(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
1 June 2006 (01.06.2006)

PCT

(10) International Publication Number
WO 2006/057904 A1

(51) International Patent Classification:
C07D 211/26 (2006.01)

(21) International Application Number:
PCT/US2005/041839

(22) International Filing Date:
18 November 2005 (18.11.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/630,246 23 November 2004 (23.11.2004) US

(71) Applicant *(for all designated States except US)*: **MERCK & CO., INC.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BOICE, Genevieve, N.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **MCWILLIAMS, J., Christopher** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **MURRY, Jerry, A.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **SAVARIN, Cecile, G.** [FR/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(74) Common Representative: **MERCK & CO., INC.**; MERCK & CO., INC., 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2006/057904 A1

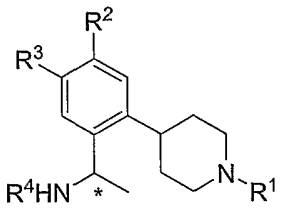
(54) Title: STEREOSELECTIVE PREPARATION OF 4-ARYL PIPERIDINE AMIDES BY ASYMMETRIC HYDROGENATION OF A PROCHIRAL ENAMIDE AND INTERMEDIATES OF THIS PROCESS

(57) Abstract: The present invention provides an efficient process for the preparation of enentiomerically enriched 4-aryl piperidine amides of structural formula (IV).

STEREOSELECTIVE PREPARATON OF 4-ARYL PIPERIDINE AMIDES BY ASYMMETRIC HYDROGENATION OF A PROCHIRAL ENAMIDE AND INTERMEDIATES OF THIS PROCESS

BACKGROUND OF THE INVENTION

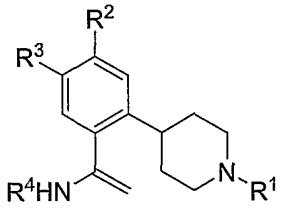
The present invention provides an efficient process for the preparation of enantiomerically enriched 4-aryl piperidine amides of structural formula (IV)



(IV)

enantiomerically enriched at the carbon atom marked with an *.

The stereoselective preparation of the compounds of formula (I) comprises the asymmetric hydrogenation of a prochiral enamide of structural formula (III):



(III)

wherein the piperidine amine is protected with R^1 or unprotected, in the presence of a rhodium, ruthenium or iridium catalyst. The use of a catalyst for the introduction of the chiral center marked with * in formula (I) is advantageous over the use of a chiral auxiliary, which requires additional steps to add and remove, and over the use of conventional syntheses based on chiral substrates or stoichiometric chiral induction and chiral separation methods, such as chromatographic resolution. The asymmetrical hydrogenation of the present invention comprises fewer steps, provides a more economical and efficient synthesis using fewer reagents and solvent, and results in less of the undesired enantiomer.

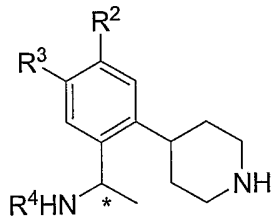
The asymmetrical hydrogenation of enamide double bonds (-C=C-N) using rhodium metal catalysts wherein the rhodium is complexed to a chiral phosphine ligand, such as rhodium Me-DuPHOS and rhodium BPE catalytic complexes, is described in: Burk, M. J. et al., *J. Org. Chem.*, vol. 63, pp. 6084-6085 (1998), and X. Zhang et al., *J. Org. Chem.*, vol. 63, pp. 8100-8101 (1998). The asymmetrical hydrogenation of enamides with rhodium cyclooctadienyl catalytic complexes has been disclosed in US 6,337,406. Methods for asymmetrically hydrogenating α-aryl enamide carbon-carbon double bonds

(C=C-N) using rhodium complexes of phosphines and rhodium binapththane complexes as catalysts have also been described in the patent literature (See US 5,919,981, US 2003/0120067, WO 99/59721, WO 01/14299, WO 02/04466, and WO 02/12253). The enantioselective hydrogenation of N-acetyl-α-arylenamides to the corresponding N-acetyl-α-arylalkylamines with MeDuPhos-Rh and MeBPE-Rh catalysts is disclosed in Burk, et al., J. Am. Chem. Soc., vol. 118, p. 5142-5143 (1996), and Zhang, et al., Chem. Rev. 103 (8) 3029-3070 (2003). Asymmetrical hydrogenations with RhBICP catalysts (See Zhang et al., J. Org. Chem., vol. 63, pp. 9590-9593 (1998)) and binaphane catalysts (See Zhang et al., Tet, Lett., vol. 43, pp. 4849-4852 (2002)) have also been disclosed. Additional methods for reducing aryl enamides with rhodium catalysts are disclosed in: Tang, W.; Zhang, X. Chem. Rev. 2003, 103, 3029-3069; Huang, et al. J. Org. Chem. 2004, 69, 7, 2355-2361; Kagan, et al. J. Organom. Chem. 1975, 90, 353-355; Gridnev, I. D. J. Am. Chem. Soc. 2001, 123, 5268-5276; Hu et al. Angew. Chem. Int. Ed. 2002, 41, 13, 2348-2350; and Jia et al. Tetrahedron Lett. 2002, 43, 5541-5544. These publications do not disclose the hydrogenation of *N*-aryl enamides in which the aryl group has an ortho piperidinyl substituent. Furthermore, asymmetrical hydrogenations of bulky ortho substituted aryl enamides do not result in adequate enantiomeric excess (ee) ratios with asymmetrical hydrogenation catalysts. (MeBPE)Rh(COD)BF4 reduces the ortho-methylphenyl enamide with only 75% ee, while the unsubstituted phenyl derivative gives 95% ee; and binaphane gives only 90% ee with the phenyl derivative, with no examples of ortho-substituted enamides given (Burk, et al., J. Am. Chem. Soc., vol. 118, p. 5142-5143 (1996).

Related approaches to the synthesis of N-acylated β-substituted enamides via the asymmetric hydrogenation of β-(acylamino)acrylates using rhodium metal precursors complexed to chiral phosphine ligands, such as rhodium Me-DuPHOS and rhodium BPE catalytic complexes are described in: (1) T. Hayashi, et al., Bull. Chem. Soc. Japan, 53: 1136-1151 (1980); (2) X. Zhang et al., J. Org. Chem., vol. 64, pp. 6907-6910 (1999); (3) W. D. Lubell, et al., Tetrahedron: Asymmetry, 2: 543-554 (1991); (4) Noyori et al, J. Am. Chem. Soc. Vol. 102, p 7932 (1980); (5) US 6,492,544; (6) US 2002/0128509; and (7) WO 03/016264. The asymmetric synthesis of β-amino acid derivatives via rhodium catalyzed hydrogenation of β-(acylamino)acrylates is disclosed, however, only moderate ees (~ 65%) were obtained with an aryl substituent in the β-(acylamino)acrylates using Rh-BICP and Rh-Me-DuPhos catalysts (Zhang et al. *J. Org. Chem.*, vol. 64, pp. 6907-6910 (1999)).

SUMMARY OF THE INVENTION

This invention is concerned with a process for preparing enantiomerically enriched compounds of structural formula (I)

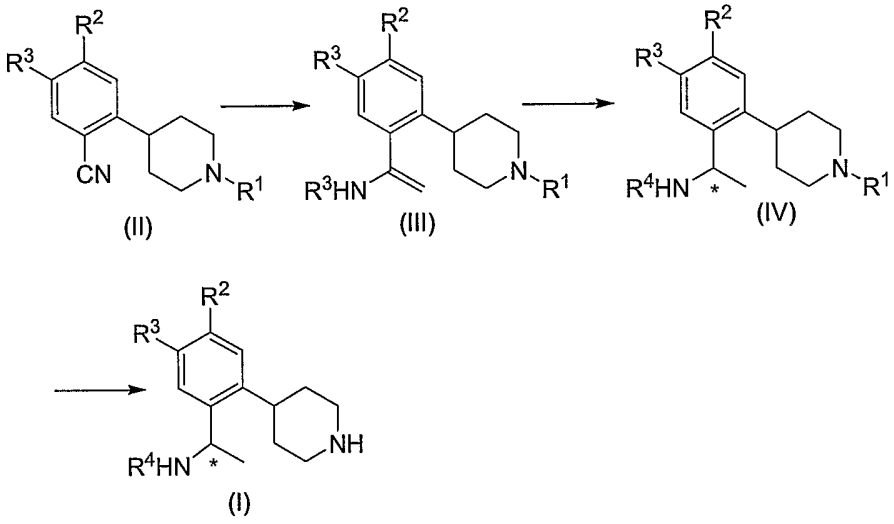


(I) ,

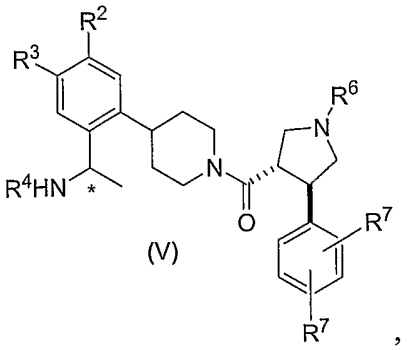
enantiomerically enriched at the carbon atom marked with an *, or a salt thereof.

The novel process and novel intermediates can be exemplified in Scheme A, which shows the preparation of 4-aryl piperidine amide (I). The preparation of nitrile (II) is disclosed in Corley, E. G. et al., J. Org. Chem. 69, 5120-23 (2004). Nitrile (II) is converted to enamide (III), followed by the reduction of the double bond of enamide (III) to give amine (IV). Finally, the R^1 protecting group of amine (IV) is cleaved to give an aryl piperidine amine of structural formula (I). Optionally, the reduction of the enamide double bond may be carried out after the R^1 protecting group of amine (IV).

Scheme A



The present invention provides intermediates useful for the preparation of compounds of structural formula (V):



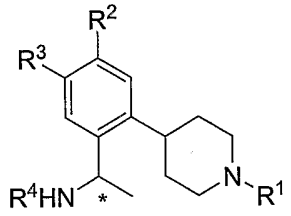
(V)

,

wherein R^2, R^3 and R^4 are as defined below, which are melanocortin receptor antagonists useful for the treatment of diseases mediated by the melanocortin 4 receptor, as disclosed in WO 02/068388.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a process for the preparation of compounds of structural formula (IV):



(IV)

enantiomerically enriched at the carbon marked with an *, or a salt thereof, wherein:

R^1 is selected from the group consisting of:

(1) -C(O)O-phenyl,
(2) -C(O)O-CH_2-phenyl,
(3) -C(O)O-*tert*-butyl,
(4) -CH_2-phenyl; and

R^2 and R^3 are independently selected from the group consisting of:

(1) hydrogen,
(2) C_{1-6} alkyl,
(3) -$(CH_2)_n$-phenyl,
(4) -$(CH_2)_n$-naphthyl,
(5) -$(CH_2)_n$-heteroaryl,
(6) -$(CH_2)_n$-heterocyclyl,
(7) -$(CH_2)_n C_{3-7}$ cycloalkyl,
(8) fluoride,

(9) chloride,
(10) OR^5,
(11) $-(CH_2)_nN(R^5)_2$,
(12) $-(CH_2)_nC{\equiv}N$,
(13) $-(CH_2)_nCO_2R^5$,
(14) NO_2,
(15) $N(R^5)_2$,
(16) $-(CH_2)_nNR^5SO_2R^5$,
(17) $-(CH_2)_nSO_2N(R^5)_2$,
(18) $-(CH_2)_nS(O)_pR^5$,
(19) $-(CH_2)_nNR^5C(O)N(R^5)_2$,
(20) $-(CH_2)_nC(O)N(R^5)_2$,
(21) $-(CH_2)_nNR^5C(O)R^5$,
(22) $-(CH_2)_nNR^5CO_2R^5$,
(23) $-(CH_2)_nNR^5C(O)$-heteroaryl,
(24) $-(CH_2)_nC(O)NR^5N(R^5)_2$,
(25) $-(CH_2)_nC(O)NR^5NR^5C(O)R^5$,
(26) $O(CH_2)_nC(O)N(R^5)_2$,
(27) CF_3,
(28) CH_2CF_3,
(29) OCF_3, and
(30) OCH_2CF_3,

wherein phenyl, naphthyl, heteroaryl, cycloalkyl, and heterocyclyl are unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, oxo, C_{1-4} alkyl, trifluoromethyl, and C_{1-4} alkoxy, and wherein any methylene (CH_2) carbon atom in R^2 and R^3 are unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and C_{1-4} alkyl, or two substituents when on the same methylene (CH_2) group are taken together with the carbon atom to which they are attached to form a cyclopropyl group;

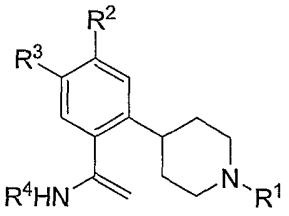
R^4 is selected from the group consisting of:

(1) $-C(O)C_{1-6}$alkyl,
(2) –C(O)cycloalkyl,
(3) $-C(O)CH_2$-phenyl,
(4) –C(O)aryl, and
(5) –C(O)heteroaryl, and

n is 0, 1 or 2;

comprising the step of:

(a) reducing the enamide double bond of the compound of structural formula (III)



(III)

wherein R^1, R^2, R^3, and R^4 are as defined above.

In one embodiment of the present invention, the enamide double bond of compound (III) of step (a) is reduced by hydrogenation in the presence of a catalyst. In a class of this embodiment, the catalyst is a rhodium, ruthenium, iridium or palladium catalyst. In another class of this embodiment the catalyst is a rhodium catalyst. In a subclass of this class, the catalyst is a rhodium catalyst of structural formula (VI):

(VI) (L)Rh(D)X

wherein:

D is an olefin, diene or triene;

X is an anion selected from the group consisting of halogen, methanesulfonate, trifluoromethanesulfonate (OTf), tetrafluoroborate (BF_4), hexafluorophosphate (PF_6), hexafluoroantimonate (SbF_6), acetylacetonate, and BARF (tetrakis(3,5-bis(trifluoromethyl)phenyl)borate; and

L is a ligand selected from the group consisting of: Binaphane, f-Binaphane, MeBPE, Me-Ketalphos, EtBPE, MeDuphos, EtDuphos, N-Me-Malphos, 1,2-bis(ethylphenyl-phosphino)benzene, 1,2-bis(methylphenylphosphino)benzene, Walphos (SL-W001-2), Pip-Monophos, EtFerrotane, EtBophoz, MeBophoz, Octahydro-pip-Monophos, Tangphos, Phanephos, Xyl-Phanephos, SL-R002-1, Taniaphos, SL-J409-2, TMBTP, and DiPAMP.

In a class of this embodiment, D is selected from the group consisting of norbornadiene, cyclooctatriene, 1,5 cyclooctadiene, and C_{1-6}alkene. In a subclass of this class, D is ethylene or propylene. In another subclass of this class, D is 1,5 cyclooctadiene. In another subclass of this class, D is norbornadiene.

In a class of this embodiment, X is a halogen selected from the group consisting of: chlorine, bromine, fluorine, and iodine. In another class of this embodiment, X is chlorine. In another class of this embodiment, X is trifluoromethanesulfonate (OTf). In another class of this embodiment, X is tetrafluoroborate (BF_4).

In a class of this embodiment, L of step (a) is selected from the group consisting of: binaphane, f-binaphane, MeKetalphos, MeBPE, EtBPE, MeDuPhos, EtDuPhos, and *N*-Me-Malphos (catASium-MN). In a subclass of this class, L is (S)-MeDuPhos. In another class of this embodiment, L is selected from the group consisting of: (R)-binaphane, (R)-f-binaphane, (S)-MeKetalphos, (S)-MeBPE, (S)-MeDuPhos, (S,S)-1,2-bis(methylphenylphosphino)benzene and *N*-Me-(S)-Malphos (or catASium-MN). In a subclass of this class, L is (S)-MeDuPhos. In another subclass of this class, L is (S)-MeBPE. In another class of this embodiment, L is (S,S)-1,2-bis(methylphenylphosphino)benzene.

In another class of this embodiment, the catalyst of step (a) is selected from the group consisting of (MeBPE)Rh(COD)BF_4, (MeDuphos)Rh(COD)BF_4, (Binaphane)-Rh(COD)BF_4, (1,2-bis(methylphenyl-phosphino)benzene)Rh(COD)BF_4, (f-Binaphane)Rh(COD)BF_4, (N-Me-Malphos)Rh(COD)BF_4, and (MeKetalphos)Rh(COD)BF_4. In a subclass of this class, the catalyst is selected from the group consisting of (S-MeBPE)Rh(COD)BF_4, (S-MeDuphos)Rh(COD)BF_4, (R-Binaphane)-Rh(COD)BF_4, (S,S-1,2-bis(methylphenyl-phosphino)benzene)Rh(COD)BF_4, (R-f-Binaphane)Rh(COD)BF_4, *N*-Me-(S)-Malphos)Rh(COD)BF_4, and (S-MeKetalphos)Rh(COD)BF_4. In another subclass of this class, the catalyst is (S-MeBPE)Rh(COD)BF_4. In another subclass of this class, the catalyst is (S-MeDuphos)-Rh(COD)BF_4. In another subclass of this class, the catalyst is (R-Binaphane)Rh(COD)BF_4. In another subclass of this embodiment, the catalyst is (S,S-1,2-bis(methylphenylphosphino)benzene)Rh(COD)BF_4.

In another embodiment of the present invention, the compound of structural formula (IV) is obtained in the hydrogenation reaction of step (a) with an enantiomeric excess of greater than 70 % ee of the "S" stereoisomer at the stereogenic center marked with * in compound (IV). In a class of this embodiment the compound of structural formula (IV) is obtained in the hydrogenation reaction of step (a) with an enantiomeric excess of greater than 85 % ee of the "S" stereoisomer at the stereogenic center marked with * in compound (IV). In another class of this embodiment the compound of structural formula (IV) is obtained in the hydrogenation reaction of step (a) with an enantiomeric excess of greater than 90 % ee of the "S" stereoisomer at the stereogenic center marked with * in compound (IV). In another class of this embodiment the compound of structural formula (IV) is obtained in the hydrogenation reaction of step (a) with an enantiomeric excess of greater than 95 % ee of the "S" stereoisomer at the stereogenic center marked with * in compound (IV). In yet another class of this embodiment the compound of structural formula (IV) is obtained in the hydrogenation reaction of step (a) with an enantiomeric excess of greater than 99 % ee of the "S" stereoisomer at the stereogenic center marked with * in compound (IV).

In another embodiment of the present invention, the hydrogenation reaction of step (a) is run in a hydrogen atmosphere at a hydrogen pressure of about 0 psig to about 1500 psig. In a subclass of this class, the hydrogenation reaction is run in a hydrogen atmosphere at a hydrogen pressure of about 5 psig to about 300 psig. In another subclass of this class, the hydrogenation reaction is run in a hydrogen

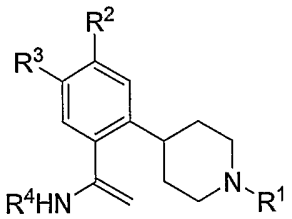
atmosphere at a hydrogen pressure of about 40 psig to about 100 psig. In another subclass of this class, the hydrogenation reaction is run at a hydrogen pressure of about 90 psig.

In another class of this embodiment, the hydrogenation reaction of step (a) is run at a temperature of between about -50°C to about 120°C. In another subclass of this subclass, the hydrogenation is run at a temperature of between about -20°C to about 50°C. In another subclass of this subclass, the hydrogenation is run at a temperature of between about 0°C to about 50°C. In another subclass of this class, the hydrogenation is run at a temperature of about 15°C to about 30°C.

In another class of this embodiment, the hydrogentation reaction of step (a) is run in a solvent selected from the group consisting of alcohol, ether, ester, aromatic hydrocarbon, non-aromatic hydrocarbon and halogenated solvent, or a mixture thereof. In a subclass of this class, the solvent is selected from the group consisting of lower alkanols, such as ethanol, methanol, ethyl acetate, methyl acetate, ethyl formate, acetone, 2-butanone, isopropyl acetate, isopropyl alcohol, 1-propanol 2-ethoxyethanol,, water, 2,2,2-trifluoroethanol, tetrahydrofuran, dichloromethane, 1,2-dichloroethane, toluene, chlorobenzene, 1,2-dichlorobenzene, nitromethane, nitroethane, 2-nitropropane, nitrobenzene, α,α,α-trifluorotoluene, and mixtures thereof. In another subclass of this class, the solvent is ethanol.

In another embodiment of the present invention, R^2 and R^3 are independently selected from the group consisting of: hydrogen, C_{1-6} alkyl, fluoride, chloride, OR^5, $-(CH_2)_nN(R^5)_2$, $-(CH_2)_nC{\equiv}N$, $-(CH_2)_nCO_2R^5$, NO_2, CF_3, CH_2CF_3, OCF_3, and OCH_2CF_3, wherein any methylene (CH_2) carbon atom in R^2 and R^3 are unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and C_{1-4} alkyl, or two substituents when on the same methylene (CH_2) group are taken together with the carbon atom to which they are attached to form a cyclopropyl group.

The present invention further relates to a process for the preparation of compounds of structural formula (III):



(III)

or a salt thereof, wherein:

R^1 is selected from the group consisting of:

(1) -C(O)O-phenyl,

(2) $-C(O)O-CH_2$-phenyl,

(3) -C(O)O-*tert*-butyl, and

(4) $-CH_2$-phenyl; and

R^2 and R^3 are independently selected from the group consisting of:

(1) hydrogen,
(2) C_{1-6} alkyl,
(3) $-(CH_2)_n$-phenyl,
(4) $-(CH_2)_n$-naphthyl,
(5) $-(CH_2)_n$-heteroaryl,
(6) $-(CH_2)_n$-heterocyclyl,
(7) $-(CH_2)_nC_{3-7}$ cycloalkyl,
(8) fluoride,
(9) chloride,
(10) OR^5,
(11) $-(CH_2)_nN(R^5)_2$,
(12) $-(CH_2)_nC{\equiv}N$,
(13) $-(CH_2)_nCO_2R^5$,
(14) NO_2,
(15) $N(R^5)_2$,
(16) $-(CH_2)_nNR^5SO_2R^5$,
(17) $-(CH_2)_nSO_2N(R^5)_2$,
(18) $-(CH_2)_nS(O)_pR^5$,
(19) $-(CH_2)_nNR^5C(O)N(R^5)_2$,
(20) $-(CH_2)_nC(O)N(R^5)_2$,
(21) $-(CH_2)_nNR^5C(O)R^5$,
(22) $-(CH_2)_nNR^5CO_2R^5$,
(23) $-(CH_2)_nNR^5C(O)$-heteroaryl,
(24) $-(CH_2)_nC(O)NR^5N(R^5)_2$,
(25) $-(CH_2)_nC(O)NR^5NR^5C(O)R^5$,
(26) $O(CH_2)_nC(O)N(R^5)_2$,
(27) CF_3,
(28) CH_2CF_3,
(29) OCF_3, and
(30) OCH_2CF_3,

wherein phenyl, naphthyl, heteroaryl, cycloalkyl, and heterocyclyl are unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, oxo, C_{1-4} alkyl, trifluoromethyl, and C_{1-4} alkoxy, and wherein any methylene (CH_2) carbon atom in R^2 and R^3 are unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and C_{1-4} alkyl, or two

substituents when on the same methylene (CH_2) group are taken together with the carbon atom to which they are attached to form a cyclopropyl group;

R^4 is selected from the group consisting of:

(1) $-C(O)C_{1-6}$alkyl,

(2) –C(O)cycloalkyl,

(3) $-C(O)CH_2$-phenyl,

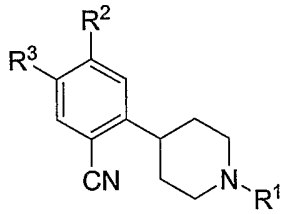
(4) –C(O)aryl, and

(5) –C(O)heteroaryl, and

n is 0, 1 or 2;

comprising the steps of:

(b) treating a compound of structural formula (II)



(II)

wherein R^1, R^2, and R^3 are as defined above, with a base, followed by an acylating agent, and

(c) isolating the resulting product.

In one embodiment of the present invention, R^1 is C(O)O-*tert*-butyl.

In another embodiment of the present invention, R^2 is hydrogen, and R^3 is chloride.

In another embodiment of the present invention, R^4 is $-C(O)CH_3$.

In yet another embodiment, R^1 is C(O)O-*tert*-butyl, R^2 is hydrogen, R^3 is chloride, and R^4 is $-C(O)CH_3$.

In another embodiment of the present invention, the base of step (b) is selected from a group consisting of methyl lithium, methyl lithium/lithium bromide complex, MeMgX wherein X is bromine, chlorine or iodine. In a class of this embodiment, the base is methyl lithium. In another class of this embodiment, the base is methyl lithium/lithium bromide complex. In another class of this embodiment, the base is methyl magnesium bromide.

In another embodiment of the present invention, step (b) further comprises a salt selected from the group consisting of BF_3-$O(CH_2CH_3)_2$, LiX and CuX, wherein X is bromine, chlorine, or iodine. In a class of this embodiment, the salt is lithium bromide. In another class of this embodiment, the salt is CuBr. In another class of this embodiment, the base is methyl lithium and the salt is lithium bromide. In another class of this embodiment, the base is methylmagnesium bromide and the base is CuBr.

In another embodiment of the present invention, the solvent of step (b) is selected from the group consisting of tetrahydrofuran, diethyl ether, methyl *tert*-butyl ether, cumene, diethoxymethane, benzene, and toluene, and mixtures thereof.

In another embodiment of the present invention, the reaction of step (b) is run at a temperature between about -50°C and about 25°C. In a class of this embodiment, the reaction temperature is between about -10°C and about -20°C.

In another embodiment of the present invention, the acylating agent in step (b) is a compound of formula (VII)

(VII) R^4-O-R^4,

wherein R^4 is selected from the group consisting of

(1) –C(O)C_{1-6}alkyl,

(2) –C(O)cycloalkyl,

(3) –C(O)CH_2-phenyl,

(4) –C(O)aryl, and

(5) –C(O)heteroaryl.

In a class of this embodiment, the acylating agent is acetic anhydride.

In another embodiment, the acylating agent in step (b) is a compound of formula (VIII)

(VIII) R^4Y,

wherein R^4 is selected from the group consisting of:

(1) –C(O)C_{1-6}alkyl,

(2) –C(O)cycloalkyl,

(3) –C(O)CH_2-phenyl,

(4) –C(O)aryl, and

(5) –C(O)heteroaryl, and

Y is selected from the group consisting of:

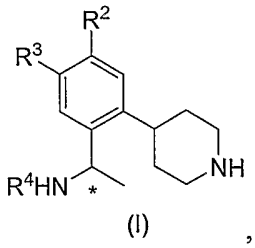
(1) Cl,

(2) Br, and

(3) I.

In a class of this embodiment, the acylating agent is acetyl chloride.

The present invention also relates to a process for the preparation of compounds of structural formula (I):



(I) ,

enantiomerically enriched at the carbon marked with an *, or a salt thereof, wherein:

R^2 and R^3 are independently selected from the group consisting of:

(1) hydrogen,
(2) C_{1-6} alkyl,
(3) $-(CH_2)_n$-phenyl,
(4) $-(CH_2)_n$-naphthyl,
(5) $-(CH_2)_n$-heteroaryl,
(6) $-(CH_2)_n$-heterocyclyl,
(7) $-(CH_2)_nC_{3-7}$ cycloalkyl,
(8) fluoride,
(9) chloride,
(10) OR^5,
(11) $-(CH_2)_nN(R^5)_2$,
(12) $-(CH_2)_nC{\equiv}N$,
(13) $-(CH_2)_nCO_2R^5$,
(14) NO_2,
(15) $N(R^5)_2$,
(16) $-(CH_2)_nNR^5SO_2R^5$,
(17) $-(CH_2)_nSO_2N(R^5)_2$,
(18) $-(CH_2)_nS(O)_pR^5$,
(19) $-(CH_2)_nNR^5C(O)N(R^5)_2$,
(20) $-(CH_2)_nC(O)N(R^5)_2$,
(21) $-(CH_2)_nNR^5C(O)R^5$,
(22) $-(CH_2)_nNR^5CO_2R^5$,
(23) $-(CH_2)_nNR^5C(O)$-heteroaryl,
(24) $-(CH_2)_nC(O)NR^5N(R^5)_2$,
(25) $-(CH_2)_nC(O)NR^5NR^5C(O)R^5$,
(26) $O(CH_2)_nC(O)N(R^5)_2$,

(27) CF_3,

(28) CH_2CF_3,

(29) OCF_3, and

(30) OCH_2CF_3,

wherein phenyl, naphthyl, heteroaryl, cycloalkyl, and heterocyclyl are unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, oxo, C_{1-4} alkyl, trifluoromethyl, and C_{1-4} alkoxy, and wherein any methylene (CH_2) carbon atom in R^2 and R^3 are unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and C_{1-4} alkyl, or two substituents when on the same methylene (CH_2) group are taken together with the carbon atom to which they are attached to form a cyclopropyl group;

R^4 is selected from the group consisting of:

(1) $-C(O)C_{1-6}$alkyl,

(2) –C(O)cycloalkyl,

(3) $-C(O)CH_2$-phenyl,

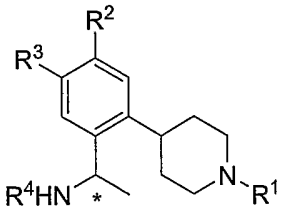
(4) –C(O)aryl, and

(5) –C(O)heteroaryl, and

n is 0, 1 or 2;

comprising the steps of:

(d) cleaving the R^1 protecting group of compound (IV)



(IV) ,

enantiomerically enriched at the carbon marked with an *, or a salt thereof,

wherein R^2, R^3, R^4 and n are as defined above, and

R^1 is selected from the group consisting of:

(1) -C(O)O-phenyl,

(2) $-C(O)O-CH_2$-phenyl,

(3) -C(O)O-*tert*-butyl, and

(4) -CH_2-phenyl; and

(e) isolating the resulting product.

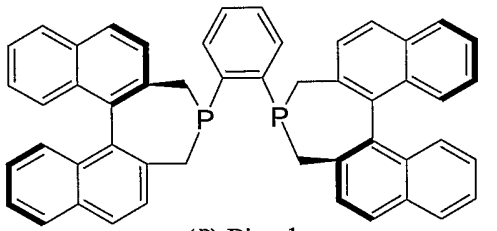
In one embodiment of the present invention, R^1 is C(O)O-*tert*-butyl. In a class of this embodiment, R^1 is cleaved by treating compound (IV) of step (d) with an acid selected from the group consisting of hydrochloric acid, hydrobromic acid, and TFA. In a subclass of this class, R^1 is -C(O)O-*tert*-butyl and the acid is hydrochloric acid.

In another embodiment of the present invention, R^1 is C(O)O-*tert*-butyl, R^2 is hydrogen, R^3 is chloride, R^4 is -$C(O)CH_3$, and R^1 is cleaved by treating compound (IV) of step (d) with an acid selected from the group consisting of hydrochloric acid, and TFA. In a class of this embodiment, the acid is hydrochloric acid.

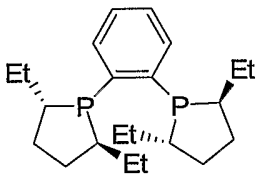
In another embodiment of the present invention, the reaction in step (d) is run at a temperature of between about 15°C to about 60°C. In a class of this embodiment, the reaction in step (d) is run at a temperature of between about 35°C to about 45°C.

In another embodiment of the present invention, the reaction in step (d) is run in a solvent selected from the group consisting of: ethanol, ethyl acetate, methylene chloride, isopropanol, acetonitrile, and mixtures thereof.

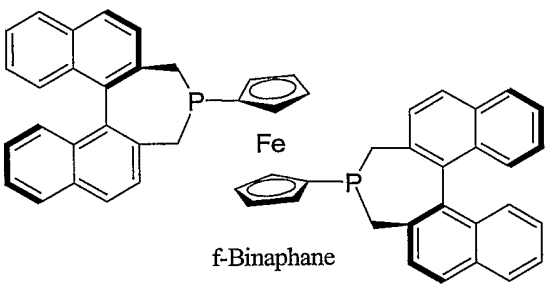
In one embodiment of the present invention, the catalyst ligands, L, useful in the methods of the present invention include, but are not limited to:



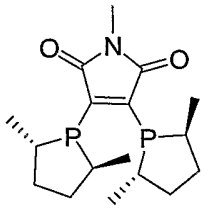
(*R*)-Binaphane



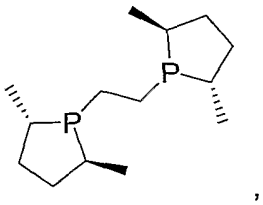
(*S*)-Et-Duphos



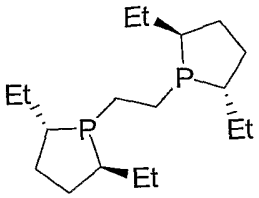
f-Binaphane



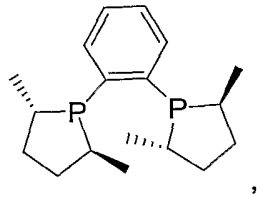
N-Me-S-Malphos
(catAXium MN)



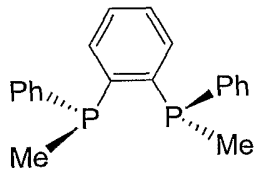
(S)-Me-BPE



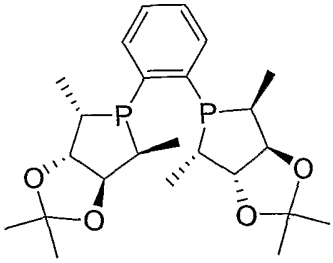
(S)-Et-BPE



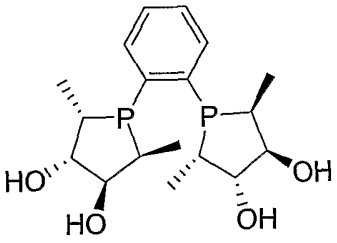
(S)-Me-Duphos



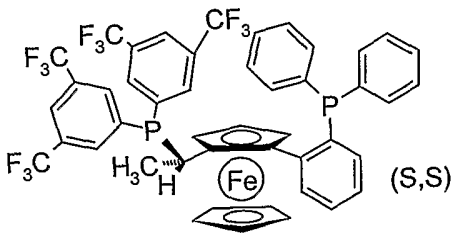
(S,S)-1,2-bis(methylphenylphosphino)benzene



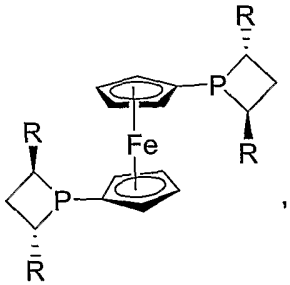
(S,S,S,S)-Me-Ketalphos



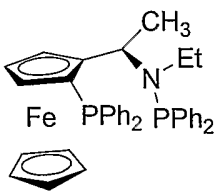
(S,S,S,S)-Rophos



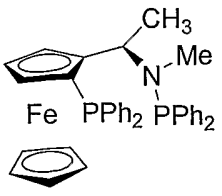
Walphos (SL-W001-2)



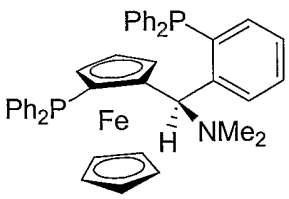
(S,S)-Et-Ferrotane R = Et
(S,S)-tBu-Ferrotane R = tBu



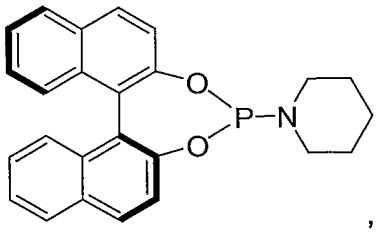
(S,S)-Et-Bophoz



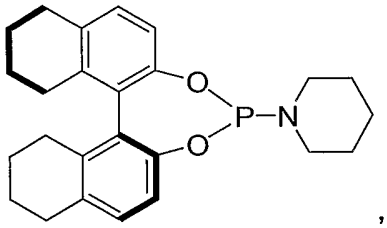
(S,S)-Me-Bophoz



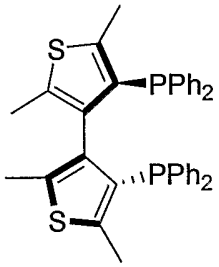
(R,S)-Taniaphos



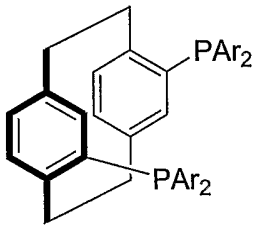
(S)-Pip-Monophos ,



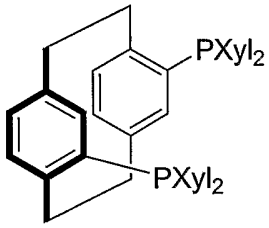
(S)-Octahydro-pip-Monophos ,



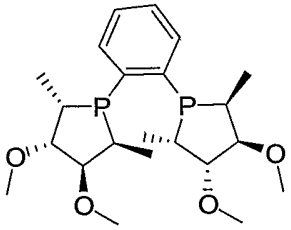
(R)-TMBTP



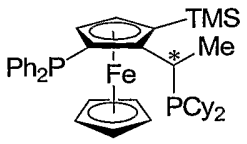
(S)-Phanephos



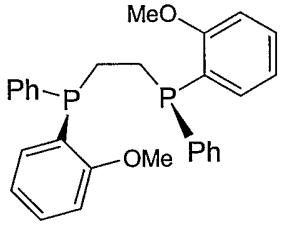
(S)-Xyl-Phanephos



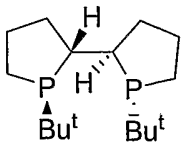
(S,S,S,S)-SL-R002-1



SL-J409-2



(R)-DiPAMP , and



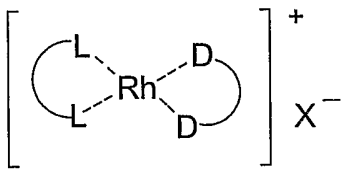
(S,S,R,R)-Tangphos .

Other catalyst ligands useful in the methods of the present invention include, but are not limited to, DIOP, DIOP analogs, CDP, BICP, bdpmi, PennPhos, aminophosphine BDPAB, Tunephos, Monophos, Josiphos, BasPhos, Malphos, Pchiral, Ulluphos, Butiphane, oBINAPO, oBIPHEP, and Binapine. Additonal catalyst ligands useful in the methods of the present invention are disclosed in the literature (See Adv. Synth. Catal., vol. 345, pp. 103-151 (2003)).

The process of the present invention contemplates that the catalyst may be either (a) generated in situ by the sequential or contemporaneous addition of a transition metal precursor and the ligand L, or a rhodium metal precursor and the ligand L to the reaction mixture; or (b) pre-formed with or without isolation and then added to the reaction mixture.

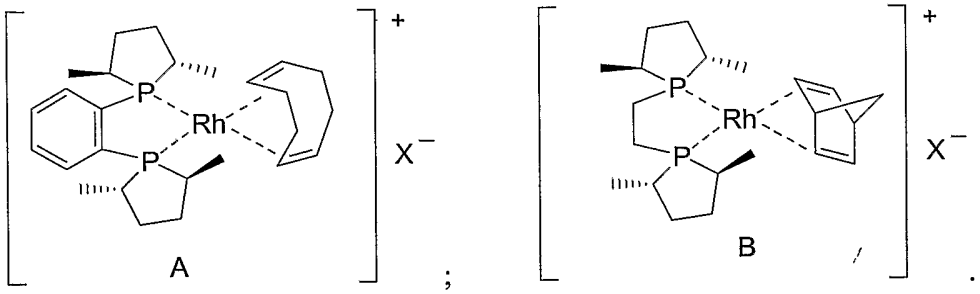
The "transition metal precursor" as used herein is $[M(monoolefin)_2X]_2$, $[M(diene)X]_2$, $[M(monoolefin)_2acetylacetonate]$, [M(diene)acetylacetonate], $[M(monoolefin)_4]X$, $[M(diolefin)X]_2$ or $[M(diolefin)_2]X$, or $[M(diene)_2]X$, wherein X is an anion selected from the group consisting of methanesulfonate, trifluoromethanesulfonate (OTf), tetrafluoroborate (BF_4), hexafluorophosphate (PF_6), and hexafluoroantimonate (SbF_6) or BARF (tetrakis(3,5-bis(trifluoromethyl)phenyl)borate, and M is rhodium (Rh), Ruthenium (Ru), Iridium (Ir) or Palladium (Pd). The term "rhodium metal precursor" as used herein refers to $[Rh(monoolefin)_2X]_2$, $[Rh(diene)X_2]_2$, $[Rh(monoolefin)_2acetylacetonate]$, [Rh(diene)acetylacetonate], $[Rh(monoolefin)_4]X$, $[Rh(diolefin)X]_2$ or $[Rh(diolefin)_2]X$, or $[Rh(diene)_2]X$, wherein X is an anion selected from halogen, methanesulfonate, trifluoromethanesulfonate (OTf), tetrafluoroborate (BF_4), hexafluorophosphate (PF_6), hexafluoroantimonate (SbF_6) or BARF (tetrakis(3,5-bis(trifluoromethyl)phenyl)borate. In one embodiment the rhodium metal precursor is $[Rh(diene)X_2]_2$, or $[Rh(diene)_2]X$. In a class of this embodiment, the rhodium metal precursor is selected from the gorup consisting of:$[Rh(cod)X]_2$, $[Rh(norbornadiene)X]_2$, $[Rh(cod)_2]X$, or $[Rh(norbornadiene)_2]X$, wherein cod = 1,5 cyclooctadiene. In a subclass of this class, the transition metal precursor is $[Rh(cod)Cl]_2$. In another subclass of this class, the transition metal precursor is $[Rh(cod)_2]Cl$. In another subclass of this class, the transition metal precursor is $[Rh(norbornadiene)_2]BF_4$. In another subclass of this class, the transition metal precursor is $[Rh(norbornadiene)BF_4]_2$.

A pre-formed catalytic complex is represented by the formula (L)Rh(D)X, wherein L is ligand and D is an olefin, diene, or triene:



where X represents an anion, such as, but not limited to, halogen (chloride, bromide, iodide, fluoride), BF_4, triflate, PF_6, SbF_6, BARF; D represents an olefin, diene or triene such as, but not limited to, a

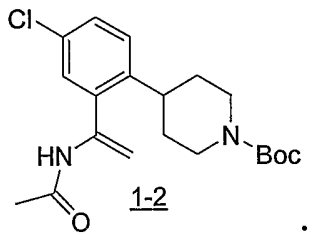
chelating monoolefin, di-olefin such as 1,4-cyclooctadiene or norbornadiene, or cyclooctatriene; and L is a ligand such as, but not limited to, binaphane, f-binaphane, Me-Ketalphos, Me-BPE, Et-BPE, Me-DuPhos, Et-DuPhos, and *N*-Me-Malphos. In the embodiment wherein D is 1,4-cyclooctadiene and L is S-MeDuphos, the complex is represented by the formula (A). In the embodiment wherein D is norbornadiene and L is S-MeDuphos, the complex is represented by the formula (B).



The ligands of formula (VI) 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 catalysts of structural formula (VI) for the asymmetric hydrogenation of a compound of formula (III). 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 carbon in a compound of formula (IV) marked with an * by the judicious choice of the chirality of the ligand of the catalyst of formula (VI).

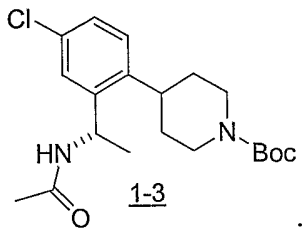
The ratio of transition metal precursor to substrate is about 0.9 to about 1.5 mol %. A preferred ratio of the transition metal precursor to substrate is about 1 mol % to about 1.1 mol %.

A further embodiment of this invention comprises the novel compound 1-2



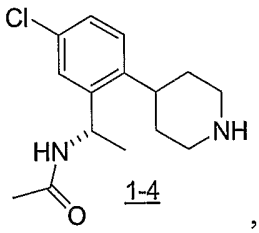
1-2

A further embodiment of this invention comprises the novel compound 1-3



1-3

A further embodiment of this invention comprises the novel compound 1-4



1-4

or a salt thereof.

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 VI with high optical purity, typically in excess of 70% ee of the "S" stereoisomer at the stereogenic carbon marked with an *. In one embodiment, compounds of formula VI are obtained with an optical purity in excess of 85% ee of the "S" stereoisomer at the stereogenic carbon marked with an *. In a class of this embodiment, compounds of formula I are obtained with an optical purity in excess of 90% ee of the "S" stereoisomer at the stereogenic carbon marked with an *. In a subclass of this class, compounds of formula I are obtained with an optical purity in excess of 95% ee of the "S" stereoisomer at the stereogenic carbon marked with an *. In another subclass of this class, compounds of formula I are obtained with an optical purity in excess of 99% ee of the "S" stereoisomer at the stereogenic carbon marked with an *.

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

The term "aryl" includes phenyl and naphthyl.

The term "heteroaryl" includes mono- and bicyclic aromatic rings containing from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulfur. "5- or 6-membered heteroaryl" represents a monocyclic heteroaromatic ring; examples thereof include thiazole, oxazole, thiophene, furan, pyrrole, imidazole, isoxazole, pyrazole, triazole, thiadiazole, tetrazole, oxadiazole, pyridine, pyridazine, pyrimidine, pyrazine, and the like. Bicyclic heteroaromatic rings include, but are not limited to, benzothiadiazole, indole, benzothiophene, benzofuran, benzimidazole, benzisoxazole, benzothiazole, quinoline, benzotriazole, benzoxazole, isoquinoline, purine, furopyridine and thienopyridine. In one embodiment of the present invention, heteroaryl is selected from the group consisting of pyridinyl, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, triazolyl, triazinyl, tetrazolyl, thiadiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxathiazolyl, pyrimidinyl, pyrazinyl, pyridazinyl, quinolyl, isoquinolyl, benzimidazolyl, benzofuryl, benzothienyl, indolyl, benzthiazolyl, and benzoxazolyl.

The term "5- or 6-membered carbocyclyl" is intended to include non-aromatic rings containing only carbon atoms such as cyclopentyl and cyclohexyl.

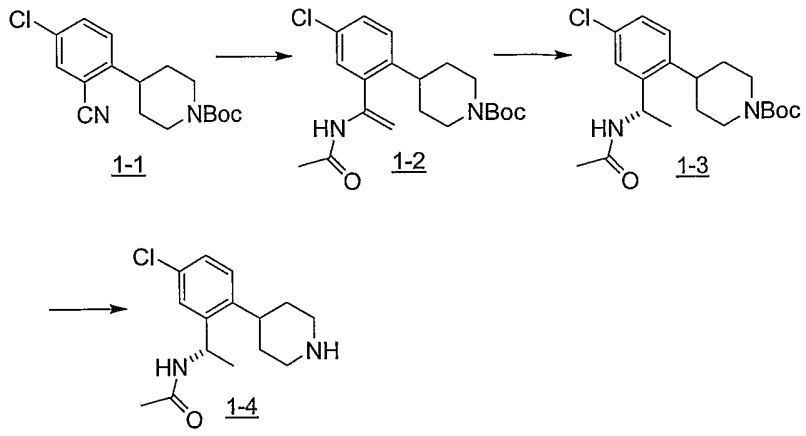
The term "5 and 6-membered heterocyclyl" is intended to include non-aromatic heterocycles containing one to four heteroatoms selected from nitrogen, oxygen and sulfur. Examples of a 5 or 6-membered heterocyclyl include piperidine, morpholine, thiamorpholine, pyrrolidine, imidazolidine, tetrahydrofuran, piperazine, and the like.

The term "olefin" or "monoolefin" is intended to include C_1-C_6 alkenes in a straight or branched configuration. Examples of such alkenes are: ethylene, propylene, butene, hexene, pentene, and the like.

Certain of the above defined terms may occur more than once in the above formula and upon such occurrence each term shall be defined independently of the other; thus for example, NR^5R^5 may represent NH_2, $NHCH_3$, $N(CH_3)CH_2CH_3$, and the like.

The process and intermediates can be exemplified with the preparation of compound 1-4 as shown in Scheme 1.

Scheme 1



As shown in Scheme 1, enamide 1-2 is prepared by the treatment of chlorobenzonitrile 1-1 with an organometallic reagent, such as methyl lithium or methyl lithium/lithium bromide complex, in the presence of a salt, such as lithium bromide, followed by the addition of an acylating agent, such as acetic anhydride or acetyl chloride, in a solvent such as ether, methyl *tert*-butyl ether, THF, toluene, cumene, or a mixture thereof, at a temperature of about -55°C to about -5°C. After warming to room temperature and aging for about 3-12 hours, the final product 1-2 is isolated. Other organometallic reagents, such as MeMgX wherein X is chloride, bromide or iodide, may be used in the conversion of nitrile 1-1 to enamide 1-2. The treatment of 1-1 with an organometallic reagent may also be run in the presence of a salt such as BF_3-$O(CH_2CH_3)_2$, LiX or CuX, wherein X is chloride, bromide or iodide.

Amide 1-3 is prepared by the asymmetric hydrogenation of enamide 1-2 in a solvent, such as toluene or a lower alkanol, for example, methanol or ethanol, with hydrogen gas under medium to high pressure, such as 5 psig to 300 psig in the presence of a rhodium catalyst, such as (S-MeBPE)Rh(COD)BF_4, (S-MeDuphos)Rh(COD)BF_4, or (R-Binaphane)Rh(COD)BF_4, until hydrogen uptake ceases. Other rhodium catalysts which may be employed in the hydrogenation reaction include, but are not limited to, the catalysts in Example 2. Additionally, ruthenium, iridium and palladium catalysts may also be used.

Free amine 1-4 is prepared by cleaving the Boc group of the Boc protected piperidine 1-3 in a solvent, such as ethanol, *iso*-propanol, EtOAc, CH_2Cl_2, or acetonitrile, with hydrochloric acid at a temperature of between about 35 °C about 45 °C until completion, followed by quenching and working up the reaction, and isolating the final product. Other acids useful to cleave the Boc protecting group include TFA, and hydrobromic acid. The Boc protecting group of piperidine 1-3 may also be removed under the standard conditions found in textbooks such as Greene, T, and Wuts, P. G. M., *Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc., New York, NY, 1991. CBZ and BOC are

commonly used protecting groups in organic synthesis, and their addition and removal conditions are known to those skilled in the art.

Abbreviations Used in the Description of the Preparation of the Compounds of the Present Invention: Ac_2O is acetic anhydride, AcCl is acetyl chloride; BARF is (tetrakis(3,5-bis(trifluoromethyl)phenyl)borate, BOC (Boc) is *tert*-butyloxycarbonyl or -CO_2-*tert*-butyl; CDI is carbonyl diimidazole; COD or cod is 1,5 cyclooctadiene; 1,2 DCB or DCB is 1,2-dichlorobenzene; 1,2 DCE or DCE is 1,2-dichloroethane; DCB is 1,2-dichlorobenzene; EtOAc is ethyl acetate; EtOH is ethanol; EDC is 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide HCl; CH_3CN is acetonitrile; equiv is equivalents; g is grams; h or hr is hour(s); H_2 is hydrogen; HCl is hydrochloric acid, HPLC is high pressure liquid chromatography; mm Hg is millimeters of mercury; IPA is isopropyl alcohol; IPAC is isopropylacetate; *i*-PrOH is isopropanol; kg is kilograms; L is liters; LiBr is lithium bromide; M is molar; mL is milliliters; Me is methyl; MeLi is methyl lithium; MeOH is methanol, mol is moles; MTBE is methyl t-butyl ether; N is normal; NBD or nbd is norbornadiene; NMP is N-methyl pyrrolidinone; NaCl is sodium chloride; $NaHCO_3$ is sodium bicarbonate; NaOH is sodium hydroxide; Na_2SO_4 is sodium sulfate; NMR is nuclear magnetic resonance; Ph (ph) is phenyl; psig is pounds per square inch guage; TFA is trifluoroacetic acid; TFE is triflouroethane; TFT is α,α,α-trifluorotoluene; THF is tetrahydrofuran; and % is percent.

Representative experimental procedures utilizing the novel process are detailed below. The following Examples are provided to illustrate the invention and is not to be construed as limiting the scope of the invention in any manner. For purposes of illustration, Example 1 is directed to the preparation of compounds 1-2, 1-3, and 1-4, but doing so is not intended to limit the present invention to a process for making those specific compounds.

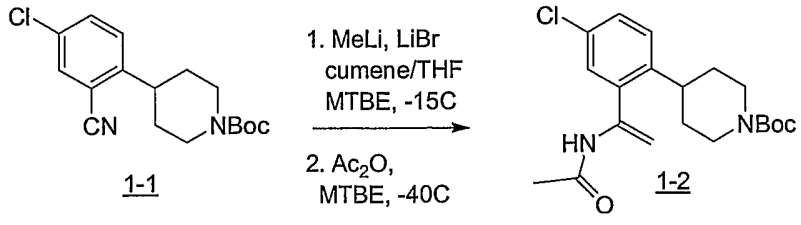
EXAMPLE 1

Preparation of Compound (1-4)

Step A: Preparation of Compound 1-1

Chlorobenzonitrile 1-1 may be prepared as shown in J. Org. Chem, vol. 69, pp. 5120-23 (2004)).

Step B: Preparation of Compound 1-2



Compound 1-2 may be prepared by the three methods described below.

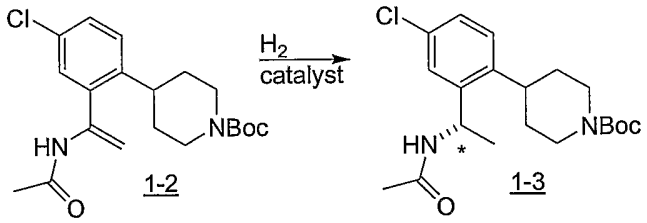
Method 1. MTBE (12 mL), LiBr (0.60 g, 6.9 mmol), and MeLi (1.1 M in cumene/THF, 6.3 mL, 6.9 mmol) were added to a flask. The mixture was cooled to -15 °C. A solution of nitrile 1-1 (2.0 g, 6.2 mmol) in MTBE (12 mL) was added keeping the reaction temperature less than -10 °C. The reaction mixture was aged at a temperature below –10 °C for 1 hour and then cooled to a temperature between -40 to -50 °C. Acetic anhydride (1.3 mL, 14.3 mmol) in MTBE (2.6 mL) was then added at a rate such that the reaction temperature remained below –30 °C. The reaction was allowed to warm to room temperature and aged overnight. To the heterogeneous mixture was added aqueous $NaHCO_3$ or K_2HPO_4 and MTBE. After stirring for 20 minutes, the aqueous layer was removed and the homogeneous organic layer was washed again with aqueous $NaHCO_3$ or K_2HPO_4. The organic layer was concentrated and solid started to crash out. Heptane was added and the slurry was aged overnight, filtered, and the resulting product washed with a mixture of heptane/MTBE, and dried under vacuum to afford the enamide 1-2.

Method 2. Nitrile 1-1 (50.0 g, 156 mmol) and MTBE (750 mL) were added to a flask. The solution was cooled to -20 °C and MeLi·LiBr (methyllithium as a complex with lithium bromide; 1.5 M in Et_2O, 119 mL, 172 mmol) was added at a rate such that the reaction temperature remained below -10 °C. The reaction mixture was aged for 1 hour at temperature below -10 °C and then cooled to -50 °C. Acetic anhydride (34 mL, 360 mmol) in MTBE (66 mL) was then added at a rate such that the reaction temperature remained below -40 °C. The reaction was allowed to warm to room temperature and aged overnight. To the heterogeneous mixture was added aqueous $NaHCO_3$ or K_2HPO_4 and MTBE. The mixture was stirred, the organic layer was separated, washed with 6.5 wt% K_2HPO_4 (aq), and then solvent switched to EtOH. The pH of the mixture was adjusted to an apparent pH of 12 with 5N NaOH. The reaction mixture was concentrated to to give enamide 1-2, which may be crystallized (2:1 EtOH:H_2O) for further purification.

Method 3. In a vessel under N_2, nitrile 1-1 was dissolved in MTBE (21.6 mL), then lithium bromide (3.2g; 37.4 mmol) and THF (18 mL) were added. The solution was cooled to -30 °C, then MeLi·LiBr (16.5 mL, 3.4M) was added at a rate such that the reaction temperature remained between -30 °C to -10 °C. The reaction was aged for 30 minutes, then cooled to -60 °C and acetic anhydride (10.8 mL) in MTBE was added at a rate such that the reaction temperature remained below -45 °C. The reaction was warmed to room temperature, aged overnight, and EtOAc and K_2HPO_4(aq) were added. The organic layer was separated, and washed with K_2HPO_4 (aq). Ecosorb C941® was added and the slurry was heated to 40 °C, aged for 2 hours and filtered. The resulting filter cake washed with two 45 mL portions of EtOAc, and the combined filtrates were solvent switched to EtOH. NaOH was added to the room temperature solution and the resulting solution was aged for 30-60 minutes, then concentrated to give a an ethanolic solution of enamide 1-2, which can be crystallized from 2:5 EtOH/H_2O (1:1 EtOH/H_2O endpoint) to give enamide 1-2. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.28 (dd, J = 8.4, 2.2 Hz, 1H), 7.20 (d, J

= 2.2 Hz, 1H), 7.17 (d, J = 8.4 Hz, 1H), 7.07 (br s, 1H), 5.97 (br s, 1H), 4.64 (br s, 1H), 4.16 (app. J = 12.8 Hz d, , 2H), 2.94 (tt, J = 11.6 Hz, 3.2 Hz, 1H), 2.78-2.62 (m, 2H), 2.00 (s, 3H), 1.67-1.51 (m, 4H), 1.44 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.6, 154.8, 142.4, 139.5, 138.8, 131.7, 129.4, 129.0, 128.1, 103.6, 79.6, 44.3, 38.2, 33.5, 28.5, 24.4. Anal. Calcd for $C_{20}H_{27}ClN_2O_3$: C, 63.40; H, 7.18; N, 7.39. Found: C, 63.59; H, 7.36; N, 7.61.

Step C: Preparation of Compound 1-3



Compound 1-3 may be prepared by the four methods described below.

Method 1. Enamide 1-2 (300 mg, 0.792 mmol) and EtOH (2.3 mL) were charged to a vial with (S-MeBPE)Rh(COD)BF_4 (0.33 mg, $5.9x10^{-4}$ mmol, 0.075 mol %). The reaction mixture was aged for 3-12 hours at 15 to 22 °C under 90 psi H_2 to give 1-3 in 87.8% enantiomeric excess of the S enantiomer at the carbon marked with an *.

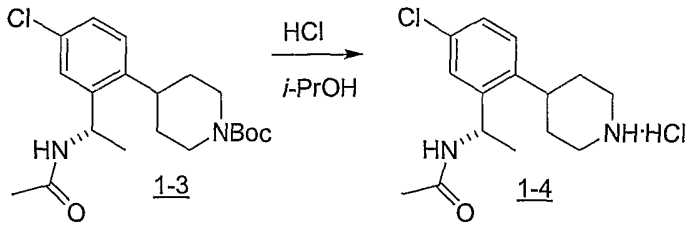
Method 2. Enamide 1-2 (300 mg, 0.792 mmol) and EtOH (2.3 mL) were charged to a vial with (S-MeDuphos)Rh(COD)BF_4 (0.48 mg, $7.9x10^{-4}$ mmol, 0.10 mol %). The reaction mixture was aged for 12 hours at 22 °C under 90 psi H_2 to give 1-3 in 83.8% enantiomeric excess of the S enantiomer at the carbon marked with an *.

Method 3. A (R-Binaphane)Rh(COD)BF_4 catalyst solution was prepared from (R)-Binaphane (24.4 mg, $3.49x10^{-2}$ mmol) and $Rh(COD)_2BF_4$, (12.9 mg, $3.1x10^{-2}$ mmol), in MeOH (4.0 mL). Enamide 1-2 (300 mg, 0.792 mmol) and EtOH (1.75 mL) were charged to a vial with an aliquot of the (R-Binaphane)-Rh(COD)BF_4 catalyst solution (0.75 mL, $5.9x10^{-3}$ mmol, 0.75 mol %). The reaction mixture was aged for 49 hours at 22 °C under 90 psi H_2 to give 1-3 in 92.9% enantiomeric excess of the S enantiomer at the carbon marked with an *.

Method 4. Enamide (10 g, 26.4 mmol) in IPA (35 mL, 3.5V) was charged as a slurry to a hydrogenator, which was then vaccum/N_2 purged 3-5 times. In a glove box, (S-MeBPE)-Rh-(COD)BF_4 (44 mg, 0.04 mmol, 0.30 mol%) in 5 mL IPA (0.5V) was introduced in the first chamber of a two-stage charging vessel, and the second chamber was filled with an IPA rinse (1.0V). The catalyst solution and the IPA rinse were sequentially added to the hydrogenator. After 3-5 vacuum/N_2 purges followed with H_2 fill, the agitation was started and the reaction mixture was aged for 1 to 16 hours at 18-22 °C under 20-90 psig H_2 to give 1-3 in greater than 99% enantiomeric excess of the S enantiomer at the carbon marked with an *.

Other catalysts that may be used in this hydrogenation reaction are shown in Example 2.

Step D: Preparation of Compound 1-4

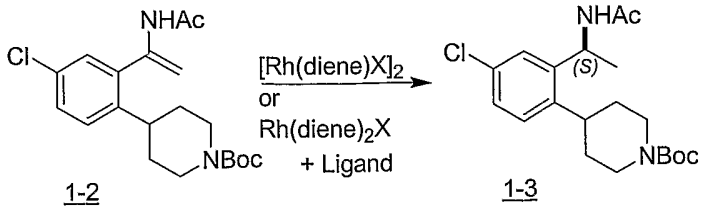


Compound 1-4 may be prepared by the two methods described below.

Method 1. The ethanol solution of Boc-acetamide 1-3 from Step B (1.3 kg, 3.4 mol, 1.0 equiv - in a total of 14.3 kg of ethanol solution), was treated with Ecosorb C-941® in ethanol (1.1 kg, 85 weight % in 3 liters of ethanol). After stirring for 3 hours at room temperature, the solution was filtered through Solka Floc® and washed with ethanol. To the resulting ethanol solution was carefully added HCl in *i*-PrOH (2.15 L, 8.7 mol, 2.6 equiv). After the addition, the reaction mixture was heated to 50 °C for 6 hours. Upon completion of the reaction, the reaction mixture was cooled to room temperature, imidazole (465 g, 6.8 mol, 2.1 equiv) was added, and the reaction mixture was concentrated to about 20 L. The solvent is then switched to CH_3CN (to give a final ratio of CH_3CN:EtOH, 10-20:1), and the mixture was stirred for 2 hours at room temperature to give a slurry. The slurry was filtered and the resulting solid cake was washed with CH_3CN (12 L). The solid was then dried in the oven under vaccum/nitrogen at room temperature to give acetamide 1-4.

Method 2. A solution of Boc-acetamide 1-3 from Step B (22 g) in isopropanol (309 mL) was treated with Ecosorb C-941® (11 g) at 40 °C for 5 hours. The resulting slurry was cooled to room temperature, filtered, and the filter cake was washed with 70 mL of isopropanol. The combined filtrate and wash were concentrated to about 125 mL under vacuum. Then 24 mL of 5.6 N HCl in isopropanol (2.6 eq) were added to the solution. The resulting solution was heated to 50 °C and seeded after 30 minutes. The mixture was allowed to age at 50 °C for 6 hours, then cooled to room temperature. Imidazole (8.3 g, 2.1 eq) was added to the reaction mixture. The slurry was aged overnight, filtered, and the filter cake was washed with three 20 mL portions of isopropanol to give acetamide 1-4 as a solid. ^{1}H NMR (d_6-DMSO, 400 MHz) δ 9.17 (br s, 2H), 8.53 (d, J = 7.6 Hz, 1H), 7.37 (d, J = 2.2 Hz, 1H), 7.28 (dd, J = 2.2, 8.4 Hz, 1H), 7.17 (d, J = 8.4 Hz, 1H), 5.16 (pent, J = 7.2 Hz, 1H), 3.43-3.30 (m, 2H), 3.19 (app t, J = 11.9 Hz, 1H), 3.07-2.94 (m, 2H), 2.10-1.95 (m, 2H), 1.85-1.65 (m, 5H), 1.29 (d, J = 6.9 Hz, 3H). ^{13}C NMR (d6-DMSO, 100 MHz) δ 168.1, 145.1, 140.3, 131.1, 127.5, 126.8, 125.4, 43.8, 43.4, 33.5, 29.6, 28.4, 22.5.

EXAMPLE 2



1-2 1-3

The hydrogenation reaction converting enamide 1-2 to alkyl amide 1-3 may be carried out with preformed rhodium catalyst, or rhodium catalyst formed in situ by adding the $[Rh(diene)X]_2$ or $Rh(diene)_2X$ precursor and the ligand to the reaction. For screening, between about 5-15 mol% of catalyst may be used. For optimized loading studies, such as with MeBPE, Binaphane, MeDuphos ligands, between 0.13 to 0.7 mol % of catalyst may be used. For in situ prepared catalysts prepared in situ, the ligand: rhodium metal precursor is between about 1.05/1.00 to about 1.10/1.00 for bidentate ligands, and between about 2.10/1.00 to about 2.20/1.00 for monodentate ligands, such as monophos derivatives. The hydrogenation reaction may be carried out between 5-300 psig, preferably between about 20 to 100 psig, more preferably about 90 psig. The reaction temperatures range from between about 0°C to 65 °C, preferably 16°C to 22 °C. The reaction times range from between about 1 hour to about 50 hours, preferably from about 1 hour to 20 hours. Solvents that may be used in the hydrogenation reaction include: EtOH, MeOH, IPA, trifluoroethane, tetrahydrofuran, 2-ethoxyethanol, 1,2 dichloroethane, 2-butanone, ethyl formate, methyl acetate, nitromethane, nitroethane, 2-nitropropane, nitrobenzene, toluene, α,α,α-trifluorotoluene, chlorobenzene, and 1,2 dichlorobenzene. The hydrogenation reactions are assayed using Chiral HPLC with a tandem column arrangement: Kromasil Silica KR100-5SIL (250 x 4.6 mm)-Chiralpak AD-H column (250 x 4.6 mm); 10% EtOH/Heptane @ 1.5 mL/min; UV @ 210 nm.

Table 1. Examples of Catalytic Hydroganation Conditions at 90 psig of H_2:

Catalyst: preformed (L)Rh(D)X or formed *in situ* from metal precursor: $[Rh(D)X]_2$ or $Rh(D)_2X$, and L	Solvent	% ee
D = COD or NBD; X = BF_4 or OTf L = Binaphane	MeOH, THF, EtOAc	94-96
D = COD; X = OTf L = f-Binaphane	EtOAc	89

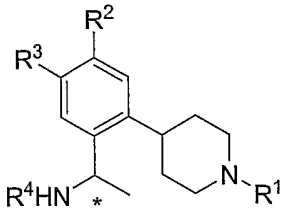
D = COD; X = OTf L = MeKetalphos	EtOAc	91
D = COD; X = BF_4 L = MeBPE	EtOH	87-90
D = COD ; X = BF_4 L = EtBPE	EtOAc	93
D = COD; X = BF_4 L = MeDuphos		84-87
D = COD ; X = OTf; L = EtDuphos	EtOAc	89
D = COD; X = BF_4 L = NMe-Malphos	1,2-dichlorobenzene	83
D = COD; X = OTf L = 1,2-bis(ethyl-phenylphosphino)-benzene	EtOH	71
D = COD; X = OTF L = Walphos (SL-W001-2)	EtOAc	63
D = ;COD X = BF_4 L = Pip-Monophos	1,2-dichlorethane	66
D = COD; X = OTf L = Et-Ferrotane	EtOAc	62
D = COD; X = OTf L = Et-Bophoz	EtOAc	60
D = COD; X = OTf L = Me-Bophoz	EtOAc	57
D = COD; X = BF_4 L = Octahydro-pip-Monophos	1,2-Dichloroethane / CH_2Cl_2	50
D = COD; X = OTf L = Tangphos	EtOAc	50
D = COD; X = OTf L = Phanephos	EtOAc	49
D = COD ; X = OTf L = Xyl-Phanephos	EtOH	51

D = COD; X = BF_4 L = SL-R002-1	EtOH	50
D = COD; X = OTf L = Taniaphos	EtOAc	46
D = COD; X = OTf L = SL-J409-2	EtOAc	49
D = COD; X = OTf L = TMBTP	EtOH	46
D = COD; X = OTf L = DiPAMP	EtOH	47

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

WHAT IS CLAIMED IS:

1. A process for preparing a compound of structural formula (IV):



(IV)

enantiomerically enriched at the carbon marked with an *, or a salt thereof,

wherein:

R^1 is selected from the group consisting of

(1) -C(O)O-phenyl,
(2) -C(O)O-CH_2-phenyl,
(3) -C(O)O-*tert*-butyl, and
(4) -CH_2-phenyl; and

R^2 and R^3 are independently selected from the group consisting of

(1) hydrogen,
(2) C_{1-6} alkyl,
(3) -$(CH_2)_n$-phenyl,
(4) -$(CH_2)_n$-naphthyl,
(5) -$(CH_2)_n$-heteroaryl,
(6) -$(CH_2)_n$-heterocyclyl,
(7) -$(CH_2)_n C_{3-7}$ cycloalkyl,
(8) fluoride,
(9) chloride,
(10) OR^5,
(11) -$(CH_2)_n N(R^5)_2$,
(12) -$(CH_2)_n C{\equiv}N$,
(13) -$(CH_2)_n CO_2R^5$,
(14) NO_2,
(15) $N(R^5)_2$,
(16) -$(CH_2)_n NR^5SO_2R^5$,
(17) -$(CH_2)_n SO_2N(R^5)_2$,

(18) -$(CH_2)_nS(O)_pR^5$,
(19) -$(CH_2)_nNR^5C(O)N(R^5)_2$,
(20) -$(CH_2)_nC(O)N(R^5)_2$,
(21) -$(CH_2)_nNR^5C(O)R^5$,
(22) -$(CH_2)_nNR^5CO_2R^5$,
(23) -$(CH_2)_nNR^5C(O)$-heteroaryl,
(24) -$(CH_2)_nC(O)NR^5N(R^5)_2$,
(25) -$(CH_2)_nC(O)NR^5NR^5C(O)R^5$,
(26) $O(CH_2)_nC(O)N(R^5)_2$,
(27) CF_3,
(28) CH_2CF_3,
(29) OCF_3, and
(30) OCH_2CF_3,

wherein phenyl, naphthyl, heteroaryl, cycloalkyl, and heterocyclyl are unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, oxo, C_{1-4} alkyl, trifluoromethyl, and C_{1-4} alkoxy, and wherein any methylene (CH_2) carbon atom in R^2 and R^3 are unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and C_{1-4} alkyl, or two substituents when on the same methylene (CH_2) group are taken together with the carbon atom to which they are attached to form a cyclopropyl group;

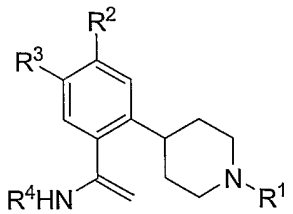
R^4 is selected from the group consisting of

(1) –C(O)C_{1-6}alkyl,
(2) –C(O)cycloalkyl,
(3) –C(O)CH_2-phenyl,
(4) –C(O)aryl, and
(5) –C(O)heteroaryl, and

n is 0, 1 or 2;

comprising the steps of:

(a) reducing the enamide double bond of the compound of structural formula (III)



(III)

wherein R^1, R^2, R^3, R^4 and n are as defined above.

2. The process of Claim 1 wherein R^1 is C(O)O-*tert*-butyl; R^2 is hydrogen, R^3 is chloride; and R^4 is $-C(O)CH_3$.

3. The process of Claim 1 wherein the enamide double bond of compound (III) is reduced by hydrogenation in the presence of a catalyst of structural formula (VI):

(VI) (L)Rh(D)X

wherein

D is an olefin, diene or triene;

X is an anion selected from the group consisting of halogen, methanesulfonate, trifluoromethanesulfonate (OTf), tetrafluoroborate (BF_4), hexafluorophosphate (PF_6), hexafluoroantimonate (SbF_6), acetylacetonate, and BARF (tetrakis(3,5-bis(trifluoromethyl)phenyl)borate; and

L is a ligand selected from the group consisting of: Binaphane, f-Binaphane, MeBPE, Me-Ketalphos, EtBPE, MeDuphos, EtDuphos, N-Me-Malphos, 1,2-bis(ethylphenyl-phosphino)benzene, 1,2-bis(methylphenylphosphino)benzene, Walphos (SL-W001-2), Pip-Monophos, EtFerrotane, EtBophoz, MeBophoz, Octahydro-pip-Monophos, Tangphos, Phanephos, Xyl-Phanephos, SL-R002-1, Taniaphos, SL-J409-2, TMBTP, and DiPAMP, either preformed, or formed in situ from a rhodium metal precursor.

4. The process of Claim 3 wherein the catalyst is selected from the group consisting of: (MeBPE)Rh(COD)BF_4, (MeDuphos)Rh(COD)BF_4, (Binaphane)Rh(COD)BF_4, (1,2-bis(methylphenyl-phosphino)benzene)Rh(COD)BF_4, (f-Binaphane)Rh(COD)BF_4, (N-Me-Malphos)Rh(COD)BF_4, and (MeKetalphos)Rh(COD)BF_4.

5. The process of Claim 3 to produce a compound of structural formula (IV) with an enantiomeric excess of the "S" stereoisomer at the carbon marked with an * comprising treating a compound of structural formula (III) with a catalyst selected from the group consisting of: (S-MeBPE)Rh(COD)BF_4, (S-MeDuphos)Rh(COD)BF_4, (R-Binaphane)-Rh(COD)BF_4, (S,S-1,2-

bis(methylphenyl-phosphino)benzene)Rh(COD)BF_4, (R-f-Binaphane)Rh(COD)BF_4, (N-Me-(S)-Malphos)Rh(COD)BF_4, and (S-MeKetalphos)Rh(COD)BF_4.

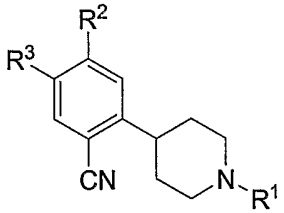
6. The process of Claim 5 wherein the catalyst is (S-MeBPE)Rh(COD)BF_4, either preformed or formed in situ.

7. The process of Claim 5 wherein the catalyst is (S-MeDuphos)Rh(COD)BF_4, either preformed or formed in situ.

8. The process of Claim 1 wherein the compound of structural formula (IV) is provided in an enantiomeric excess of greater than 85 % ee of the "S" stereoisomer at the carbon marked with an *.

9. The process of Claim 1 further comprising the steps of:

(b) treating a compound of structural formula (II)



(II)

wherein:

R^1 is selected from the group consisting of

(5) -C(O)O-phenyl,
(6) -C(O)O-CH_2-phenyl,
(7) -C(O)O-*tert*-butyl, and
(8) -CH_2-phenyl; and

R^2 and R^3 are independently selected from the group consisting of

(1) hydrogen,
(2) C_{1-6} alkyl,
(3) -$(CH_2)_n$-phenyl,
(4) -$(CH_2)_n$-naphthyl,
(5) -$(CH_2)_n$-heteroaryl,
(6) -$(CH_2)_n$-heterocyclyl,

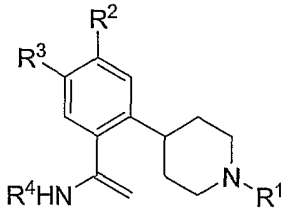
(7) -$(CH_2)_nC_{3-7}$ cycloalkyl,
(8) fluoride,
(9) chloride,
(10) OR^5,
(11) -$(CH_2)_nN(R^5)_2$,
(12) -$(CH_2)_nC{\equiv}N$,
(13) -$(CH_2)_nCO_2R^5$,
(14) NO_2,
(15) $N(R^5)_2$,
(16) -$(CH_2)_nNR^5SO_2R^5$,
(17) -$(CH_2)_nSO_2N(R^5)_2$,
(18) -$(CH_2)_nS(O)_pR^5$,
(19) -$(CH_2)_nNR^5C(O)N(R^5)_2$,
(20) -$(CH_2)_nC(O)N(R^5)_2$,
(21) -$(CH_2)_nNR^5C(O)R^5$,
(22) -$(CH_2)_nNR^5CO_2R^5$,
(23) -$(CH_2)_nNR^5C(O)$-heteroaryl,
(24) -$(CH_2)_nC(O)NR^5N(R^5)_2$,
(25) -$(CH_2)_nC(O)NR^5NR^5C(O)R^5$,
(26) $O(CH_2)_nC(O)N(R^5)_2$,
(27) CF_3,
(28) CH_2CF_3,
(29) OCF_3, and
(30) OCH_2CF_3,

wherein phenyl, naphthyl, heteroaryl, cycloalkyl, and heterocyclyl are unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, oxo, C_{1-4} alkyl, trifluoromethyl, and C_{1-4} alkoxy, and wherein any methylene (CH_2) carbon atom in R^2 and R^3 are unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and C_{1-4} alkyl, or two substituents when on the same methylene (CH_2) group are taken together with the carbon atom to which they are attached to form a cyclopropyl group; and

n is 0, 1 or 2;

with a base, followed by an acylating agent, and

(c) isolating the resulting product of structural formula (III):



(III)

wherein R^1, R^2, R^3 and n are as defined above, and

R^4 is selected from the group consisting of:

(1) $-C(O)C_{1-6}$alkyl,

(2) –C(O)cycloalkyl,

(3) $-C(O)CH_2$-phenyl,

(4) –C(O)aryl, and

(5) –C(O)heteroaryl.

10. The process of Claim 9 wherein R^1 is C(O)O-*tert*-butyl; R^2 is hydrogen, R^3 is chloride; and R^4 is $-C(O)CH_3$.

11. The process of Claim 10 wherein the base of step (b) is selected from a group consisting of methyl lithium, methyl lithium/lithium bromide complex, and methyl magnesium halide, wherein halide bromine, chlorine, or iodine.

12. The process of Claim 11 further comprising a salt selected from the group consisting of: lithium halide or copper halide, wherein halide is bromine, chlorine, or iodine.

13. The process of Claim 11 wherein the base is methyl lithium.

14. The process of Claim 13 further comprising lithium bromide.

15. The process of Claim 9 wherein the acylating agent of step (b) is a compound of formula (VII)

(VII) R^4-O-R^4,

wherein R^4 is selected from the group consisting of:

(1) $-C(O)C_{1-6}$alkyl,

(2) –C(O)cycloalkyl,

(3) –C(O)CH_2-phenyl,

(4) –C(O)aryl, and

(5) –C(O)heteroaryl.

16. The process of Claim 15 wherein the acylating agent is acetic anhydride.

17. The process of Claim 9 wherein the acylating agent is a compound of formula (VIII):

(VIII) R^4Y,

wherein R^4 is selected from the group consisting of:

(1) –C(O)C_{1-6}alkyl,

(2) –C(O)cycloalkyl,

(3) –C(O)CH_2-phenyl,

(4) –C(O)aryl, and

(5) –C(O)heteroaryl, and

Y is selected from the group consisting of:

(1) Cl,

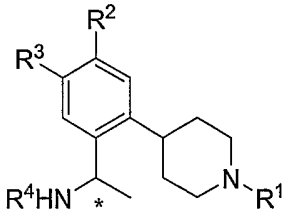
(2) Br, and

(3) I.

18. The process of Claim 17 wherein the acylating agent is acetyl chloride.

19. The process of Claim 1 further comprising the steps of:

(d) cleaving the R^1 protecting group of compound (IV)



(IV) ,

wherein:

R^1 is selected from the group consisting of:

(1) -C(O)O-phenyl,

(2) -C(O)O-CH_2-phenyl,

(3) -C(O)O-*tert*-butyl, and

(4) -CH_2-phenyl; and

R^2 and R^3 are independently selected from the group consisting of

(1) hydrogen,

(2) C_{1-6} alkyl,

(3) -$(CH_2)_n$-phenyl,

(4) -$(CH_2)_n$-naphthyl,

(5) -$(CH_2)_n$-heteroaryl,

(6) -$(CH_2)_n$-heterocyclyl,

(7) -$(CH_2)_nC_{3-7}$ cycloalkyl,

(8) fluoride,

(9) chloride,

(10) OR^5,

(11) -$(CH_2)_nN(R^5)_2$,

(12) -$(CH_2)_nC{\equiv}N$,

(13) -$(CH_2)_nCO_2R^5$,

(14) NO_2,

(15) $N(R^5)_2$,

(16) -$(CH_2)_nNR^5SO_2R^5$,

(17) -$(CH_2)_nSO_2N(R^5)_2$,

(18) -$(CH_2)_nS(O)_pR^5$,

(19) -$(CH_2)_nNR^5C(O)N(R^5)_2$,

(20) -$(CH_2)_nC(O)N(R^5)_2$,

(21) -$(CH_2)_nNR^5C(O)R^5$,

(22) -$(CH_2)_nNR^5CO_2R^5$,

(23) -$(CH_2)_nNR^5C(O)$-heteroaryl,

(24) -$(CH_2)_nC(O)NR^5N(R^5)_2$,

(25) -$(CH_2)_nC(O)NR^5NR^5C(O)R^5$,

(26) $O(CH_2)_nC(O)N(R^5)_2$,

(27) CF_3,

(28) CH_2CF_3,

(29) OCF_3, and

(30) OCH_2CF_3,

wherein phenyl, naphthyl, heteroaryl, cycloalkyl, and heterocyclyl are unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, oxo, C_{1-4} alkyl, trifluoromethyl, and C_{1-4} alkoxy, and wherein any methylene (CH_2) carbon atom in R^2 and R^3 are unsubstituted or

substituted with one to two groups independently selected from halogen, hydroxy, and C_{1-4} alkyl, or two substituents when on the same methylene (CH_2) group are taken together with the carbon atom to which they are attached to form a cyclopropyl group;

R^4 is selected from the group consisting of

(1) –C(O)C_{1-6}alkyl,

(2) –C(O)cycloalkyl,

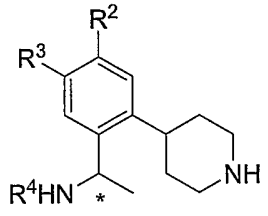
(3) –C(O)CH_2-phenyl,

(4) –C(O)aryl, and

(5) –C(O)heteroaryl, and

n is 0, 1 or 2; and

(e) isolating the resulting product of structural formula (I)



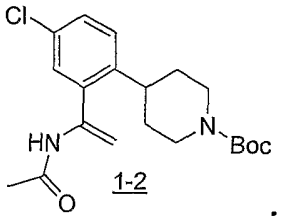
(I)

enantiomerically enriched at the carbon marked with an *, or a salt thereof, wherein R^2, R^3, R^4 and n are as defined above.

20. The process of Claim 19 wherein R^1 is C(O)O-*tert*-butyl, R^2 is hydrogen, R^3 is chloride, R^4 is -C(O)CH_3, and R^1 is cleaved by treating compound (IV) of step (d) with an acid selected from the group consisting of hydrochloric acid, hydrobromic acid, and trifluoroacetic acid.

21. The process of Claim 20 wherein the acid is hydrochloric acid.

22. The compound 1-2



1-2

.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2005/041839

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D211/26

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BEILSTEIN Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2003/225060 A1 (MERCK & CO) 4 December 2003 (2003-12-04) page 37 - page 38; compounds 3-8	1-22
A	HUANG ET AL: "A Novel Class of P-O Monophosphite Ligands Derived from D-Mannitol: Broad Applications in Highly Enantioselective Rh-Catalyzed Hydrogenations" JOURNAL OF ORGANIC CHEMISTRY, vol. 69, 27 February 2004 (2004-02-27), pages 2355-2361, XP002374252 cited in the application page 2357; tables	1-22
P,A	WO 2005/009950 A (MERCK & CO) 3 February 2005 (2005-02-03) pages 69,70 pages 78,80	1-22

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 March 2006	12/04/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Cortés, J

INTERNATIONAL SEARCH REPORT

In nal application No
PCT/US2005/041839

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2003225060 A1	04-12-2003	NONE	
WO 2005009950 A	03-02-2005	AU 2004259717 A1	03-02-2005