(19) DANMARK

(10) DK/EP 2411385 T3

(12) Oversættelse af europæisk patentskrift

Patent- og Varemærkestyrelsen

(51) Int.Cl.: *C 07 D 413/12 (2006.01)*

(45) Oversættelsen bekendtgjort den: **2015-08-17**

(80) Dato for Den Europæiske Patentmyndigheds bekendtgørelse om meddelelse af patentet: **2015-08-05**

(86) Europæisk ansøgning nr.: **10709535.8**

(86) Europæisk indleveringsdag: **2010-03-19**

(87) Den europæiske ansøgnings publiceringsdag: **2012-02-01**

(86) International ansøgning nr.: **EP2010053598**

(87) Internationalt publikationsnr.: **WO2010108861**

(30) Prioritet: **2009-03-24 EP 09156074** **2009-12-07 EP 09178220**

(84) Designerede stater: **AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO SE SI SK SM TR**

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(54) Benævnelse: **FREMGANGSMÅDE TIL FREMSTILLINGEN AF PROPIONSYREDERIVATER**

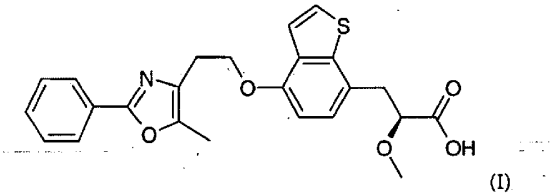
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Fortsættes ...

DESCRIPTION

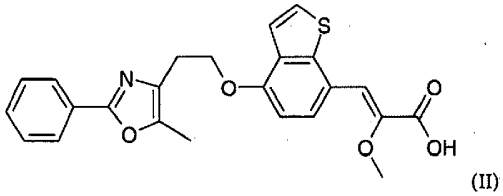
[0001] The present invention is concerned with a novel process for the preparation of (S)-2-methoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-propionic acid or a salt thereof.

[0002] Herein is described a process for the preparation of a compound of formula (I)



(I)

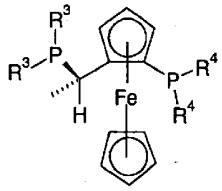
or a salt thereof, wherein a compound of formula (II)



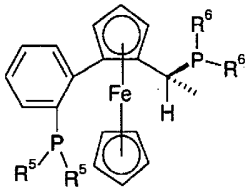
(II)

or a salt thereof is hydrogenated

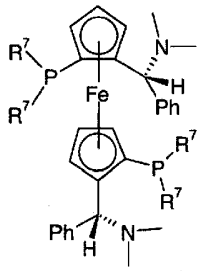
1. (a) in the presence of a catalyst comprising iridium; or
2. (b) in the presence of a catalyst comprising ruthenium and a compound of formula (IV), (V), (VI) or (VII)



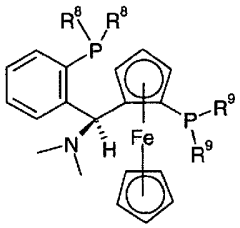
(IV);



(V);



(VI); or



(VII);

wherein

R^3 is alkyl, cycloalkyl or aryl;

R^4 is cycloalkyl, aryl or heteroaryl;

R^5 is cycloalkyl or aryl;

R^6 is cycloalkyl or aryl;

R^7 is cycloalkyl or aryl;

R^8 is cycloalkyl or aryl; and

R^9 is cycloalkyl or aryl.

[0003] The compound of formula (I) is known in the art and is described for example in international application WO 02/092084. It

is especially useful for the prophylaxis and/or treatment of diabetes mellitus type I and II.

[0004] Further background information can be found in WO 2005/030764, which mentions the preparation of chirial propionic acid derivatives.

[0005] The process according to the invention allows the synthesis of the compound of formula (I) with high enantiomeric excess. It can be performed in dichloromethane and the use of complex solvent mixtures can be avoided. The process with the catalyst comprising iridium gives particularly high yield and high enantiomeric excess of the compound of formula (I). Furthermore, optically pure compound of formula (I) is obtained without the use of multiple crystallization of diastereomeric salts.

[0006] The term "catalyst" refers to a complex of ruthenium or iridium respectively with a chiral ligand. In such ruthenium complexes, ruthenium is preferably characterised by the oxidation number II. In such iridium complexes, iridium is preferably characterized by the oxidation number I.

[0007] The term "alkyl" refers to a branched or straight chain monovalent alkyl radical of one to eight carbon atoms, preferably one to four carbon atoms. This term is further exemplified by such radicals as methyl, ethyl, *n*-propyl, *iso*-propyl, *iso*-butyl, *n*-butyl, *tert*-butyl and the like with methyl, *tert*-butyl and *iso*-propyl being preferred.

[0008] The term "alkoxy," refers to the group alkyl-O-. A preferred alkoxy group is methoxy.

[0009] The term "cycloalkyl" refers to a monovalent carbocyclic radical of 3 to 10 carbon atoms, preferably 3 to 6 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. Cyclohexyl is a preferred cycloalkyl.

[0010] The term "aryl" relates to the phenyl or naphthyl group, preferably the phenyl group, which can optionally be mono- or multiply-substituted, particularly mono-, di- or tri-substituted by halogen, hydroxy, CN, CF_3, NO_2, NH_2, N(H, alkyl), $N(alkyl)_2$, carboxy, aminocarbonyl, alkyl, alkoxy, phenyl and/or phenyloxy. Preferred substituents are halogen, alkyl, CF_3 and alkoxy, particularly alkyl, CF_3 and alkoxy.

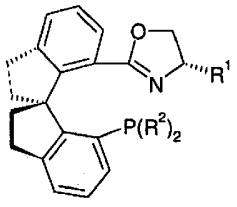
[0011] The term "heteroaryl" refers to an aromatic 5- or 6-membered ring which can comprise 1, 2 or 3 atoms selected from nitrogen, oxygen and/or sulphur such as furyl, pyridyl, 1,2-, 1,3- and 1,4-diazinyl, thienyl, isoxazolyl, oxazolyl, imidazolyl, or pyrrolyl. The term "heteroaryl" further refers to bicyclic aromatic groups comprising two 5- or 6-membered rings, in which one or both rings can comprise 1, 2 or 3 atoms selected from nitrogen, oxygen or sulphur such as e.g. indole or quinoline, or partially hydrogenated bicyclic aromatic groups such as e.g. indolinyl. A heteroaryl group may have a substitution pattern as described earlier in connection with the term "aryl". Preferred heteroaryl groups are 2-thienyl and 2-furyl. 2-Furyl is particularly preferred.

[0012] The term "halide" refers to a halogen atom bearing a negative charge such as fluoride, chloride, bromide and iodide.

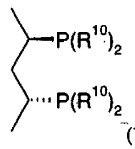
[0013] The term "pharmaceutically acceptable salts" embraces salts of the compound of formula (I) with pharmaceutically acceptable bases such as alkali salts, e.g. Na- and K-salts, alkaline earth salts, e.g. Ca- and Mg-salts, and ammonium or alkyl-substituted ammonium salts, such as e.g. trimethylammonium salts. A preferred pharmaceutically acceptable salt of the compound of formula (I) is the sodium salt.

[0014] The term "η^5" means eta5 as used normaly in coordination chemistry. It indicates the number of electrons shared between a metal center and a ligand in a coordination compound or complex.

[0015] A process is herein described wherein the above defined catalyst comprises iridium and a compound of formula (III), (VIII) or (IX)

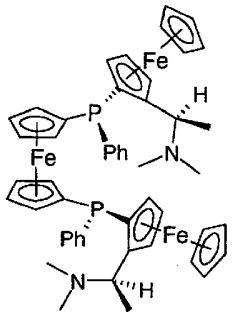


(III);



(VIII);

or



(IX);

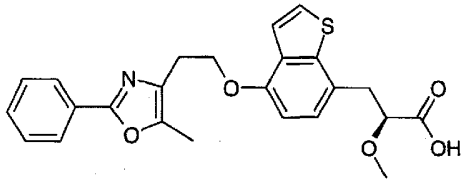
wherein

R^1 is hydrogen, alkyl, aryl or arylalkyl;

R^2 is aryl; and

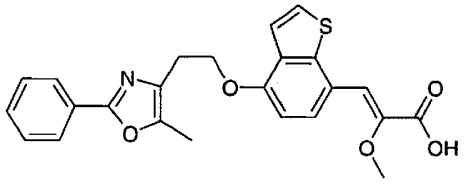
R^{10} is aryl.

[0016] The invention thus relates to a process for the preparation of a compound of formula (I)



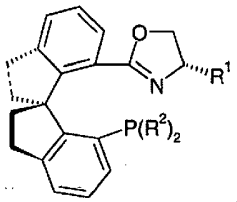
(I)

or a salt thereof, wherein a compound of formula (II)



(II)

or a salt thereof is hydrogenated in the presence of a catalyst comprising iridium;
wherein the catalyst comprises iridium and a compound of formula (III)



(III)

wherein

R^1 is hydrogen, *iso*-propyl or benzyl; and

R^2 is phenyl, 3,5-di-methylphenyl or 3,5-di-*tert*-butyl-phenyl.

Also described is a process as defined above wherein R^{10} is 3,5-di-methyl-phenyl.

[0017] The compound of formula (IX) is (S,R,R)'-1,1'-bis-[((1-N,N-dimethylamino) ethylferrocenyl)(phenylphosphino)]ferrocene.

[0018] (S,S)-[1,3-dimethyl-1,3-propanediyl] bis[di-(3,5-dimethylphenyl)phosphine] is herein described as a compound of formula (VIII).

[0019] Particularly preferred is a process according to the invention wherein the compound of formula (III) is

(Sa,S)-7-[4,5-Dihydro-4-benzyloxazol-2-yl]-7'-diphenylphosphino-1,1'-spirobiindane;
(Sa,S)-7-[4,5-Dihydro-4-benzyloxazol-2-yl]-7'-di(3,5-di-methylphenyl)phosphino-1'1-spirobiindane;
(Sa,S)-7-[4,5-Dihydro-4-benzyloxazol-2-yl]-7'-di(3,5-di-tert-butylphenyl) phosphino-1,1'-spirobiindane;
(Sa,S)-7-[4,5-Dihydro-4-phenyloxazol-2-yl]-7'-di(3,5-di-tert-butylphenyl) phosphino-1,1'-spirobiindane;
(Sa,S)-7-[4,5-Dihydro-4-isopropyloxazol-2-yl]-7'-di(3,5-di-tert-butylphenyl) phosphino-1,1'-spirobiindane; or
(Sa)-7-[4,5-Dihydrooxazol-2-yl]-7,-di(3,5-di-tert-butylphenyl)phosphino-1,1'-spirobiindane.

[0020] Further preferred is a process according to the invention wherein the compound of formula (III) is
(Sa,S)-7-[4,5-Dihydro-4-benzyloxazol-2-yl]-7'-di(3,5-di-tert-butylphenyl) phosphino-1,1'-spirobiindane;
(Sa,S)-7-[4,5-Dihydro-4-isopropyloxazol-2-yl]-7'-di(3,5-di-tert-butylphenyl) phosphino-1,1'-spirobiindane; or
(Sa)-7-[4,5-Dihydrooxazol-2-yl]-7'-di(3,5-di-tert-butylphenyl)phosphino-1,1'-spirobiindane.

[0021] Moreover, preferred is a process as defined above wherein the catalyst is $Ir(L^1)(L^2)_nY$
wherein

L^1 is a compound of formula (III) as defined above;

L^2 is cyclooctene, 1,5-cyclooctadiene, ethylene, 1,5-hexadiene or norbornadiene;

Y is chloride, iodide, bromide, fluoride, trifluoroacetate, tetrafluoroborate, tetrakis[3,5-bis(trifluoromethyl)phenyl]borate, tetraphenylborate, hexafluoroantimonate, hexafluorophosphate, triflate, mesylate, perchlorate, perbromate, periodate, nitrate, hydrogen sulfate or acetylacetonate; and

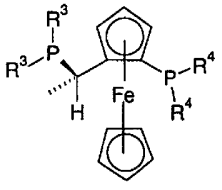
n is 1 or 2.

Y is preferably chloride, tetrafluoroborate, hexafluorophosphate or tetrakis[3,5-bis(trifluoromethyl)phenyl]borate, more preferably tetrafluoroborate or tetrakis[3,5-bis(trifluoromethyl)phenyl]borate.

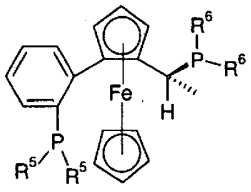
n is preferably 1.

[0022] In particular, preferred is a process according to the invention wherein the catalyst is
[Ir((S,S)-7-[4,5-dihydro-4-benzyloxazol-2-yl]-7'-di(3,5-di-tert-butylphenyl) phosphino-1,1'-spirobiindane)(1,5-cyclooctadiene)][tetrakis[3,5-bis(trifluoromethyl)phenyl]borate];
[Ir((S,S)-7-[4,5-dihydro-4-isopropyloxazol-2-yl]-7'-di(3,5-di-tert-butylphenyl) phosphino-1,1'-spirobiindane)(1,5-cyclooctadiene)][tetrakis[3,5-bis(trifluoromethyl)phenyl]borate]; or
[Ir((S)-7-[4,5-dihydrooxazol-2-yl]-7'-di(3,5-di-tert-butylphenyl)phosphino-1,1'-spirobiindane)(1,5-cyclooctadiene)][tetrakis[3,5-bis(trifluoromethyl)phenyl]borate].

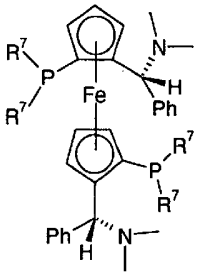
[0023] Also described is a process as defined above wherein the catalyst comprises ruthenium and a compound of formula (IV), (V), (VI) or (VII)



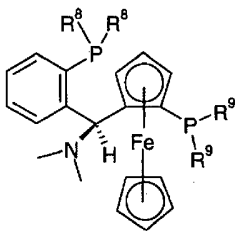
(IV);



(V);



(VI); or



(VII);

wherein R^3 to R^9 are as defined above.

R^3 is can be alkyl, cyclohexyl, phenyl, alkylphenyl or dialkylphenyl.

[0024] In particular, in the process described above, R^3 can be *tert*-butyl, cyclohexyl, phenyl, 2-methyl-phenyl or 3,5-di-methyl-phenyl.

[0025] Moreover, R^4 can be alkyl, cyclohexyl, phenyl, naphtyl, furyl or phenyl substituted with one to three substituents independently selected from trifluoromethyl, alkyl and alkoxy.

[0026] A process as defined above wherein R^4 is *tert*-butyl, cyclohexyl, phenyl, 3,5-di-trifluoromethyl-phenyl, 4-trifluoromethyl-phenyl, 3,5-di-methyl-4-methoxy-phenyl, 1-naphtyl or 2-furyl is also described.

[0027] R^5 can be cyclohexyl, phenyl or phenyl substituted with one to three substituents independently selected from alkyl and alkoxy.

[0028] Furthermore, a process as defined above wherein R^5 is phenyl, cyclohexyl, 3,5-di-methyl-4-methoxy-phenyl or 3,5-di-methyl-phenyl is also described.

[0029] R^6 is can be cyclohexyl, norbornyl, phenyl or phenyl substituted with one to three substituents independently selected from alkyl and trifluoromethyl.

[0030] Moreover, descibed is a process as defined above wherein R^6 is phenyl, cyclohexyl, 3,5-di-methyl-phenyl, 3,5-di-trifluoromethyl-phenyl or norbornyl.

[0031] R^7 can be cyclohexyl, phenyl or phenyl substituted with one to three substituents independently selected from alkyl, trifluoromethyl and alkoxy.

[0032] Also described is a process as defined above wherein R^7 is cyclohexyl, phenyl, 3,5-di-methyl-phenyl, 3,5-di-trifluoromethyl-phenyl, 3,5-di-methyl-4-methoxy-phenyl or 2-methyl-phenyl.

[0033] A process as defined above wherein R^8 is cyclohexyl or phenyl is also described.

[0034] A process as defined above wherein R^9 is cyclohexyl or phenyl is further described.

[0035] Further described is a process as defined above wherein the compound of formula (IV), (V), (VI), (VII) or (VIII) is
(S)-1-[(R)-2-(Diphenylphosphino)ferrocenyl]ethyldi-tert-butylphosphine;
(S)-1-[(R)-2-(Dicyclohexylphosphino)ferrocenyl]ethyldi-tert-butylphosphine;
(S)-1-[(R)-2-(Di-(4-trifluoromethylphenyl)phosphino)ferrocenyl]ethyldi-tert-butyl phosphine;
(S)-1-[(R)-2-(Di-(3,5-dimethyl-4-methoxyphenyl)phosphino)ferrocenyl]ethyldi-tert-butylphosphine;
(S)-1-[(R)-2-(Di-2-furylphosphino)ferrocenyl]ethyldi-tert-butylphosphine;
(αR,αR)-2,2'-Bis(α-N,N-dimethylaminophenylmethyl)-(S,S)-1,1'-bis(diphenylphosphino)ferrocene;
(αR,αR)-2,2'-Bis(α-N,N-dimethylaminophenylmethyl)-(S,S)-1,1'-bis[di(3,5-dimethyl-4-methoxyphenyl)phosphino]ferrocene;
(R)-1-Diphenylphosphino-2-[(S)-α-(N,N-dimethylamino)-o-diphenylphosphinophenyl)methyl]ferrocene;
(S)-1-[(S)-2-(2'-Diphenylphosphinophenyl)ferrocenyl]ethyldi(bis-3,5-trifluoromethyl phenyl)phosphine;
(R)-1-[(R)-2-(2'-Dicyclohexylphosphinophenyl)ferrocenyl]ethyldi(bis-3,5-trifluoromethylphenyl)phosphine; or
(R)-1-[(R)-2-(2'-Diphenylphosphinophenyl)ferrocenyl]ethyldi-(2-norbornyl)phosphine.

[0036] Moreover, further described is a process as defined above wherein the compound of formula (IV), (V), (VI) or (VII) is
(S)-1-[(R)-2-(Diphenylphosphino)ferrocenyl]ethyldi-tert-butylphosphine; or
(S)-1-[(R)-2-(Di-(3,5-dimethyl-4-methoxyphenyl)phosphino)ferrocenyl]ethyldi-tert-butylphosphine.

[0037] In particular, a process as defined above is described wherein the catalyst is $Ru(L^3)(L^4)(L^5)_mY_p$

wherein,

L^3 is a compound of formula (IV), (V), (VI) or (VII) as defined above;

L^4 is η^5-2,4-dimethylpentadienyl, cyclopentadienyl or η^5-2,3,4-trimethylpenta-dienyl;

L^5 is halide, acetonitrile, diethyl ether, water, acetone, tetrahydrofuran, dioxane, pyridine, imidazole or thiophene;

Y is tetrakis[3,5-bis(trifluoromethyl)phenyl]borate, tetrafluoroborate, tetraphenylborate, hexafluoroantimonate, hexafluorophosphate, triflate, mesylate, hydrogen sulfate or perchlorate;

m is 0 or 1; and

pis 0 or 1.

L^5 can be iodine.

m can be 1. p can be 1.

[0038] A process as defined above is decribed wherein the catalyst is

[Ru(η^5-2,4-dimethylpentadienyl)((S)-1-[(R)-2-(diphenylphosphino)ferrocenyl] ethyldi-tert-butylphosphine)(acetonitrile)] [tetrafluoroborate];

[Ru(η^5-2,4-dimethylpentadienyl)((S)-1-[(R)-2-(dicyclohexylphosphino)ferrocenyl] ethyldi-tert-butylphosphine)(acetonitrile)] [tetrafluoroborate];

[Ru(η^5-2,4-dimethylpentadienyl)((S)-1-[(R)-2-(di-(4-trifluoromethylphenyl) phosphino)ferrocenyl]ethyldi-tert-butylphosphine) (acetonitrile)] [tetrafluoroborate];

[Ru(η^5-2,4-dimethylpentadienyl)((S)-1-[(R)-2-(di-(3,5-dimethyl-4-methoxyphenyl) phosphino)ferrocenyl]ethyldi-tert-butylphosphine)(acetonitrile)] [tetrafluoroborate] ;

[Ru(η^5-2,4-dimethylpentadienyl)((S)-1-[(R)-2-(di-2-furylphosphino)ferrocenyl] ethyldi-tert-butylphosphine)(acetonitrile)] [tetrafluoroborate];

[Ru(η^5-2,4-dimethylpentadienyl)((αR,αR)-2,2'-bis(α-N,N-dimethylaminophenylmethyl)-(S,S)-1,1'-bis(diphenylphosphino)ferrocene) (acetonitrile)] [tetrafluoroborate];

[Ru(η^5-2,4-dimethylpentadienyl)((αR,αR)-2,2'-bis(α-N,N-dimethylaminophenylmethyl)-(S,S)-1,1'-bis[di(3,5-dimethyl-4-methoxyphenyl) phosphino]ferrocene)(acetonitrile)] [tetrafluoroborate];

[Rul(η^5-2,4-dimethylpentadienyl)((R)-1-diphenylphosphino-2-[(S)-α-(N,N-dimethylamino)-o-diphenylphosphinophenyl)methyl]ferrocene)];

[Ru(η^5-2,4-dimethylpentadienyl)((S)-1-[(S)-2-(2'-diphenylphosphinophenyl) ferrocenyl]ethyldi(bis-3,5-trifluoromethylphenyl)phosphine)(acetonitrile)] [tetrafluoroborate];

[Ru(η^5-2,4-dimethylpentadienyl)((R)-1-[(R)-2-(2'-dicyclohexylphosphinophenyl) ferrocenyl]ethyldi(bis-3,5-trifluoromethylphenyl)phosphine)(acetonitrile)] [tetrafluoroborate]; or

[Ru(η^5-2,4-dimethylpentadienyl)((R)-1-[(R)-2-(2'-diphenylphosphinophenyl) ferrocenyl]ethyldi-(2-norbornyl)phosphine) (acetonitrile)] [tetrafluoroborate].

[0039] A process as defined above is described wherein the catalyst is

[Ru(η^5-2,4-dimethylpentadienyl)((S)-1-[(R)-2-(diphenylphosphino)ferrocenyl] ethyldi-tert-butylphosphine)(acetonitrile)] [tetrafluoroborate]; or

[Ru(η^5-2,4-dimethylpentadienyl)((S)-1-[(R)-2-(di-(3,5-dimethyl-4-methoxyphenyl) phosphino)ferrocenyl]ethyldi-tert-butylphosphine)(acetonitrile)] [tetrafluoroborate].

[0040] The compound of formula (II) can be hydrogenated under a pressure of hydrogen gaz.

[0041] When an iridium catalyst is used, the process is preferably carried out at a temperature of 10 to 120°C, more preferably 40 to 100°C, particularly preferably 60 to 80°C.

[0042] When a catalyst comprising iridium is used, the process is preferably carried out in a solvent selected from alcohols,

fluorinated alcohols, tetrahydrofuran, methyl-tetrahydrofuran, dichloromethane, dialkyl ethers, aromatic solvents such as benzene, toluene, CF_3-C_6H_5, mono- and poly-fluorinated aromatic solvents and mixtures thereof, more preferred in methanol, tetrahydrofuran, dichloromethane and mixtures thereof, most preferably in methanol/tetrahydrofuran 3:2.

[0043] When a catalyst comprising iridium is used, the process is preferably carried out under a hydrogen pressure range of 1 to 200 bar, more preferably 10 to 100 bar, particularly preferably 40 to 60 bar.

[0044] When a catalyst comprising iridium is used, the substrate-to-catalyst ratio (mol/mol) is preferably 10 to 50000, more preferably between 100 and 10000, particularly preferably between 1000 and 5000.

[0045] When a catalyst comprising ruthenium is used, the process is preferably carried out at a temperature of 10 to 120°C, more preferably 20 to 80°C, particularly preferably 30 to 50°C.

[0046] When a catalyst comprising ruthenium is used, the process is preferably carried out in a solvent selected from alcohols, tetrahydrofuran, dichloromethane, fluorinated alcohols, methyl-tetrahydrofuran, ethers and mixtures thereof, preferably methanol, tetrahydrofuran, dichloromethane and mixtures thereof, more preferably in a mixture dichloromethane/tetrahydrofuran 1:1 or in dichloromethane and particularly preferably in dichloromethane.

[0047] When a catalyst comprising ruthenium is used, the process is preferably carried out under an hydrogen pressure of 1 to 200 bar, more preferably 10 to 100 bar, particularly preferably 40 to 60 bar.

[0048] When a catalyst comprising ruthenium is used, the substrate-to-catalyst ratio (mol/mol) is preferably 10 to 50000, more preferably 100 to 10000, particularly preferably 1000 to 5000.

[0049] The preferred (S) configuration of the compound of formula (I) has been obtained with the ligands disclosed in the tables in the experimental part. Should a chiral ligand or catalyst afford preferentially the compound of formula (I) with the (R) configuration, it is clear that the ligand or catalyst with the opposite configuration should be used in order to obtain the compound of formula (I) with the (S) configuration. Both enantiomers of the chiral ligands are equally well accessible.

[0050] Furthermore, the invention also relates to the use of a catalyst as defined above for the preparation of a compound of formula (I) as defined above.

[0051] The catalysts for use in the above process may be prepared by reacting a compound of formula $[Ir(L)Cl]_2$, $[Ir(L)_2]$ BARF or $[Ir(L)_2]BF_4$ where L denotes a neutral ligand, e.g. COD with the desired ligand of formula (III), (IX), (X) or (XI), e.g. (S,S)-3,5-Xyl-Skewphos or (S,R,R)-TRIFER, in an appropriate solvent, such as e.g. dichloromethane or methanol. The catalyst may be used after isolation or as prepared in situ. The ligands of formula (III), (IX), (X) or (XI) can be prepared by methods known per se, e.g. The compounds $[Ir(COD)Cl]_2$ and $[Ir^+(COD)_2]BF_4$ are either commercially available, e.g. from Strem Chemicals Inc., Newburgport, Mass. USA or can be prepared according to to methods known perse, e.g. J. Herde et al., Inorg. Syn. 1974,18-20 or M. Green et al., J. Chem. Soc. 1971,2334-2337.

[0052] The term "neutral ligand" as used herein denotes a readily exchangeable ligand such as an olefin, e.g. ethylene, propylene, cyclooctene, 1,5-hexadiene, norbornadiene, 1,5-cyclooctadiene, a nitrile such as acetonitrile or benzonitrile, or also a solvent such as e.g. tetrahydrofuran, toluene etc. Where more than one such ligand is present, these can also be different from each other. A preferred neutral ligand is cyclooctadiene.

Examples

Abbreviations

[0053]

η^5-2,4-DMP = η^5-2,4-dimethylpentadienyl,

THF = tetrahydrofuran,

NCMe = acetonitrile,

TFA = trifluoroacetic acid,

COD = 1,5-cyclooctadiene,

BARF = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate,

r.t. = room temperature,

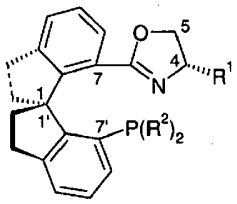
S/C = substrate-to-catalyst ratio (mol /mol),

HPLC = high pressure liquid chromatography,

ee = enantiomeric excess = [(S)-(R)]/[(S)+(R)].

[0054] All ferrocenyl-diphosphine ligands are commercially available from Solvias AG, CH-4002 Basel. The ruthenium complexes are commercially available from Umicore AG, D-63457 Hanau-Wolfgang or can be prepared according to O. Briel et al. in "Catalysis of Organic Reactions", 2009, 203, CRC Press, Boca Raton. The oxazoline-monophosphine ligands (SIPHOX ligands) and their corresponding iridium complexes are commercially available from Nankai University, Tianjin 300071 China or can be prepared according to Q.L. Zhou et al. J. Am. Chem. Soc. 2008, 130, 8584. Xyl-Skewphos and 3,5-tBu-MeOBIPHEP are commercially available from Solvias AG, CH-4002 Basel. TRIFER is commercially available from Phoenix Chemicals, 34 Thursby Rod., Bromborough, Wirral CH62, 3PW, United Kingdom (UK) or can be prepared according to P. McCormack et al. Angew. Chem. Int. Ed. 2007, 46, 4141-44.

[0055] The atom numbering of SIPHOX ligands is shown below:



Chiral phosphorus Ligands

[0056]

Acronyms	***Chemical Name***
Ph-Bn-SIPHOX	7-[4,5-Dihydro-4-benzyloxazol-2-yl]-7'-diphenylphosphino-1,1'-spirobiindane
Xyl-Bn-SIPHOX	7-[4,5-Dihydro-4-benzyloxazol-2-yl]-7'-di(3,5-di-methylphenyl)phosphino-1,1'-spirobiindane
DBT-Bn-SIPHOX	7-[4,5-Dihydro-4-benzyloxazol-2-yl]-7'-di(3,5-di-tert-butylphenyl) phosphino-1,1'-spirobiindane
DBT-Ph-SIPHOX	7-[4,5-Dihydro-4-phenyloxazol-2-yl]-7'-di(3,5-di-tert-butylphenyl) phosphino-1,1'-spirobiindane
DBT-iPr-SIPHOX	7-[4,5-Dihydro-4-isopropyloxazol-2-yl]-7'-di(3,5-di-tert-butylphenyl) phosphino-1,1'-spirobiindane
DBT-H-SIPHOX	7-[4,5-Dihydrooxazol-2-yl]-7'-di(3,5-di-tert-butylphenyl)phosphino-1,1'-spirobiindane
TRIFER	1,1'-Bis-[((1-N,N-dimethylamino)ethylferrocenyl)(phenylphosphi-no)]ferrocene
Xyl-Skewphos	[1,3-Dimethyl-1,3-propanediyl]bis[di-(3,5-dimethylphenyl)phosphine]

Acronyms	***Chemical Name***
PPF-$PtBu_2$	1-[2-(Diphenylphosphino)ferrocenyl] ethyldi-tert.- butylphosphine
Cy_2PF-$PtBu_2$	1-[2-(Dicyclohexylphosphino)ferrocenyl]ethyldi-tert.-butylphosphine
$(4\text{-}CF_3Ph)_2$PF-$PtBu_2$	1-[2-(Di-(4-trifluoromethylphenyl) phosphino)ferrocenyl]ethyldi-tert.-butyl phosphine

Acronyms	*Chemical Name*
$(3,5\text{-}Me_2\text{-}4\text{-}MeOPh)_2PF\text{-}PtBu_2$	1-[2-(Di-(3,5-dimethyl-4-methoxy phenyl)phosphino)ferrocenyl]ethyldi-tert.-butylphosphine
$2\text{-}Fur_2PF\text{-}PtBu_2$	1-[2-(Di-2-furylphosphino)ferrocenyl]ethyldi-tert.-butylphosphine
$NMe_2\text{-}PPh_2$-Mandyphos	2,2'-Bis(α-N,N-dimethylaminophenylmethyl)-1,1'-bis(diphenylphosphino) ferrocene
$NMe_2\text{-}P(3,5\text{-}Me\text{-}4\text{-}MeOPh)_2$-Mandyphos	2,2'-Bis(α-N,N-dimethylaminophenylmethyl)-1,1'-bis[di(3,5-dimethyl-4-methoxyphenyl)-phosphino] ferrocene
$PPPhCHNMe_2$-F-PP	1-Diphenylphosphino-2-[α-(N,N-dimethylamino)-o-diphenylphosphinophenyl) methyl] ferrocene
$PPPhFCHCH_3\text{-}P(3,5\text{-}CF_3Ph)_2$	1-[2-(2'-Diphenylphosphinophenyl) ferrocenyl] -ethyldi(bis-3,5-trifluoromethyl phenyl)phosphine
$Cy_2PPhFCH\ CH_3P(3,5\text{-}CF_3Ph)_2$	1-[2-(2'-Dicyclohexylphosphino phenyl)ferrocenyl] ethyldi(bis-3,5-trifluoromethylphenyl)phosphine
$PPPhFCHCH_3\text{-}P(Norbornyl)_2$	1-[2-(2'-Diphenylphosphinophenyl) ferrocenyl]ethyldi-(2-norbornyl)phosphine

Synthesis of Iridium Metal Complexes: Reference Examples 1a-1b

Reference Example 1.a: Preparation of [Ir((S,S)-Xyl-Skewphos)(COD)]BF_4

[0057] A 25-ml Schlenk tube was charged with 100 mg of (S,S)-Xyl-Skewphos (0.18 mmol), 60 mg of $[Ir(COD)Cl]_2$ (0.09 mmol) and 5 ml of dichloromethane. To the formed dark red solution, 35 mg of silver tetrafluoroborate (0.18 mmol) was added in two protions and the resulting suspension was stirred for 2 hours at r.t. The reaction mixture was filtered over dicalite speedex and the filter cake was washed with 6 ml of dichloromethane. The combined filtrates were rotary evaporated to dryness (50°C/5 mbar). The formed crude product was washed with 8 ml of hexane and dried over high vacuum to afford 563 mg (85%) of [Ir((S,S)-Xyl-Skewphos)(COD)]BF_4 as a red solid. FT-MS: 853.4 m/z [Ir((S,S)-Xyl-Skewphos)(COD)]$^+$,^{31}P-NMR ($CDCl_3$): 14.6 ppm (s).

Reference Example 1.b: Preparation of [Ir((S,R,R)-Trifer)(COD)]BARF

[0058] A 100-ml Schlenk tube was charged with 400 mg of (S,R,R)-TRIFER (0.44 mmol), 584 mg of $Ir(COD)_2$]BARF (0.46 mmol) and 40 ml of methanol. The formed orange solution was stirred for 5 hours at r.t. Then, 12 ml of water was added and the formed crystals were filtered off. The filter cake was washed with 32 ml of a mixture of methanol/water (4:1) and dried over high vacuum to afford 804 mg (88%) of [Ir((S,R,R)-TRIFER)(COD)]BARF as orange crystals. FT-MS: 1213.2 m/z [Ir((S,R,R)-TRIFER)(COD)]$^+$. ^{31}P-NMR ($CDCl_3$): 6.2 ppm (s).

Synthesis of 2-Methoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-propionic acid via asymmetric hydrogenation of (Z)-2-methoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-acrylic acid: Examples 2-19 & Comparative Example A

Example 2

[0059] In a glove box (O_2 content ≤ 2 ppm), a 185- ml stainless steel autoclave was charged with 2.00 g of (Z)-2-methoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-acrylic acid (4.59 mmol), 35.9 mg of [Ir((S,S)-DBT-Bn-SIPHOX)(COD)]BARF (0.018 mmol, S/C 250), 24 ml of methanol, 16 ml of tetrahydrofuran and 0.12 ml of (S)-1-phenylethylamine (0.93 mmol). The autoclave was sealed and the hydrogenation was run at 60°C under 30 bar of hydrogen. After 16 h the autoclave was

opened and the yellowish solution was rotary evaporated to dryness (50°C/5 mbar) to afford crude (S)-2-methoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-propionic acid (Acid I) as a white solid with a chemical purity of 99.6 % (>99.9% conversion) and an enantiomeric purity of 99.5%.

[0060] HPLC method for chemical purity (area-%, (S)-phenylethylamine not included): YMC-Pack Pro C18, 150 x 4.6 mm; mobile phase A: mobile phase A: water with 0.1% TFA, B: NCMe with 0.1% TFA, 22°C, 2 ml/min, isocratic A/B 51/49% during 10 min, gradient from 51/49% to 5/95% within 10 min and 5 min at 5/95%, 285 nm. Retention times: 11.2 min (S)- and (R)-2-methoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-propionic acid; 12.4 min (E)-2-methoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-acrylic acid; 14.0 min (Z)-2-methoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-acrylic acid.

[0061] HPLC method for ee determination (area-%): Chiralpak-ADH column, 25 cm x 4.6 mm, 85% heptane /10% ethanol with 0.4% trifluoroacetic acid, flow 0.7 ml/min, 30°C, 270 nm. Retention times: 22.4 min (R)-2-methoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-propionic acid; 26.3 min (S)-2-methoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-propionic acid.

Examples 3.1-3.4

[0062] In an analogous manner to Example 2 the following hydrogenations were performed at 60°C under 30 bar of hydrogen (reaction time: 16 h) using iridium complexes of general formula [Ir(Phosphorous Ligand)(COD)]BARF as catalysts to afford crude 2-methoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-propionic acid (Acid I) as listed in Table 1.

Table 1

Exp. No.	Phosphorus Ligand	Conv. [%]	Acid I Purity [%]	Acid I Ee [%] / Configuration
3.1	(S,S)-Xyl-Bn-SIPHOX)	99.8	97.6	88.9 / S
3.2	(S,S)-DBT-Ph-SIPHOX)	99.9	99.4	98.0 / S
3.3	(S,S)-DBT-iPr-SIPHOX)	>99.9	99.3	99.3 / S
3.4	(S)-DBT-H-SIPHOX)	>99.9	98.3	99.3 / S

Example 4

[0063] In a glove box (O_2 content ≤ 2 ppm), a 185- ml stainless steel autoclave was charged with 2.00 g of (Z)-2-methoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-acrylic acid (4.59 mmol), 8.96 mg of [Ir(S,S)-DBT-Bn-SIPHOX)(COD)]BARF (0.0046 mmol, S/C 1'000), 24 ml of methanol, 16 ml of tetrahydrofuran and 0.12 ml of (S)-1-phenylethylamine (0.93 mmol). The autoclave was sealed and the hydrogenation was run at 60°C under 30 bar of hydrogen. After 16 h the autoclave was opened and the yellowish solution was rotary evaporated to dryness (50°C/5 mbar) to afford the crude (S)-2-methoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-propionic acid (Acid I) as a white solid with a chemical purity of 99.2 % (99.8% conversion) and an enantiomeric purity of 99.3%.

Examples 5.1-5.2

[0064] In an analogous manner to Example 4 the following hydrogenations were performed at 60°C under 30 bar of hydrogen (reaction time: 16 h) using iridium complexes of general formula [Ir(Phosphorus Ligand)(COD)]BARF as catalysts to afford crude 2-methoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-propionic acid (Acid I) as listed in Table 2.

Table 2

Exp. No.	Phosphorus Ligand	Conv. [%]	Acid I Purity [%]	Acid I Ee [%] / Configuration
5.1	(S,S)-DBT-iPr-SIPHOX)	99.9	99.5	98.7 / S
5.2	(S)-DBT-H-SIPHOX)	99.9	98.1	99.3 / S

Example 6

[0065] In a glove box (O_2 content ≤ 2 ppm), a 185- ml stainless steel autoclave was charged with 2.00 g of (Z)-2-methoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-acrylic acid (4.59 mmol), 4.48 mg of [Ir((S,S)-DBT-Bn-SIPHOX)(COD)]BARF (0.0023 mmol, S/C 2'000), 24 ml of methanol, 16 ml of tetrahydrofuran and 0.12 ml of (S)-1-phenylethylamine (0.93 mmol). The autoclave was sealed and the hydrogenation was run at 60°C for 20 h and subsequently 80°C for 2 h under 30 bar of hydrogen. After the autoclave was opened and the yellowish solution was rotary evaporated to dryness (50°C/5 mbar) to afford crude (S)-2-methoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-propionic acid (Acid I) as a white solid with a chemical purity of 99.2 % (>99.9% conversion) and an enantiomeric purity of 99.4%.

Example 7

[0066] In a glove box (O_2 content ≤ 2 ppm), a 185- ml stainless steel autoclave was charged with 2.00 g of (Z)-2-methoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-acrylic acid (4.59 mmol), 8.96 mg of [Ir((S,S)-DBT-Bn-SIPHOX)(COD)]BARF (0.0046 mmol, S/C 1'000), 24 ml of methanol, 16 ml of tetrahydrofuran and 0.12 ml of (S)-1-phenylethylamine (0.93 mmol). The autoclave was sealed and the hydrogenation was run at 60°C for 8 h and subsequently 80°C for 2 h under 30 bar of hydrogen. After the autoclave was opened and the yellowish solution was rotary evaporated to dryness (50°C/5 mbar) to afford 2.24 g of the crude (S)-2-methoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-propionic acid (Acid I) as a white solid with a chemical purity of 99.2 % (>99.9% conversion) and an enantiomeric purity of 99.2%. The crude product was dissolved in 50 ml of ethyl acetate. 10 ml of water and 3 ml of 2M aqueous HCl were added and the biphasic mixture was stirred at 55°C for 15 min. The organic layer was separated, the aqueous layer extracted with 20 ml of ethyl acetate and the combined organic layers stirred over 0.5 g of carcoal (Darko KB) at r.t. for 30 min. After filtration over celite, the colorless solution was dried over 3 g of sodium sulfate and evaporated to dryness (40°C/10 mbar). The crude product was dissolved in 50 ml of isopropyl acetate at reflux (oil bath temp. 100°C) and allowed to cool to room temperature whereby crystallization started sponanously. The formed crystals were filtered off, washed with 10 ml of isopropyl acetate and dried at 60°C/10mbar for 2 h to yield 1.40 g (70%) of pure (S)-2-methoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-propionic acid (Acid I) as a white crystals with a chemical purity of 99.8 % and an enantiomeric purity of >99.9%ee.

Example 8

[0067] In a glove box(O_2 content ≤ 2 ppm), a 185- ml stainless steel autoclave was charged with 2.00 g of (Z)-2-methoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-acrylic acid (4.59 mmol), 4.48 mg of [Ir((S,S)-DBT-Bn-SIPHOX)(COD)]BARF (0.0023 mmol, S/C 2'000), 24 ml of methanol, 16 ml of tetrahydrofuran and 0.12 ml of (S)-1-phenylethylamine (0.93 mmol). The autoclave was sealed and the hydrogenation was run at 60°C for 20 h and subsequently 80°C for 2 h under 10 bar of hydrogen. After the autoclave was opened and the yellowish solution was rotary evaporated to dryness (50°C/5 mbar) to afford crude (S)-2-methoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-propionic acid (Acid I) as a white solid with a chemical purity of 98.9% (>99.9% conversion) and an enantiomeric purity of 99.6%.

Reference Example 9

[0068] In an analogous manner to Example 4 the following hydrogenation was performed at 40°C under 30 bar of hydrogen (reaction time: 16 h) using [Ir({S,S)-Xyl-Skewphos)(COD)]BF_4 (S/C 1'000) as catalysts to afford crude (S)-2-methoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-propionic acid (Acid I) as a white solid with a chemical purity of 98.8 % (99.4% conversion) and an enantiomeric purity of 85%.

Reference Example 10

[0069] In an analogous manner to Example 2 the following hydrogenation was performed at 60°C under 30 bar of hydrogen (reaction time: 16 h) using [Ir((S,R,R)-Trifer)(COD)]BARF (S/C 250) as catalysts to afford crude (R)-2-methoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-propionic acid (Acid I) as a white solid with a chemical purity of 98.0 % (>99.9% conversion) and an enantiomeric purity of 86%.

Reference Example 11

[0070] In a glove box (02 content ≤ 2 ppm), a 50- ml stainless steel autoclave was charged with 1.00 g of (Z)-2-methoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-acrylic acid (2.30 mmol),1.99 mg of [Ru(
(
5-2,4-DMP)((R)-(S)-PPF-PtBu2)(NCMe)]BF4 (0.0023 mmol, S/C 1'000) 12 ml of methanol, 8 ml of dichloromethane and 0.06 ml of (S)-1-phenylethylamine (0.47 mmol). The autoclave was sealed and the hydrogenation was run at 40°C under 30 bar of hydrogen. After 16 h the autoclave was opened and the yellowish solution was rotary evaporated to dryness (50°C/5 mbar) to afford the crude (R)-2-methoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-propionic acid (Acid I) as a white solid with a chemical purity of 99.6 % (>99.9% conversion) and an enantiomeric purity of 89%.

[0071] HPLC method for chemical purity (area-%, (S)-phenylethylamine not included): YMC-Pack Pro C18, 150 x 4.6 mm; mobile phase A: mobile phase A: water with 0.1% TFA, B: NCMe with 0.1% TFA, 22°C, 2 ml/min, isocratic A/B 51/49% during 10 min, gradient from 51/49% to 5/95% within 10 min and 5 min at 5/95%, 285 nm. Retention times: 11.2 min (S)- and (R)-2-methoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-propionic acid; 12.4 min (E)-2-methoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-acrylic acid; 14.0 min (Z)-2-methoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-acrylic acid.

[0072] HPLC method for ee determination (area-%): Chiralpak-ADH column, 25 cm x 4.6 mm, 90% heptane /10% ethanol with 0.5% trifluoroacetic acid, flow 0.7 ml/min, 30°C, 270 nm. Retention times: 22.1 min (R)-2-methoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-propionic acid; 26.0 min (S)-2-methoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-propionic acid.

Reference Examples 12.1-12.5

[0073] In an analogous manner to Example 11 the following hydrogenations were performed at 40°C under 30 bar of hydrogen (reaction time: 16 h) using ruthenium complexes of general formula [Ru(η^5-2,4-DMP)(Phosphorous Ligand)(NCMe)]BF_4 as catalysts to afford crude 2-methoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-propionic acid (Acid I) as listed in Table 3.

Table 3

Exp. No.	Phosphorus Ligand	Conv. [%]	Acid I Purity [%]	Acid I Ee [%] / Configuration
12.1	(R)-(R)-PPPhFCHCH$_3$-P(Norbornyl)$_2$	>99.9	97.1	69/S
12.2	(R)-(R)-Cy$_2$PPhFCH-CH$_3$P(3,5-CF$_3$Ph)$_2$	>99.9	99.4	79/S
12.3	(R)-(S)-NMe$_2$-PPh$_2$-Mandyphos	99.6	99.1	69/S
12.4	(R)-(S)-NMe$_2$-P(3,5-Me-4-MeOPh)$_2$-Mandyphos	99.3	98.8	70/S
12.5	(R)-(R)-PPPhFCHCH$_3$-P(3,5-CF$_3$Ph)$_2$	>99.9	99.6	58/R

Reference Example 13

[0074] In an analogous manner to Example 11 the following hydrogenations were performed at 40°C under 30 bar of hydrogen (reaction time: 16 h) using ruthenium complexe [RuI(η^5-2,4-DMP)((S)-(R)-PPPhCHNMe$_2$F-PP)] as catalysts to afford crude (S)-2-methoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-propionic acid (Acid I) as a white solid with a chemical purity of 98.7 % (99.2% conversion) and an enantiomeric purity of 46%.

Reference Example 14

[0075] In a glove box (O_2 content ≤ 2 ppm), a 50- ml stainless steel autoclave was charged with 2.26 mg of [Ru(η^5-2,4-DMP)((S)-(R)-(3,5-Me_2-4-MeOPh)$_2$PF-PtBu_2)(NCMe)]BF_4 (0.0023 mmol, S/C 1'000) and 6 ml of dichloromethane. The resulting violet solution was stirred for 2 h at r.t. Then, 1.00 g of (Z)-2-methoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-acrylic acid (2.30 mmol), 4 ml of dichloromethane, 10 ml of THF and 0.06 ml of (S)-1-phenylethylamine (0.47 mmol) were added. The autoclave was sealed and the hydrogenation was run under stirring at 40°C under 30 bar of hydrogen. After 16 h the autoclave was opened and the yellowish solution was rotary evaporated to dryness (50°C/5 mbar) to afford the crude (S)-2-methoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-propionic acid (Acid I) as a white solid with a chemical purity of 99.5 % (>99.9% conversion) and an enantiomeric purity of 87%.

Reference Example 15

[0076] In an analogous manner to Example 14 the following hydrogenations were performed at 40°C under 30 bar of hydrogen (reaction time: 16 h) using ruthenium complexe [Ru(η^5-2,4-DMP)((S)-(R)-2-Fur$_2$PF-PtBu_2)(NCMe)]BF_4 as catalysts to afford crude (S)-2-methoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-propionic acid (Acid I) as a white solid with a chemical purity of 99.3 % (>99.9% conversion) and an enantiomeric purity of 73%.

Reference Example 16

[0077] In a glove box (O_2 content ≤ 2 ppm), a 50-ml stainless steel autoclave was charged with 1.99 mg of [Ru(η^5-2,4-DMP)((R)-(S)-PPF-PtBu_2)(NCMe)]BF_4 (0.0023 mmol, S/C 1'000) and 5 ml of dichloromethane. The resulting violet solution was stirred for 2 h at r.t. Then, 1.00 g of (Z)-2-methoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-acrylic acid (2.30 mmol), 2.5 ml of dichloromethane, 7.5 ml of THF and 0.06 ml of (S)-1-phenylethylamine (0.47 mmol) were added. The autoclave was sealed and the hydrogenation was run under stirring at 40°C under 30 bar of hydrogen. After 16 h the autoclave was opened and the yellowish solution was rotary evaporated to dryness (50°C/5 mbar) to afford (R)-2-methoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-propionic acid (Acid I) as a white solid with a chemical purity of 99.2 % (>99.9% conversion) and an enantiomeric purity of 90%.

Reference Examples 17.1-17.2

[0078] In an analogous manner to Example 16 the following hydrogenations were performed at 40°C under 30 bar of hydrogen (reaction time: 16 h) using ruthenium complexes of general formula [Ru(η^5-2,4-DMP)(Phosphorus Ligand)(NCMe)]BF_4 as catalysts to afford crude 2-methoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-propionic acid (Acid I) as listed in Table 4.

Table 4

Exp. No.	Phosphorus Ligand	Conv. [%]	Acid I Purity [%]	Acid I Ee [%] / Configuration
17.1	(S)-(R)-Cy$_2$PF-PtBu_2	98.7	98.6	74/S
17.2	(S)-(R)-(4-CF_3Ph)$_2$PF-PtBu_2	99.9	99.6	84/S

Reference Example 18

[0079] In a glove box (O_2 content ≤ 2 ppm), a 50-ml stainless steel autoclave was charged with 0.66 mg of [Ru(η^5-2,4-DMP)((R)-(S)-PPF-PtBu_2)(NCMe)]BF_4(0.0008 mmol, S/C 3'000) and 5 ml of dichloromethane. The resulting violet solution was stirred for 2 h at r.t. Then, 1.00 g of (Z)-2-methoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-acrylic acid (2.30 mmol), 2.5 ml of dichloromethane, 7.5 ml of THF and 0.06 ml of (S)-1-phenylethylamine (0.47 mmol) were added. The autoclave was sealed and the hydrogenation was run under stirring at 40°C under 30 bar of hydrogen. After 16 h the autoclave was opened and the yellowish solution was rotary evaporated to dryness (50°C/5 mbar) to afford (R)-2-methoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-propionic acid (Acid I) as a white solid with a chemical purity of 99.5 % (99.9% conversion) and an enantiomeric purity of 89%.

Reference Example 19

[0080] In a glove box (O_2 content ≤ 2 ppm), a 50-ml stainless steel autoclave was charged with 0.66 mg of [Ru(η^5-2,4-DMP)((R)-(S)-PPF-PtBu_2)(NCMe)]BF_4 (0.0008 mmol, S/C 3'000) and 5 ml of dichloromethane. The resulting violet solution was stirred for 2 h at r.t. Then, 1.00 g of (Z)-2-methoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-acrylic acid (2.30 mmol), 10 ml of dichloromethane and 0.06 ml of (S)-1-phenylethylamine (0.47 mmol) were added. The autoclave was sealed and the hydrogenation was run under stirring at 40°C under 30 bar of hydrogen. After 16 h the autoclave was opened and the yellowish solution was rotary evaporated to dryness (50°C/5 mbar) to afford (R)-2-methoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-propionic acid (Acid I) as a white solid with a chemical purity of 99.5 % (99.9% conversion) and an enantiomeric purity of 90%.

Comparative Example A

[0081] In a glove box (O_2 content ≤ 2 ppm), a 50-ml stainless steel autoclave was charged with 0.62 mg of [Ru$(OAc)_2$((S)-TMBTP)] (0.0008 mmol, S/C 3'000) (prepared according to EP 1,670,792 B1; TMBTP = 2,2',5,5'-Tetramethyl-4,4'-bis(diphenylphosphino)-3,3'-bithiophene) and 5 ml of methanol. The resulting orange solution was stirred for 2 h at r.t. Then, 1.00 g of (Z)-2-methoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-acrylic acid (2.30 mmol), 4 ml of methanol, 6 ml of THF and 0.06 ml of (S)-1-phenylethylamine (0.47 mmol) were added. The autoclave was sealed and the hydrogenation was run under stirring at 40°C under 30 bar of hydrogen. After 16 h the autoclave was opened and the yellowish solution was rotary evaporated to dryness (50°C/5 mbar) to afford crude (S)-2-methoxy-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzo[b]thiophen-7-yl}-propionic acid (Acid I) as a white solid with a chemical purity of 99.7 % (99.9% conversion) and an enantiomeric purity of 89%.

REFERENCES CITED IN THE DESCRIPTION

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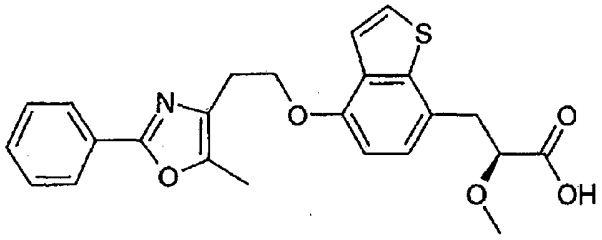
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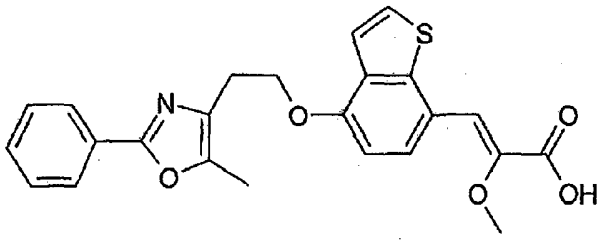
Patentkrav

1. Fremgangsmåde til fremstilling af en forbindelse med formel (I)



(I)

eller et salt deraf, hvor en forbindelse med formel (II)

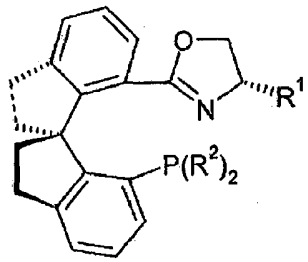


(II)

eller et salt deraf hydrogeneres

i tilstedeværelse af en katalysator omfattende iridium;

hvor katalysatoren omfatter iridium og en forbindelse med formel (III)



(III)

hvor R^1 er hydrogen, iso-propyl, phenyl eller benzyl; og

hvor R^2 er phenyl, 3,5-di-methylphenyl eller 3,5-di-*tert*-butyl-phenyl.

2. Fremgangsmåde ifølge krav 1, hvor forbindelsen med formel (III) er (Sa,S)-7-[4,5-dihydro-4-benzyloxazol-2-yl]-7'-diphenylphosphino-1,1'-spirobiindan;

(Sa,S)-7-[4,5-dihydro-4-benzyloxazol-2-yl]-7'-di(3,5-di-methylphenyl)phosphino-1,1'-spirobiindan;

(Sa,S)-7-[4,5-dihydro-4-benzyloxazol-2-yl]-7'-di(3,5-di-tert-butylphenyl) phosphino-1,1'-spirobiindan;
(Sa,S)-7-[4,5-dihydro-4-phenyloxazol-2-yl]-7'-di(3,5-di-tert-butylphenyl) phosphino-1,1'-spirobiindan;
(Sa,S)-7-[4,5-dihydro-4-isopropyloxazol-2-yl]-7'-di(3,5-di-tert-butylphenyl) phosphino-1,1'-spirobiindan; eller
(Sa)-7-[4,5-dihydrooxazol-2-yl]-7'-di(3,5-di-tert-butylphenyl)phosphino-1,1'-spirobiindan.

3. Fremgangsmåde ifølge krav 1 eller 2, hvor forbindelsen med formel (III) er (Sa,S)-7-[4,5-dihydro-4-benzyloxazol-2-yl]-7'-di(3,5-di-tert-butylphenyl) phosphino-1,1'-spirobiindan;
(Sa,S)-7-[4,5-dihydro-4-isopropyloxazol-2-yl]-7'-di(3,5-di-tert-butylphenyl) phosphino-1,1'-spirobiindan; eller
(Sa)-7-[4,5-dihydrooxazol-2-yl]-7'-di(3,5-di-tert-butylphenyl)phosphino-1,1'-spirobiindan.

4. Fremgangsmåde ifølge et hvilket som helst af kravene 1 til 3, hvor katalysatoren er $Ir(L^1)(L^2)_nY$
hvor

L^1 er en forbindelse med formel (III) ifølge et hvilket som helst af kravene 1 til 3;

L^2 er cycloocten, 1,5-cyclooctadien, ethylen, 1,5-hexadien eller norbornadien;

Y er chlorid, iodid, bromid, fluorid, trifluoracetat, tetrafluorborat, tetrakis[3,5-bis(trifluormethyl)phenyl]borat, tetraphenylborat, hexafluorantimonat, hexafluorphosphat, triflat, mesylat, perchlorat, perbromat, periodat, nitrat, hydrogensulfat eller acetylacetonat; og

n er 1 eller 2.

5. Fremgangsmåde ifølge et hvilket som helst af kravene 1 til 4, hvor katalysatoren er
[Ir((S,S)-7-[4,5-dihydro-4-benzyloxazol-2-yl]-7'-di(-3,5-di-tert-butylphenyl) phosphino-1,1'-spirobiindan)(1,5-cyclooctadien)][tetrakis[3,5-bis(trifluormethyl)phenyl]borat];
[Ir((S,S)-7-[4,5-dihydro-4-isopropyloxazol-2-yl]-7'-di(3,5-di-tert-butylphenyl) phosphino-1,1'-spirobiindan)(1,5-cyclooctadien)][tetrakis[3,5-bis(trifluormethyl)phenyl]borat]; eller
[Ir((S)-7-[4,5-dihydrooxazol-2-yl]-7'-di(3,5-di-tert-butylphenyl)phosphino-1,1'-spirobiindan)(1,5-cyclooctadien)][tetrakis[3,5-bis(trifluormethyl)phenyl]borat].

6. Anvendelsen af en katalysator ifølge et hvilket som helst af kravene 1 til 5 til fremstillingen af en forbindelse med formel (I) ifølge krav 1.