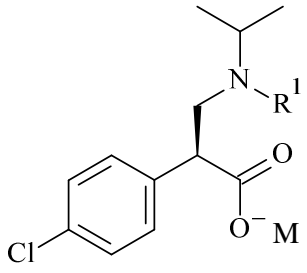
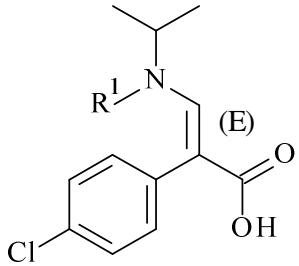
M is a metal ion selected from an alkali metal ion.

In one aspect, the present disclosure refers to a process for the preparation of a compound of formula (II)



(II)

comprising the asymmetric hydrogenation of a compound of formula (IV)



(IV)

using a metal complex catalyst (C) wherein

R^1 is an amino-protecting group selected from the list of benzyl, benzyloxycarbonyl (carbobenzyloxy, CBZ), 9-Fluorenylmethyloxycarbonyl (Fmoc), p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, tert-butoxycarbonyl (BOC), and trifluoroacetyl; and

M is an alkali metal ion; and

wherein the metal complex catalyst (C) is a ruthenium complex catalyst selected from a compound of formula (C1), (C2) or (C3):

$Ru(Z)_2D$ (C1)

$[Ru(Z)_{2-p}(D)(L)_m](Y)_p$ (C2)

Ru(E)(E')(D)(F) (C3)

wherein:

D is a chiral phosphine ligand;

L is a neutral ligand selected from C_{2-7} alkene, cyclooctene, 1,3-hexadiene, norbornadiene, 1,5-cyclooctadiene, benzene, hexamethylbenzene, 1,3,5-trimethylbenzene, p-cymene, tetrahydrofuran, dimethylformamide, acetonitrile, benzonitrile, acetone, toluene and methanol;

Z is an anionic ligand selected from hydride, fluoride, chloride, bromide, η^5-2,4-pentadienyl, η^5-2,4-dimethyl-pentadienyl or the group A-COO^-,

with the proviso that when two Z are attached to the Ru atom they can either be the same or different;

A is C_{1-7} alkyl, C_{1-7} haloalkyl, aryl, or haloaryl;

Y is a non-coordinating anion selected from fluoride, chloride, bromide, iodide, BF_4^-, ClO_4^-, SbF_6^-, PF_6^-, $B(phenyl)_4^-$, $B(3,5\text{-di-trifluoromethyl-phenyl})_4^-$, $CF_3SO_3^-$, and $C_6H_5SO_3^-$;

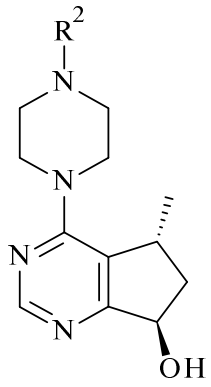
F is an optionally chiral diamine;

E and E' are both halogen ions, or E is hydride and E' is BH_4^-;

m is 1, 2, 3 or 4; and

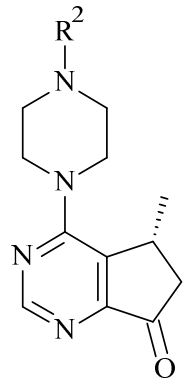
p is 1 or 2.

In one aspect, the present disclosure refers to a process for the manufacture of compounds of formula (III)



(III)

comprising the asymmetric reduction of the compound of formula (V)



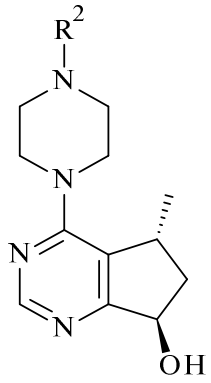
(V)

catalyzed by an oxidoreductase, wherein R^2 is an amino-protecting group selected from the list of benzyl, benzyloxycarbonyl (carbobenzyloxy, CBZ), 9-Fluorenylmethyloxycarbonyl (Fmoc), p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, tert-butoxycarbonyl (BOC), and trifluoroacetyl;

wherein the asymmetric reduction is catalyzed by the oxidoreductase in the presence of a cofactor; and

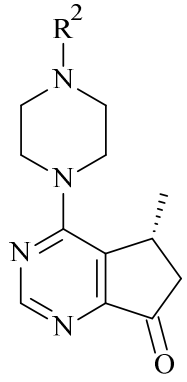
wherein the cofactor is in situ regenerated by substrate-coupled cofactor regeneration using a secondary alcohol as cosubstrate.

In one aspect, the present disclosure refers to a process for the manufacture of compounds of formula (III)



(III)

comprising the asymmetric reduction of the compound of formula (V)



(V)

catalyzed by an oxidoreductase, wherein R^2 is an amino-protecting group selected from the list of benzyl, benzyloxycarbonyl (carbobenzyloxy, CBZ), 9-Fluorenylmethyloxycarbonyl (Fmoc), p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, tert-butoxycarbonyl (BOC), and trifluoroacetyl;

wherein the asymmetric reduction is catalyzed by the oxidoreductase in the presence of a cofactor; and

wherein the oxidoreductase is a diastereoselective NADPH-dependent oxidoreductase selected from the list of KRED-NADPH-111, KRED-NADPH-112, KRED-NADPH-113, KRED-NADPH-114, KRED-NADPH-115, KRED-NADPH-121, KRED-NADPH-123, KRED-NADPH-145, KRED-NADPH-155, A231, KRED-NADPH-

136, KRED-X1, KRED-X2, KRED-X1-P1B06, KRED-X1.1-P1F01, KRED-X1.1-P1H10, KRED-X1.1-P1G11, KRED-X1.1-P1C04, KRED-X1.1-P1C11, and KRED-X1.1-P1C08 or a variant thereof.

Detailed description of the invention

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the invention, suitable methods and materials are described below.

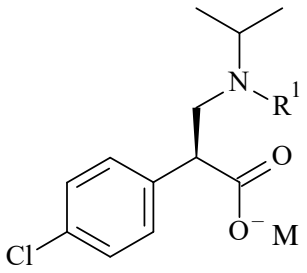
The nomenclature used in this Application is based on IUPAC systematic nomenclature, unless indicated otherwise.

Any open valency appearing on a carbon, oxygen, sulfur or nitrogen atom in the structures herein indicates the presence of a hydrogen, unless indicated otherwise.

When indicating the number of substituents, the term “one or more” refers to the range from one substituent to the highest possible number of substitution, i.e. replacement of one hydrogen up to replacement of all hydrogens by substituents.

Claims

1. A compound of formula (II)



(II)

wherein

R^1 is an amino-protecting group selected from the list of benzyl, benzyloxycarbonyl (carbobenzyloxy, CBZ), 9-Fluorenylmethyloxycarbonyl (Fmoc), p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, tert-butoxycarbonyl (BOC), and trifluoroacetyl; and

M is a metal ion selected from an alkali metal ion.

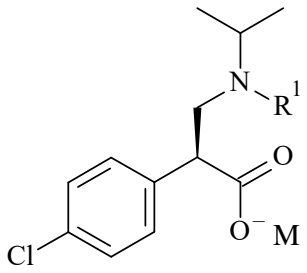
2. The compound of claim 1, wherein M is Li^+, K^+ or Na^+.

3. The compound of claim 1, wherein M is Na^+.

4. The compound of claim 1, wherein R^1 is tert-butoxycarbonyl (BOC).

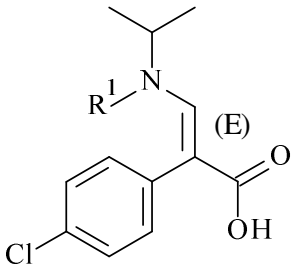
5. The compound of claim 1 that is sodium (S)-3-(tert-butoxycarbonyl(isopropyl)amino)-2-(4-chlorophenyl)propanoate.

6. A process for the preparation of a compound of formula (II)



(II)

comprising the asymmetric hydrogenation of a compound of formula (IV)



(IV)

using a metal complex catalyst (C) wherein

R^1 is an amino-protecting group selected from the list of benzyl, benzyloxycarbonyl (carbobenzyloxy, CBZ), 9-Fluorenylmethyloxycarbonyl (Fmoc), p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, tert-butoxycarbonyl (BOC), and trifluoroacetyl; and

M is an alkali metal ion; and

wherein the metal complex catalyst (C) is a ruthenium complex catalyst selected from a compound of formula (C1), (C2) or (C3):

$Ru(Z)_2D$ (C1)

$[Ru(Z)_{2-p}(D)(L)_m](Y)_p$ (C2)

Ru(E)(E')(D)(F) (C3)

wherein:

D is a chiral phosphine ligand;

L is a neutral ligand selected from C_{2-7} alkene, cyclooctene, 1,3-hexadiene, norbornadiene, 1,5-cyclooctadiene, benzene, hexamethylbenzene, 1,3,5-trimethylbenzene, p-cymene, tetrahydrofuran, dimethylformamide, acetonitrile, benzonitrile, acetone, toluene and methanol;

Z is an anionic ligand selected from hydride, fluoride, chloride, bromide, η^5-2,4-pentadienyl, η^5-2,4-dimethyl-pentadienyl or the group $A\text{-}COO^-$,
with the proviso that when two Z are attached to the Ru atom they can either be the same or different;

A is C_{1-7} alkyl, C_{1-7} haloalkyl, aryl, or haloaryl;

Y is a non-coordinating anion selected from fluoride, chloride, bromide, iodide, BF_4^-, ClO_4^-, SbF_6^-, PF_6^-, $B(phenyl)_4^-$, $B(3,5\text{-di-trifluoromethyl-phenyl})_4^-$, $CF_3SO_3^-$, and $C_6H_5SO_3^-$;

F is an optionally chiral diamine;

E and E' are both halogen ions, or E is hydride and E' is BH_4^-;

m is 1, 2, 3 or 4; and

p is 1 or 2.

7. The process according to claim 6, wherein the ruthenium complex catalysts is $Ru(Z)_2D$, wherein Z and D are as defined in claim 6.

8. The process according to claim 6, wherein the anionic ligand (Z) is TFA.

9. The process according to claim 6, wherein the neutral ligand (L) is independently selected from benzene (C_6H_6), p-cymene (pCym), and acetonitrile (AN).

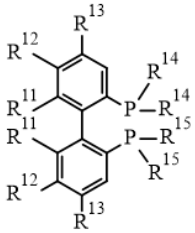
10. The process according to claim 6, wherein the non-coordinating anion (Y) is selected from chloride, bromide, iodide and BF_4^-.

11. The process according to claim 6, wherein m is 1 or 4.

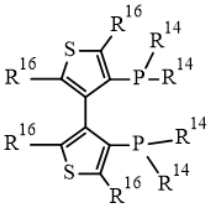
12. The process according to claim 6, wherein E and E' are both chloride.

13. The process according to claim 6, wherein the chiral diamine F is (1S,2S)-1,2-diphenylethylenediamine (S,S-DPEN).

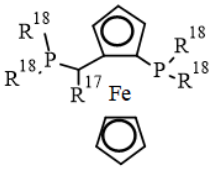
14. The process according to claim 6, wherein the chiral phosphine ligand D is selected from a compound of formula (D1) to (D12):



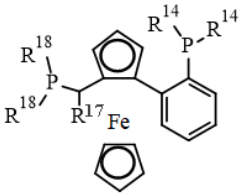
(D1)



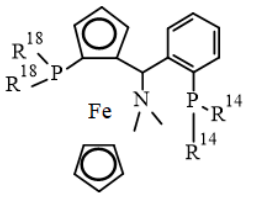
(D2)



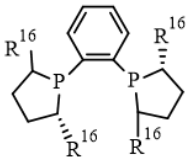
(D3)



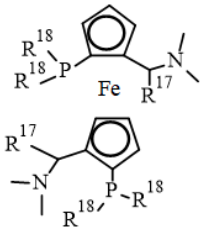
(D4)



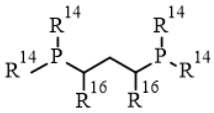
(D5)



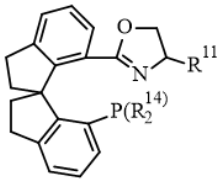
(D6)



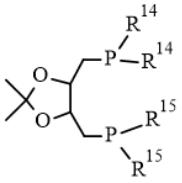
(D7)



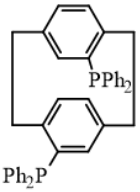
(D8)



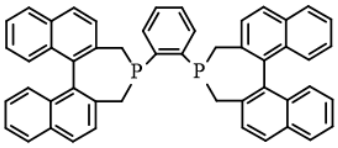
(D9)



(D10)



(D11)



(D12)

wherein:

R^{11} is C_{1-7} alkyl, C_{1-7} alkoxy, hydroxy or C_{1-7} alkyl-C(O)O-;

R^{12} and R^{13} are each independently hydrogen, C_{1-7} alkyl, C_{1-7} alkoxy or di(C_{1-7} alkyl)amino; or

R^{11} and R^{12} which are attached to the same phenyl group, or R^{12} and R^{13} which are attached to the same phenyl group taken together are -X-$(CH_2)_r$-Y-, wherein X is -O-, or -C(O)O-, Y is -O-, -N(lower-alkyl)-, or -CF_2- and r is an integer from 1 to 6; or

two R^{11} taken together are -O-$(CH_2)_s$-O- or O-$CH(CH_3)$-$(CH_2)_s$-$CH(CH_3)$-O-, wherein s is an integer from 1 to 6; or

R^{11} and R^{12}, or R^{12} and R^{13}, together with the carbon atoms to which they are attached, form a naphthyl, tetrahydronaphthyl or dibenzofuran ring;

R^{14} and R^{15} are each independently C_{1-7} alkyl, C_{3-8} cycloalkyl, phenyl, naphthyl or heteroaryl, optionally substituted with 1 to 7 substituents independently selected from the group consisting of C_{1-7} alkyl, C_{1-7} alkoxy, di(C_{1-7} alkyl)amino, morpholinyl, phenyl, tri(C_{1-7} alkyl)silyl, C_{1-7} alkoxycarbonyl, hydroxycarbonyl, hydroxysulfonyl, $(CH_2)_t$-OH and $(CH_2)_t$-NH_2, wherein t is an integer from 1 to 6;

R^{16} is C_{1-7} alkyl;

R^{17} is C_{1-7} alkyl; and

R^{18} independently is aryl, heteroaryl, C_{3-8} cycloalkyl or C_{1-7} alkyl.

15. The process according to claim 14, wherein the chiral phosphine ligand (D) is selected from the compound of formula (D1).

16. The process according to claim 6, wherein the chiral phosphine ligand (D) is selected from (R)-3,5-Xyl-BINAP, (R)-BINAP, (S)-2-Furyl-MeOBIPHEP, (S)-BINAP, (S)-BIPHEMP, (S)-MeOBIPHEP, (S)-pTol-BINAP), (S)-TMBTP and (S,S)-iPr-DUPHOS.

17. The process according to claim 6, wherein the ruthenium complex catalyst is selected from the group of:

$Ru(TFA)_2$((R)-3,5-Xyl-BINAP),

$Ru(OAc)_2$((S)-2-Furyl-MeOBIPHEP),

$Ru(OAc)_2$((S)-BINAP),

$[Ru(OAc)_2$((S)-BINAP)]$AlCl_3$,

$Ru(TFA)_2$((S)-BINAP),

$Ru(TFA)_2$((*S*)-BINAPHANE),

$Ru(TFA)_2$((S)-BIPHEMP),

$Ru(OAc)_2$((S)-MeOBIPHEP),

$Ru(TFA)_2$((S)-TMBTP),

$Ru(TFA)_2$((S,S)-iPr-DUPHOS),

$[Ru$((R)-BINAP)(pCym)(AN)$](BF_4)_2$,

$[RuBr$((S)-BINAP)$(C_6H_6)]Br$,

$[RuCl$((S)-BINAP)$(C_6H_6)]BF_4$,

$[RuI$((S)-BINAP)$(C_6H_6)]I$,

$[Ru$((S)-BINAP)(AN))$_4](BF_4)_2$, and

$RuCl_2$((S)-pTol-BINAP)(S,S-DPEN).

18. The process according to claim 6, wherein the ruthenium complex catalyst is $Ru(TFA)_2$((S)-BINAP).

19. The process according to claim 6, wherein the asymmetric hydrogenation of a compound of formula (IV) is carried out in a solvent selected from alcohols, hydrocarbons, chlorinated hydrocarbons, fluorinated and polyfluorinated aliphatic or aromatic hydrocarbons, supercritical or liquid carbon dioxide, THF, water or mixtures thereof.

20. The process according to claim 6, wherein the asymmetric hydrogenation of a compound of formula (IV) is carried out in a solvent selected from the list of MeOH, EtOH, i-PrOH, EtOH/cyclopentyl methyl ether, EtOH/CH_2Cl_2, EtOH/EtOAc, EtOH/THF, EtOH/H_2O, CH_2Cl_2 and THF.

21. The process according to claim 6, wherein the asymmetric hydrogenation of a compound of formula (IV) further comprises one or more additives selected from the list of $LiBF_4$, $LiPF_6$, LiO_3SCF_3, HBF_4, HCl, H_2SO_4, and CH_3SO_3H.

22. The process according to claim 6, wherein the asymmetric hydrogenation of a compound of formula (IV) is carried out under hydrogen pressure of 1 to 150 bar.

23. The process according to claim 6, wherein the asymmetric hydrogenation of a compound of formula (IV) is carried out under hydrogen pressure of 10 to 30 bar.

24. The process according to claim 6, wherein the asymmetric hydrogenation of a compound of formula (IV) is carried out at a substrate IV/metal complex catalyst ratio (S/C) of 5 to 100’000.

25. The process according to claim 6, wherein the asymmetric hydrogenation of a compound of formula (IV) is carried out at a substrate IV/metal complex catalyst ratio (S/C) of 100 to 15’000.

26. The process according to claim 6, followed by forming a salt by adding to the hydrogenation reaction mixture of IV and the metal complex catalyst, an alcoholic solution of a metal alkoxide of formula $C_{1\text{-}7}$ alkyl-OM.

27. The process according to claim 26, wherein the metal alkoxide employed in the salt forming step is MeOM, EtOM, iPrOM, nPrOM, nBuOM, iBuOM, or tBuOM.

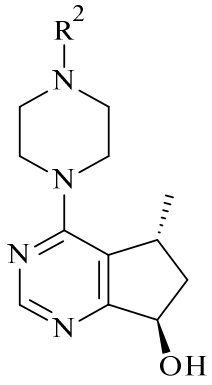
28. The process according to claim 6, wherein M is Li^+, K^+, or Na^+.

29. The process according to claim 6, wherein M is Na^+.

30. The process according to claim 6, wherein R^1 is tert-butoxycarbonyl (BOC).

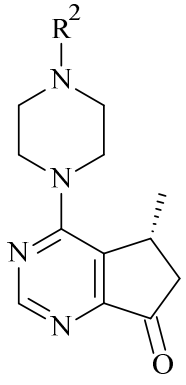
31. The process according to claim 6, wherein the compound of formula (II) is sodium (S)-3-(tert-butoxycarbonyl(isopropyl)amino)-2-(4-chlorophenyl)propanoate and the compound of formula (IV) is (E)-3-(tert-butoxycarbonyl(isopropyl)amino)-2-(4-chlorophenyl)acrylic acid.

32. A process for the manufacture of compounds of formula (III)



(III)

comprising the asymmetric reduction of the compound of formula (V)



(V)

catalyzed by an oxidoreductase, wherein R^2 is an amino-protecting group selected from the list of benzyl, benzyloxycarbonyl (carbobenzyloxy, CBZ), 9-

Fluorenylmethyloxycarbonyl (Fmoc), p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, tert-butoxycarbonyl (BOC), and trifluoroacetyl;
wherein the asymmetric reduction is catalyzed by the oxidoreductase in the presence of a cofactor; and
wherein the cofactor is in situ regenerated by substrate-coupled cofactor regeneration using a secondary alcohol as cosubstrate.

33. The process according to claim 32, wherein R^2 is tert-butoxycarbonyl (BOC).

34. The process according to claim 32 or 33, wherein the oxidoreductase catalyzes the asymmetric reduction of a compound of formula (V) to a compound of formula (III) with a diastereoselectivity of at least 95% diastereomeric excess (de).

35. The process according to any one of claims 32 to 34, wherein the oxidoreductase catalyzes the asymmetric reduction of a compound of formula (V) to a compound of formula (III) with a diastereoselectivity of at least 98% de.

36. The process according to any one of claims 32 to 35, wherein the cofactor which is oxidized in the asymmetric reduction of a compound of formula (V) to a compound of formula (III) is NADH or NADPH.

37. The process according to any one of claims 32 to 36, wherein the secondary alcohol as cosubstrate for the substrate coupled regeneration is selected from 2-propanol, 2-butanol, butan-1.4-diol, 2-pentanol, pentan-1,5-diol, 4-methyl-2-pentanol, 2-hexanol, hexan-1,5-diol, 2-heptanol, or 2-octanol.

38. The process according to claim 37, wherein the secondary alcohol as cosubstrate for the substrate-coupled cofactor regeneration is 2-propanol.

39. The process according to any one of claims 32 to 38, wherein the oxidoreductase is a diastereoselective NADPH-dependent oxidoreductase selected from the list of KRED-NADPH-111, KRED-NADPH-112, KRED-NADPH-113, KRED-NADPH-114, KRED-NADPH-115, KRED-NADPH-121, KRED-NADPH-123, KRED-NADPH-145, KRED-NADPH-155, A231, KRED-NADPH-136, KRED-X1, KRED-X2, KRED-X1-P1B06,

KRED-X1.1-P1F01, KRED-X1.1-P1H10, KRED-X1.1-P1G11, KRED-X1.1-P1C04, KRED-X1.1-P1C11, and KRED-X1.1-P1C08.

40. The process according to any one of claims 32 to 39, wherein the oxidoreductase is a diastereoselective NADPH-dependent oxidoreductase selected from the list of KRED-X1, KRED-X2, KRED-X1-P1B06, KRED-X1.1-P1F01, KRED-X1.1-P1H10, KRED-X1.1-P1G11, KRED-X1.1-P1C04, KRED-X1.1-P1C11, and KRED-X1.1-P1C08.

41. The process according to any one of claims 32 to 40, wherein the oxidoreductase is a diastereoselective NADPH-dependent oxidoreductase selected from the list of KRED-X1, KRED-X2, KRED-X1-P1B06, KRED-X1.1-P1C04 and KRED-X1.1-P1F01.

42. The process according to any one of claims 32 to 41, wherein the oxidoreductase is a diastereoselective NADPH-dependent oxidoreductase selected from the list of KRED-X1.1-P1C04 and KRED-X1.1-P1F01.

43. The process according to any one of claims 32 to 42, wherein the asymmetric reduction of a compound of formula (V) to a compound of formula (III) is performed in an aqueous medium in the presence of one or more organic cosolvents.

44. The process according to claim 43, wherein the organic cosolvents are present in a total concentration from 1 to 50 %V.

45. The process according to claim 43, the organic cosolvents are present in a total concentration from 5 to 30 %V.

46. The process according to any one of claims 43 to 45, wherein the organic cosolvents are selected from the list of glycerol, 2-propanol, diethylether, tert-butylmethylether, diisopropylether, dibutylether, methyl tetrahydrofurane, ethylacetate, butylacetat, toluene, heptane, hexane, cyclohexene and mixtures thereof.

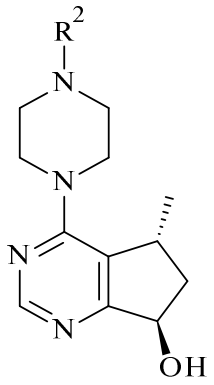
47. The process according to any one of claims 43 to 46, wherein the organic cosolvent is 2-propanol.

48. The process according to any one of claims 32 to 42, wherein the asymmetric reduction of a compound of formula (V) to a compound of formula (III) is performed in an aqueous buffer.

49. The process according to claim 48, wherein the buffer is 2-(N-morpholino)ethanesulfonic acid (MES) or potassium dihydrogen phosphate (PBS).

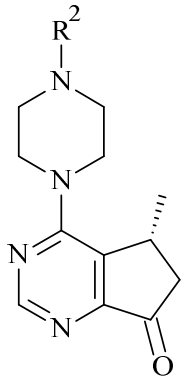
50. The process according to any one of claims 34 to 49, followed by work up by extraction or by filtration.

51. A process for the manufacture of compounds of formula (III)



(III)

comprising the asymmetric reduction of the compound of formula (V)



(V)

catalyzed by an oxidoreductase, wherein R^2 is an amino-protecting group selected from the list of benzyl, benzyloxycarbonyl (carbobenzyloxy, CBZ), 9-

Fluorenylmethyloxycarbonyl (Fmoc), p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, tert-butoxycarbonyl (BOC), and trifluoroacetyl;

wherein the asymmetric reduction is catalyzed by the oxidoreductase in the presence of a cofactor; and

wherein the oxidoreductase is a diastereoselective NADPH-dependent oxidoreductase selected from the list of KRED-NADPH-111, KRED-NADPH-112, KRED-NADPH-113, KRED-NADPH-114, KRED-NADPH-115, KRED-NADPH-121, KRED-NADPH-123, KRED-NADPH-145, KRED-NADPH-155, A231, KRED-NADPH-136, KRED-X1, KRED-X2, KRED-X1-P1B06, KRED-X1.1-P1F01, KRED-X1.1-P1H10, KRED-X1.1-P1G11, KRED-X1.1-P1C04, KRED-X1.1-P1C11, and KRED-X1.1-P1C08 or a variant thereof.

52. The process according to claim 51, wherein the oxidoreductase is a diastereoselective NADPH-dependent oxidoreductase selected from the list of KRED-X1, KRED-X2, KRED-X1-P1B06, KRED-X1.1-P1F01, KRED-X1.1-P1H10, KRED-X1.1-P1G11, KRED-X1.1-P1C04, KRED-X1.1-P1C11, and KRED-X1.1-P1C08 or a variant thereof.

53. The process according to claim 51, wherein the oxidoreductase is a diastereoselective NADPH-dependent oxidoreductase selected from the list of KRED-X1, KRED-X2, KRED-X1-P1B06, KRED-X1.1-P1C04 and KRED-X1.1-P1F01 or a variant thereof.

54. The process according to claim 51, wherein the oxidoreductase is a diastereoselective NADPH-dependent oxidoreductase selected from the list of KRED-X1.1-P1C04 and KRED-X1.1-P1F01 or a variant thereof.

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