

R_1 is selected from C_{3-7} cycloalkyl, C_{1-6} alkyl, and C_{1-6} fluoroalkyl; and

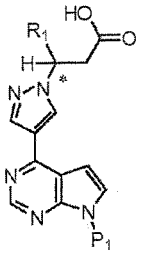
P_1 is a protecting group.

13. A process according to claim 12, wherein said dehydrating conditions comprises trichloroacetyl chloride in the presence of triethylamine.

14. A process according to any one of claims 2 to 9, wherein R_2 is $-C(=O)O-R_3$.

15. A process according to any one of claims 2 to 9, wherein R_2 is $-C(=O)OCH_3$.

16. A process according to claim 14 or 15, further comprising reacting said compound of Formula I with a metal hydroxide to form a compound of Formula Ic:



Ic

wherein:

* indicates a chiral carbon;

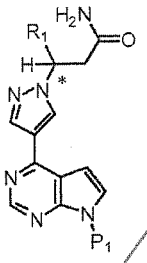
R_1 is selected from C_{3-7} cycloalkyl, C_{1-6} alkyl, and C_{1-6} fluoroalkyl; and

P_1 is a protecting group.

17. A process according to claim 16, wherein said metal hydroxide is an alkali metal hydroxide or an alkaline earth hydroxide.

18. A process according to claim 16, wherein said metal hydroxide is lithium hydroxide.

19. A process according to any one of claims 16 to 18, further comprising reacting said compound of Formula Ic with ammonia or ammonium hydroxide in the presence of a coupling reagent to form a compound of Formula Ib:



Ib

wherein:

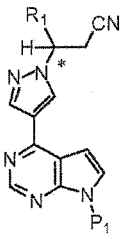
* indicates a chiral carbon;

R_1 is selected from C_{3-7} cycloalkyl, C_{1-6} alkyl, and C_{1-6} fluoroalkyl; and

P_1 is a protecting group.

20. A process according to claim 19, wherein said coupling agent is N,N-carbonyldiimidazole.

21. A process according to any one of claims 19 to 20, further comprising reacting said compound of Formula Ib under dehydrating conditions to form a compound of Formula Ia:



Ia

~~wherein:~~

~~* indicates a chiral carbon;~~

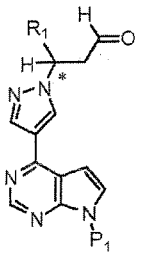
~~R_1 is selected from C_{3-7} cycloalkyl, C_{1-6} alkyl, and C_{1-6} fluoroalkyl; and~~

~~P_1 is a protecting group.~~

~~22. A process according to any one of claims 2 to 21, wherein P_1 is $-CH_2OC(=O)C(CH_3)_3$ or $-CH_2OCH_2CH_2Si(CH_3)_3$.~~

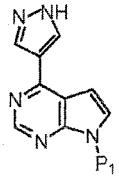
~~23. A process according to any one of claims 2 to 22, wherein R_1 is cyclopentyl.~~

1. ~~24.~~ A process of preparing a composition comprising an enantiomeric excess of a (R)- or (S)-enantiomer of a compound of Formula Id:



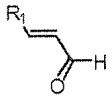
Id

comprising reacting a compound of Formula IV:



IV

with a compound of Formula V:



V

in the presence of a chiral amine and an organic acid;

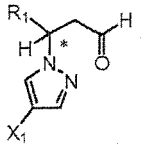
wherein:

* indicates a chiral carbon;

R_1 is selected from C_{3-7} cycloalkyl, C_{1-6} alkyl, and C_{1-6} fluoroalkyl; and

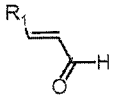
P_1 is a protecting group.

2. ~~25.~~ A process of preparing a composition comprising an enantiomeric excess of a (R)- or (S)-enantiomer of a compound of Formula VI:



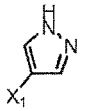
VI

comprising reacting a compound of Formula V:



V

with a compound of Formula VII:



VII

in the presence of a chiral amine and an organic acid;

wherein:

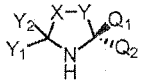
* indicates a chiral carbon;

R_1 is selected from C_{3-7} cycloalkyl, C_{1-6} alkyl, and C_{1-6} fluoroalkyl; and

X_1 is halogen.

3. ~~26.~~ A process according to claim ~~24~~ 1 or ~~25~~ 2, wherein said organic acid is p-toluenesulfonic acid.

4. ~~27.~~ A process according to any one of claims ~~24~~ 1 to ~~26~~ 3, wherein said chiral amine is a (R)- or (S)-enantiomer of a compound of Formula A-1:



A-1

wherein:

X is CY_3Y_4 and Y is CY_5Y_6; or

X is S or NY_7 and Y is CY_5Y_6; or

X is CY_3Y_4 and Y is S;

Q_1 and Q_2 are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, carboxy, C_{1-6} alkylcarboxamide, C_{1-6} alkoxycarbonyl, and phenyl; wherein said C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkylcarboxamide, C_{1-6} alkoxycarbonyl, and phenyl are each optionally substituted by 1, 2, or 3 groups independently selected from hydroxyl, carboxy, tri-C_{1-6} alkylsilyl, tri-C_{1-6} alkylsilyloxy, C_{6-10} aryl, C_{6-10} arylamino, C_{1-9} heteroaryl, and C_{1-9} heteroarylamino; wherein said C_{6-10} aryl, C_{6-10} arylamino, C_{1-9} heteroaryl, and C_{1-9} heteroarylamino are each optionally substituted by 1, 2, 3, or 4 groups independently selected from halogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; and

Y_1, Y_2, Y_3, Y_4, Y_5, Y_6 are each independently selected from H, hydroxyl, carboxy, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxycarbonyl, and phenyl; or

Y_1 and Y_2 together form oxo; or

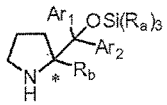
Y_3 and Y_4 together form oxo; or

Y_5 and Y_6 together form oxo; or

Y_1 and Y_2, together with the carbon to which they are attached, form a 5- or 6-membered cycloalkyl ring; or

Q_1 and Y_5, together with the carbon atoms to which they are attached, form a 5- or 6-membered cycloalkyl ring.

5. ~~28.~~ A process of any one of claims 1 ~~24~~ to 3 ~~26~~, wherein said chiral amine is a (R)- or (S)-enantiomer of a compound of Formula A-2:



A-2

wherein

* is a chiral carbon having a (*R*)- or (*S*)-configuration;

Ar_1 and Ar_2 are each independently C_{6-10} aryl, which is optionally substituted by 1, 2, 3, or 4 groups independently selected from C_{1-6} alkyl and C_{1-6} haloalkyl;

each R_a are independently selected from C_{1-6} alkyl; and

R_b is selected from H, C_{1-6} alkyl, and C_{1-6} haloalkyl.

6. ~~29.~~ A process according to claim 5 ~~28~~, wherein:

Ar_1 and Ar_2 are each independently phenyl, which is optionally substituted by 1, 2, 3, or 4 groups independently selected from methyl and trifluoromethyl;

each R_a is independently selected from methyl, ethyl, or t-butyl;

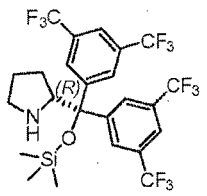
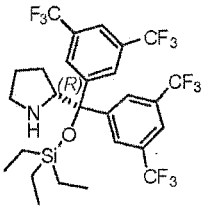
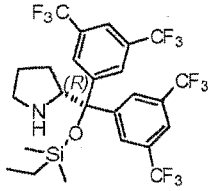
R_b is H.

7. ~~30.~~ A process according to any one of claims 1 ~~24~~ to 3 ~~26~~, wherein said chiral amine is a (*R*)- or (*S*)-enantiomer of a compound selected from proline, prolinamide, prolyl-L-leucine, prolyl-L-alanine, prolylglycine, prolyl-L-phenylalanine, diphenylpyrrolidine, dibenzylpyrrolidine, N-(1-methylethyl)-pyrrolidinecarboxamide, 2-(anilinomethyl)pyrrolidine, 2-[bis(3,5-dimethylphenyl)methyl]pyrrolidine, diphenyl(pyrrolidin-2-yl)methanol, prolinol, 4-thiazolidinecarboxylic acid, trans-3-hydroxyproline, trans-4-hydroxyproline, 4-benzyl-1-methyl-imidazolidine-2-carboxylic acid, 1-methyl-4-phenyl-imidazolidine-2-carboxylic acid, 4,5-octahydro-benzoimidazole-2-carboxylic acid, 4,5-diphenyl-imidazolidine-2-carboxylic acid, N1-methyl-3-phenylpropane-1,2-diamine, 1,2-diphenylethanediamine, 1-methyl-4-(1-methyl-1H-indol-3-ylmethyl)-imidazolidine-2-carboxylic acid, 4-benzyl-1-methyl-imidazolidine-2-carboxylic acid, 1,2-cyclohexanediamine, 2-phenyl-thiazolidine-4-carboxylic acid, tert-leucine methyl ester, 5-benzyl-2,2,3-trimethyl-imidazoline-4-one, methyl prolinate, 4,5-diphenylimidazolidine, 2-cyclohexyl-4,5-diphenylimidazolidine, 2-{bis-[3,5-bis(trifluoromethyl)phenyl]-trimethylsilanyloxy-methyl}-pyrrolidine, 2-{bis-[3,5-dimethylphenyl]-trimethylsilanyloxy-methyl}-pyrrolidine, 2-{diphenyl-trimethylsilanyloxy-methyl}-pyrrolidine, 2-{bis[naphth-2-yl]-trimethylsilanyloxy-methyl}-pyrrolidine, 2-{tert-butyldimethylsilyloxy-diphenyl-methyl}-pyrrolidine, 2-{bis-[3,5- bis(trifluoromethyl)phenyl]-triethylsilanyloxy-methyl}-pyrrolidine, and 2-{bis-[3,5-

bis(trifluoromethyl)phenyl]-ethyl-dimethylsilyloxy-methyl}-pyrrolidine; wherein the (*R*)- or (*S*)-configuration is at the carbon adjacent to a NH group in said compound.

8. ~~31.~~ A process according to any one of claims ~~27~~ 4 to ~~30~~ 7, wherein said chiral amine is the (R)-enantiomer.

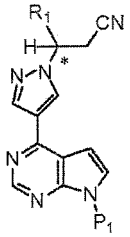
9. ~~32.~~ A process according to any one of claims ~~24~~ 1 to ~~26~~ 3, wherein said chiral amine is selected from one of the following compounds:

10. ~~33.~~ A process according to any one of claims ~~24~~ 1 to ~~32~~ 9, wherein said enantiomeric excess is equal to or greater than about 90%.

11. ~~34.~~ A process according to any one of claims ~~24~~ 1 to ~~32~~ 9, wherein said enantiomeric excess is equal to or greater than about 99%.

12. ~~35.~~ A process according to claim ~~24~~ 1, further comprising treating said compound of Formula Id with ammonia or ammonium hydroxide and iodine to form said compound of Formula Ia:



Ia

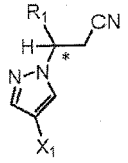
wherein:

* indicates a chiral carbon;

R_1 is selected from C_{3-7} cycloalkyl, C_{1-6} alkyl, and C_{1-6} fluoroalkyl; and

P_1 is a protecting group.

13. ~~36.~~ A process according to claim 2, ~~25~~, further comprising treating said compound of Formula VI with ammonia or ammonium hydroxide and iodine to form said compound of Formula VIII:



VIII

wherein:

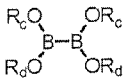
* indicates a chiral carbon;

R_1 is selected from C_{3-7} cycloalkyl, C_{1-6} alkyl, and C_{1-6} fluoroalkyl;

P_1 is a protecting group; and

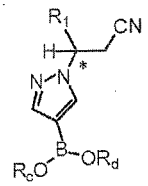
X_1 is halogen.

14. ~~37.~~ A process according to claim 13, ~~36~~, further comprising reacting said compound of Formula VIII with a compound of Formula B-1:



B-1

to form a compound of Formula IX:



IX

wherein:

* indicates a chiral carbon;

R_1 is selected from C_{3-7} cycloalkyl, C_{1-6} alkyl, and C_{1-6} fluoroalkyl;

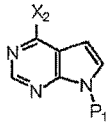
X_1 is halo; and

R_c and R_d are each independently selected from H and C_{1-6} alkyl; or

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

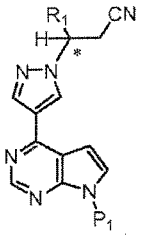
15. ~~38.~~ A process according to claim 14, ~~37~~, wherein said compound of Formula B-1 is 4,4,5,5,4',4',5',5'-octamethyl-[2,2']bis[1,3,2-dioxaborolanyl].

16. ~~39.~~ A process according to claim 14 or 15, ~~37 or 38,~~ further comprising reacting said compound of Formula IX with a compound of Formula X:



X

in the presence of a palladium catalyst and a base to form a compound of Formula Ia:



Ia

wherein:

* indicates a chiral carbon;

R_1 is selected from C_{3-7} cycloalkyl, C_{1-6} alkyl, and C_{1-6} fluoroalkyl;

X_2 is a tosylate group, a triflate group, iodo, chloro, or bromo;

P_1 is a protecting group; and

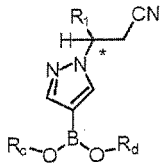
R_c and R_d are each independently selected from H and C_{1-6} alkyl; or

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

17. ~~40.~~ A process according to any one of claims ~~24~~, ~~26~~ to ~~35~~, and ~~24~~ to ~~39~~, wherein P_1 is $-CH_2OC(=O)C(CH_3)_3$ or $-CH_2OCH_2CH_2Si(CH_3)_3$.

18. ~~41.~~ A process according to any one of claims ~~24~~ to ~~40~~, wherein R_1 is cyclopentyl.

19. ~~42.~~ A composition comprising an enantiomeric excess of a (R)- or (S)-enantiomer of a compound of Formula IX:



IX

wherein:

* indicates a chiral carbon;

R_1 is selected from C_{3-7} cycloalkyl, C_{1-6} alkyl, and C_{1-6} fluoroalkyl; and

R_c and R_d are each independently C_{1-6} alkyl; or

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

20. ~~43.~~ A composition according to claim ~~42~~, wherein R_1 is cyclopentyl.

21. ~~44.~~ A process of preparing a composition according to claim ~~42~~ or ~~43~~, comprising passing a composition comprising a racemate of a compound of Formula IX through a chiral chromatography unit using a mobile phase and collecting a composition comprising an enantiomeric excess of the (R)- or (S)-enantiomer of a compound of Formula IX.

22. ~~45.~~ A process according to claim ~~44~~, wherein the mobile phase comprises ethanol and hexanes, wherein said ethanol is present in an amount of about 25% to about 10% by volume.

19 22

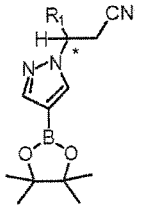
23. ~~46.~~ A process according to claim ~~42~~ or ~~45~~, wherein said chromatography unit is a stimulated moving bed (SMB) chromatography unit equipped with a set of eight columns or a chiral column unit, wherein each column is packed with a chiral stationary phase.

23

24. ~~47.~~ A process according to claim ~~46~~, wherein said chiral stationary phase is cellulose modified chiral stationary phase.

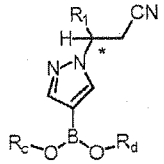
21 24

25. ~~48.~~ A process according to any one of claims ~~44~~ to ~~47~~, wherein said compound of Formula IX has the formula:



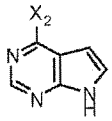
21 25

26. ~~49.~~ A process according to any one of claims ~~44~~ to ~~48~~, further comprising reacting the compound of Formula IX:



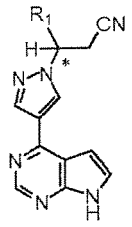
IX

with a compound of Formula XI:



XI

in the presence of a palladium catalyst, base, and a solvent to form a composition comprising an enantiomeric excess of the (R)- or (S)-enantiomer of a compound of Formula III:



III

wherein:

* is a chiral carbon;

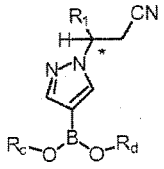
X_2 is a tosylate group, a triflate group, iodo, chloro, or bromo;

R_1 is selected from C_{3-7} cycloalkyl, C_{1-6} alkyl, and C_{1-6} fluoroalkyl; and

R_c and R_d are each independently C_{1-6} alkyl; or

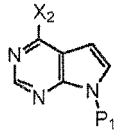
R_c and R_d, together with the oxygen atoms to which they are attached and the boron atom to which the oxygen atoms are attached, form a 5- to 6-membered heterocyclic ring, which is optionally substituted with 1, 2, 3, or 4 C_{1-4} alkyl groups.

27. ~~50.~~ A process according to any one of claims ~~44~~ 21 to ~~48~~ 25, further comprising reacting the compound of Formula IX:



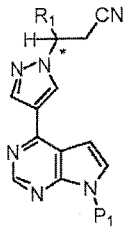
IX

with a compound of Formula X:



X

in the presence of a palladium catalyst, base, and a solvent under conditions and for a time sufficient to form a composition comprising an enantiomeric excess of the (R)- or (S)-enantiomer of a compound of Formula Ia:



Ia

wherein:

* indicates a chiral carbon;

R_1 is selected from C_{3-7} cycloalkyl, C_{1-6} alkyl, and C_{1-6} fluoroalkyl;

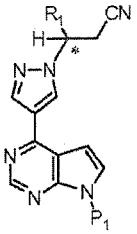
R_c and R_d are each independently C_{1-6} alkyl; or

R_c and R_d, together with the oxygen atoms to which they are attached and the boron atom to which the oxygen atoms are attached, form a 5- to 6-membered heterocyclic ring, which is optionally substituted with 1, 2, 3, or 4 C_{1-4} alkyl groups;

X_2 is a tosylate group, a triflate group, iodo, chloro, or bromo; and

P_1 is a protecting group.

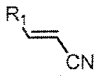
28. ~~51.~~ A process of preparing a composition comprising a racemate of a compound of Formula Ia:



Ia

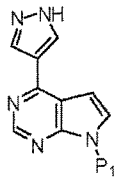
comprising:

a) treating a composition comprising an enantiomeric excess of the (R)- or (S)-enantiomer of a compound of Formula Ia with a compound of Formula D-1:



D-1

in the presence of a first base under conditions sufficient to form a compound of Formula IV:



IV

and

(b) reacting a compound of Formula IV with a compound of Formula D-1 in the presence of a second base;

wherein:

* is a chiral carbon;

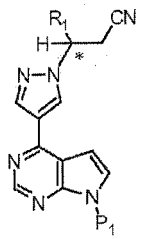
P_1 is a protecting group; and

R_1 is selected from C_{3-7} cycloalkyl, C_{1-6} alkyl, and C_{1-6} fluoroalkyl.

29. ~~52.~~ A process according to claim 28, wherein said first base is cesium carbonate.

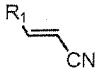
30. ~~53.~~ A process according to claim 28 or 29, wherein said second base is 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

31. ~~54.~~ A process of preparing a composition comprising a racemate of a compound of Formula Ia:



Ia

comprising treating a composition comprising an enantiomeric excess of the (R)- or (S)-enantiomer of a compound of Formula Ia with a compound of Formula D-1:



D-1

in the presence of a base under conditions sufficient to form said racemate of said compound of Formula Ia;

wherein:

* is a chiral carbon;

P_1 is a protecting group; and

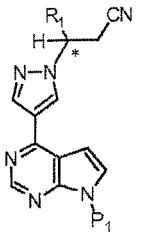
R_1 is selected from C_{3-7} cycloalkyl, C_{1-6} alkyl, and C_{1-6} fluoroalkyl.

31

32. ~~55.~~ A process according to claim ~~54~~, wherein said base is potassium t-butoxide.

28 32

33. ~~56.~~ A process according to any one of claims ~~51~~ to ~~55~~, further comprising preparing a composition comprising an enantiomeric excess of the (R)- or (S)-enantiomer of a compound of Formula Ia:



Ia

comprising passing a composition comprising a racemate of a compound of Formula Ia through a chiral chromatography unit using a mobile phase and collecting a composition comprising an enantiomeric excess of the (R)- or (S)-enantiomer of a compound of Formula Ia;

wherein:

* is a chiral carbon;

R_1 is selected from C_{3-7} cycloalkyl, C_{1-6} alkyl, and C_{1-6} fluoroalkyl; and

P_1 is a protecting group.

33

34. ~~57.~~ A process according to claim ~~56~~, wherein the mobile phase comprises isopropanol and hexanes, wherein said isopropanol is present in an amount of about 25% to about 10% by volume.

33 34

35. ~~58.~~ A process according to any one of claims ~~56~~ to ~~57~~, wherein said chromatography unit is a stimulated moving bed (SMB) chromatography unit equipped with a set of eight columns or a chiral column unit, wherein each column is packed with a chiral stationary phase.

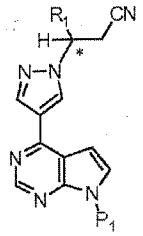
28 35

36. ~~59.~~ A process according to any one of claims ~~51~~ to ~~58~~, wherein P_1 is $-CH_2OC(=O)C(CH_3)_3$ or $-CH_2OCH_2CH_2Si(CH_3)_3$.

28 36

37. ~~60.~~ A process according to any one of claims ~~51~~ to ~~60~~, wherein R_1 is cyclopentyl.

38. ~~61.~~ A process of preparing a composition comprising an enantiomeric excess of a (R)- or (S)-enantiomer of a compound of Formula Ia:



Ia

comprising:

(a) reacting a composition comprising a racemate of a compound of Formula Ia with a chiral acid in the presence of a solvent to form a salt of a compound of Formula Ia;

(b) separating a composition comprising an enantiomer excess of a chiral salt of the (R)- or (S)-enantiomer of the compound of Formula Ia; and

(c) treating said chiral salt with a base to form a composition comprising an enantiomeric excess of the (R)- or (S)-enantiomer of the compound of Formula Ia;

wherein:

* is a chiral carbon;

R_1 is selected from C_{3-7} cycloalkyl, C_{1-6} alkyl, and C_{1-6} fluoroalkyl; and

P_1 is a protecting group.

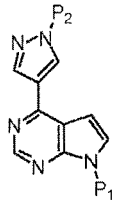
39. 62. A process according to claim 38 61, wherein said chiral acid is selected from optically active forms of mandelic acid, 2-chloromandelic acid, camphorsulfonic acid, tartaric acid, lactic acid, malic acid, 3-bromocamphor-8-sulfonic acid, 3-bromocamphor-10-sulfonic acid, 10-camphorsulfonic acid, dibenzoyl tartaric acid, di-p-toluoyltartaric acid, 2-amino-7,7-dimethylbicyclop[2,2,1]heptan-1-methylene sulfonic acid, and 2-acrylamide-7,7-dimethylbicyclo[2,2,1] heptan-1-methylene sulfonic acid.

40. 63. A process according to claim 38 61, wherein said chiral acid is (+)-dibenzoyl-D-tartaric acid.

41. 64. A process according to any one of claims 38 61 to 40 63, wherein P_1 is $-CH_2OC(=O)C(CH_3)_3$ or $-CH_2OCH_2CH_2Si(CH_3)_3$.

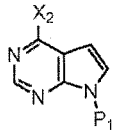
42. 65. A process according to any one of claims 38 61 to 41 64, wherein R_1 is cyclopentyl.

43. 66. A process of preparing a compound of Formula XII:



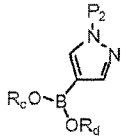
XII

comprising reacting a compound of Formula X:



X

with a compound of Formula XIII:



XIII

in the presence of a palladium catalyst, base, and a solvent, to form a compound of Formula XII.

wherein:

* is a chiral carbon;

X_2 is a tosylate group, a triflate group, iodo, chloro, or bromo;

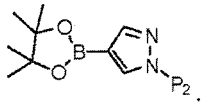
R_1 is selected from C_{3-7} cycloalkyl, C_{1-6} alkyl, and C_{1-6} fluoroalkyl; and

R_c and R_d are each independently H or C_{1-6} alkyl; or

R_c and R_d, together with the oxygen atoms to which they are attached and the boron atom to which the oxygen atoms are attached, form a 5- to 6-membered heterocyclic ring, which is optionally substituted with 1, 2, 3, or 4 C_{1-4} alkyl groups; and

P_1 and P_2 are each independently a protecting group.

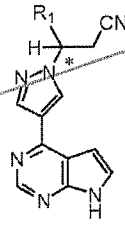
44. ~~67.~~ A process according to claim 43 ~~66~~, wherein said compound of Formula XIII has formula:



45. ~~68.~~ A process according to any one of claims 43 ~~66~~ to 44 ~~67~~, wherein P_1 is $-CH_2OC(=O)C(CH_3)_3$ or $-CH_2OCH_2CH_2Si(CH_3)_3$.

46. ~~69.~~ A process according to any one of claims 43 ~~66~~ to 45 ~~68~~, wherein P_2 is 1-(ethoxy)ethyl.

~~70. A process according to any one of claims 10, 12, 13, 21, 35, 39, 50, and 56 to 63, further comprising reacting said compound of Formula Ia under deprotection conditions to form a compound of Formula III:~~



~~III~~

~~* is a chiral carbon;~~

R_1 is selected from C_{3-7} cycloalkyl, C_{1-6} alkyl, and C_{1-6} fluoroalkyl; and

P_1 is a protecting group.

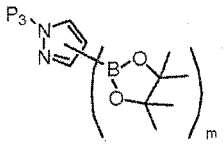
71. A process according to claim 70, wherein P_1 is $-CH_2OC(=O)C(CH_3)_3$ or $-CH_2OCH_2CH_2Si(CH_3)_3$.

72. A process according to claim 70 or 71, wherein R_1 is cyclopentyl.

73. A process according to claim 70 or 71, wherein said compound of Formula III is (3R)-3-cyclopentyl-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]propanenitrile.

74. A process according to any one of claims 70 to 73, further comprising reacting the compound of Formula III with phosphoric acid to form a phosphate salt of said compound of Formula III.

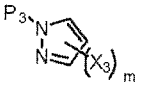
47. ~~75.~~ A process for preparing a compound of Formula XVI:



XVI

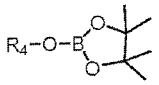
comprising:

(a) reacting a compound of Formula XVIII



XVIII

with about 1 or more equivalents of an C_{1-6} alkyl Grignard reagent or C_{1-6} alkyl lithium reagent followed by treating with about 1 or more equivalents of compound of Formula XVII:



XVII

and

(b) optionally, reprotecting the product of step (a) to give a compound of Formula XVI;

wherein:

P_3 is a protecting group;

X_3 is halogen;

R_4 is C_{1-6} alkyl; and

m is an integer selected from 1 and 2.

47

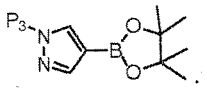
48. ~~76.~~ A process according to claim ~~75~~, wherein X_3 is iodo or bromo.

47 48

49. ~~77.~~ A process according to claim ~~75~~ or ~~76~~, wherein P_3 is 1-(ethoxy)ethyl.

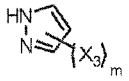
47 49

50. ~~78.~~ A process according to any one of claims ~~75~~ to ~~77~~, wherein said compound of Formula XVI has formula:



47 50

51. ~~79.~~ A process according to any one of claims ~~75~~ to ~~78~~, further comprising a method for preparing a compound of Formula XVIII, comprising protecting a compound of Formula XIX:



XIX

wherein:

P_3 is a protecting group;

X_3 is halogen; and

m is an integer selected from 1 and 2.

47 51

52. ~~80.~~ A process according to any one of claims ~~75~~ to ~~79~~, further comprising preparing said compound of Formula XIX by a process comprising reacting 1H-pyrazole with a halogenating agent, wherein:

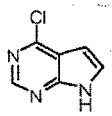
X_3 is halogen; and

m is an integer selected from 1 and 2.

47 52

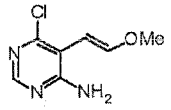
53. ~~81.~~ A process according to any one of claims ~~75~~ to ~~80~~, wherein said halogenating agent is selected from N-bromosuccinimide or N-iodosuccinimide.

54. ~~82.~~ A process for preparing a compound of Formula XIa:



XIa

comprising treating a compound of Formula F-1:



F-1

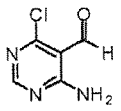
with acid under conditions sufficient to form a compound of Formula XIa.

54

55. ~~83.~~ A process according to claim ~~82~~, wherein said acid is aqueous concentrated hydrochloric acid.

54 55

56. ~~84.~~ The process according to any one of claims ~~82~~ to ~~83~~, further comprising preparing said compound of Formula F-1 by a process comprising reacting a compound of Formula F-2:

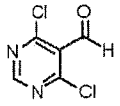


F-2

with about 1 or more equivalents of a Wittig-type reagent having a ylide of formula $-CH_2OCH_3$ in the presence of a base.

54 56

57. ~~85.~~ The process according to any one of claims ~~82~~ to ~~84~~, further comprising preparing said compound of Formula F-1 by a process comprising reacting a compound of F-3:

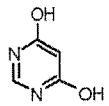


F-3

with about 2 or more equivalents of ammonia in a solvent.

54 57

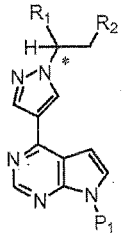
58. ~~86.~~ The process according to any one of claims ~~82~~ to ~~85~~, further comprising preparing said compound of Formula F-1 by a process comprising reacting a compound of F-4:



F-4

with a chlorinating agent.

59. ~~87.~~ A composition comprising an enantiomeric excess of a (R)- or (S)-enantiomer of a compound of Formula I:



I

wherein:

* indicates a chiral carbon;

R_1 is selected from C_{3-7} cycloalkyl, C_{1-6} alkyl, and C_{1-6} fluoroalkyl;

R_2 is selected from $-C(=O)-NH_2$, $-C(=O)O-R_3$, $-C(=O)OH$, and $-C(=O)H$;

R_3 is selected from C_{1-4} alkyl or C_{1-4} fluoroalkyl; and

P_1 is a protecting group.

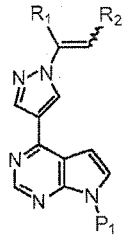
59

60. ~~88.~~ A composition according to claim ~~87~~, wherein P_1 is $-CH_2OC(=O)C(CH_3)_3$ or $-CH_2OCH_2CH_2Si(CH_3)_3$.

59 60

61. ~~89.~~ A composition according to claim ~~87~~ or ~~88~~, wherein R_1 is cyclopentyl.

~~90. A compound of Formula II:~~



II

wherein:

R_1 is selected from C_{3-7} cycloalkyl, C_{1-6} alkyl, and C_{1-6} fluoroalkyl;

R_2 is selected from $-C(=O)-NH_2$ and $-C(=O)O-R_3$;

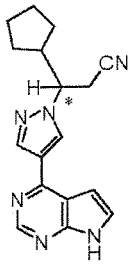
R_3 is selected from C_{1-4} alkyl or C_{1-4} fluoroalkyl; and

P_1 is a protecting group.

91. A compound according to claim 90, wherein P_1 is $-CH_2OC(=O)C(CH_3)_3$ or $-CH_2OCH_2CH_2Si(CH_3)_3$.

92. A compound according to claim 90 or 91, wherein R_1 is cyclopentyl.

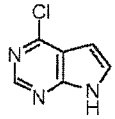
~~93. A process of preparing a composition comprising an enantiomeric excess of equal to or greater than 90 % of the (R)-enantiomer of a compound of formula III:~~



III'

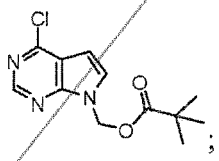
comprising:

(a) treating a compound of Formula XI':



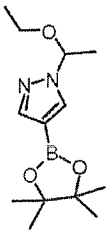
XI'

with sodium hydride and N-pivaloyloxymethyl chloride to form a compound of Formula X':



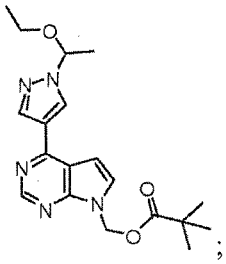
X'

(b) treating said compound of Formula X' with a compound of Formula XIII':



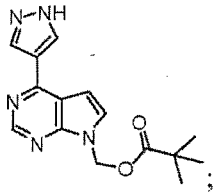
XIII'

in the presence of Pd(triphenylphosphine)$_4$, potassium carbonate, and a solvent, to form a compound of Formula XII':



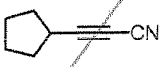
XII'

(c) reacting said compound of Formula XII' under deprotection conditions to give a compound of Formula IV':



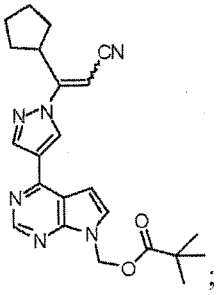
IV'

(d) reacting said compound of Formula IV" with a compound of Formula XIV':



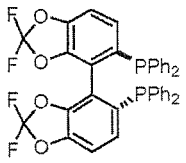
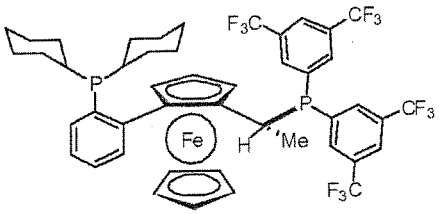
XIV'

in the presence of 1,8-diaza-bicyclo[5.4.0]undec-7-ene to give a compound of Formula II':

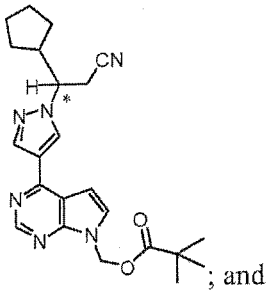


II'

(e) reacting said compound of Formula II' with hydrogen gas in the presence of $[Rh(COD)_2]CF_3SO_3$ and a chiral phosphine ligand selected from:

to form a compound of Formula I':

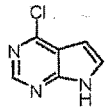

; and

I'

(f) reacting said compound of Formula I' under deprotection conditions to form said compound of Formula III';

wherein * indicates a chiral carbon.

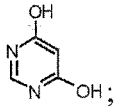
94. The process of claim 93, further comprising preparing said compound of Formula XI':



XI'

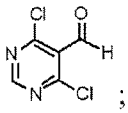
comprising:

(i) reacting a compound of F-4:


;

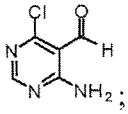
F-4

with from about three to about five equivalents of $POCl_3$ in the presence of about one to about two equivalents of dimethylformamide to form a compound of Formula F-3:


;

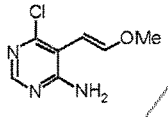
F-3

(ii) reacting said compound of F-3 with about two equivalents of ammonia in methanol to form a compound of Formula F-2:


;

F-2

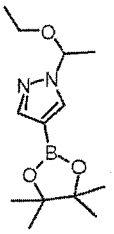
(iii) reacting said compound of Formula F-2 with from about 1 to about 1.5 equivalents of a Wittig-type reagent of formula $[Ph_3P^+(CH_2OCH_3)]Cl^-$, wherein Ph is phenyl, in the presence of from about 1 to about 1.5 equivalents of potassium tert-butoxide to form a compound of Formula F-1:


; and

F-1

(iv) treating said compound of Formula F-1 with aqueous concentrated hydrochloric acid in tetrahydrofuran at reflux to form compound of Formula XI'.

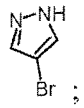
95. The process of claim 93, further comprising preparing said compound of Formula XIII':



XIII'

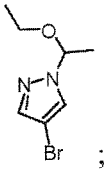
comprising:

(i) reacting 1H-pyrazole with N-bromosuccinimide to form a compound of Formula XIX';



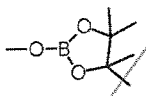
XIX'

(ii) protecting said compound of Formula XIX to form a compound of Formula XVIII':



XVIII'

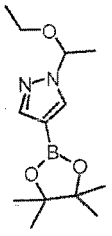
(iii) reacting said compound of Formula XVIII' with about one or more equivalents of a isopropylmagnesium chloride followed by treating with about one or more equivalents of compound of Formula XVII':



XVII'

to form a compound of Formula XIII'.

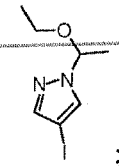
96. The process of claim 93, further comprising preparing said compound of Formula XIII':



XIII'

comprising:

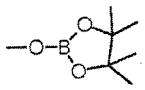
(i) protecting 4-iodo-1H-pyrazole to form a compound of Formula XVIII":



; and

XVIII"

(ii) reacting a compound of Formula XVIII" with about one or more equivalents of a isopropylmagnesium chloride in tetrahydrofuran followed by treating with about one or more equivalents of compound of Formula XVII':



XVII'

to form a compound of Formula XIII'.

97. The process of claim 93, wherein, in step (e):

the solvent is 2,2,2-trifluoroethanol (TFE);

the hydrogenation catalyst loading is about 0.005 to about 0.01 mol %;

the ratio of said compound of Formula II to said hydrogenation catalyst is from about 20000/1 to about 10000/1;

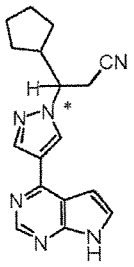
the hydrogen pressure is from about 7 to about 60 bar;

the reacting is run at a temperature from about room temperature to about 75 °C;

the reacting is run until the conversion of said compound of Formula II to said compound of Formula is about equal to or greater than 99.5%; and

~~the reacting is from about 10 to about 25 hours.~~

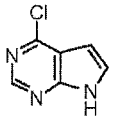
62. ~~98.~~ A process of preparing a composition comprising an enantiomeric excess of the (R)-enantiomer of a compound of Formula III':



III'

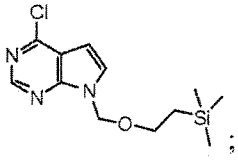
comprising:

(a) treating a compound of Formula XI':



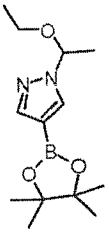
XI'

with sodium hydride and 2-(trimethylsilyl)ethoxymethyl to form a compound of Formula X":



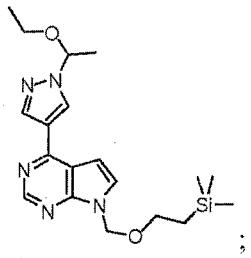
X"

(b) treating said compound of Formula X" with a compound of Formula XIII':



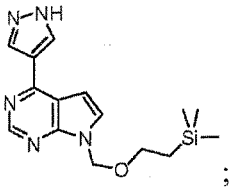
XIII'

in the presence of Pd(triphenylphosphine)$_4$, potassium carbonate, and a solvent, to form a compound of Formula XII":



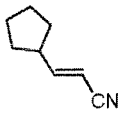
XII"

(c) reacting said compound of Formula XII" under deprotection conditions to form a compound of Formula IV":



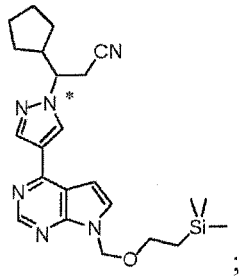
IV"

(d) reacting said compound of Formula IV" with a compound of Formula D-1':



D-1'

under conditions sufficient to form a composition comprising a racemate of a compound of Formula I":



I"

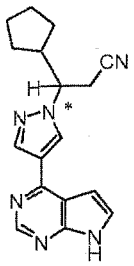
(e) passing said composition comprising said racemate of said compound of Formula I" through a chiral chromatography unit using a mobile phase and

collecting a composition comprising an enantiomeric excess of the (R)-enantiomer of said compound of Formula I"; and

(f) reacting said compound of Formula I" with lithium tetrafluoroborate, followed by aqueous ammonium hydroxide to form a composition comprising an enantiomeric excess of the (R)-enantiomer of said compound of Formula III';

wherein * is a chiral carbon.

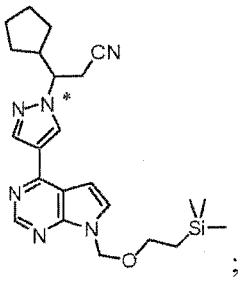
63. A process of preparing a composition comprising an enantiomeric excess of the (R)-enantiomer of a compound of Formula III':



III'

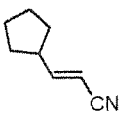
comprising:

(a) treating a composition comprising an enantiomeric excess of the (S)-enantiomer of a compound of Formula I":



I"

with a compound of Formula D-1':



D-1'

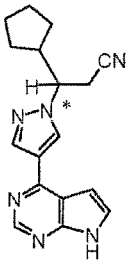
in the presence of cesium carbonate in acetonitrile under conditions sufficient to form the racemate of the compound of Formula I";

(b) passing said composition comprising said racemate of said compound of Formula I" through a chiral chromatography unit using a mobile phase and collecting a composition comprising an enantiomeric excess of the (R)-enantiomer of said compound of Formula I"; and

(c) reacting said compound of Formula I" with lithium tetrafluoroborate, followed by aqueous ammonium hydroxide to form a composition comprising an enantiomeric excess of the (R)-enantiomer of said compound of Formula III';

wherein * is a chiral carbon.

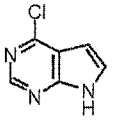
64. ~~100.~~ A process of preparing a composition comprising an enantiomeric excess of the (R)-enantiomer of a compound of Formula III':



III'

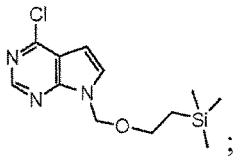
comprising:

(a) treating a compound of Formula XI':



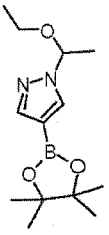
XI'

with sodium hydride and 2-(trimethylsilyl)ethoxymethyl to form a compound of Formula X":



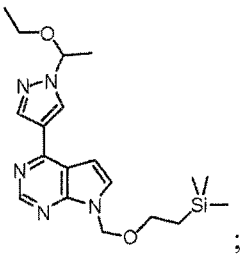
X"

(b) treating said compound of Formula X" with a compound of Formula XIII':



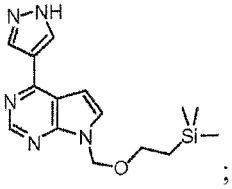
XIII'

in the presence of Pd(triphenylphosphine)$_4$, potassium carbonate, and a solvent, to form a compound of Formula XII":



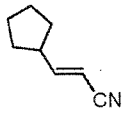
XII"

(c) reacting said compound of Formula XII" under deprotection conditions to form a compound of Formula IV":



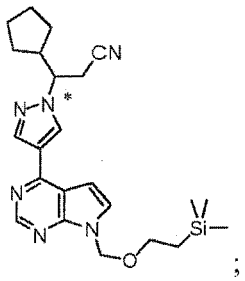
IV"

(d) reacting said compound of Formula IV" with a compound of Formula D-1':



D-1'

under conditions sufficient to form a composition comprising a racemate of a compound of Formula I":



;

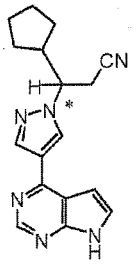
I"

(e) passing said composition comprising said racemate of said compound of Formula I" through a chiral chromatography unit using a mobile phase and collecting a composition comprising an enantiomeric excess of the (R)-enantiomer of said compound of Formula I"; and

(f) reacting said compound of Formula I" with boron trifluoride diethyl etherate, followed by aqueous ammonium hydroxide to form a composition comprising an enantiomeric excess of the (R)-enantiomer of said compound of Formula III';

wherein * is a chiral carbon.

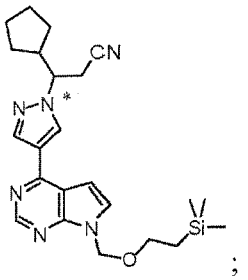
65. ~~101.~~ A process of preparing a composition comprising an enantiomeric excess of the (R)-enantiomer of a compound of Formula III':



III'

comprising:

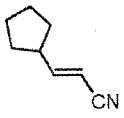
(a) treating a composition comprising an enantiomeric excess of the (S)-enantiomer of a compound of Formula I":



;

I"

with a compound of Formula D-1':



D-1'

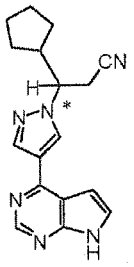
in the presence of cesium carbonate in acetonitrile under conditions sufficient to form the racemate of the compound of Formula I";

(b) passing said composition comprising said racemate of said compound of Formula I" through a chiral chromatography unit using a mobile phase and collecting a composition comprising an enantiomeric excess of the (R)-enantiomer of said compound of Formula I"; and

(c) reacting said compound of Formula I" with boron trifluoride diethyl etherate, followed by aqueous ammonium hydroxide to form a composition comprising an enantiomeric excess of the (R)-enantiomer of said compound of Formula III';

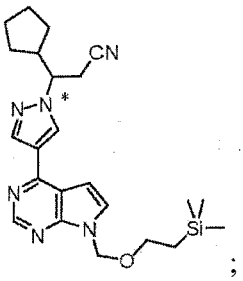
wherein * is a chiral carbon.

66. ~~102.~~ A process of preparing a composition comprising an enantiomeric excess of the (R)-enantiomer of a compound of Formula III':



III'

comprising: reacting said compound of Formula I" :



;

I"

with boron trifluoride diethyl etherate, followed by aqueous ammonium hydroxide to form a composition comprising an enantiomeric excess of the (R)-enantiomer of said compound of Formula III'; wherein * is a chiral carbon.

67. ~~103.~~ A process for preparing (3R)-cyclopentyl-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)pyrazol-1-yl]propionitrile phosphate salt comprising reacting (3R)-cyclopentyl-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)pyrazol-1-yl]propionitrile with phosphoric acid in the presence of 2-propanol and dichloromethane.

68. ~~104.~~ A method of purifying (3R)-cyclopentyl-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)pyrazol-1-yl]propionitrile phosphate salt comprising recrystallizing (3R)-cyclopentyl-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)pyrazol-1-yl]propionitrile phosphate salt from a solvent mixture comprising methanol, 2-propanol, and n-heptane.

69. ~~105.~~ The method of claim 68 ~~104~~ wherein said 2-propanol and n-heptane are added to a mixture of (3R)-cyclopentyl-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)pyrazol-1-yl]propionitrile phosphate salt in methanol.