We Claim:

1. A method for preparing 5-((*tert*-butoxycarbonyl)aminomethyl)-2-fluorobenzene-boronic acid, comprising boronation of 4-(*tert*-butoxycarbonyl)aminomethyl)-fluorobenzene with a boronic acid forming agent under boronation conditions, and then quenching the resultant mixture with an aqueous acid to yield 5-((*tert*-butoxycarbonyl)aminomethyl)-2-fluoro-benzeneboronic acid.

2. The method of claim 1 wherein the boronation conditions uses a superbase.

3. The method of claim 2 wherein the superbase is a combination of an organolithium reagent of formula RLi where R is an alkyl or aryl group having 1-12 carbons and a bulky potassium alkoxide such as potassium *tert*-butoxide or potassium *tert*-pentoxide and the like.

4. The method of claim 3 wherein the superbase is a combination of *n*-butyllithium and potassium *tert*-butoxide.

5. The method of claim 1 wherein the boronation conditions uses a boronic acid forming agent which is a trialkyl boronate.

6. The method of claim 5 wherein the trialkyl boronate is selected from trimethyl borate, triethyl borate, tripropyl borate, triisopropyl borate, tributylborate and the like.

7. The method of claim 6 wherein the trialkyl boronate is triisopropyl borate.

8. The method of claim 1 wherein the boronation conditions uses a boronation solvent which is an ether solvent selected from diethyl ether, THF, 2-methyltetrahydrofuran, MTBE, dimethoxyethane and the like.

9. The method of claim 8 wherein the ether solvent is THF.

10. The method of claim 1 wherein the boronation conditions uses a boronation reaction temperature from about -100°C to about -30°C.

11. The method of claim 10 wherein the boronation reaction temperature is from about –70 to about -45 °C.

12. The method of claim 1 wherein the aqueous acid is HCl or H_3PO_4.

13. The method of claim 12 wherein the aqueous acid is HCl.

14. A method for preparing (4-fluoro-3-pyridin-4-yl-benzyl)-carbamic acid *tert*-butyl ester comprising coupling 5-((*tert*-butoxycarbonyl)aminomethyl)-2-fluorobenzeneboronic acid according to claim 1 and a 4-halopyridine under Suzuki coupling conditions to yield 4-fluoro-3-pyridin-4-yl-benzyl)-carbamic acid *tert*-butyl ester.

15. The method according to claim 14 wherein the Suzuki coupling conditions uses a Suzuki coupling solvent selected from an alcoholic solvent with a boiling point of at least that of *i*-propyl alcohol, polar aprotic solvent, or ether solvent, or mixture of any of the aforesaid mentioned solvents and water or toluene.

16. The method according to claim 15 wherein the Suzuki coupling solvent is an ether solvent selected from THF, toluene, 2-methylTHF, or dimethoxyethane.

17. The method according to claim 16 wherein the ether solvent is dimethoxyethane.

18. The method according to claim 14 wherein the Suzuki coupling conditions uses a Suzuki catalyst selected from Pd catalyst such as $Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$, $Pd_2(dba)_3$, $PdCl_2dppf$, $Pd(dtbpf)Cl_2$, or the like; or Pd catalyst such as $Pd(OAc)_2$, $Pd_2(dba)_3$ or the like in conjunction with a phosphine ligand such as PPh_3, dppf, *t*-Bu_3P, $P(Cy)_3$ or the like, and a strong base.

19. The method according to claim 18 wherein the Suzuki coupling catalyst is $Pd(PPh_3)_4$.

20. The method according to claim 14 wherein the Suzuki coupling conditions uses a Suzuki coupling reaction temperature of from about 60°C to about 100°C.

21. The method according to claim 20 wherein the Suzuki coupling reaction temperature is at about 85°C.

22. The method in claim 14 wherein the 4-halopyridine is 4-chloropyridine.

23. A method for preparing (4-fluoro-3-piperidin-4-yl-benzyl)-carbamic acid *tert*-butyl ester hydrochloride (I), comprising reducing (4-fluoro-3-pyridin-4-yl-benzyl)-carbamic acid *tert*-butyl ester according to claim 11 under hydrogenation reducing conditions, and then followed by HCl work-up to yield fluoro-3-piperidin-4-yl-benzyl)-carbamic acid *tert*-butyl ester hydrochloride.

24. The method according to claim 18 wherein the hydrogenation reducing conditions uses a hydrogenation catalyst selected from Pt/C, PtO_2, Pd/C, $Pd(OH)_2$, Rh/C and the like, with or without added inorganic acid such as HCl and the like, or organic acid such as acetic acid and the like.

25. The method according to claim 24 wherein the hydrogenation catalyst is PtO_2.

26. The method according to claim 18 wherein the hydrogenation reducing conditions uses a hydrogenation solvent selected from an ester solvent such as EtOAc, i-PrOAc, BuOAc and the like; alcohol solvent such as methanol, ethanol, isopropyl alcohol and the like; or AcOH; or a mixture of an alcohol or ester solvent and water and acetic acid.

27. The method according to claim 26 wherein the hydrogenation solvent *i* –PrOAc.

28. The method according to claim 18 wherein the hydrogenation reducing conditions uses a hydrogenation reaction temperature from about 10 to about 60 °C.

29. The method according to claim 18 wherein the hydrogenation reaction temperature is at about ambient temperature.

30. The method according to claim 18 wherein the hydrogenation reducing conditions uses a hydrogenation pressure from about 10 to about 1000 psi.

31. The method in claim 30 wherein the hydrogenation pressure is from about 50 to about 60 psi.

Claims

What is claimed is:

1. A method for preparing 5-((tert-butoxycarbonyl)aminomethyl)-2-fluorobenzene-boronic acid, comprising boronation of 4-(tert-butoxycarbonyl)aminomethyl)-fluorobenzene with a boronic acid forming agent under boronation conditions, and then quenching the resultant mixture with an aqueous acid to yield 5-((tert-butoxycarbonyl)aminomethyl)-2-fluoro-benzeneboronic acid.

2. The method of claim 1 wherein the boronation conditions uses a superbase.

3. The method of claim 2 wherein the superbase is a combination of an organolithium reagent of formula RLi where R is an alkyl or aryl group having 1-12 carbons and a bulky potassium alkoxide such as potassium tert-butoxide or potassium tert-pentoxide and the like.

4. The method of claim 3 wherein the superbase is a combination of n-butyllithium and potassium tert-butoxide.

5. The method of claim 1 wherein the boronation conditions uses a boronic acid forming agent which is a trialkyl boronate.

6. The method of claim 5 wherein the trialkyl boronate is selected from trimethyl borate, triethyl borate, tripropyl borate, triisopropyl borate, tributylborate and the like.

7. The method of claim 6 wherein the trialkyl boronate is triisopropyl borate.

8. The method of claim 1 wherein the boronation conditions uses a boronation solvent which is an ether solvent selected from diethyl ether, THF, 2-methyltetrahydrofuran, MTBE, dimethoxyethane and the like.

9. The method of claim 8 wherein the ether solvent is THF.

10. The method of claim 1 wherein the boronation conditions uses a boronation reaction temperature from about −100° C. to about −30° C.

11. The method of claim 10 wherein the boronation reaction temperature is from about −70° C. to about −45° C.

12. The method of claim 1 wherein the aqueous acid is HCl or H_3PO_4.

13. The method of claim 12 wherein the aqueous acid is HCl.

14. A method for preparing (4-fluoro-3-pyridin-4-yl-benzyl)-carbamic acid tert-butyl ester comprising coupling 5-((tert-butoxycarbonyl)aminomethyl)-2-fluorobenzeneboronic acid prepared according to claim 1 and a 4-halopyridine under Suzuki coupling conditions to yield 4-fluoro-3-pyridin-4-yl-benzyl)-carbamic acid tert-butyl ester.

15. The method according to claim 14 wherein the Suzuki coupling conditions uses a Suzuki coupling solvent selected from an alcoholic solvent with a boiling point of at least that of i-propyl alcohol, polar aprotic solvent, or ether solvent, or mixture of any of the aforesaid mentioned solvents and water or toluene.

16. The method according to claim 15 wherein the Suzuki coupling solvent is an ether solvent selected from THF, toluene, 2-methylTHF, or dimethoxyethane.

17. The method according to claim 16 wherein the ether solvent is dimethoxyethane.

18. The method according to claim 14 wherein the Suzuki coupling conditions uses a Suzuki catalyst selected from Pd catalyst such as $Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$, $Pd_2(dba)_3$, $PdCl_2dppf$, $Pd(dtbpf)Cl_2$, or the like; or Pd catalyst such as $Pd(OAc)_2$, $Pd_2(dba)_3$ or the like in conjunction with a phosphine ligand such as PPh_3, dppf, t-Bu_3P, $P(Cy)_3$ or the like, and a strong base.

19. The method according to claim 18 wherein the Suzuki coupling catalyst is $Pd(PPh_3)_4$.

20. The method according to claim 14 wherein the Suzuki coupling conditions uses a Suzuki coupling reaction temperature of from about 60° C. to about 100° C.

21. The method according to claim 20 wherein the Suzuki coupling reaction temperature is at about 85° C.

22. The method in claim 14 wherein the 4-halopyridine is 4-chloropyridine.

23. A method for preparing (4-fluoro-3-piperidin-4-yl-benzyl)-carbamic acid tert-butyl ester hydrochloride (I), comprising reducing (4-fluoro-3-pyridin-4-yl-benzyl)-carbamic acid tert-butyl ester prepared according to claim 14 under hydrogenation reducing conditions, and then followed by HCl work-up to yield fluoro-3-piperidin-4-yl-benzyl)-carbamic acid tert-butyl ester hydrochloride.

24. The method according to claim 23 wherein the hydrogenation reducing conditions uses a hydrogenation catalyst selected from Pt/C, PtO_2, Pd/C, $Pd(OH)_2$, Rh/C and the like, with or without added inorganic acid such as HCl and the like, or organic acid such as acetic acid and the like.

25. The method according to claim 24 wherein the hydrogenation catalyst is PtO_2.

26. The method according to claim 23 wherein the hydrogenation reducing conditions uses a hydrogenation solvent selected from an ester solvent such as EtOAc, i-PrOAc, BuOAc and the like; alcohol solvent such as methanol, ethanol, isopropyl alcohol and the like; or AcOH; or a mixture of an alcohol or ester solvent and water and acetic acid.

27. The method according to claim 26 wherein the hydrogenation solvent i-PrOAc.

28. The method according to claim 23 wherein the hydrogenation reducing conditions uses a hydrogenation reaction temperature from about 10 to about 60° C.

29. The method according to claim 23 wherein the hydrogenation reaction temperature is at about ambient temperature.

30. The method according to claim 23 wherein the hydrogenation reducing conditions uses a hydrogenation pressure from about 10 to about 1000 psi.

31. The method according to claim 30 wherein the hydrogenation pressure is from about 50 to about 60 psi.