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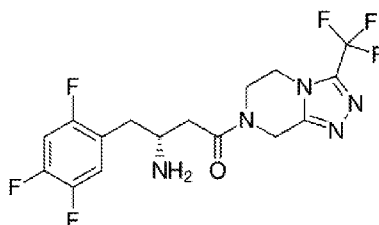
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(54) Title: HIGHLY EFFICIENT PROCESS FOR THE PREPARATION OF SITAGLIPTIN VIA RHODIUM CATALYZED ASYMMETRIC HYDROGENATION



Formula Ia

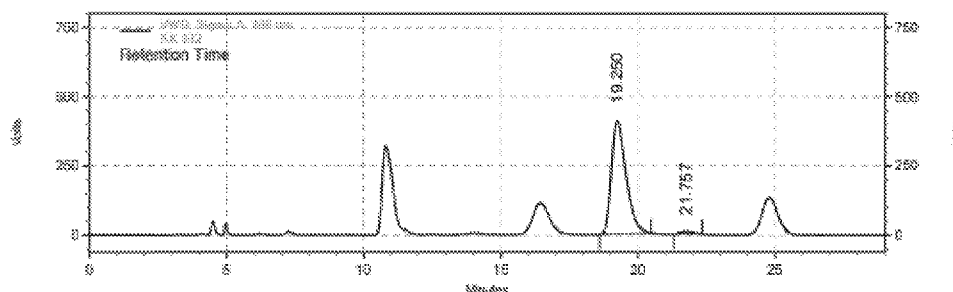


Fig. 1

(57) Abstract: The present invention provides highly efficient process for the preparation of enantiomerically enriched Sitagliptin of Formula (Ia). More particularly, a direct rhodium catalyzed asymmetric hydrogenation in the presence of bis-phosphine chiral ligand has been developed to yield enantiopure Sitagliptin product with the highest enantiomeric excess of 85-99.9%.



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HIGHLY EFFICIENT PROCESS FOR THE PREPARATION OF SITAGLIPTIN VIA RHODIUM CATALYZED ASYMMETRIC HYDROGENATION

FIELD OF THE INVENTION

5 The present invention provides highly efficient process for the preparation of enantiomerically enriched Sitagliptin. More particularly, a direct rhodium catalyzed asymmetric hydrogenation in the presence of bis-phosphine chiral ligand has been developed to yield enantiopure Sitagliptin product with the highest enantiomeric excess of 85-99.9%.

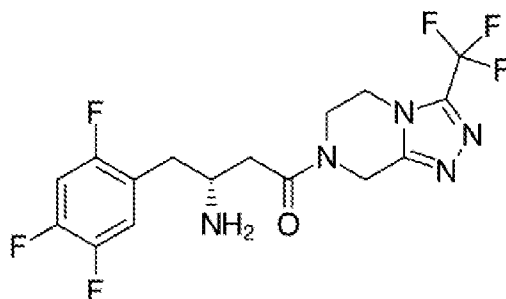
10 BACKGROUND AND PRIOR ART OF THE INVENTION

Beta amino acids and its derivatives have lot of medicinal significance. Beta amino acids are also present in peptides and different heterocycles. In beta amino acids, the amino group is linked to the beta carbon. Different free forms and derivatives of beta amino acid exhibit interesting pharmacological effects. Many methods of syntheses and transformations have
15 been explored to obtain enantiomerically pure product of beta amino acid derivative. Still it is a challenge in organic synthesis to develop a process for the preparation of beta amino acids with high enantiomeric excess, when different functional groups are bonded to the beta carbon in order to maintain the chirality.

Many API's exhibiting antibiotic, antifungal, cytotoxic, and other pharmacological
20 properties comprise the product of the present invention, a chiral beta-amino acid derivatives. They are therefore frequently used chiral building blocks in organic synthesis.

Another important application is the substitution of unnatural alpha- and beta-amino acids in biologically active peptides, which greatly enhance the understanding of enzyme mechanisms, protein conformations and properties related to molecular recognition, and for
25 obtaining peptides with increased potency and enzymatic stability.

More preferably, here the beta amino acid compound is Sitagliptin Formula Ia. Sitagliptin is chemically known as (*R*)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine and marketed as a phosphate salt under trade name JANUVIA by Merck.

**Formula Ia**

Sitagliptin is used possibly with other medications to control high blood sugar. It is used in people with type 2 diabetes. Controlling high blood sugar helps prevent kidney damage, blindness, nerve problems, loss of limbs, and sexual function problems. Proper control of diabetes may also lessen your risk of a heart attack or stroke. Sitagliptin is a diabetes drug that works by increasing levels of natural substances called incretins. Incretins help to control blood sugar by increasing insulin release, especially after a meal. It also decreases the amount of sugar in liver.

J. Org. Process Res. Dev. 2005, 9, 634–639 describes lengthy multi step reaction process giving only 52% yield of sitagliptin. However, in this transformation selective separation of (E/Z) isomers was problematic as well as overall approach was multi-step.

J. Am. Chem. Soc. 2009, 131(32): p. 11316-11317 reports direct asymmetric reductive amination to sitagliptin with 96% yield and 99.5% enantiomeric excess, which is achieved by using Ruthenium metal and (R)-dm-segphos as ligand in presence of acidic additives like acetic acid, benzoic acid, salicylic acid, chloroacetic acid etc.

PCT application WO2005097733 describes the process for the preparation of beta amino acid derivatives including sitagliptin using Ru catalyst in the presence of chiral mono- or bis-phosphene ligands. But this application specifically does not include ferrocenyl bisphosphene ligands with Ru catalyst for asymmetric hydrogenation, in its description.

Sitagliptin is an important active ingredient for diabetic patients. Therefore, highly enantioselective, low cost synthesis of this API is always in need. The present invention provides such atom economic single step protocol like asymmetric hydrogenation which provides an unprecedented enantiomeric excess of 90% and above. It reduces the cost of the process also by generating the desired active catalyst in-situ, circumventing the need of separate synthesis and isolation of active catalyst.

OBJECTS OF THE INVENTION

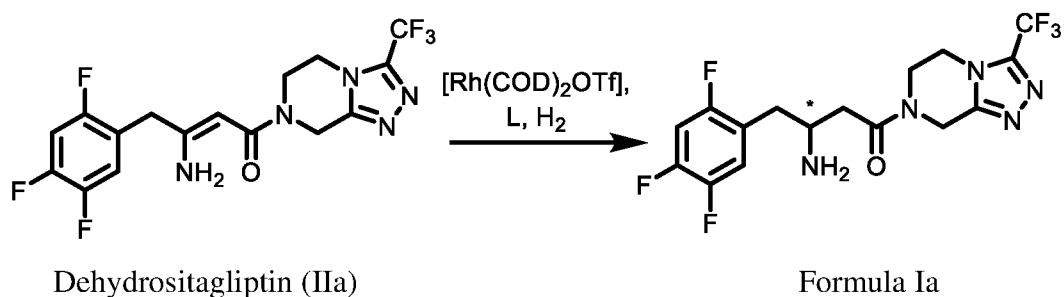
Main objectives of the present invention is to provide a highly efficient process for the preparation of enantiomerically enriched Sitagliptin.

Another objective of the present invention is to provide a direct rhodium catalyzed asymmetric hydrogenation in the presence of bis-phosphine chiral ligand to yield enantiopure Sitagliptin product with the highest enantiomeric excess of 85-99.9%.

An another objectives of the present invention is to provide process for the preparation of beta amino acid derivatives of Formula (I), more preferably Sitagliptin of Formula (Ia), via highly enantioselective asymmetric hydrogenation with in-situ generated catalyst by using Rh-catalyst in the presence of ferrocenyl bisphosphene ligands, which provides enantiopure Sitagliptin of Formula (Ia) with the highest enantiomeric excess of 85-99.9%.

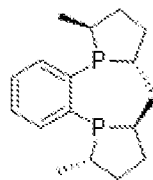
SUMMARY OF THE INVENTION

Accordingly, the present invention relates to a process for the preparation of sitagliptin, compound of Formula (Ia) by enantioselective asymmetric hydrogenation of dehydrositagliptin of Formula (IIa) employing rhodium catalyst on bisphosphine ferrocenyl ligands of Formula L, to obtain enantiomeric excess in the range of 85-99.9%;



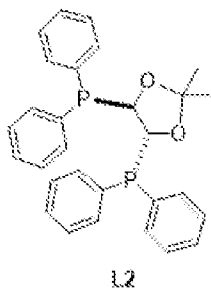
, said bisphosphine ferrocenyl ligands are selected from the group consisting of Formula L1-L8 are:

a) L1 : 1,2-bis(2,5-dimethylphospholan-1-yl)benzene

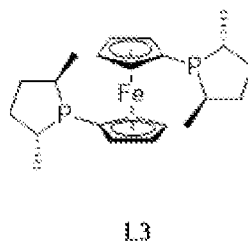


L1

b) L2 : (2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(diphenylphosphane)

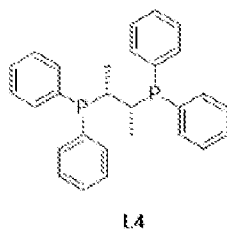


c) L3 : 1,1'-Bis[2,5-dimethylphospholano]ferrocene

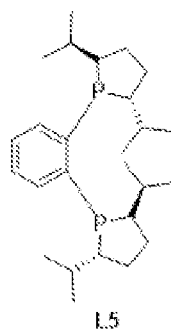


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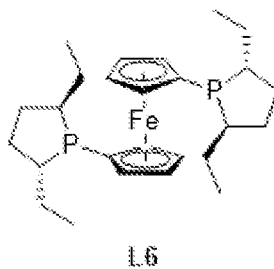
d) L4 : butane-2,3-diylbis(diphenylphosphane)



e) L5 : 1,2-bis(2,5-diisopropylphospholan-1-yl)benzene

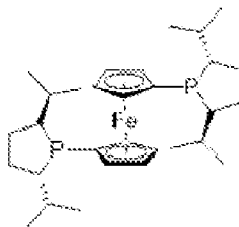


f) L6 : 1,1'-Bis[2,5-diethylphospholano]ferrocene



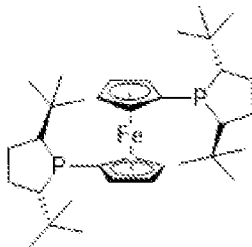
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g) L7 : 1,1'-Bis(2,5-di-isopropylphospholano)ferrocene



L7

h) L8 : 1,1'-Bis((2,5)-2,5-di-ter-butylphospholano)ferrocene



L8

5 wherein, the process for the preparation of sitagliptin, compound of Formula (Ia) comprises the steps of:

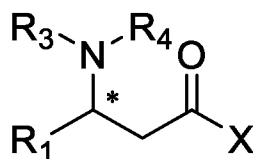
- i) mixing compound of Formula (IIa) with rhodium catalyst, ferrocenyl bisphosphine ligand L, and additive to obtained reaction mixture;
- 10 ii) adding solvent in the reaction mixture of step i) in the inert atmosphere of argon and stirring at a temperature of 25°C for an hour to obtained reaction slurry;
- 15 iii) maintaining the reaction slurry as obtained in step ii) under hydrogen pressure of 10-30 bar at a temperature of 35°C -90°C for 17-24 hrs into autoclave followed by cooling at a temperature of 25°C of step iii) and releasing the pressure to obtained reaction mixture 2;
- iv) passing the reaction mixture 2 of step iii) through neutral alumina bed followed by collecting the filtrate and drying the residue to afford compound of Formula (Ia).

In an embodiment of the present invention, the rhodium catalyst is [Rh(COD)₂OTf].

20 In another embodiment of the present invention, the additive is selected from the group consisting of salicylic acid, acetic acid, ammonium chloride, phosphoric acid, ammonium salicylate, tetramethyl ammonium iodide, tetraethyl ammonium iodide, tetra butyl ammonium bromide, butyl phosphoric acid, dibutyl phosphate, tributyl phosphate.

In yet another embodiment, the solvent selected from the group consisting of methanol, dichloromethane, tetrahydrofuran, trifluoroethanol, toluene, 1,4-dioxane and ethyl acetate.

In another embodiment, the preparation of beta amino acid derivatives of Formula (I), more preferably Sitagliptin of Formula (Ia), with the highest enantiomeric excess of 85-99.9%,



Formula I

wherein, the carbon atom marked with an '*' is enantiomerically enriched;

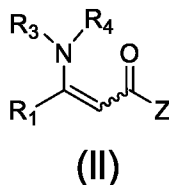
X is OR₂, SR₂, or NR₂R₂';

R₁ is alkyl, aryl, heteroaryl, aralkyl, or optionally substituted heteroaryl;

R₂ and R₂' are each independently selected from the group comprising of hydrogen, alkyl, aryl, aralkyl; or R₂ and R₂' together with the nitrogen atom to which they are attached may form a 4- to 7-membered optionally substituted ring system optionally containing an additional heteroatom selected from O, S, N, NH, and NC₁₋₄ alkyl; and said heterocyclic ring system being optionally fused with a 5-to 6-membered saturated or aromatic carbocyclic ring system or 5-to 6-membered saturated or aromatic heterocyclic ring system containing one to three heteroatoms selected from O, S, N, NH, and NC₁₋₄ alkyl, said fused ring system being unsubstituted or substituted;

R₃ and R₄ are independently selected from the group comprising of -H, alkyl, -COCH₃.

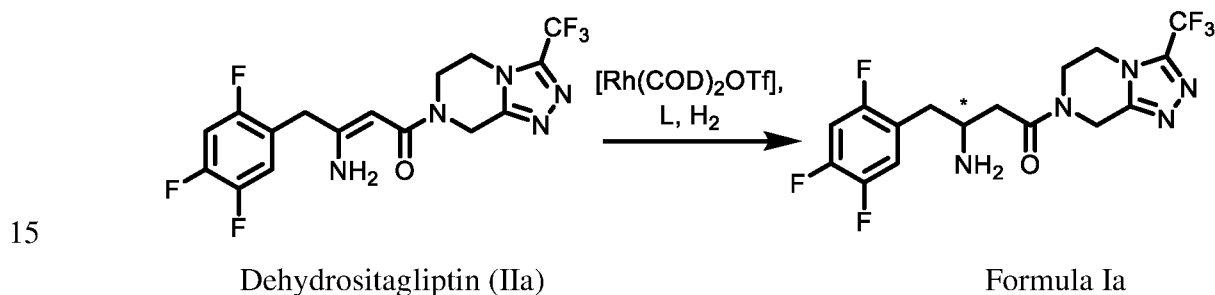
The process of the present invention relates to a highly enantioselective rhodium metal catalyzed asymmetric hydrogenation of a prochiral enamine of compound of structural Formula II in the presence of bisphosphine ferrocenyl ligand of Formula L to provide chiral beta amino acid derivatives of structural Formula I, more preferably compound of Formula Ia.



In still another embodiment, the bisphosphine ferrocenyl ligand of Formula L is selected from the group of ligands L1-L8;

- a) L1 : 1,2-bis(2,5-dimethylphospholan-1-yl)benzene
- b) L2 : (2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(diphenylphosphane)
- 5 c) L3 : 1,1'-Bis[2,5-dimethylphospholano]ferrocene
- d) L4 : butane-2,3-diylbis(diphenylphosphane)
- e) L5 : 1,2-bis(2,5-diisopropylphospholan-1-yl)benzene
- f) L6 : 1,1'-Bis[2,5-diethylphospholano]ferrocene
- g) L7 : 1,1'-Bis(2,5-di-isopropylphospholano)ferrocene
- 10 h) L8 : 1,1'-Bis((2,5)-2,5-di-ter-butylphospholano)ferrocene

In yet another embodiment, the present embodiment provides general process for the preparation of Sitagliptin, compound of Formula Ia. Asymmetric hydrogenation of dehydrositagliptin to sitagliptin of Formula Ia is shown below in synthetic scheme-1.



Scheme-1

BRIEF DESCRIPTION OF THE DRAWINGS

20 **Figure-1** describes HPLC chromatogram of enantiopure sitagliptin.

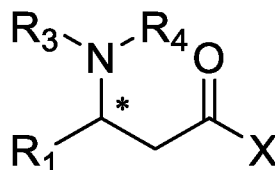
Figure-2 relates to the HPLC chromatogram of racemic sitagliptin

Figure 3 describes the HPLC chromatogram of dehydrositagliptin

DETAILED DESCRIPTION OF THE INVENTION

25 It is to be understood that the figures, schemes and descriptions of the present invention have been simplified to illustrate elements that are relevant for a clear understanding of the invention. The detailed description will be provided herein below with reference to the attached drawings, and schemes.

In view of the above, the present invention provides a process for the preparation of beta amino acid derivatives of Formula (I), more preferably Sitagliptin of Formula (Ia), with the highest enantiomeric excess of 85-99.9%,



Formula I

wherein, the carbon atom marked with an '*' is enantiomerically enriched;

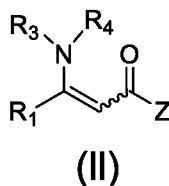
X is OR₂, SR₂, or NR₂R₂';

R₁ is alkyl, aryl, heteroaryl, aralkyl, or optionally substituted heteroaryl;

R₂ and R₂' are each independently selected from the group comprising of hydrogen, alkyl, aryl, aralkyl; or R₂ and R₂' together with the nitrogen atom to which they are attached may form a 4- to 7-membered optionally substituted ring system optionally containing an additional heteroatom selected from O, S, N, NH, and NC₁₋₄ alkyl; and said heterocyclic ring system being optionally fused with a 5-to 6-membered saturated or aromatic carbocyclic ring system or 5-to 6-membered saturated or aromatic heterocyclic ring system containing one to three heteroatoms selected from O, S, N, NH, and NC₁₋₄ alkyl, said fused ring system being unsubstituted or substituted;

R₃ and R₄ are independently selected from the group comprising of -H, alkyl, -COCH₃.

The process of the present invention relates to a highly enantioselective rhodium metal catalyzed asymmetric hydrogenation of a prochiral enamine of compound of structural Formula II in the presence of bisphosphine ferrocenyl ligand of Formula L to provide chiral beta amino acid derivatives of structural Formula I, more preferably compound of Formula Ia.

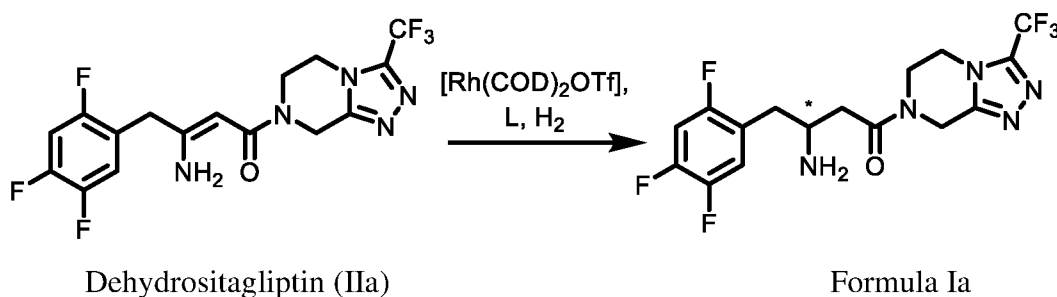


The general process to afford compound of Formula (I) comprises of following steps;

- i) mixing compound of formula II with rhodium catalyst, ferrocenyl bisphosphine ligand L, and additive;

- ii) adding suitable solvent in the reaction mixture of step i) in the inert atmosphere of argon and stirring at suitable temperature for an hour;
- iii) maintaining the reaction mixture under suitable hydrogen pressure at suitable temperature for 24 hrs into autoclave;
- iv) cooling the reaction mixture to a temperature in the range of 25-35°C of step iii) and releasing the pressure;
- v) passing the reaction mixture through neutral alumina bed;
- vi) collecting the filtrate and drying the residue to afford compound of Formula (I).

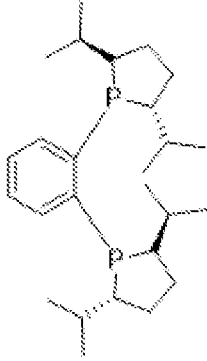
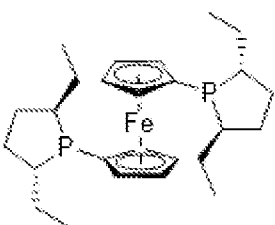
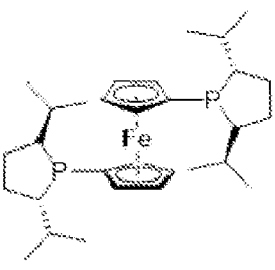
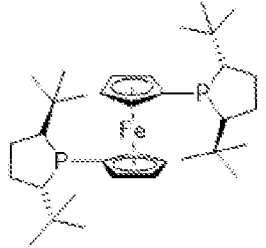
More particularly, the present embodiment provides above general process for the preparation of Sitagliptin, compound of Formula Ia. Asymmetric hydrogenation of dehydrositagliptin to sitagliptin of Formula Ia is shown below in synthetic scheme-1.



Scheme-1

The bisphosphine ferrocenyl ligand of Formula L is selected from the group of ligands L1-L8 represented below;

L1 1,2-bis(2,5-dimethylphospholan-1-yl)benzene	L2 (2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(diphenylphosphane)	L3 1,1'-Bis[2,5-dimethylphospholano]ferrocene	L4 butane-2,3-diylbis(diphenylphosphane)
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 L5 1,2-bis(2,5-diisopropylphospholan-1-yl)benzene	 L6 1,1'-Bis[2,5-diethylphospholano]ferrocene	 L7 1,1'-Bis(2,5-diisopropylphospholano)ferrocene	 L8 1,1'-Bis((2,5)-2,5-di-tert-butylphospholano)ferrocene
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In an aspect of the present embodiment involves a an additives at step i) of the process, which may be selected from the group comprising of Salicylic acid, Acetic acid, Ammonium chloride, Phosphoric acid, Ammonium salicylate, Tetra methyl ammonium iodide, Tetraethyl ammonium iodide, Tetra butyl ammonium bromide, Butyl phosphoric acid, Dibutyl phosphate, Tributyl phosphate.

Another aspect of the present embodiment involves a suitable solvent at step ii) of the process, suitable solvents may include alcohol solvents. Alcohol solvents, which may include methanol, ethanol, isopropanol, or mixtures thereof. In particularly useful embodiments, methanol is used as a solvent at step ii).

Suitable temperature for stirring the reaction mass at step ii) may be 20°C-40°C, more preferably 25°C-35°C.

Suitable temperature for maintaining the reaction mixture at step iii) may be 35°C-95°C, preferably 60°C-80°C, more preferably 70°-80°C.

Suitable hydrogen pressure for maintaining reaction mixture at step iii) may be 20 bar-40 bar, more preferably 30 bar.

Asymmetric hydrogenation of dehydrositagliptin is carried out using bis-phosphine ligands of Formulas L1 to L8, as shown above, with Rh precursor [Rh(COD)₂OTf]. Several experiments have been conducted by using different reaction parameters and ligands L1 to L8. Results of these experiments are summarized in Table 1.

Table 1 : Rhodium catalyzed asymmetric hydrogenation of dehydrositagliptin to sitagliptin.^a

Ex. No.	Ligand	Solvent	Press (bar)	Additives	Temp (°C)	Time (hrs)	Conv (%)	ee (%)
Ligand Screening								
1	L1	Methanol	20	NH ₄ Cl	50	17	00	00
2	L2	Methanol	20	NH ₄ Cl	50	17	00	00
3	L3	Methanol	20	NH ₄ Cl	50	17	20	85
4	L4	Methanol	20	NH ₄ Cl	50	17	00	00
Solvent Screening								
5	L3	Methanol	20	NH ₄ Cl	60	18	30	85
6	L3	DCM	20	NH ₄ Cl	60	18	00	00
7	L3	THF	20	NH ₄ Cl	60	18	00	00
8	L3	TFE	20	NH ₄ Cl	60	18	6	2
9	L3	Toluene	20	NH ₄ Cl	60	18	00	00
10	L3	1,4-dioxane	20	NH ₄ Cl	60	18	00	00
11	L3	EtOAc	20	NH ₄ Cl	60	18	00	00
Temperature Screening								
12	L3	Methanol	20	NH ₄ Cl	50	17	20	85
13	L3	Methanol	20	NH ₄ Cl	60	17	30	85
14	L3	Methanol	20	NH ₄ Cl	70	17	68	87
15	L3	Methanol	20	NH ₄ Cl	80	17	80	88
16	L3	Methanol	20	NH ₄ Cl	90	17	90	80
Pressure Screening								
17	L3	Methanol	10	NH ₄ Cl	70	24	00	00
18	L3	Methanol	20	NH ₄ Cl	70	24	30	85
19	L3	Methanol	30	NH ₄ Cl	70	24	90	87
Additive Screening								

20	L3	Methanol	30	NH ₄ Cl	70	24	90	87
21	L3	Methanol	30	CH ₃ CO ₂ H	70	24	74	85
22	L3	Methanol	30	H ₃ PO ₄	70	24	94	88
23	L3	Methanol	30	-	70	24	50	90
^a Conditions: Substrate (dehydrositagliptin): 85.11 mg; [Rh(COD) ₂ OTf]: 1 mg (1 mol%); Ligand/Rh: 1.1; Additive/Rh: 1; Solvent: 2 ml; conversion and enantiomeric excess is determined by chiral HPLC.								

Screening of Additives								
24	L6	Methanol	30	-	70	24	32	79
25	L6	Methanol	30	NH ₄ Cl	70	24	30	84
26	L6	Methanol	30	Acetic acid	70	24	20	84
27	L6	Methanol	30	H ₃ PO ₄	70	24	30	86
28	L6	Methanol	30	Salicylic acid	70	24	69	85
Screening of temperature								
29	L6	Methanol	30	Salicylic acid	70	24	69	85
30	L6	Methanol	30	Salicylic acid	80	24	98	86
Screening of catalyst loading								
31	L6 1 mol%	Methanol	30	NH ₄ Cl	70	24	65	84
32	L6 2 mol%	Methanol	30	NH ₄ Cl	70	24	90	88
33	L6 3 mol%	Methanol	30	NH ₄ Cl	70	24	91	85
34	L6 4 mol%	Methanol	30	NH ₄ Cl	70	24	99	85

35	L6 5 mol%	Methanol	30	NH ₄ Cl	70	24	99	85
Screening of Additives								
36	L7 1 mol%	Methanol	30	-	60	18	10	80
37	L7 1 mol%	Methanol	30	Salicylic acid	60	18	70	90
38	L7 1 mol%	Methanol	30	Acetic acid	60	18	10	94
39	L7 1 mol%	Methanol	30	NH ₄ Cl	60	18	30	91
40	L7 1 mol%	Methanol	30	H ₃ PO ₄	60	18	5	87
41	L7 1 mol%	Methanol	30	Ammonium salicylate	60	18	20	89
42	L7 1 mol%	Methanol	30	Tetramethyl ammonium iodide	60	18	-	-
43	L7 1 mol%	Methanol	30	Tetraethyl ammonium iodide	60	18	-	-
44	L7 1 mol%	Methanol	30	Tetra butyl ammonium bromide	60	18	-	-
45	L7 1 mol%	Methanol	30	Butyl phosphoric acid	70	24	34	89
46	L7 1 mol%	Methanol	30	Dibutyl phosphate	70	24	63	90
47	L7 1 mol%	Methanol	30	Tributyl phosphate	70	24	5	83

48	L7 1 mol%	Methanol	30	Formic acid	70	24	15	89
49	L7 1 mol%	Methanol	30	Sodium benzoate	70	24	10	66
50	L7 1 mol%	Methanol	30	Pyridinium p-toluene sulphate	70	24	14	80
Screening of Temperature								
51	L7 1 mol%	Methanol	30	Salicylic acid	70	18	95	92
52	L7 1 mol%	Methanol	30	Salicylic acid	60	18	95	94
53	L7 1 mol%	Methanol	30	Salicylic acid	50	18	90	95
54	L7 1 mol%	Methanol	30	Salicylic acid	45	18	85	98
55	L7 1 mol%	Methanol	30	Salicylic acid	40	18	60	95
56	L7 1 mol%	Methanol	30	Salicylic acid	35	18	10	96

GENERAL INFORMATION

All manipulations were carried out under an inert atmosphere of argon using standard Schlenk line techniques or m-Braun glove box. Solvents were dried by standard procedures unless otherwise mentioned. Ferrocene bis-phosphine ligands and $[\text{Rh}(\text{COD})_2\text{OTf}]$ were purchased from Sigma-Aldrich. While 1,1'-Bis(2,5-di-isopropylphospholano)ferrocene was purchased from Stream chemicals. Hydrogen gas (H_2) was supplied by Ms. Vadilal Chemicals Ltd., Pune, India. All other reagents/chemicals, solvents were purchased from local suppliers (Spectrochem Pvt. Ltd.; Avra Synthesis Pvt. Ltd.; Thomas Baker Pvt. Ltd.

etc). Asymmetric hydrogenation was performed in Amar Equipment Pvt. Ltd. high-pressure reactor equipped with pressure regulators and safety rupture valve.

Solution NMR spectra were recorded on a Bruker Advance 200, 400 and 500 MHz instruments at 298 K unless mentioned otherwise. Chemical shifts are referenced to external reference TMS (^1H). Coupling constants are given as absolute values. Multiplicities are given as follows s: singlet, d: doublet, t: triplet, m: multiplet. The enantiomeric excess and conversion to sitagliptin was determined by chiral HPLC on an Agilent Technologies 1260 Infinity instrument with Chiralpak IC column (250 mm $\times$ 4.6mm $\times$ 5 μm).

The following high performance liquid chromatographic (HPLC) conditions were used to determine percent conversion to product & optical purity of the sitagliptin product:

Column: Chiral Pak IC (250 mm $\times$ 4.6mm $\times$ 5 μm)

Eluent: n-Hexane: Ethanol: Diethyl amine (80:20:0.1)

Gradient: Isocratic

Flow rate: 1ml/min

Injection volume: 10 μL

UV detection: 266nm

Column temp.: ambient

Retention times: RT's may vary by ± 0.5 min

Dehydrositagliptin: 24.793 min

Racemic: 19.25 min & 21.757 min

Impurity: 16.440 min

Salicylic acid: 10.810 min

EXAMPLES

The following examples, which include preferred embodiments, will serve to illustrate the practice of this invention, it being understood that the particulars shown are by way of example and for purpose of illustrative discussion of preferred embodiments of the invention.

Example-1: General process for the synthesis of sitagliptin from dehydrositagliptin:

In a 5 ml reaction vial equipped with septa and inlet needle, dehydrositagliptin (100 eq. 85.11 mg), $[\text{Rh}(\text{COD})_2\text{OTf}]$ (1 eq. 1 mg), ligand L (1.05 eq.) and additive (1 eq.) were added in the glove box. Reaction vial was then transferred in a large Schlenk type container and was then taken out from the glove box. 2 ml dry methanol was added to the vial in inert atmosphere

and the resultant reaction slurry was stirred for 1 hour at 25°C. After that, the reaction vial was kept in an autoclave and the autoclave was purged three times by using hydrogen gas pressure (40 bars). Finally, the autoclave was pressurized to 30 bar of hydrogen pressure and the hydrogenation was continued at 50-70°C for 18 hrs. Then autoclave was cooled to 25°C, excess pressure was released and the autoclave was opened. The vials were taken out from autoclave reactor. The thus obtained reaction mixture was passed through neutral alumina bed, the filtrate was collect and dried to yield residue. The resultant residue was then analyzed by HPLC or NMR spectroscopy. ¹H NMR (400 MHz CDCl₃) δ = 7.10 (m, 1H), 6.89 (m, 1H), 4.89 (s, 2H), 4.21 (t, 2H) 4.06 (t, 2H), 3.36 (t, 1H), 3.25 (t, 1H), 2.79 (s, 1H), 2.32 (t, 1H), 2.00 (t, 1H).

HPLC: (Ref: Figure 1)

VWD: Signal A, 266 nm Results				
Retention Time	Area	Area %	Height	Height %
20.53	129681411	98.78	3064393	98.27
23.35	1604318	1.22	53969	1.73
Totals	131285729	100.00	3118362	100.00

Example-2: Process for the synthesis of sitagliptin from dehydrositagliptin using ligand of formula L3:

In a 5 ml reaction vial equipped with septa and inlet needle, dehydrositagliptin (100 eq. 85.11 mg), [Rh(COD)₂OTf] (1 eq. 1 mg), ligand L3 (1.05 eq.) and additive (1 eq.) were added in the glove box. Reaction vial was then kept in a large Schlenk type container and was then taken out from the glove box. 2 ml dry methanol was added to the vial in inert atmosphere and the resultant reaction slurry was stirred for 1 hour at 25°C. After that, the reaction vial was kept in an autoclave and the autoclave was purged three times by using hydrogen gas pressure (40 bars). Finally, the autoclave was pressurized to 30 bar hydrogen pressure and the hydrogenation was continued at 70°C for 18 hrs period. After 18 hrs, the autoclave was cooled to 25°C, excess pressure was released and the autoclave was opened. The vials were taken out from autoclave reactor. The thus obtained reaction mixture was passed through neutral alumina bed, the filtrate was collect and dried to yield residue. The resultant residue was then analyzed by HPLC or NMR spectroscopy.

Example-3: Process for the synthesis of sitagliptin from dehydrositagliptin using ligand of formula L7:

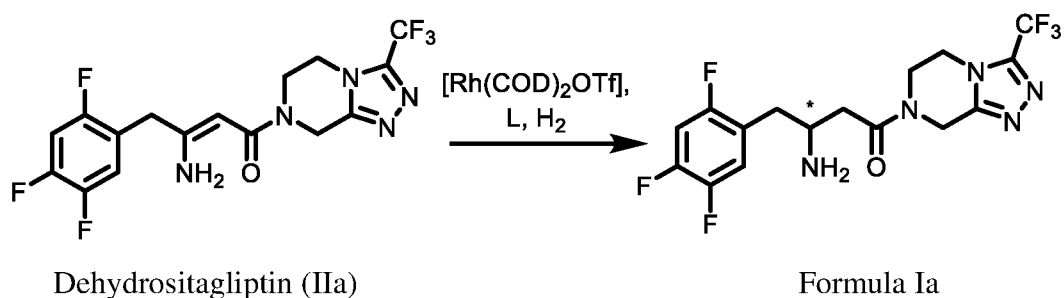
In a 5 ml reaction vial equipped with septa and inlet needle, dehydrositagliptin (100 mol%, 85.11 mg), [Rh(COD)₂OTf] (1 mol%), ligand L7 (1.1 mol%) and additive (150 mol%) were added in the glove box. Reaction vial was then kept in a large Schlenk type container and was then taken out from the glove box. 2 ml dry methanol was added to the vial in inert atmosphere and the resultant reaction slurry was stirred for 1 hour at 25°C. After that reaction vial was kept in an autoclave and the autoclave was purged three times by using hydrogen gas pressure (40 bars). Finally, the autoclave was pressurized to 30 bar hydrogen pressure and the hydrogenation was continued at 50°C for 18 hrs period. After 18 hrs, the autoclave was cooled to 25°C, excess pressure was released and the autoclave was opened. The vials were taken out from autoclave reactor. The thus obtained reaction mixture was passed through neutral alumina bed, the filtrate was collect and dried to yield residue. The resultant residue was then analyzed by HPLC or NMR spectroscopy.

ADVANTAGES OF THE PRESENT INVENTION

- Atom economic single step protocol of process
- An unprecedented enantiomeric excess of 85-99.9% is observed
- The desired active catalyst is in-situ generated, circumventing the need of separate synthesis and isolation of active catalyst
- Sitagliptin presented in Formula (Ia) is a new class of oral anti-hyperglycemic drug known as a DPP-4 inhibitor or incretin enhancer for the treatment of Type 2 diabetes mellitus (T2DM)
- Sitagliptin can also be used in combination drugs without any adverse effects.

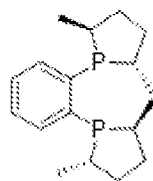
WE CLAIM

1. A process for preparation of sitagliptin compound of Formula (Ia) by enantioselective asymmetric hydrogenation of dehydrositagliptin of Formula (IIa) employing rhodium catalyst on bisphosphine ferrocenyl ligands of Formula L, to obtain enantiomeric excess in the range of 85-99.9%;



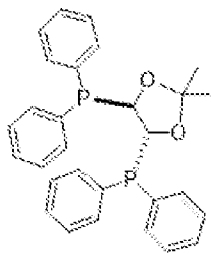
said bisphosphine ferrocenyl ligands of Formula L1-L8 are:

- a) L1 : 1,2-bis(2,5-dimethylphospholan-1-yl)benzene



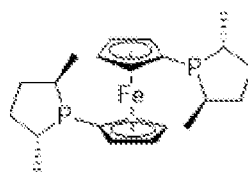
L1

- b) L2 : (2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(diphenylphosphane)



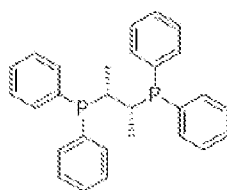
L2

- c) L3 : 1,1'-Bis[2,5-dimethylphospholano]ferrocene



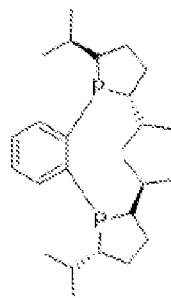
L3

- d) L4 : butane-2,3-diylbis(diphenylphosphane)



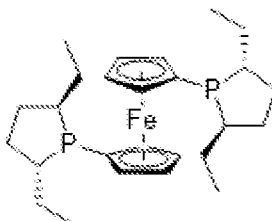
L4

e) L5 : 1,2-bis(2,5-diisopropylphospholan-1-yl)benzene



L5

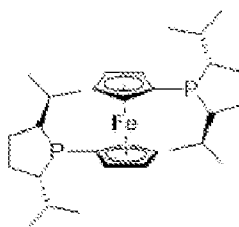
f) L6 : 1,1'-Bis[2,5-diethylphospholano]ferrocene



L6

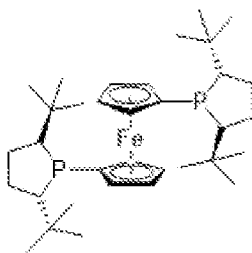
5

g) L7 : 1,1'-Bis(2,5-di-isopropylphospholano)ferrocene



L7

h) L8 : 1,1'-Bis((2,5)-2,5-di-ter-butylphospholano)ferrocene



L8

wherein, the process for the preparation of sitagliptin, compound of Formula (Ia) comprises the steps of:

- i) mixing compound of Formula (IIa) with rhodium catalyst, ferrocenyl bisphosphine ligand L, and additive;
- 5 ii) adding solvent in the reaction mixture of step i) in the inert atmosphere of argon and stirring at a temperature of 25°C for an hour to obtain reaction slurry;
- 10 iii) maintaining the reaction slurry as obtained in step ii) under hydrogen pressure of 10-30 bar at a temperature of 35°C -90°C for 17-24 hrs into autoclave followed by cooling at a temperature of 25°C of step iii) and releasing the pressure to obtain reaction mixture;
- iv) passing the reaction mixture of step iii) through neutral alumina bed followed by collecting the filtrate and drying the residue to afford compound of Formula (Ia).
2. The process as claimed in claim 1, wherein the rhodium precursor is $[\text{Rh}(\text{COD})_2\text{OTf}]$.
3. The process as claimed in claim 2, wherein the additive is selected from the group
15 consisting of salicylic acid, acetic acid, ammonium chloride, phosphoric acid, ammonium salicylate, tetramethyl ammonium iodide, tetraethyl ammonium iodide, tetra butyl ammonium bromide, butyl phosphoric acid, dibutyl phosphate, tributyl phosphate.
4. The process as claimed in claim 2, wherein the solvent selected from the group
20 consisting of methanol, dichloromethane, tetrahydrofuran, trifluoroethanol, toluene, 1,4-dioxane and ethyl acetate.

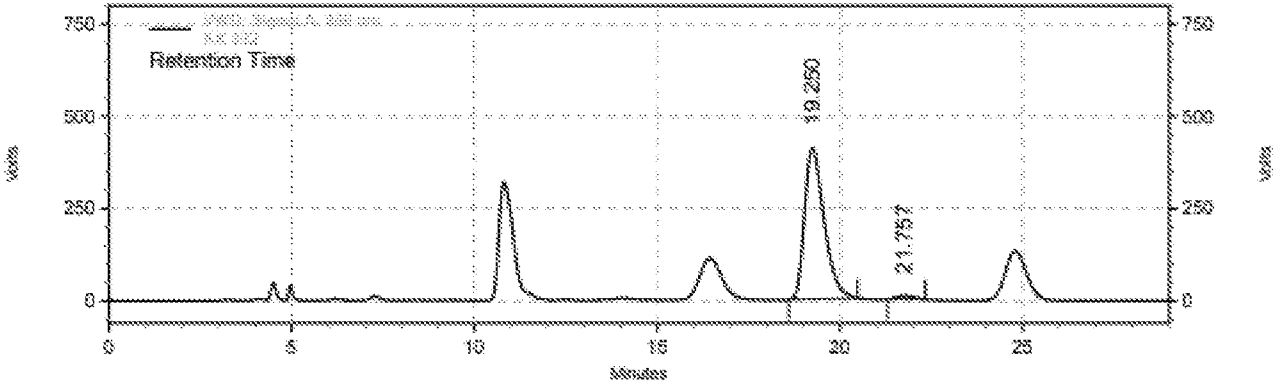


Fig. 1

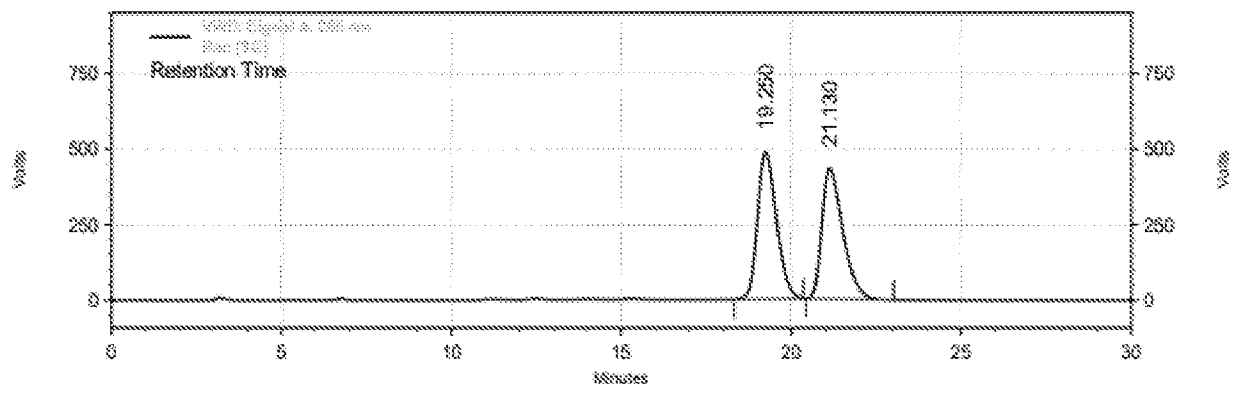


Fig. 1

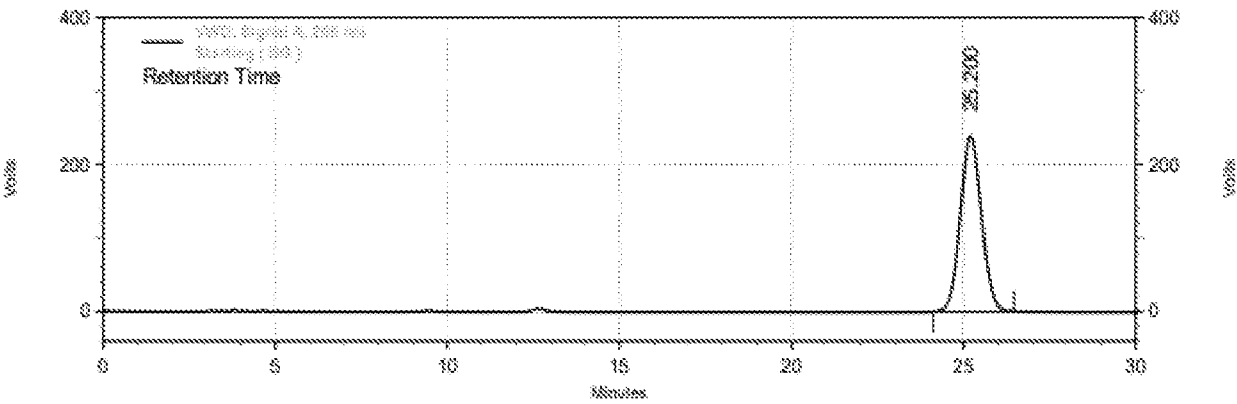


Fig. 3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2019/050896

A. CLASSIFICATION OF SUBJECT MATTER
C07D487/04 Version=2020.01

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 practicable, search terms used)

Total Patent One, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2005097733 A1 (MERCK & CO. INC.) 20 OCTOBER 2005 (20.10.2005) *See pages 17 and 23; scheme-2; claims*	1-4
Y	Hansen Karl B. Et. Al, "Highly Efficient Asymmetric Synthesis of Sitagliptin", J. Am. Chem. Soc., vol. 131, 2009, pp. 8798-8804. DOI: 10.1055/s-0029-1218332. *abstract; page 8800; table 1, entry 11* FAMILY: [NONE]	1-4
Y	Mark J. Burk and Gross F, Michael, "New Chiral 1,1-Bis(Phospholano)ferrocene Ligands for Asymmetric Catalysis", Tetrahedron Letters, Vol. 35(50), 1994, pp. 9363-9366. https://doi.org/10.1016/S0040-4039(00)78543-1 . *table 1; ligands 5 and 6; pages 9364-65; scheme-2* FAMILY: [NONE]	1-4

☐ 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

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"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

"I" 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

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"&" document member of the same patent family

Date of the actual completion of the international search

18-03-2020

Date of mailing of the international search report

18-03-2020

Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IN2019/050896

Citation	Pub.Date	Family	Pub.Date
WO 2005097733 A1	20-10-2005	EP 1735269 A1	27-12-2006
		US 7495123 B2	24-02-2009