

TITLE OF THE INVENTION

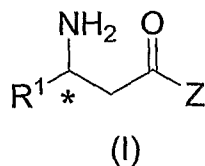
PROCESS TO CHIRAL BETA AMINO ACID DERIVATIVES BY ASYMMETRIC
HYDROGENATION

5 FIELD OF THE INVENTION

The present invention relates to a process for the efficient preparation of enantiomerically enriched beta amino acid derivatives which are useful in the asymmetric synthesis of biologically active molecules. The process comprises an enantioselective hydrogenation of a prochiral beta-amino acrylic acid derivative substrate in the presence of an ammonium salt and a transition metal precursor complexed
10 with a chiral ferrocenyl diphosphine ligand.

BACKGROUND OF THE INVENTION

The present invention provides an efficient process for the preparation of an enantiomerically enriched beta amino acid derivative of structural formula I:



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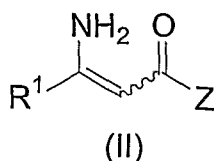
having the (*R*)- or (*S*)-configuration at the stereogenic center marked with an *; wherein

Z is OR², SR², or NR²R³;

R¹ is C₁₋₈ alkyl, aryl, heteroaryl, aryl-C₁₋₂ alkyl, or heteroaryl-C₁₋₂ alkyl;

R² and R³ are each independently hydrogen, C₁₋₈ alkyl, aryl, or aryl-C₁₋₂ alkyl; or R² and R³ together
20 with the nitrogen atom to which they are attached form a 4- to 7-membered heterocyclic ring system optionally containing an additional heteroatom selected from O, S, and NC₁₋₄ alkyl, said heterocyclic ring system being optionally fused with a 5- to 6-membered saturated or aromatic carbocyclic ring system or a 5- to 6-membered saturated or aromatic heterocyclic ring system containing one to two heteroatoms selected from O, S, and NC₁₋₄ alkyl, said fused ring system being unsubstituted or substituted with one
25 to two substituents independently selected from hydroxy, amino, fluoro, C₁₋₄ alkyl, C₁₋₄ alkoxy, and trifluoromethyl.

The process of the present invention relates to a method for the preparation of chiral beta amino acid derivatives of structural formula I in an efficient enantioselective fashion *via* transition metal-catalyzed asymmetric hydrogenation of a prochiral enamine of structural formula II:



wherein the amino group is unprotected, in the presence of an ammonium salt and a transition metal precursor complexed to a chiral ferrocenyl diphosphine ligand.

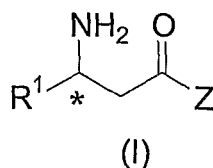
Methods for asymmetrically reducing enamine carbon-carbon double bonds (C=C-N) using chiral ferrocenyl diphosphines as ligands complexed to a rhodium or iridium precursor have been described in the patent literature (See U.S. Patent No. 5,563,309 issued Oct. 8, 1996 to Ciba-Geigy Corp. and the related family of patents and patent applications). A related approach to *N*-acylated beta amino acids using a rhodium Me-DuPHOS catalytic complex has also been published (U.S. 2002/0128509 published on Sept. 12, 2002 assigned to Degussa AG). The following publications also describe the asymmetric hydrogenation of *N*-acylated beta-amino acrylic acids with rhodium metal precursors complexed to a chiral phosphine ligand: (1) T. Hayashi, et al., Bull. Chem. Soc. Japan, 53: 1136-1151 (1980); (2) G. Zhu et al., J. Org. Chem., 64: 6907-6910 (1999); and (3) W. D. Lubell, et al., Tetrahedron: Asymmetry, 2: 543-554 (1991). In these publications all the examples provided have the amino group in the beta amino acrylic acid derivative substrate protected as an acetamide derivative. The requirement for amine protection introduces two additional chemical steps into the sequence, namely protection and deprotection, and the synthesis of the protected substrate may also be difficult. The process of the present invention circumvents the need for protecting the primary amino group in the substrate for the asymmetric hydrogenation reaction and proceeds with excellent reactivity and enantioselectivity.

20 SUMMARY OF THE INVENTION

The present invention is concerned with a process for the preparation of enantiomerically enriched beta amino acid derivatives of structural formula I. The process utilizes an asymmetric hydrogenation of a prochiral beta amino acrylic acid derivative, wherein the primary amino group is unprotected, in the presence of an ammonium salt and a transition metal precursor complexed with a chiral ferrocenyl diphosphine ligand. The process of the present invention is applicable to the preparation of beta amino acid derivatives on a pilot plant or industrial scale. The beta amino acids are useful to prepare a wide variety of biologically active molecules.

DETAILED DESCRIPTION OF THE INVENTION

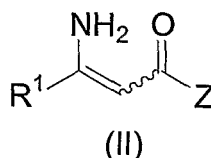
The present invention provides an efficient process for the preparation of an enantiomerically enriched beta amino acid derivative of structural formula I:



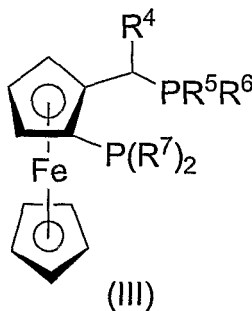
having the (*R*)- or (*S*)-configuration at the stereogenic center marked with an *;
 in an enantiomeric excess of at least 70% over the opposite enantiomer, wherein
 Z is OR², SR², or NR²R³;

- 5 R¹ is C₁₋₈ alkyl, aryl, heteroaryl, aryl-C₁₋₂ alkyl, or heteroaryl-C₁₋₂ alkyl;
 R² and R³ are each independently hydrogen, C₁₋₈ alkyl, aryl, or aryl-C₁₋₂ alkyl; or R² and R³ together
 with the nitrogen atom to which they are attached form a 4- to 7-membered heterocyclic ring system
 optionally containing an additional heteroatom selected from O, S, NH, and NC₁₋₄ alkyl, said
 heterocyclic ring being unsubstituted or substituted with one to three substituents independently selected
 10 from oxo, hydroxy, halogen, C₁₋₄ alkoxy, and C₁₋₄ alkyl wherein alkyl and alkoxy are unsubstituted or
 substituted with one to five fluorines; and said heterocyclic ring system being optionally fused with a 5-
 to 6-membered saturated or aromatic carbocyclic ring system or a 5- to 6-membered saturated or aromatic
 heterocyclic ring system containing one to two heteroatoms selected from O, S, and NC₀₋₄ alkyl, said
 fused ring system being unsubstituted or substituted with one to two substituents selected from hydroxy,
 15 amino, fluorine, C₁₋₄ alkyl, C₁₋₄ alkoxy, and trifluoromethyl.

The process of the present invention comprises the step of hydrogenating a prochiral
 enamine of structural formula II:



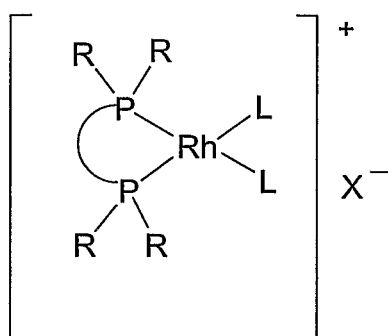
- in a suitable organic solvent in the presence of an ammonium salt and a transition metal precursor
 20 complexed to a chiral ferrocenyl diphosphine ligand of structural formula III:



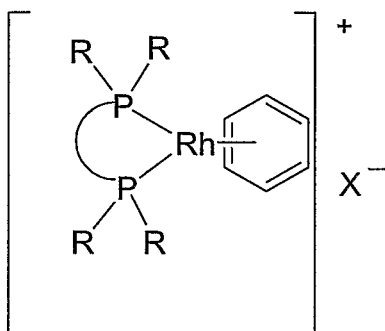
wherein R⁴ is C₁₋₄ alkyl or aryl;

R⁵ and R⁶ are each independently C₁₋₆ alkyl, C₅₋₁₂ cycloalkyl, or aryl; and
 R⁷ is C₁₋₄ alkyl or unsubstituted phenyl.

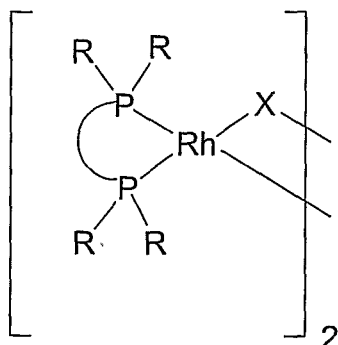
The process of the present invention contemplates that the catalytic complex of the transition metal precursor and the chiral ferrocenyl diphosphine ligand may be either (a) generated *in situ*
 5 by the sequential or contemporaneous addition of the transition metal species and the chiral ferrocenyl diphosphine ligand to the reaction mixture or (b) pre-formed with or without isolation and then added to the reaction mixture. A pre-formed catalytic complex is represented by the formula:



10 where X represents a non-coordinating anion, such as trifluoromethanesulfonate, tetrafluoroborate, and hexafluorophosphate, and L is a neutral ligand such as an olefin (or chelating di-olefin such as 1,5-cyclooctadiene or norbornadiene) or a solvent molecule (such as MeOH and TFE). In the case where olefin is arene, the complex is represented by the formula:

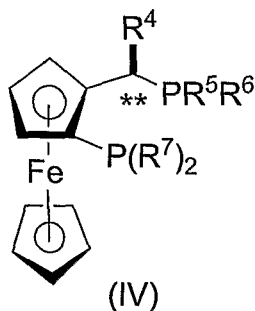


15 The pre-formed catalytic complex in the case where X represents halogen is represented by the formula:

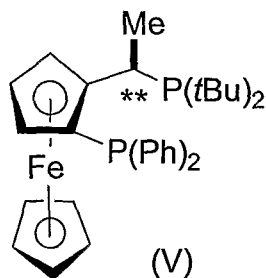


The ligands of structural formula III are known in the art as Josiphos ligands and are commercially available from Solvias AG, Basel, Switzerland.

In one embodiment of the ligands of formula III useful in the process of the present invention, the carbon stereogenic center marked with an ** has the (*R*)-configuration as depicted in formula IV:

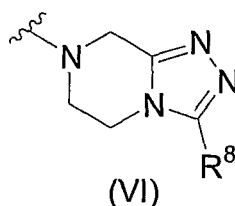


In another embodiment of the ligands of formula III useful in the process of the present invention, R⁴ is C₁₋₂ alkyl, R⁵ and R⁶ are C₁₋₄ alkyl, and R⁷ is unsubstituted phenyl. In a class of this embodiment, R⁴ is methyl, R⁵ and R⁶ are *t*-butyl, and R⁷ is unsubstituted phenyl. The latter ligand is known in the art as *t*-butyl Josiphos. Commercially available forms of the *t*-butyl Josiphos ligand are the *S,R* and *R,S* enantiomeric forms. *R,S-t*-butyl Josiphos is {(*R*)-1-[(*S*)-(diphenylphosphino)ferrocenyl]}ethyl-di-*tert*-butylphosphine of formula V below:



The ferrocenyl diphosphine ligands of formula III have two centers of asymmetry, and the process of the present invention is intended to encompass the use of single enantiomers, individual diastereomers, and mixtures of diastereomers thereof. The present invention is meant to comprehend the use of all such isomeric forms of the ligands of structural formula III for the asymmetric hydrogenation of a compound of formula II. The facial enantioselectivity of the hydrogenation reaction will depend on the particular stereoisomer of the ligand that is employed in the reaction. It is possible to control the configuration at the newly formed stereogenic center in a compound of formula I marked with an * by the judicious choice of the chirality of the ferrocenyl diphosphine ligand of formula III.

In one embodiment of the substrate for the process of the present invention, R^1 is benzyl wherein the phenyl group of benzyl is unsubstituted or substituted one to three substituents selected from the group consisting of fluorine, trifluoromethyl, and trifluoromethoxy. In another embodiment of the process of the present invention, Z is OR^2 or NR^2R^3 . In a class of this embodiment, NR^2R^3 is a heterocycle of the structural formula VI:



wherein R^8 is hydrogen or C_{1-4} alkyl which is unsubstituted or substituted with one to five fluorines. In another class of this embodiment, Z is OR^2 .

In another embodiment of the substrate for the process of the present invention, R^1 is 6-methoxy-pyridin-3-yl and Z is C_{1-4} alkoxy. In a class of this embodiment, Z is methoxy or ethoxy.

The asymmetric hydrogenation reaction of the present invention is carried out in a suitable organic solvent. Suitable organic solvents include lower alkanols, such as methanol, ethanol, isopropyl alcohol, hexafluoroisopropyl alcohol, phenol, 2,2,2-trifluoroethanol (TFE), and mixtures thereof; tetrahydrofuran; methyl *t*-butyl ether; and mixtures thereof.

The asymmetric hydrogenation reaction is also carried out in the presence of about 0.01 to about 10 mol % (relative to the prochiral enamine substrate of formula II) of an ammonium salt. In one embodiment the ammonium salt is an ammonium halide salt selected from the group consisting of ammonium chloride, ammonium bromide, and ammonium iodide. In a class of this embodiment the ammonium halide salt is ammonium chloride. In another embodiment the ammonium salt is an ammonium carboxylate salt such as ammonium acetate and ammonium formate. In another embodiment the ratio of the ammonium salt to prochiral enamine substrate is about 0.05 to about 5 mol %.

The reaction temperature for the reaction may be in the range of about 10 °C to about 90 °C. A preferred temperature range for the reaction is about 45 °C to about 65 °C.

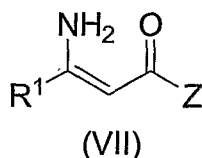
The hydrogenation reaction can be performed at a hydrogen pressure range of about 20 psig to about 1500 psig. A preferred hydrogen pressure range is about 80 psig to about 200 psig.

The transition metal precursor is $[M(\text{monoolefin})_2\text{Cl}]_2$, $[M(\text{diolefin})\text{Cl}]_2$, $[M(\text{monoolefin})_2\text{acetylacetonate}]$, $[M(\text{diolefin})\text{acetylacetonate}]$, $[M(\text{monoolefin})_4]\text{X}$, or $[M(\text{diolefin})_2]\text{X}$ wherein X is a non-coordinating anion selected from the group consisting of methanesulfonate, trifluoromethanesulfonate (Tf), tetrafluoroborate (BF_4), hexafluorophosphate (PF_6), and hexafluoroantimonate (SbF_6), and M is rhodium (Rh) or iridium (Ir). Transition metal precursors where M is ruthenium (Ru) are $[M(\text{arene})\text{Cl}]_2$, $[M(\text{diolefin})\text{Cl}]_n$, or $[M(\text{diolefin})(\eta^3\text{-2-methyl-1-propenyl})_2]$. In one embodiment the transition metal precursor is $[\text{Rh}(\text{cod})\text{Cl}]_2$, $[\text{Rh}(\text{norbornadiene})\text{Cl}]_2$, $[\text{Rh}(\text{cod})_2]\text{X}$, or $[\text{Rh}(\text{norbornadiene})_2]\text{X}$. In a class of this embodiment, the transition metal precursor is $[\text{Rh}(\text{cod})\text{Cl}]_2$.

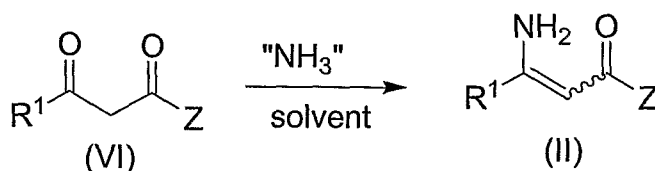
The ratio of transition metal precursor to substrate is about 0.01 to about 10 mol %. A preferred ratio of the transition metal precursor to substrate is about 0.05 mol % to about 0.4 mol %.

The beta amino acrylic acid derivative substrates of formula II for the asymmetric hydrogenation contain an olefinic double bond, and unless specified otherwise, are meant to include both *E* and *Z* geometric isomers or mixtures thereof as starting materials. The squiggly bond in the substrate of structural formula II signifies either the *Z* or *E* geometric isomer or a mixture thereof.

In one embodiment of the present invention, the geometric configuration of the double bond in the beta amino acrylic acid derivative substrate for the asymmetric hydrogenation reaction is the *Z*-configuration as depicted in formula VII:



The beta amino acrylate esters of formula II ($Z = \text{OR}^2$ or SR^2) for the asymmetric hydrogenation reaction of the present invention can be prepared from a beta-keto ester of structural formula VI in high yield by reaction with a source of ammonia in a suitable organic solvent such as methanol, ethanol, isopropyl alcohol, tetrahydrofuran, and aqueous mixtures thereof.



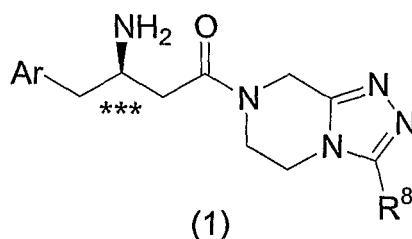
Sources of ammonia " NH_3 " include ammonium acetate, ammonium hydroxide, ammonium formate, ammonium lactate, ammonium citrate dibasic, ammonium carbonate, ammonium carbamate, and

ammonium benzoate. In one embodiment the source of ammonia is ammonium acetate. The beta-keto esters can be prepared as described by D.W. Brooks et al., Angew. Chem. Int. Ed. Engl., 18: 72 (1979).

The beta amino acrylamides can be prepared from the corresponding esters via amide exchange as described in Org. Syn. Collect., Vol. 3, p. 108.

5 The process of the present invention can be carried out without the need for isolating the intermediate of structural formula II.

Another embodiment of the present invention concerns a process for the preparation of a compound of structural formula 1:



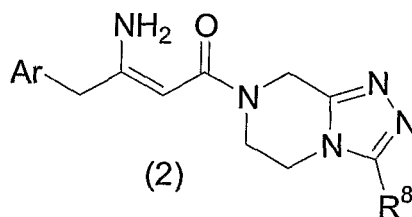
10 having the (*R*)-configuration at the stereogenic center marked with an ***;
in an enantiomeric excess of at least 70% over the enantiomer having the opposite (*S*)-configuration,
wherein

Ar is phenyl which is unsubstituted or substituted with one to five substituents independently selected from the group consisting of fluorine, trifluoromethyl, and trifluoromethoxy; and

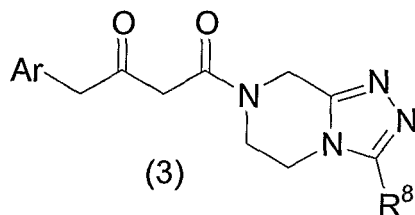
15 R⁸ is hydrogen or C₁₋₄ alkyl unsubstituted or substituted with one to five fluorines;

comprising the steps of:

(a) producing a compound of structural formula 2:

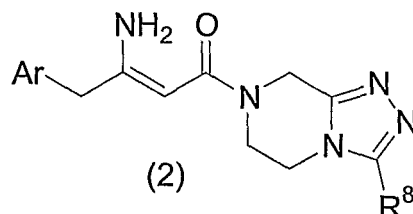


by treating a compound of structural formula 3:

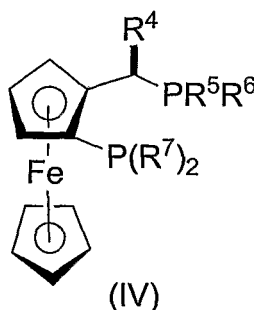


with a source of ammonia in a suitable organic solvent; and

(b) hydrogenating a compound of structural formula 2:



in a suitable organic solvent in the presence of an ammonium salt and a rhodium metal precursor
 5 complexed to a chiral ferrocenyl diphosphine of structural formula IV:



wherein R^4 is C_{1-4} alkyl or aryl;

R^5 and R^6 are each independently C_{1-6} alkyl, C_{5-12} cycloalkyl, or aryl; and

R^7 is C_{1-4} alkyl or unsubstituted phenyl.

10 In a class of this embodiment, Ar is 2,5-difluorophenyl or 2,4,5-trifluorophenyl. In a subclass of this class, R^8 is trifluoromethyl.

In another class of this embodiment, the rhodium metal precursor is chloro(1,5-cyclooctadiene)rhodium(I) dimer $\{[Rh(cod)Cl]_2\}$.

15 In another class of this embodiment, R^4 is methyl, R^5 and R^6 are both *t*-butyl, and R^7 is unsubstituted phenyl. In a subclass of this class, the rhodium metal precursor is chloro(1,5-cyclooctadiene)rhodium(I) dimer.

20 In yet another class of this embodiment, R^4 is methyl, R^5 and R^6 are both *t*-butyl, R^7 is unsubstituted phenyl, Ar is 2,5-difluorophenyl or 2,4,5-trifluorophenyl, R^8 is trifluoromethyl, and the rhodium metal precursor is chloro(1,5-cyclooctadiene)rhodium(I) dimer. In a subclass of this class, the ammonium salt is ammonium chloride.

The process steps can be carried out without the need for isolating the intermediate of structural formula (2). In one embodiment, both chemical transformations are carried out in the same reaction vessel in the presence of an ammonium salt. In a class of this embodiment the ammonium salt is selected from the group consisting of ammonium acetate, ammonium hydroxide, ammonium formate,

ammonium lactate, ammonium citrate dibasic, ammonium carbonate, ammonium carbamate, and ammonium benzoate. In a subclass of this class the ammonium salt is ammonium formate.

In another embodiment the compound of structural formula 1 is obtained with an enantiomeric excess of greater than 90%. In a class of this embodiment the compound of structural formula 1 is obtained with an enantiomeric excess of greater than 95%.

Compounds of structural formula 1 are disclosed in WO 03/004498 (published 16 January 2003) as inhibitors of dipeptidyl peptidase-IV which are useful for the treatment of Type 2 diabetes.

Throughout the instant application, the following terms have the indicated meanings:

The term "% enantiomeric excess" (abbreviated "ee") shall mean the % major enantiomer less the % minor enantiomer. Thus, a 70% enantiomeric excess corresponds to formation of 85% of one enantiomer and 15% of the other. The term "enantiomeric excess" is synonymous with the term "optical purity."

The process of the present invention provides compounds of structural formula I with high optical purity, typically in excess of 70% ee. In one embodiment, compounds of formula I are obtained with an optical purity in excess of 80% ee. In a class of this embodiment, compounds of formula I are obtained with an optical purity in excess of 90% ee. In a subclass of this class, compounds of formula I are obtained with an optical purity in excess of 95% ee.

The term "enantioselective" shall mean a reaction in which one enantiomer is produced (or destroyed) more rapidly than the other, resulting in the predominance of the favored enantiomer in the mixture of products.

The alkyl groups specified above are intended to include those alkyl groups of the designated length in either a straight or branched configuration. Exemplary of such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tertiary butyl, pentyl, isopentyl, hexyl, isohexyl, and the like. The alkyl groups are unsubstituted or substituted with one to three groups independently selected from the group consisting of halogen, hydroxy, carboxy, aminocarbonyl, amino, C₁₋₄ alkoxy, and C₁₋₄ alkylthio.

The term "cycloalkyl" is intended to mean cyclic rings of alkanes of five to twelve total carbon atoms, or any number within this range (i.e., cyclopentyl, cyclohexyl, cycloheptyl, etc).

The term "halogen" is intended to include the halogen atoms fluorine, chlorine, bromine, and iodine.

The abbreviation "cod" means "1,5-cyclooctadiene."

The term "aryl" includes phenyl and naphthyl. "Aryl" is unsubstituted or substituted with one to five substituents independently selected from fluoro, hydroxy, trifluoromethyl, amino, C₁₋₄ alkyl, and C₁₋₄ alkoxy.

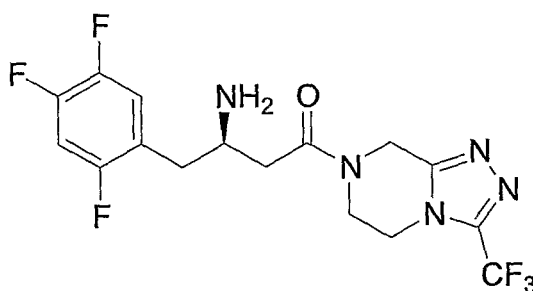
The term "arene" refers to benzene, naphthalene, and *o*-, *m*-, or *p*-isopropyltoluene (*o*, *m*, or *p*-cymene).

The term "olefin" refers to a acyclic or cyclic hydrocarbon containing one or more double bonds including aromatic cyclic hydrocarbons. The term includes, but is not limited to, 1,5-cyclooctadiene and norbornadiene ("nbd").

The term "heteroaryl" means a 5- or 6-membered aromatic heterocycle that contains at least one ring heteroatom selected from O, S and N. Heteroaryls also include heteroaryls fused to other kinds of rings, such as aryls, cycloalkyls and heterocycles that are not aromatic. Examples of heteroaryl groups include, but are not limited to, pyrrolyl, isoxazolyl, isothiazolyl, pyrazolyl, pyridinyl, oxazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, thiadiazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, furyl, triazinyl, thienyl, pyrimidinyl, pyrazinyl, benzisoxazolyl, benzoxazolyl, benzothiazolyl, benzothiadiazolyl, dihydrobenzofuranyl, indolyl, pyridazinyl, indazolyl, isoindolyl, dihydrobenzothienyl, indolizyl, cinnolyl, phthalazinyl, quinazolinyl, naphthyridinyl, carbazolyl, benzodioxolyl, quinoxalinyl, purinyl, furazanyl, isobenzylfuranyl, benzimidazolyl, benzofuranyl, benzothienyl, quinolyl, indolyl, isoquinolyl, and dibenzofuranyl. "Heteroaryl" is unsubstituted or substituted with one to five substituents independently selected from fluoro, hydroxy, trifluoromethyl, amino, C₁₋₄ alkyl, and C₁₋₄ alkoxy.

Representative experimental procedures utilizing the novel process are detailed below. The following Examples are for the purposes of illustration only and are not intended to limit the process of the present invention to the specific conditions for making these particular compounds.

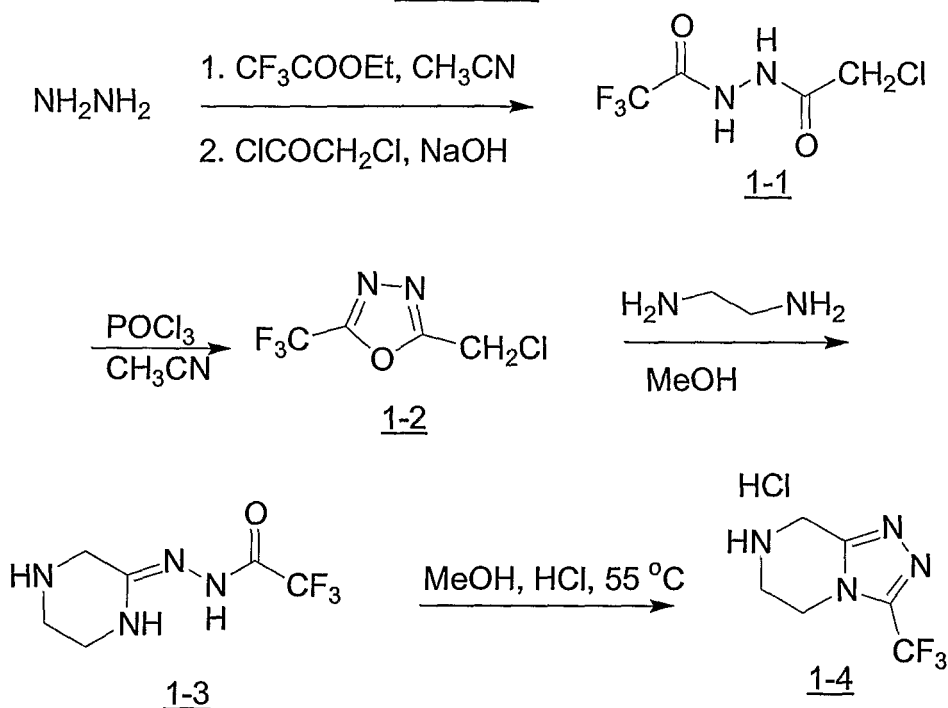
EXAMPLE 1



(2R)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine (2-5)

Preparation of 3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyrazine, hydrochloride salt (1-4)

Scheme 1

Step A: Preparation of bishydrazide (1-1)

Hydrazine (20.1 g, 35 wt% in water, 0.22 mol) was mixed with 310 mL of acetonitrile.

- 5 31.5 g of ethyl trifluoroacetate (0.22 mol) was added over 60 min. The internal temperature was increased to 25 °C from 14 °C. The resulting solution was aged at 22 - 25 °C for 60 min. The solution was cooled to 7 °C. 17.9 g of 50 wt% aqueous NaOH (0.22 mol) and 25.3 g of chloroacetyl chloride (0.22 mol) were added simultaneously over 130 min at a temperature below 16 °C. When the reaction was complete, the mixture was vacuum distilled to remove water and ethanol at 27 ~ 30 °C and under 26
- 10 ~ 27 in Hg vacuum. During the distillation, 720 mL of acetonitrile was added slowly to maintain constant volume (approximately 500 mL). The slurry was filtered to remove sodium chloride. The cake was rinsed with about 100 mL of acetonitrile. Removal of the solvent afforded bis-hydrazide 1-1.
¹H-NMR (400 MHz, DMSO-*d*₆): δ 4.2 (s, 2H), 10.7 (s, 1H), and 11.6 (s, 1H) ppm.
¹³C-NMR (100 MHz, DMSO-*d*₆): δ 41.0, 116.1 (q, J = 362 Hz), 155.8 (q, J = 50 Hz), and 165.4 ppm.

15

Step B: Preparation of 5-(trifluoromethyl)-2-(chloromethyl)-1,3,4-oxadiazole (1-2)

- Bishydrazide 1-1 from Step A (43.2 g, 0.21 mol) in ACN (82 mL) was cooled to 5 °C. Phosphorus oxychloride (32.2 g, 0.21 mol) was added, maintaining the temperature below 10 °C. The mixture was heated to 80 °C and aged at this temperature for 24 h until HPLC showed less than 2 area% of 1-1. In a separate vessel, 260 mL of IPAc and 250 mL of water were mixed and cooled to 0 °C. The
- 20

reaction slurry was charged to the quench keeping the internal temperature below 10 °C. After the addition, the mixture was agitated vigorously for 30 min, the temperature was increased to room temperature and the aqueous layer was cut. The organic layer was then washed with 215 mL of water, 215 mL of 5 wt% aqueous sodium bicarbonate and finally 215 mL of 20 wt% aqueous brine solution.

- 5 Volatiles were removed by distillation at 75-80 mm Hg, 55 °C to afford an oil which could be used directly in Step C without further purification. Otherwise the product can be purified by distillation to afford 1-2.

¹H-NMR (400 MHz, CDCl₃): δ 4.8 (s, 2H) ppm.

¹³C-NMR (100 MHz, CDCl₃): δ 32.1, 115.8 (q, J = 337 Hz), 156.2 (q, J = 50 Hz), and 164.4 ppm.

10

Step C: Preparation of N-[(2Z)-piperazin-2-ylidene]trifluoroacetohydrazide (1-3)

To a solution of ethylenediamine (33.1 g, 0.55 mol) in methanol (150 mL) cooled at -20 °C was added distilled oxadiazole 1-2 from Step B (29.8 g, 0.16 mol) while keeping the internal temperature at -20 °C. After the addition was complete, the resulting slurry was aged at -20 °C for 1 h.

- 15 Ethanol (225 mL) was then charged and the slurry slowly warmed to -5 °C. After 60 min at -5 °C, the slurry was filtered and washed with ethanol (60 mL) at -5 °C. Amidine 1-3 was obtained as a white solid.

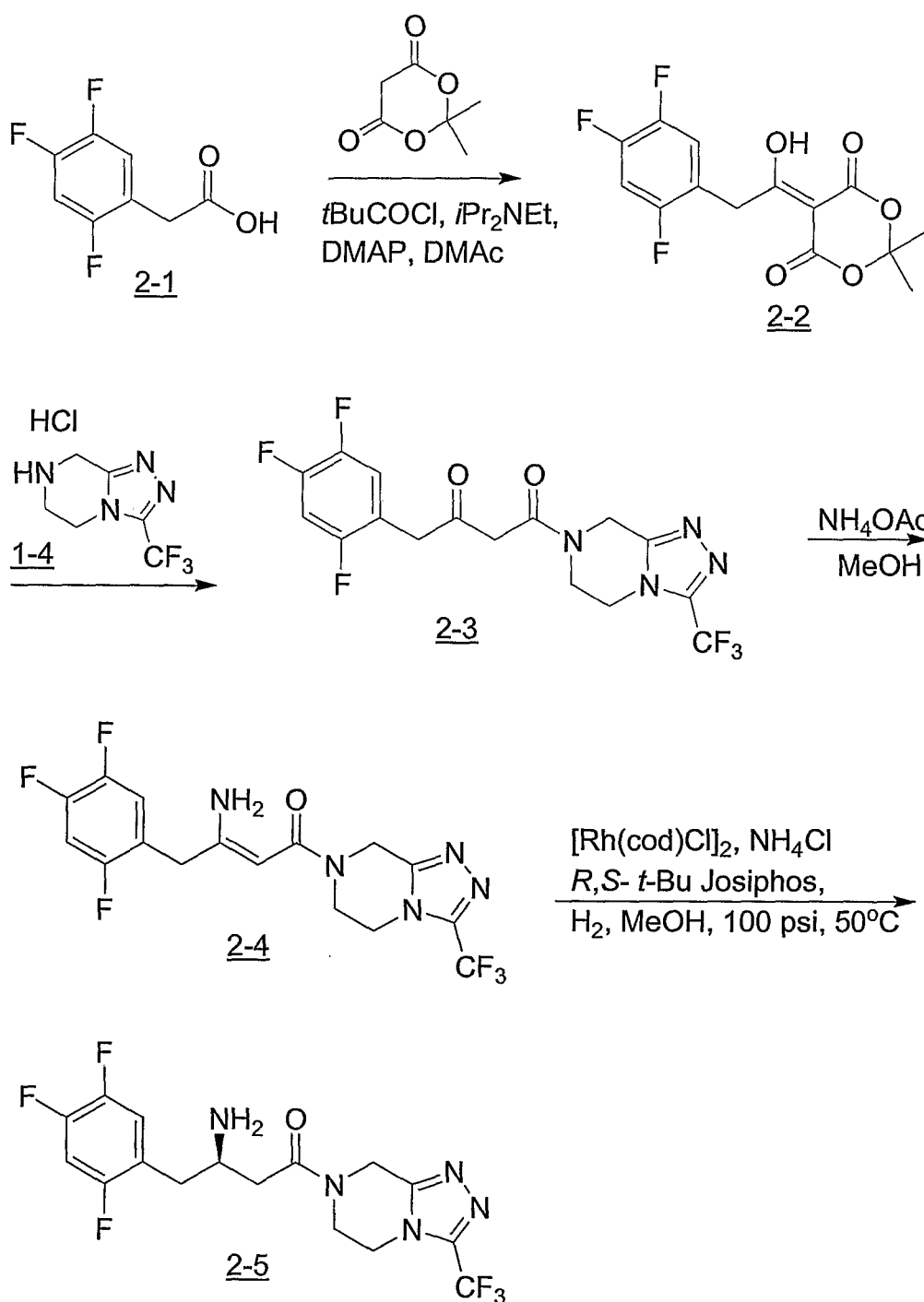
¹H-NMR (400 MHz, DMSO-*d*₆): δ 2.9 (t, 2H), 3.2 (t, 2H), 3.6 (s, 2H), and 8.3 (b, 1H) ppm. ¹³C-NMR (100 MHz, DMSO-*d*₆): δ 40.8, 42.0, 43.3, 119.3 (q, J = 350 Hz), 154.2, and 156.2 (q, J = 38 Hz) ppm.

20

Step D: Preparation of 3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyrazine, hydrochloride salt (1-4)

A suspension of amidine 1-3 (27.3 g, 0.13 mol) in 110 mL of methanol was warmed to 55 °C. 37% Hydrochloric acid (11.2 mL, 0.14 mol) was added over 15 min at this temperature. During the addition, all solids dissolved resulting in a clear solution. The reaction was aged for 30 min. The solution was cooled down to 20 °C and aged at this temperature until a seed bed formed (10 min to 1 h). 300 mL of MTBE was charged at 20 °C over 1 h. The resulting slurry was cooled to 2 °C, aged for 30 min and filtered. Solids were washed with 50 mL of ethanol:MTBE (1:3) and dried under vacuum at 45 °C.

- 25
30 ¹H-NMR (400 MHz, DMSO-*d*₆): δ 3.6 (t, 2H), 4.4 (t, 2H), 4.6 (s, 2H), and 10.6 (b, 2H) ppm; ¹³C-NMR (100 MHz, DMSO-*d*₆): δ 39.4, 39.6, 41.0, 118.6 (q, J = 325 Hz), 142.9 (q, J = 50 Hz), and 148.8 ppm.

Scheme 2

Step A: Preparation of 4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3- α]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-one (**2-3**)

2,4,5-Trifluorophenylacetic acid (**2-1**) (150 g, 0.789 mol), Meldrum's acid (125 g, 0.868 mol), and 4-(dimethylamino)pyridine (DMAP) (7.7 g, 0.063 mol) were charged into a 5 L three-neck

flask. *N,N*-Dimethylacetamide (DMAc) (525 mL) was added in one portion at room temperature to dissolve the solids. *N,N*-diisopropylethylamine (282 mL, 1.62 mol) was added in one portion at room temperature while maintaining the temperature below 40 °C. Pivaloyl chloride (107 mL, 0.868 mol) was added dropwise over 1 to 2 h while maintaining the temperature between 0 and 5 °C. The reaction mixture was aged at 5 °C for 1 h. Triazole hydrochloride 1-4 (180 g, 0.789 mol) was added in one portion at 40-50 °C. The reaction solution was aged at 70 °C for several h. 5% Aqueous sodium hydrogencarbonate solution (625 mL) was then added dropwise at 20 – 45 °C. The batch was seeded and aged at 20 – 30 °C for 1-2 h. Then an additional 525 mL of 5% aqueous sodium hydrogencarbonate solution was added dropwise over 2-3 h. After aging several h at room temperature, the slurry was cooled to 0 – 5 °C and aged 1 h before filtering the solid. The wet cake was displacement-washed with 20% aqueous DMAc (300 mL), followed by an additional two batches of 20% aqueous DMAc (400 mL), and finally water (400 mL). The cake was suction-dried at room temperature.

Step B: Preparation of (2Z)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)but-2-en-2-amine (2-4)

A 5 L round-bottom flask was charged with methanol (100 mL), the ketoamide 2-3 (200 g), and ammonium acetate (110.4 g). Methanol (180 mL) and 28% aqueous ammonium hydroxide (58.6 mL) were then added keeping the temperature below 30 °C during the addition. Additional methanol (100 mL) was added to the reaction mixture. The mixture was heated at reflux temperature and aged for 2 h. The reaction was cooled to room temperature and then to about 5 °C in an ice-bath. After 30 min, the solid was filtered and dried to afford 2-4 as a solid; m.p. 271.2 °C.

Step C: Preparation of (2R)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine (2-5)

Into a 250 ml flask were charged chloro(1,5-cyclooctadiene)rhodium(I) dimer {[Rh(cod)Cl]₂} (46 mg, 0.093 mmol) and (*R,S*) *t*-butyl Josiphos (106 mg, 0.196 mmol), ammonium chloride (12.5 mg, 0.234 mmol), and enamine amide (25 g, 61.8 mmol) under a nitrogen atmosphere. Degassed MeOH was then added (225 mL) and the mixture was stirred at room temperature for 1 h. The slurry was transferred into a hydrogenator under nitrogen. After degassing three times, the enamine amide was hydrogenated under 100 psi hydrogen gas at 50 °C for 18 h. Assay yield was determined by HPLC to be 97% and optical purity to be 94% ee.

The optical purity was further enhanced in the following manner. The methanol solution from the hydrogenation reaction (18 g in 180 mL MeOH) was concentrated and switched to methyl *t*-butyl ether (MTBE) (45 mL). Into this solution was added aqueous H₃PO₄ solution (0.5 M, 95 mL).

After separation of the layers, 3*N* NaOH (35 mL) was added to the water layer, which was then extracted

with MTBE (180 mL + 100 mL). The MTBE solution was concentrated and solvent switched to hot toluene (180 mL, about 75 °C). The hot toluene solution was then allowed to cool to 0 °C slowly (5 – 10 h). The crystals were isolated by filtration (98 – 99% ee); m.p. 114.1 – 115.7 °C.

¹H NMR (300 MHz, CD₃CN): δ 7.26 (m), 7.08 (m), 4.90 (s), 4.89 (s), 4.14 (m), 3.95 (m), 3.40 (m), 2.68 (m), 2.49 (m), 1.40 (bs).

Compound 2-5 exists as amide bond rotamers. Unless indicated, the major and minor rotamers are grouped together since the carbon-13 signals are not well resolved:

¹³C NMR (CD₃CN): δ 171.8, 157.4 (ddd, J_{CF} = 242.4, 9.2, 2.5 Hz), 152.2 (major), 151.8 (minor), 149.3 (ddd; J_{CF} = 246.7, 14.2, 12.9 Hz), 147.4 (ddd, J_{CF} = 241.2, 12.3, 3.7 Hz), 144.2 (q, J_{CF} = 38.8 Hz), 124.6 (ddd, J_{CF} = 18.5, 5.9, 4.0 Hz), 120.4 (dd, J_{CF} = 19.1, 6.2 Hz), 119.8 (q, J_{CF} = 268.9 Hz), 106.2 (dd, J_{CF} = 29.5, 20.9 Hz), 50.1, 44.8, 44.3 (minor), 43.2 (minor), 42.4, 41.6 (minor), 41.4, 39.6, 38.5 (minor), 36.9.

EXAMPLE 2

Preparation of (2*R*)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine (2-5)

Into a 1-mL reactor were charged chloro(1,5-cyclooctadiene)rhodium(I) dimer {[Rh(cod)Cl]₂} (0.074 mg, 0.15 μmol) and (*R,S*) *t*-butyl Josiphos (0.179 mg, 0.033 μmol), ammonium formate (6.6 mg, 0.15 mmol), and keto amide 2-3 (6.1 mg, 15 μmol) under a nitrogen atmosphere.

Degassed MeOH was then added (200 μL) and the mixture was stirred at 55 °C for 5 h in a pressure vessel under nitrogen. The mixture was then hydrogenated under 250 psi hydrogen gas at 55 °C for 20 h. Assay yield was determined by HPLC to be 91% and optical purity to be 95% ee.

The following high-performance liquid chromatographic (HPLC) conditions were used to determine percent conversion to product:

Column: Agilent Extend C18, 150 mm x 4.6 mm

Eluent: Solvent A: 80/20 vol% Water/Methanol 10 mM TRIS pH 9

Solvent B: 20/80 vol% Water/Methanol 10 mM TRIS pH 9

Gradient: 0 min 55% A : 45% B

8 min 24% A : 76% B

15 min 24% A : 76% B

Flow rate: 2 mL/min

Injection Vol.: 5 μL

UV detection: 215 nm

Column temp.: 23 °C

Retention times: compound 2.4: 5.9 min
compound 2.5: 4.2 min.

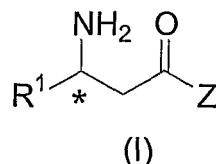
The following high-performance liquid chromatographic (HPLC) conditions were used to determine optical purity:

- 5 Column: Chirapak, AD-H, 250 mm x 4.6 mm
Eluent: 60/40/0.1/0.1 vol/vol Ethanol/hexanes/diethylamine/water
Isochratic Run Time: 24 min
Flow rate: 0.8 mL/min
Injection Vol.: 10 μ L
- 10 UV detection: 268 nm
Column temp.: 35 $^{\circ}$ C
Retention times: (*R*)-amine 2-5: 7.5 min
(*S*)-amine: 14.5 min

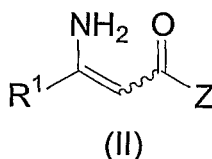
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WHAT IS CLAIMED IS:

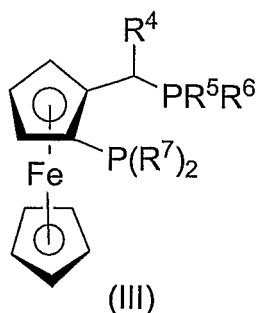
1. A process for preparing a compound of structural formula I:



- 5 having the (*R*)- or (*S*)- configuration at the stereogenic center marked with an *;
 in an enantiomeric excess of at least 70% over the opposite enantiomer, wherein
 Z is OR², SR², or NR²R³;
 R¹ is C₁₋₈ alkyl, aryl, heteroaryl, aryl-C₁₋₂ alkyl, or heteroaryl-C₁₋₂ alkyl;
 R² and R³ are each independently hydrogen, C₁₋₈ alkyl, aryl, or aryl-C₁₋₂ alkyl; or R² and R³ together
 10 with the nitrogen atom to which they are attached form a 4- to 7-membered heterocyclic ring system
 optionally containing an additional heteroatom selected from O, S, NH, and NC₁₋₄ alkyl, said
 heterocyclic ring being unsubstituted or substituted with one to three substituents independently selected
 from oxo, hydroxy, halogen, C₁₋₄ alkoxy, and C₁₋₄ alkyl wherein alkyl and alkoxy are unsubstituted or
 substituted with one to five fluorines; and said heterocyclic ring system being optionally fused with a 5-
 15 to 6-membered saturated or aromatic carbocyclic ring system or a 5- to 6-membered saturated or aromatic
 heterocyclic ring system containing one to two heteroatoms selected from O, S, and NC₀₋₄ alkyl, said
 fused ring system being unsubstituted or substituted with one to two substituents selected from hydroxy,
 amino, fluorine, C₁₋₄ alkyl, C₁₋₄ alkoxy, and trifluoromethyl;
 comprising the step of hydrogenating a prochiral enamine of structural formula II:



20 in a suitable organic solvent in the presence of an ammonium salt and a transition metal precursor
 complexed to a chiral ferrocenyl diphosphine ligand of structural formula III:



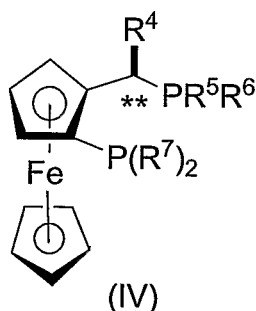
wherein R^4 is C_{1-4} alkyl or aryl;

R^5 and R^6 are each independently C_{1-6} alkyl, C_{5-12} cycloalkyl, or aryl; and

R^7 is C_{1-4} alkyl or unsubstituted phenyl.

5

2. The process of Claim 1 wherein said ferrocenyl diphosphine ligand is of structural formula IV:



wherein the stereogenic center marked with an ** has the (*R*)-configuration.

10

3. The process of Claim 2 wherein R^4 is C_{1-2} alkyl, R^5 and R^6 are C_{1-4} alkyl, and R^7 is unsubstituted phenyl.

4. The process of Claim 3 wherein R^4 is methyl, R^5 and R^6 are *t*-butyl, and R^7 is unsubstituted phenyl.

15

5. The process of Claim 1 wherein said ammonium salt is ammonium chloride.

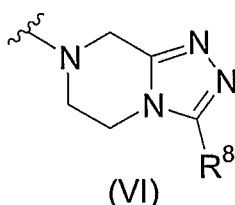
6. The process of Claim 1 wherein R^1 is benzyl wherein the phenyl group of benzyl is unsubstituted or substituted one to three substituents selected from the group consisting of fluorine, trifluoromethyl, and trifluoromethoxy.

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7. The process of Claim 1 wherein Z is OR² or NR²R³.

8. The process of Claim 7 wherein NR²R³ is a heterocycle of the structural formula

VI:

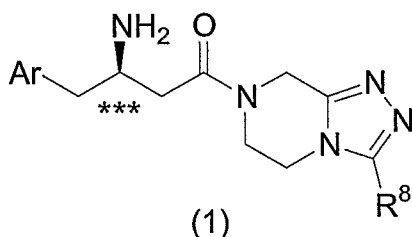


wherein R⁸ is hydrogen or C₁₋₄ alkyl which is unsubstituted or substituted with one to five fluorines.

9. The process of Claim 1 wherein said transition metal precursor is [M(cod)Cl]₂, [M(norbornadiene)Cl]₂, [M(cod)₂]X, or [M(norbornadiene)₂]X wherein X is methanesulfonate, trifluoromethanesulfonate, tetrafluoroborate, hexafluorophosphate, or hexafluoroantimonate and M is rhodium or iridium.

10. The process of Claim 9 wherein said transition metal precursor is [Rh(cod)Cl]₂.

11. A process for preparing a compound of structural formula 1:



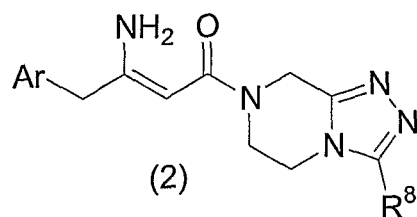
having the (*R*)-configuration at the stereogenic center marked with an ***;

in an enantiomeric excess of at least 70% over the enantiomer having the opposite (*S*)-configuration; wherein

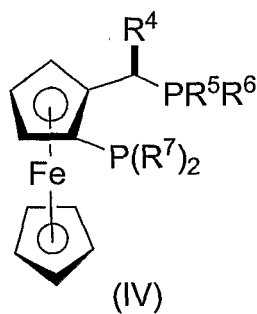
Ar is phenyl which is unsubstituted or substituted with one to five substituents independently selected from the group consisting of fluorine, trifluoromethyl, and trifluoromethoxy; and R⁸ is hydrogen or C₁₋₄ alkyl unsubstituted or substituted with one to five fluorines;

comprising the step of:

hydrogenating a compound of structural formula 2:

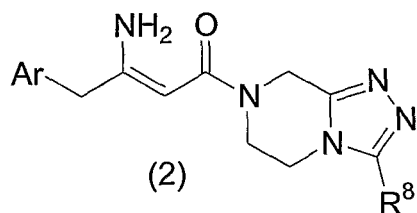


in a suitable organic solvent in the presence of an ammonium salt and a rhodium metal precursor complexed to a chiral ferrocenyl disphosphine of structural formula IV:

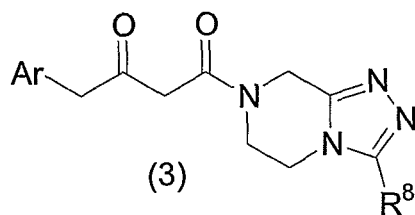


- 5 wherein R^4 is C_{1-4} alkyl or aryl;
 R^5 and R^6 are each independently C_{1-6} alkyl, C_{5-12} cycloalkyl, or aryl; and
 R^7 is C_{1-4} alkyl or unsubstituted phenyl.

12. The process of Claim 11 additionally comprising the step of producing a
 10 compound of structural formula 2:



by treating a compound of structural formula 3:



with a source of ammonia in a suitable organic solvent.

13. The process of Claim 11 wherein Ar is 2,5-difluorophenyl or 2,4,5-trifluorophenyl and R⁸ is trifluoromethyl.

14. The process of Claim 11 wherein said rhodium metal precursor is [Rh(cod)Cl]₂.

15. The process of Claim 11 wherein R⁴ is methyl, R⁵ and R⁶ are both *t*-butyl, and R⁷ is unsubstituted phenyl.

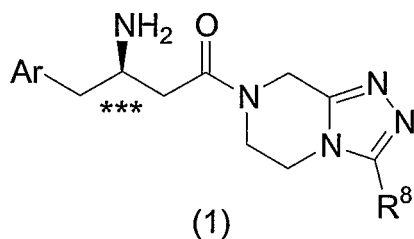
16. The process of Claim 15 wherein said rhodium metal precursor is [Rh(cod)Cl]₂.

17. The process of Claim 11 wherein R⁴ is methyl, R⁵ and R⁶ are both *t*-butyl, R⁷ is unsubstituted phenyl, Ar is 2,5-difluorophenyl or 2,4,5-trifluorophenyl, R⁸ is trifluoromethyl, and the rhodium metal precursor is chloro(1,5-cyclooctadiene)rhodium(I) dimer.

18. The process of Claim 17 wherein said ammonium salt is ammonium chloride.

19. The process of Claim 12 wherein said source of ammonia is ammonium acetate.

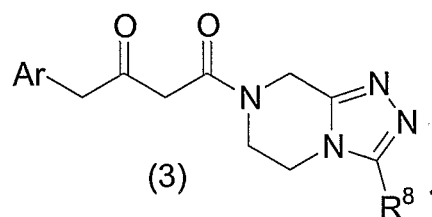
20. A process for preparing a compound of structural formula 1:



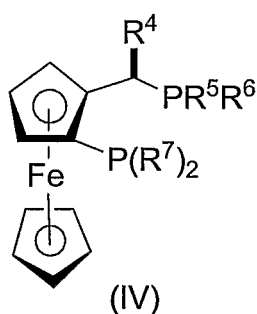
having the (*R*)-configuration at the stereogenic center marked with an ***;
in an enantiomeric excess of at least 70% over the enantiomer having the opposite (*S*)-configuration;
wherein

Ar is phenyl which is unsubstituted or substituted with one to five substituents independently selected from the group consisting of fluorine, trifluoromethyl, and trifluoromethoxy; and
R⁸ is hydrogen or C₁₋₄ alkyl unsubstituted or substituted with one to five fluorines;

comprising the step of subjecting a compound of structural formula 3:



with an ammonium salt in a suitable organic solvent under a hydrogen atmosphere in the presence of a rhodium metal precursor complexed to a chiral ferrocenyl diphosphine of structural formula IV:



- 5 wherein R⁴ is C₁₋₄ alkyl or aryl;
 R⁵ and R⁶ are each independently C₁₋₆ alkyl, C₅₋₁₂ cycloalkyl, or aryl; and
 R⁷ is C₁₋₄ alkyl or unsubstituted phenyl.

21. The process of Claim 20 wherein said ammonium salt is selected from the group
 10 consisting of ammonium acetate, ammonium hydroxide, ammonium formate, ammonium lactate,
 ammonium citrate dibasic, ammonium carbonate, ammonium carbamate, and ammonium benzoate.