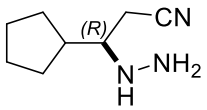
What is claimed is:

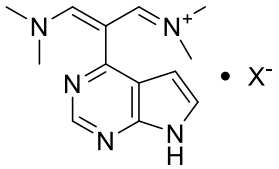
1. A process of preparing ruxolitinib, or a salt thereof, comprising:

reacting a compound of formula 3:



3,

or a salt thereof, with a reagent which is salt of formula 2a:



2a

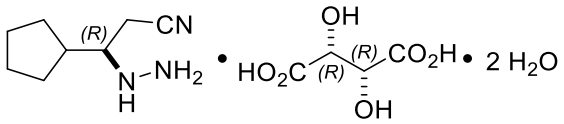
wherein X^- is a counter anion.

2. The process of claim 1, wherein the compound of formula 3, or the salt thereof, is a chiral salt of the compound of formula 3.

3. The process of claim 2, wherein the chiral salt is prepared by reacting the compound of formula 3 with an optically active form of an acid selected from 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.

4. The process of claim 2, wherein the chiral salt is the L-(+)-tartrate salt of the compound of formula 3.

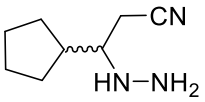
5. The process of claim 2, wherein the compound of formula 3, or the salt thereof, has formula 3a:



3a.

6. The process of any one of claims 4-5, wherein the L-tartrate salt of formula 3 is prepared by a process comprising:

reacting compound 7a:

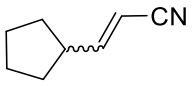


7a

with L-tartaric acid.

7. The process of claim 6, wherein the compound of formula 7a is prepared by a process comprising:

reacting the compound of formula 6a:



6a

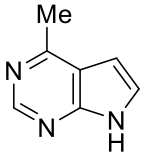
with hydrazine.

8. The process of any one of claims 1-7, wherein X^- is selected from Cl^-, BF_4^-, PF_6^-, AsF_6^-, SbF_6^-, and ClO_4^-.

9. The process of any one of claims 1-7, wherein X^- is Cl^-.

10. The process of any one of claims 1-9, wherein the salt of formula 2a is prepared by a process comprising:

reacting the compound of formula 1a:



1a,

or a salt thereof, with a Vilsmeier reagent formed from dimethylformamide.

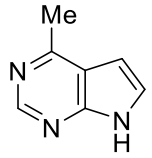
11. The process of claim 10, wherein the Vilsmeier reagent is prepared by a process comprising reacting dimethylformamide with a chlorinating agent.

12. The process of claim 11, wherein the chlorinating agent is selected from oxalyl chloride, phosphorus oxychloride, and triphosgene.

13. The process of claim 11, wherein the chlorinating agent is oxalyl chloride.

14. The process of any one of claims 1-13, wherein the salt of formula 2a, wherein X^- is Cl^-, is prepared by a process comprising:

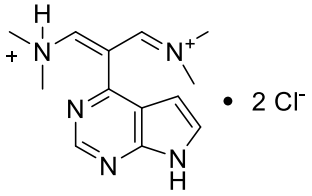
reacting the compound of formula 1a:



1a,

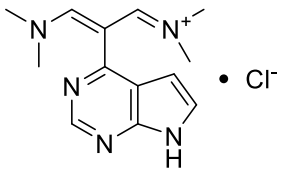
or a salt thereof, with a Vilsmeier reagent formed from dimethylformamide; and

reacting a salt of formula 2d:



2d

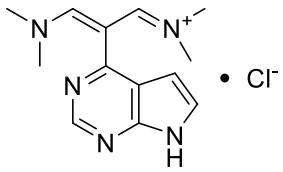
with a base to form a salt of formula 2c:



2c

wherein the Vilsmeier reagent is prepared by a process comprising reacting dimethylformamide with a chlorinating agent.

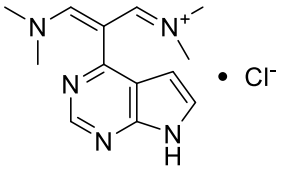
15. The process of any one of claims 10-13, wherein the reacting with the Vilsmeier reagent produces a salt of formula 2c:



2c.

16. The process of any one of claims 14-15, further comprising:

reacting the salt of formula 2c:



2c,

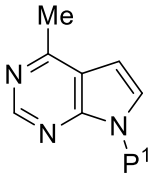
with a salt of formula M^+X^- to form the salt of formula 2a, wherein:

M^+ is a counter cation; and

X^- is a counter anion other than Cl^-.

17. The process of any one of claims 10-16, wherein the compound of formula 1a, or the salt thereof, is prepared by a process comprising:

deprotecting a compound of formula 1aP:



1aP

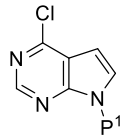
wherein P^1 is an amino protecting group.

18. The process of claim 17, wherein P^1 is selected from $(R^1)_3Si$, wherein R^1 is $C_{1\text{-}6}$ alkyl.

19. The process of claim 18, wherein R^1 is methyl, ethyl, propyl, isopropyl, butyl or t-butyl.

20 The process of any one of claims 17-19, wherein the compound of formula 1aP is prepared by a process comprising:

reacting a compound of formula 2P:



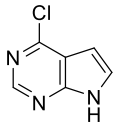
2P

with MeMgBr in the presence of a Grignard catalyst,

wherein P^1 is an amino protecting group.

21. The process of claim 20, wherein the compound of formula 2P is prepared by a process comprising:

protecting a compound of formula 12a:



12a

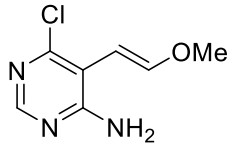
to form the compound of formula 2P.

22. The process of claim 21, wherein the protecting comprises reacting the compound of formula 12a with an alkali metal hydride and P^1-Y, wherein Y is halo.

23. The process of claim 22, wherein P^1-Y is $(R^1)_3$Si-Y, wherein Y is halo and R^1 is C_{1-6} alkyl.

24. The process of any one of claims 21-23, wherein the compound of formula 12a is prepared by a process comprising:

reacting a compound of formula 11a:

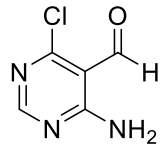


11a

or a salt thereof, with a strong acid.

25. The process of claim 24, wherein the compound of formula 11a, or a salt thereof, is prepared by a process comprising:

reacting a compound of formula 10a:

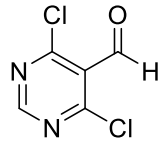


10a

or a salt thereof, with (methoxymethyl)triphenylphosphonium chloride and a base.

26. The process of claim 25, wherein the compound of formula 10a, or a salt thereof, is prepared by a process comprising:

reacting a compound of formula 9a:

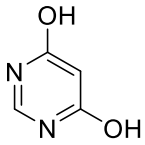


9a

with ammonia.

27. The process of claim 26, wherein the compound of formula 9a is prepared by a process comprising:

reacting a compound of formula 8a:



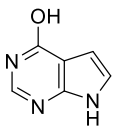
8a

with a Vilsmeier reagent formed from dimethylformamide.

28. The process of claim 27, wherein the Vilsmeier reagent is prepared by a process comprising reacting dimethylformamide with a chlorinating agent.

29. The process of any one of claims 21-23, wherein the compound of formula 12a is prepared by a process comprising:

reacting a compound of formula 15a:

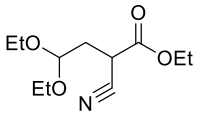


15a

with a chlorinating agent.

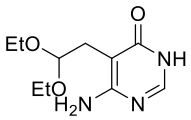
30. The process of claim 29, wherein the compound of formula 15a is prepared by a process comprising:

(i) reacting a compound of formula 14a:



14a

with formamidine acetate and an alkali metal hydroxide to generate a compound of formula 14aa:

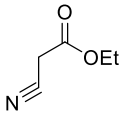


14aa; and

(ii) reacting the compound of formula 14aa with a strong acid.

31. The process of claim 30, wherein the compound of formula 14a is prepared by a process comprising:

reacting a compound of formula 13a:

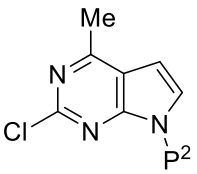


13a

with bromoacetaldehyde diethyl acetal and sodium tert-amyloxide.

32. The process of any one of claims 10-16, wherein the compound of formula 1a, or the salt thereof, is prepared by a process comprising:

reducing a compound of formula 23P:



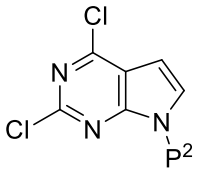
23P

wherein P^2 is an amino protecting group.

33. The process of claim 32, wherein the reducing of the compound of formula 23P is accomplished by a process comprising reacting the compound of formula 23P with hydrogen gas in the presence of a catalyst.

34. The process of any one of claims 32-33, wherein the compound of formula 23P is prepared by a process comprising:

reacting a compound of formula 22P:



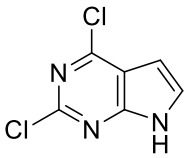
22P

with MeMgBr in the presence of a Grignard catalyst,

wherein P^2 is an amino protecting group.

35. The process of claim 34, wherein the compound of formula 22P is prepared by a process comprising:

protecting a compound of formula 22a:



22a,

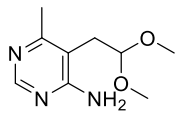
to form the compound of formula 22P.

36. The process of claim 35, wherein the protecting comprises reacting the compound of formula 22a with an alkali metal hydride and P^2-Y, wherein Y is halo.

37. The process of claim 36, wherein P^2 is $(R^1)_3Si$, wherein R^1 is C_{1-6} alkyl.

38. The process of any one of claims 10-16, wherein the compound of formula 1a, or the salt thereof, is prepared by a process comprising:

reacting a compound of formula 18a:

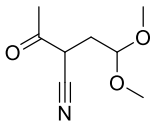


18a

with an acid to form the compound of formula 1a.

39. The process of claim 38, wherein the compound of formula 18a, or a salt thereof, is prepared by a process comprising:

reacting a compound of formula 17a:

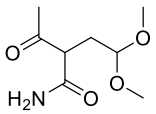


17a

with formamidine acetate and triethyl orthoformate to form the compound of formula 18a.

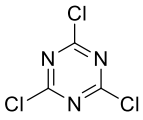
40. The process of claim 39, wherein the compound of formula 17a, or a salt thereof, is prepared by a process comprising:

reacting a compound of formula 20a:



20a

with a compound of formula 21a:

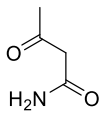


21a

to form the compound of formula 17a.

41. The process of claim 40, wherein the compound of formula 20a, or a salt thereof, is prepared by a process comprising:

reacting a compound of formula 19a:



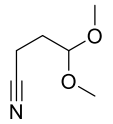
19a

with bromo-1,1-dimethoxyethane and a base to form the compound of formula 20a.

42. The process of claim 41, wherein the base is an alkali metal carbonate.

43. The process of claim 39, wherein the compound of formula 17a, or a salt thereof, is prepared by a process comprising:

reacting a compound of formula 16a:



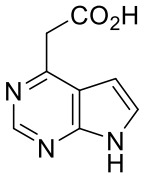
16a

with ethyl acetate and a base to form the compound of formula 17a.

44. The process of claim 43, wherein the base is an alkali metal alkoxide.

45. The process of any one of claims 1-9, wherein the salt of formula 2a is prepared by a process comprising:

reacting the compound of formula 5a:



5a,

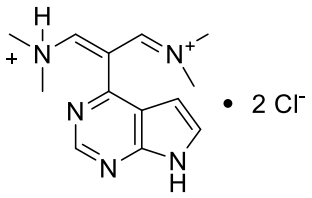
or a salt thereof, with a Vilsmeier reagent formed from dimethylformamide.

46. The process of claim 45, wherein the Vilsmeier reagent is prepared by a process comprising reacting dimethylformamide with a chlorinating agent.

47. The process of claim 46, wherein the chlorinating agent is selected from oxalyl chloride, phosphorus oxychloride, and triphosgene.

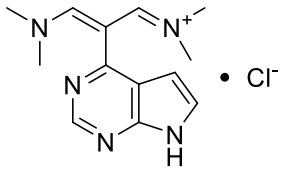
48. The process of claim 46, wherein the chlorinating agent is oxalyl chloride.

49. The process of claim 45, further comprising reacting the salt of formula 2d:



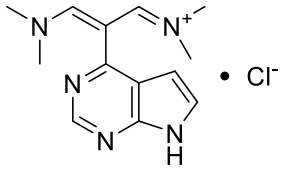
2d

with a base to form a salt of formula 2c:



2c.

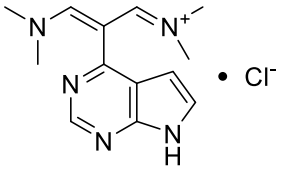
50. The process of any one of claims 45-48, wherein the reacting with the Vilsmeier reagent produces a salt of formula 2c:



2c.

51. The process of any one of claims 49-50, further comprising:

reacting the salt of formula 2c:



2c,

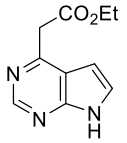
with a salt of formula M^+X^- to form the salt of formula 2a, wherein:

M^+ is a counter cation; and

X^- is a counter anion other than Cl^-.

52. The process of any one of claims 45-51, wherein the compound of formula 5a, or the salt thereof, is prepared by a process comprising:

hydrolyzing a compound of formula 27a:



27a

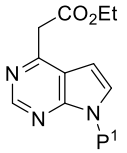
in water in the presence of a base.

53. The process of claim 52, wherein the base, present for the hydrolyzing of the compound of formula 27a, is sodium hydroxide; and the compound of formula 5a, or the salt thereof, is a sodium salt of the compound of formula 5a.

54. The process of claim 53, further comprising reacting the sodium salt of the compound of formula 5a with a strong acid.

55. The process of any one of claims 52-54, wherein the compound of formula 27a is prepared by a process comprising:

reacting a compound of formula 26P:



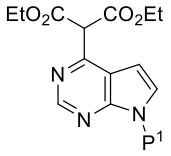
26P

with a strong acid, wherein P^1 is an amino protecting group.

56. The process of claim 55, wherein P^1 is p-toluenesulfonyl.

57. The process of any one of claims 55-56, wherein the compound of formula 26P is prepared by a process comprising:

reacting a compound of formula 25P:

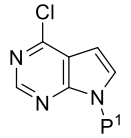


25P

with an alkali metal alkoxide to form the compound of formula 26P, wherein P^1 is an amino protecting group.

58. The process of claim 57, wherein the compound of formula 25P is prepared by a process comprising:

reacting a compound of formula 2P:

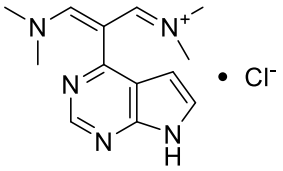


2P

with diethyl malonate and a base, wherein P^1 is an amino protecting group.

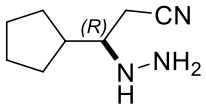
59. The process of claim 1, wherein the ruxolitinib phosphate is prepared by a process comprising reacting the ruxolitinib with phosphoric acid.

60. A process of preparing ruxolitinib, or a salt thereof, comprising reacting a salt of formula 2c:



2c,

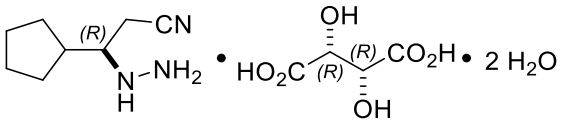
with a L-(+)-tartrate salt of a compound of formula 3:



3,

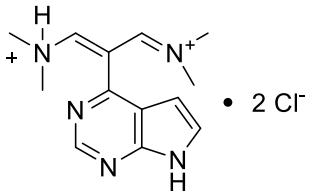
to form the ruxolitinib, or the salt thereof.

61. The process of claim 60, wherein the L-(+)-tartrate salt of a compound of formula 3 is a salt of formula 3a:



3a.

62. The process of claim 61, wherein the salt of formula 2c is prepared by a process comprising reacting a salt of formula 2d:

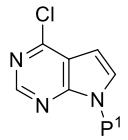


2d

with a base to form the salt of formula 2c.

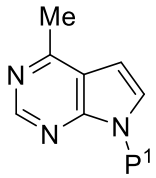
63. The process of claim 62, wherein the salt of formula 2d is prepared by a process comprising:

(a) reacting a compound of formula 2P:



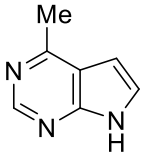
2P

with MeMgBr in the presence of a Grignard catalyst to form a compound of formula 1aP:



1aP

(b) deprotecting the compound of formula 1aP to form a compound of formula 1a:



1a

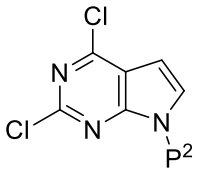
or a salt thereof; and

(c) reacting the compound of formula 1a, or the salt thereof, with a Vilsmeier reagent formed from dimethylformamide and a chlorinating agent to form the salt of formula 2d;

wherein P^1 is an amino protecting group.

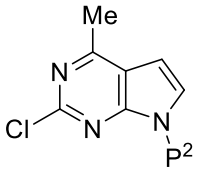
64. The process of claim 62, wherein the salt of formula 2d is prepared by a process comprising:

(a) reacting a compound of formula 22P:



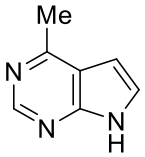
22P

with MeMgBr in the presence of a Grignard catalyst to form a compound of formula 23P:



23P;

(b) reducing the compound of formula 23P to form a compound of formula 1a:



1a

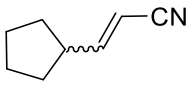
or a salt thereof; and

(c) reacting the compound of formula 1a, or the salt thereof, with a Vilsmeier reagent formed from dimethylformamide and a chlorinating agent to form the salt of formula 2d;

wherein P^2 is an amino protecting group.

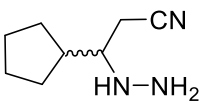
65. The process of any one of claims 61-64, wherein the salt of formula 3a is prepared by a process comprising:

(a) reacting a compound of formula 6a:



6a

with hydrazine to form a compound of formula 7a:



7a; and

(b) reacting the compound of formula 7a with L-tartaric acid to form the salt of formula 3a.

66. The process of claim 63, wherein the chlorinating agent is selected from oxalyl chloride, phosphorus oxychloride, and triphosgene.

67. The process of claim 63, wherein the chlorinating agent is oxalyl chloride.

68. The process of claim 49, wherein the chlorinating agent is selected from oxalyl chloride, phosphorus oxychloride, and triphosgene.

69. The process of claim 49, wherein the chlorinating agent is oxalyl chloride.