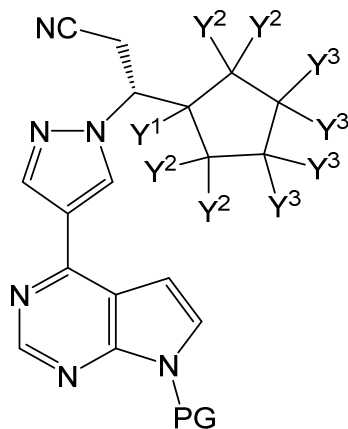


CLAIMS

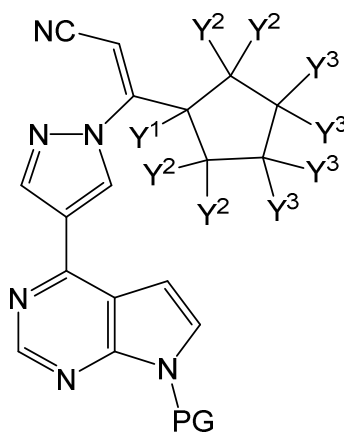
~~What is claimed is:~~

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



Formula I;

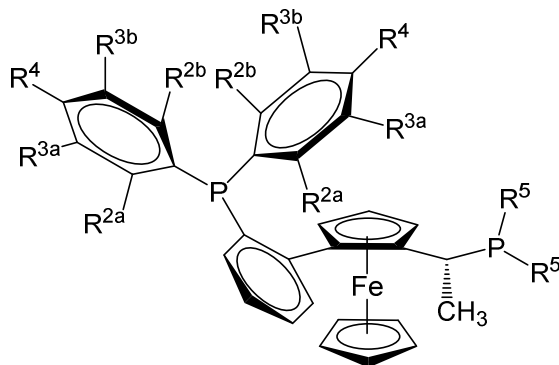
wherein Y¹ is hydrogen or deuterium, each Y² is the same and is hydrogen or deuterium, each Y³ is the same and is hydrogen or deuterium; and PG is hydrogen or a protecting group selected from pivaloyloxymethyl (POM), 2-(trimethylsilyl)ethoxymethyl (SEM), benzyl (Bn), *p*-methoxybenzyl (PMB), 3,4-dimethoxybenzyl (DMPM), 2,4-dimethoxybenzyl, benzenesulfonyl, tosyl (Ts), *t*-butoxycarbonyl (BOC), methoxycarbonyl (MOC), benzyloxycarbonyl (CBz), 1-naphthalenesulfonate (1-napsyl), 4-nitrobenzenesulfonyl (*p*-nosyl), and 2,4,6-trimethylphenylsulfonyl; comprising the step of reacting a compound of Formula II:



Formula II;

wherein each of Y¹, Y², Y³, and PG is defined as in Formula I;

with hydrogen gas in the presence of a hydrogenation catalyst comprising rhodium and a chiral phosphine ligand (L) according to Formula III:



Formula III;

wherein each of R^{2a} , R^{2b} , R^{3a} , R^{3b} , and R^4 is independently selected from hydrogen, methyl, methoxy, and trifluoromethyl; and R^5 is secondary alkyl, tertiary alkyl, or cycloalkyl.

2. The process according to claim 1, wherein each of Y^1 , Y^2 , and Y^3 is hydrogen; or
3. ~~The process according to claim 1,~~ wherein Y^1 is hydrogen, and each of Y^2 and Y^3 is deuterium.
43. The process according to ~~any one of claims 1-3~~ claim 1 or 2, wherein PG is tosyl; or
5. ~~The process according to any one of claims 1-3,~~ wherein PG is hydrogen.
64. The process according to any one of claims 1-3 ~~1-5~~, wherein R^5 is selected from norbornyl, cyclohexyl, cyclopentyl, and *tert*-butyl.
75. The process according to any one of claims 1-4 ~~1-6~~, wherein each of R^{2a} , R^{2b} , R^{3a} , R^{3b} , and R^4 is hydrogen.

~~8~~6. The process according to any one of claims ~~1-4-1-6~~, wherein each of R^{2a} , R^{2b} , and R^4 is hydrogen, and R^{3a} and R^{3b} are each methyl or each trifluoromethyl.

~~9~~7. The process according to any one of claims ~~1-4-1-6~~, wherein each of R^{2a} and R^{2b} is hydrogen, R^4 is methoxy, and R^{3a} and R^{3b} are each methyl.

~~10~~8. The process according to any one of claims ~~1-4-1-6~~, wherein each of R^{2a} , R^{2b} , R^{3a} , and R^{3b} is hydrogen, and R^4 is methoxy, trifluoromethyl, or methyl.

~~11~~9. The process according to any one of claims ~~1-4-1-6~~, wherein each of R^{3a} , R^{3b} , and R^4 is hydrogen, each R^{2a} is hydrogen and each R^{2b} is methyl.

~~12~~10. The process according to any one of claims ~~1-5-1-7~~, wherein each of R^{2a} , R^{2b} , R^{3a} , R^{3b} , and R^4 is hydrogen, and R^5 is norbornyl.

~~13~~11. The process according to any one of claims ~~1-5-1-7~~, wherein each of R^{2a} , R^{2b} , R^{3a} , R^{3b} , and R^4 is hydrogen, and R^5 is cyclohexyl.

~~14~~12. The process according to any one of claims ~~1-11-1-13~~, wherein the hydrogenation catalyst is formed by mixing a rhodium pre-catalyst of the formula $[Rh(L_1)(L_2)]^+NC^-$ with the chiral phosphine ligand (L) of Formula III; wherein L_1 and L_2 are the same or different, L_1 and L_2 are each independently a pair of monodentate ligands or a bidentate ligand, wherein the monodentate ligand is selected from an alkene ligand and a solvent ligand, wherein the bidentate ligand is a diene; and wherein NC^- is a non-coordinating counterion selected from tetrafluoroborate, triflate, hexafluorophosphate, hexafluoroantimonate, and perchlorate.

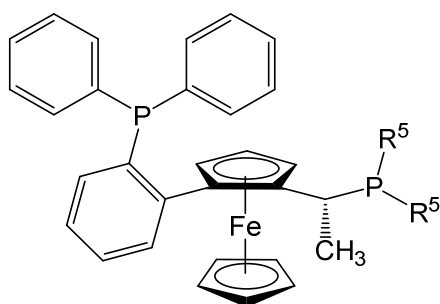
~~15~~13. The process according to claim ~~12-14~~, wherein the alkene ligand is selected from ethylene, cyclooctene, and norbornene.

~~16~~14. The process according to claim ~~12~~14, wherein the solvent ligand is selected from acetonitrile, tetrahydrofuran, 2-methyltetrahydrofuran, methanol, ethanol, trifluoroethanol, and isopropanol.

~~17~~15. The process according to claim ~~12~~14, wherein the diene ligand is selected from 1,5-cyclooctadiene (COD), 1,5-hexadiene, and norbornadiene.

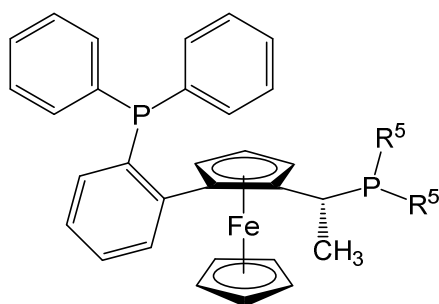
~~18~~16. The process according to claim ~~12~~14, wherein the rhodium pre-catalyst is $[\text{Rh}(\text{COD})_2]^+\text{BF}_4^-$.

~~19~~17. The process according to any one of claims ~~1-5 and 11-16~~1-5 and 11-16 ~~1-7 and 13-18~~, wherein the hydrogenation catalyst comprises $[\text{Rh}(\text{L}_1)(\text{L})]^+\text{BF}_4^-$, wherein (L_1) is a pair of monodentate ligands or a bidentate ligand, and (L) is:



CAS # 565184-29-4; wherein R⁵ is cyclohexyl.

~~20~~18. The process according to any one of claims ~~1-5, 10 and 12-16~~1-5, 10 and 12-16 ~~1-7, 12, and 14-18~~, wherein the hydrogenation catalyst comprises $[\text{Rh}(\text{L}_1)(\text{L})]^+\text{BF}_4^-$, wherein (L_1) is a pair of monodentate ligands or a bidentate ligand, and (L) is:



CAS # 849925-29-7; wherein R⁵ is norbornyl.

~~21~~19. The process according to any one of claims ~~1-18~~1-20, wherein the step of reacting is performed in a solvent.

~~22~~20. The process according to claim ~~19-21~~19-21, wherein the solvent is selected from dichloromethane, tetrahydrofuran, 2-methyltetrahydrofuran, methanol, ethanol, trifluoroethanol, isopropanol, ethyl acetate, isopropyl acetate, and mixtures thereof.

~~23~~21. The process according to any one of claims ~~1-20~~1-20, wherein the hydrogen gas is present at a pressure of 20 bar or less; or

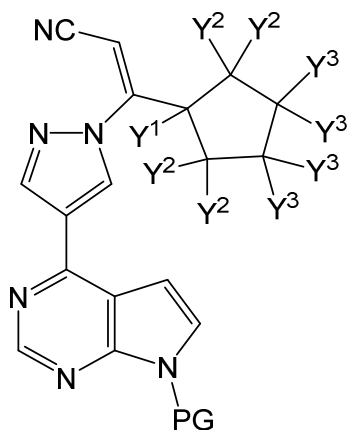
~~24.~~ The process according to any one of claims ~~1-22~~1-22, wherein the hydrogen gas is present at a pressure of 10 bar or less.

~~25~~22. The process according to any one of claims ~~1-21~~1-21, wherein the compound of Formula I has an enantiomeric excess of the (*R*)-enantiomer of at least 90%; or

~~26.~~ The process according to any one of claims ~~1-24~~1-24, wherein the compound of Formula I has an enantiomeric excess of the (*R*)-enantiomer of at least 95%; or

~~27.~~ The process according to any one of claims ~~1-24~~1-24, wherein the compound of Formula I has an enantiomeric excess of the (*R*)-enantiomer of at least 97%.

~~28~~23. A compound of Formula II:



Formula II;

wherein Y^1 is hydrogen or deuterium, each Y^2 is the same and is hydrogen or deuterium, each Y^3 is the same and is hydrogen or deuterium; and PG is hydrogen or a protecting group selected from ~~pivaloyloxymethyl (POM), 2-(trimethylsilyl)ethoxymethyl (SEM), benzyl (Bn),~~ *p*-methoxybenzyl (PMB), 3,4-dimethoxybenzyl (DMPM), 2,4-dimethoxybenzyl, benzenesulfonyl, tosyl (Ts), *t*-butoxycarbonyl (BOC), methoxycarbonyl (MOC), benzyloxycarbonyl (CBz), 1-naphthalenesulfonate (1-napsyl), 4-nitrobenzenesulfonyl (*p*-nosyl), and 2,4,6-trimethylphenylsulfonyl.

~~29~~24. The compound of claim ~~23-28~~, wherein Y^1 is hydrogen; and each of Y^2 and Y^3 is deuterium;
;

~~30. The compound of claim 28,~~ wherein each of Y^1 and Y^3 is hydrogen; and each Y^2 is deuterium;
;or

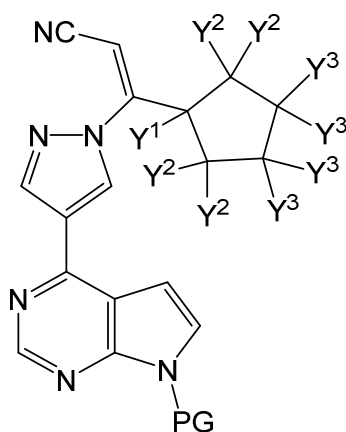
~~31. The compound of claim 28,~~ wherein each of Y^1 and Y^2 is hydrogen; and each Y^3 is deuterium.

~~32~~25. The compound of ~~any one of claims claim 23 or 24-28-31,~~ wherein PG is tosyl (Ts);
;or

~~33.~~ The compound of any one of claims ~~28-31~~, wherein PG is hydrogen.

~~34~~26. A reaction mixture comprising:

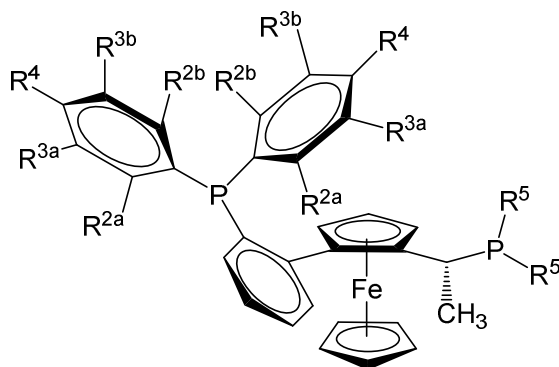
a. a compound of Formula II:



Formula II;

wherein Y¹ is hydrogen or deuterium, each Y² is the same and is hydrogen or deuterium, each Y³ is the same and is hydrogen or deuterium; and PG is hydrogen or a protecting group selected from pivaloyloxymethyl (POM), 2-(trimethylsilyl)ethoxymethyl (SEM), benzyl (Bn), *p*-methoxybenzyl (PMB), 3,4-dimethoxybenzyl (DMPM), 2,4-dimethoxybenzyl, benzenesulfonyl, tosyl (Ts), *t*-butoxycarbonyl (BOC), methoxycarbonyl (MOC), benzyloxycarbonyl (CBz), 1-naphthalenesulfonate (1-napsyl), 4-nitrobenzenesulfonyl (*p*-nosyl), and 2,4,6-trimethylphenylsulfonyl;

b. a hydrogenation catalyst comprising rhodium and a chiral phosphine ligand (L) according to Formula III:



Formula III;

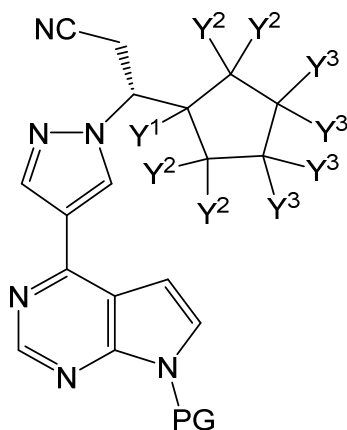
wherein each of R^{2a} , R^{2b} , R^{3a} , R^{3b} , and R^4 is independently selected from hydrogen, methyl, methoxy, and trifluoromethyl; and R^5 is secondary alkyl, tertiary alkyl, or cycloalkyl; and

- c. a solvent selected from dichloromethane, tetrahydrofuran, 2-methyltetrahydrofuran, methanol, ethanol, trifluoroethanol, isopropanol, ethyl acetate, isopropyl acetate, and mixtures thereof.

3527. The reaction mixture of claim 26-34, wherein each of R^{2a} , R^{2b} , R^{3a} , R^{3b} , and R^4 is hydrogen, and R^5 is selected from norbornyl, cyclohexyl, cyclopentyl, and *tert*-butyl.

3628. A process for increasing the enantiomeric excess of a compound of Formula I comprising the steps of:

providing a compound of Formula I:



Formula I;

wherein Y¹ is hydrogen or deuterium, each Y² is the same and is hydrogen or deuterium, each Y³ is the same and is hydrogen or deuterium, PG is tosyl (Ts), and having a starting enantiomeric excess of the (*R*)-enantiomer of at least 70%;

dissolving the compound in aqueous ethanol, and

crystallizing the compound to provide a final enantiomeric excess of the (*R*)-enantiomer of at least 98%.

~~37~~29. The process of claim ~~36~~28, wherein Y¹ is hydrogen, and each of Y² and Y³ is deuterium;
or

~~38.~~ ~~The process of claim 36,~~ wherein each of Y¹, Y², and Y³ is hydrogen.

~~39~~30. The process of ~~any one of claims~~ claim 28 or 29~~36-38~~, wherein the aqueous ethanol is 95% ethanol.

~~40~~31. The process of any one of claims ~~28-30~~36-39, wherein the step of crystallizing comprises forming a hemihydrate of the compound of Formula I.

~~41~~32. The process of any one of claims ~~28-31~~36-40, wherein the starting enantiomeric excess is at least 86% and the final enantiomeric excess is at least 98.8%~~;~~ or

~~42.~~ ~~The process of any one of claims 36-40,~~ wherein the starting enantiomeric excess is at least 94% and the final enantiomeric excess is at least 99%.

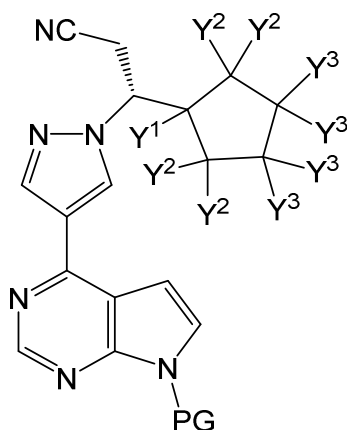
~~43~~33. The process of any one of claims ~~28-32~~36-42, further comprising the step of removing the tosyl group.

4434. The process of claim ~~33-43~~, wherein the tosyl group is removed by treating with potassium hydroxide.

4535. The process of ~~any one of claims~~claim 33 or 34 ~~43-44~~, further comprising the step of forming a pharmaceutically acceptable salt of the compound of Formula I.

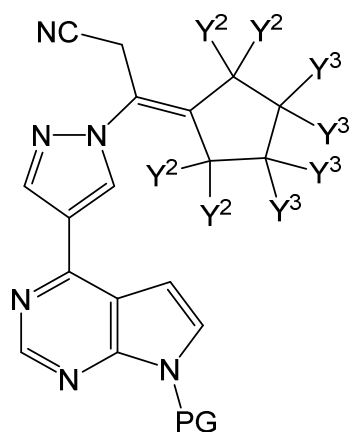
4636. The process of claim ~~35-45~~, wherein a phosphoric acid salt of the compound of Formula I is formed by treating with phosphoric acid.

4737. A process for preparing a compound of Formula I:



Formula I;

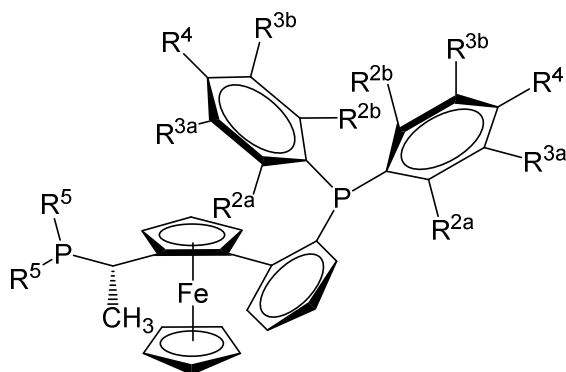
wherein Y¹ is hydrogen or deuterium, each Y² is the same and is hydrogen or deuterium, each Y³ is the same and is hydrogen or deuterium; and PG is hydrogen or a protecting group selected from pivaloyloxymethyl (POM), 2-(trimethylsilyl)ethoxymethyl (SEM), benzyl (Bn), *p*-methoxybenzyl (PMB), 3,4-dimethoxybenzyl (DMPM), 2,4-dimethoxybenzyl, benzenesulfonyl, tosyl (Ts), *t*-butoxycarbonyl (BOC), methoxycarbonyl (MOC), benzyloxycarbonyl (CBz), 1-naphthalenesulfonate (1-napsyl), 4-nitrobenzenesulfonyl (*p*-nosyl), and 2,4,6-trimethylphenylsulfonyl; comprising the step of reacting a compound of Formula VII:



Formula VII;

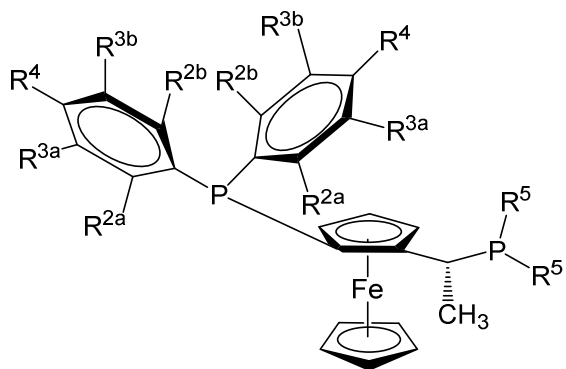
wherein each of Y^2 , Y^3 , and PG is defined as in Formula I;

with hydrogen gas in the presence of a hydrogenation catalyst comprising rhodium and a chiral phosphine ligand according to Formula VI or Formula VIII:



Formula VI;

wherein each of R^{2a} , R^{2b} , R^{3a} , R^{3b} , and R^4 is independently selected from hydrogen, methyl, methoxy, and trifluoromethyl; and R^5 is phenyl; or



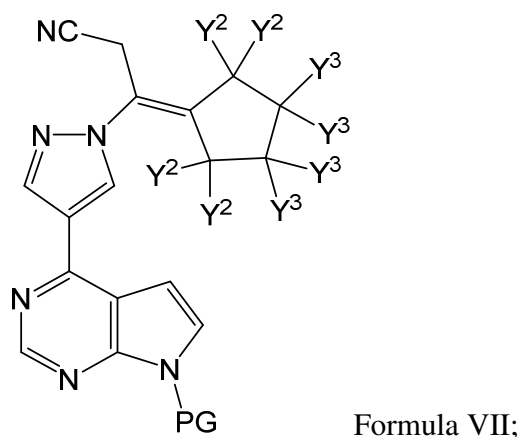
Formula VIII;

wherein each of R^{2a} , R^{2b} , R^{3a} , R^{3b} , and R^4 is independently selected from hydrogen, methyl, methoxy, and trifluoromethyl; and R^5 is *tert*-butyl.

~~48~~38. The process of claim ~~47~~37, wherein PG is tosyl (Ts); or

~~49.~~ The process of claim ~~47~~, wherein PG is hydrogen.

~~50~~39. A compound of Formula VII:



wherein each Y^2 is the same and is hydrogen or deuterium, each Y^3 is the same and is hydrogen or deuterium; and PG is ~~hydrogen or~~ a protecting group selected from pivaloyloxymethyl (POM), ~~2-(trimethylsilyl)ethoxymethyl (SEM),~~ benzyl (Bn), *p*-methoxybenzyl (PMB), 3,4-dimethoxybenzyl (DMPM), 2,4-dimethoxybenzyl, benzenesulfonyl, tosyl (Ts), *t*-butoxycarbonyl (BOC), methoxycarbonyl (MOC), benzyloxycarbonyl (CBz), 1-naphthalenesulfonate (1-napsyl), 4-nitrobenzenesulfonyl (*p*-nosyl), and 2,4,6-trimethylphenylsulfonyl.

~~51~~40. The compound of claim ~~39~~50, wherein each Y^2 is deuterium; and each Y^3 is hydrogen; or

~~52.~~ The compound of claim ~~50~~, wherein each Y^2 is hydrogen; and each Y^3 is deuterium; or

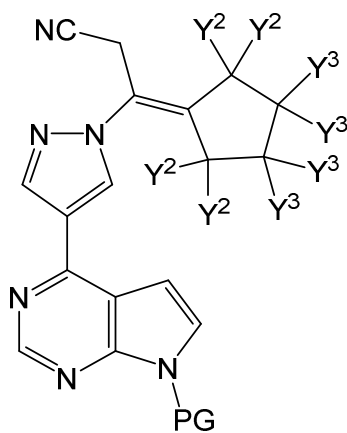
~~53.~~ The compound of claim ~~50~~, wherein each Y^2 and each Y^3 is deuterium.

~~5441.~~ The compound of ~~any one of claims 39 or 40–50–53,~~ wherein PG is tosyl (Ts).

~~55.~~ ~~The compound of any one of claims 50–53, wherein PG is hydrogen.~~

~~5642.~~ A reaction mixture comprising:

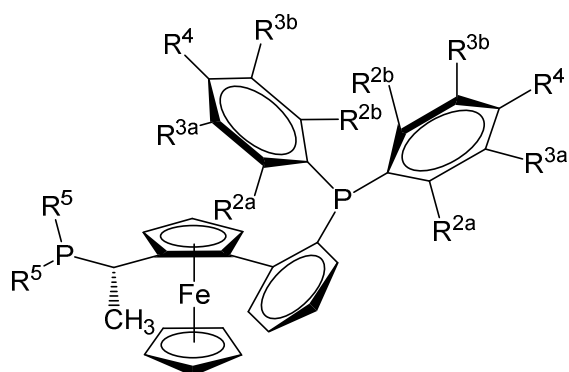
a. a compound of Formula VII:



Formula VII;

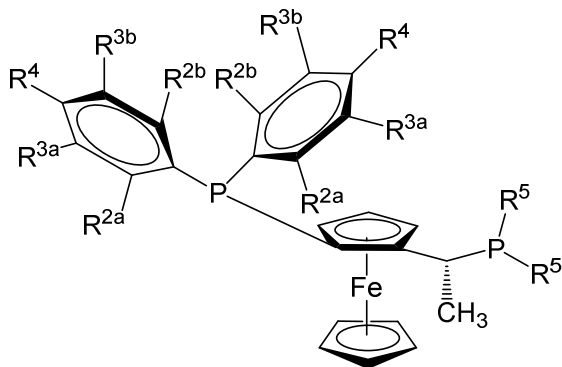
wherein each Y² is the same and is hydrogen or deuterium, each Y³ is the same and is hydrogen or deuterium; and PG is hydrogen or a protecting group selected from pivaloyloxymethyl (POM), 2-(trimethylsilyl)ethoxymethyl (SEM), benzyl (Bn), *p*-methoxybenzyl (PMB), 3,4-dimethoxybenzyl (DMPM), 2,4-dimethoxybenzyl, benzenesulfonyl, tosyl (Ts), *t*-butoxycarbonyl (BOC), methoxycarbonyl (MOC), benzyloxycarbonyl (CBz), 1-naphthalenesulfonate (1-napsyl), 4-nitrobenzenesulfonyl (*p*-nosyl), and 2,4,6-trimethylphenylsulfonyl;

b. a hydrogenation catalyst comprising rhodium and a chiral phosphine ligand according to Formula VI or Formula VIII:



Formula VI;

wherein each of R^{2a} , R^{2b} , R^{3a} , R^{3b} , and R^4 is independently selected from hydrogen, methyl, methoxy, and trifluoromethyl; and R^5 is phenyl; or



Formula VIII;

wherein each of R^{2a} , R^{2b} , R^{3a} , R^{3b} , and R^4 is independently selected from hydrogen, methyl, methoxy, and trifluoromethyl; and R^5 is *tert*-butyl; and

- c. a solvent selected from dichloromethane, tetrahydrofuran, 2-methyltetrahydrofuran, methanol, ethanol, trifluoroethanol, isopropanol, ethyl acetate, isopropyl acetate, and mixtures thereof.