



(11) **EP 1 724 251 B1**

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:
16.09.2015 Bulletin 2015/38

(21) Application number: **05704190.7**

(22) Date of filing: **27.01.2005**

(51) Int Cl.:
C07C 45/00 ^(2006.01) **B01J 31/14** ^(2006.01)
C07C 45/75 ^(2006.01) **C07C 49/497** ^(2006.01)
C07C 49/733 ^(2006.01) **C07C 49/82** ^(2006.01)
C07C 327/22 ^(2006.01)

(86) International application number:
PCT/JP2005/001086

(87) International publication number:
WO 2005/073156 (11.08.2005 Gazette 2005/32)

(54) **PROCESS FOR THE PRODUCTION OF OPTICALLY ACTIVE HYDROXYMETHYLATED COMPOUNDS**

VERFAHREN ZUR HERSTELLUNG OPTISCH AKTIVER HYDROXYMETHYLIERTER VERBINDUNGEN

PROCEDE POUR LA FABRICATION DE COMPOSES HYDROXYMETHYLES OPTIQUEMENT ACTIFS

(84) Designated Contracting States:
CH DE FR GB LI

(30) Priority: **30.01.2004 JP 2004023338**

(43) Date of publication of application:
22.11.2006 Bulletin 2006/47

(73) Proprietor: **Japan Science and Technology Agency**
Kawaguchi-shi,
Saitama 332-0012 (JP)

(72) Inventors:
• **KOBAYASHI, Shu**
Chiyoda-ku, Tokyo 1010048 (JP)
• **MANABE, Kei**
Bunkyo-ku, Tokyo 1130033 (JP)

(74) Representative: **Wilson Gunn**
Blackfriars House
The Parsonage
5th Floor
Manchester M3 2JA (GB)

(56) References cited:
JP-A- 6 166 652 JP-A- 6 256 248
JP-A- 2001 252 570

- **ISHIKAWA, SHUNPEI ET AL: "Catalytic asymmetric hydroxymethylation of silicon enolates using an aqueous solution of formaldehyde with a chiral scandium complex" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY , 126(39), 12236-12237 CODEN: JACSAT; ISSN: 0002-7863, 2004, XP003003389**
- **KOBAYASHI, SHU ET AL: "Lanthanide Triflates as Water- Tolerant Lewis Acids. Activation of Commercial Formaldehyde Solution and Use in the Aldol Reaction of Silyl Enol Ethers with Aldehydes in Aqueous Media" JOURNAL OF ORGANIC CHEMISTRY , 59(13), 3590-6 CODEN: JOCEAH; ISSN: 0022-3263, 1994, XP002460718**
- **BOLM, CARSTEN ET AL: "Optically active bipyridine in asymmetric catalysis" ANGEWANDTE CHEMIE , 102(2), 206-8 CODEN: ANCEAD; ISSN: 0044-8249, 1990, XP002460719**
- **DENMARK S.E. ET AL: 'Catalytic, Enantioselective Aldol Additions to Ketones' JOURNAL OF THE AMERICAN CHEMICAL SOCIETY vol. 124, no. 6, 2002, pages 4233 - 4235, XP002983764**
- **Hoi-Lun Kwong ET AL: "Chiral bipyridine-copper (II) complex. Crystal structure and catalytic activity in asymmetric cyclopropanation", Journal of the Chemical Society, Dalton Transactions, no. 6, 1 January 1998 (1998-01-01), pages 1043-1046, XP55006690, ISSN: 0300-9246, DOI: 10.1039/a706754b**

Note: Within nine months of the publication of the mention of the grant of the European patent in the European Patent Bulletin, any person may give notice to the European Patent Office of opposition to that patent, in accordance with the Implementing Regulations. Notice of opposition shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

- Hoi-Lun Kwong ET AL: "Chiral zinc(II) bipyridine complex. Crystal structure and catalytic activity in asymmetric allylation reaction", *New Journal of Chemistry*, vol. 23, no. 6, 1 January 1999 (1999-01-01), pages 629-632, XP55006691, ISSN: 1144-0546, DOI: 10.1039/a902177i

Description

Field of the Invention

5 **[0001]** The present invention relates to an asymmetric hydroxymethylation reaction and more particularly to a production method for an optically active hydroxymethylated compound and a catalyst thereof.

Prior Art

10 **[0002]** The reaction between a silicon enolate and formaldehyde under the presence of a Lewis acid is a useful method to synthesize α -hydroxymethyl carbonyl compounds. However, a catalytic asymmetric reaction is extremely difficult to achieve, and examples with high selectivity have not been reported (References 1 to 5).

[0003]

15 Reference 1:

Manabe, K.; Ishikawa, S.; Hamada, T.; Kobayashi, S. Tetrahedron 2003, 59, 10439.

Reference 2:

20

Ozasa, N.; Wadamoto, M.; Ishihara, K.; Yamamoto, H. Synlett 2003, 2219.

Reference 3:

25

Kuwano, R. et al., Chem. Commun. 1998, 71.

Reference 4:

30

Casas, J. et al., Tetrahedron Lett. 2004, 45, 6117.

Reference 5:

35

Bolm, C.; Ewald, M.; Felder, M.; Schlingloff, G. Chem. Ber. 1992, 125, 1169.
Denmark and Fan have reported catalytic, enantioselective aldol additions to ketones (J. Am. Chem. Soc. 2002, 124, 4233-4235). JP 2001252570A relates to a chiral rare earth metallic catalyst and asymmetric aldol reaction process. JP 6166652A and JP 6256248A both relate to the production of an aldol compound.

Problems to be solved by the Invention

40 **[0004]** The present invention presents a catalyst that allows an asymmetric hydroxymethylation reaction to proceed with excellent asymmetric selectivity and a production method for optically active hydroxymethylated compounds using the catalyst.

Means to solve the Problems

45

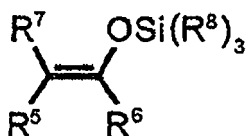
[0005] The inventors discovered that a catalytic asymmetrical hydroxymethylation reaction proceeded with excellent stereoselectivity when a combination of chiral ligands (see Reference 3) and a scandium triflate was used. The present invention was completed based on the discovery. A commercially available aqueous formaldehyde solution (formalin) can be used directly to the reaction.

50 **[0006]** The catalytic system of the present invention is not only useful in the synthesis of optically active materials but also can provide an important direction for the development of catalytic asymmetric reactions in aqueous media.

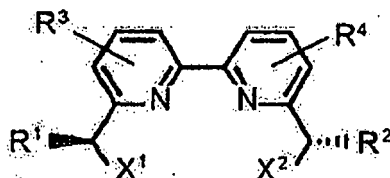
[0007] That is, the present invention is a method for producing an optically active hydroxymethylated compound, comprising reacting a silicon enolate and formaldehyde, in the presence of a catalyst, in an aqueous solution or a mixed solvent of water and an organic solvent,

55

wherein the silicon enolate is represented by the following formula (chemical formula 2):



wherein R⁵ is a hydrogen atom or an alkyl group, R⁶ is an alkyl group, an alkyl aryl group, or an aryl group, in which R⁵ and R⁶ may together form a five or six membered ring comprising carbon atoms and optional hetero atoms, R⁷ is a hydrogen atom, an alkyl group, an alkyl aryl group or an aryl group and the groups R⁸, which may be identical or different, are each alkyl groups, and the catalyst is obtained by mixing a ligand or its symmetric isomer and a Lewis acid, wherein the ligand is represented by the following formula (chemical formula 1):



wherein R¹ and R², may be identical or different, are hydrogen atoms, alkyl groups or aryl groups, at least one of R¹ and R² contains at least three carbon atoms, R³ and R⁴, may be identical or different, are hydrogen atoms, alkyl groups containing one to four carbon atoms or alkoxy groups, X¹ and X², may be identical or different, are represented by -OH, -SH or -NHR¹¹, wherein R¹¹ is a hydrogen atom or an alkyl group, and the Lewis acid is represented by MY_n, wherein M is Cu, Zn, Fe, Sc or a lanthanoid element, Y is a halogen atom, OAc, OCOCF₃, ClO₄, SbF₆, PF₆ or OSO₂CF₃ and n is 2 or 3.

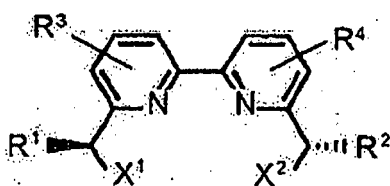
Brief Description of the Drawings

[0008]

Figure 1 shows a synthetic route for Ligand 1.
Figure 2 shows a synthetic route for Ligand 2.

Detailed Description of the Invention

[0009] The catalyst used in the present invention is obtained by mixing a ligand having the following structure (chemical formula 1):



and a Lewis acid represented by MY_n.

[0010] R¹ and R² represent hydrogen atoms, alkyl groups or aryl groups, preferably alkyl groups or aryl groups. They may be identical or different, preferably identical. At least one of R¹ or R² needs to be bulky and, more specifically, needs to contain at least three carbon atoms.

[0011] R³ and R⁴ represent hydrogen atoms or alkyl or alkoxy groups having one to four carbon atoms but are preferably hydrogen atoms. They may be identical or different, preferably identical.

[0012] X¹ and X² represent -OH, -SH or -NHR¹¹, preferably -OH, where R¹¹ represents a hydrogen atom or an alkyl group with a hydrogen atom preferred, and the number of carbon atoms in the alkyl groups is 1 to 3.

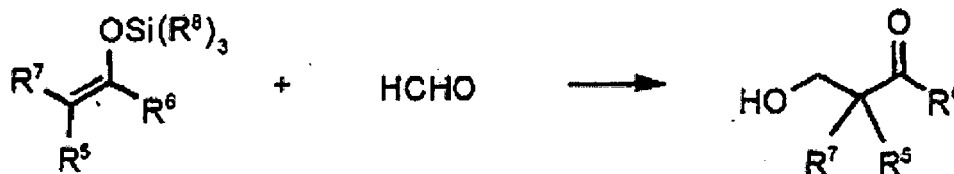
[0013] M represents Cu (divalent), Fe (divalent or trivalent), Sc (trivalent) or lanthanoid elements (⁵⁷La to ⁷¹Lu) (trivalent) but preferably represents Sc.

[0014] n represents an integer corresponding to the valence of M and represents 2 or 3.

[0015] Y represents a halogen atom, OAc, OCOCF₃, ClO₄, SbF₆, PF₆ or OSO₂CF₃(OTf), preferably OTf.

[0016] When this ligand and a Lewis acid represented by MY_n are mixed in a solvent, a catalyst is formed by coordinating M in the ligand. H_2O -DME, H_2O - CH_3CN , H_2O -THF, H_2O -1, 4-dioxane, H_2O -EtOH, H_2O -MeOH, H_2O -PrOH, water and the like may be cited as the solvent used. Each concentrations in the solvent is preferably from about 0.01 mole/liter to about 0.1 mole/liter.

[0017] In the present invention, this catalyst is used in asymmetric hydroxymethylation reactions of formaldehyde and a silicon enolate as described below (chemical formula 3):



[0018] R^5 to R^7 are as described below:

R^5 represents a hydrogen atom or an alkyl group, and R^6 represents an alkyl groups, an alkyl aryl groups, or an aryl group. However, R^5 and R^6 may together form a five to six membered ring, the ring may optionally contain a hetero atom the R^7 represents a hydrogen atom, an alkyl group, an alkyl aryl group, or an aryl group.

[0019] R^8 represents an alkyl group. They may each be identical or different, but the preference is for them to be identical. R^8 is preferably an alkyl group containing one to three carbon atoms and most preferably a methyl group.

[0020] This reaction is conducted in an aqueous solution or a mixed solvent of water and an organic solvent. At this point, dimethoxy ethane (DME), tetrahydrofuran (THF), acetonitrile, dioxane, alcohols containing no more than four carbon atoms and the like may be cited as the organic solvent that readily blends with water used in the mixed solvent with water. DME, THF, acetonitrile and dioxane are preferred examples. The mix ratio of an organic solvent and water is not particularly restricted, but the mixture generally contains at least 1% by weight of water and the presence of at least 5% by weight is more preferred.

[0021] The amount of the aqueous solution or mixed solvent used should be appropriately considered. Ordinarily, however, the use of the amount necessary to dissolve the starting material substances and the catalyst, for example, from two times the weight to fifty times the weight is considered.

[0022] The HCHO/silicon enolate molar ratio in a reaction solution is from 0.1 to 10, more preferably about 0.5 to 2. In addition, the catalyst is used at from 1% by mole to 50% by mole, more preferably from 5% by mole to 20% by mole in the reaction system.

[0023] The reaction temperature is ordinarily form $-40^\circ C$ to ambient temperature, more preferably from $-20^\circ C$ to $0^\circ C$.

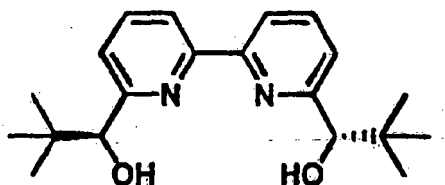
[0024] The reaction time may be selected appropriately and from 0.5 hours to sixty hours, for example, is selected.

[0025] An optically active hydroxymethylated compound is formed by this reaction in excellent yield and selectivity.

[0026] The present invention is illustrated below by using examples, but these are not intended to restrict the scope of the present invention.

Production Example 1

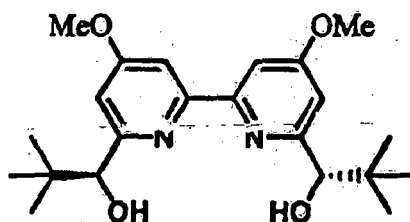
[0027] A ligand (henceforth referred to as "the ligand 1") having the structure shown by the formula below (chemical formula 4) was prepared according to the method described in Reference 5. The synthesis route is shown in Figure 1.



[0028] After treating 2,6-dibromopyridine (1) in ether using n-butyl lithium, compound (2) was obtained through acylation using pivalonitrile. The carbonyl group of the compound (2) was reduced stereoselectively using (-)-DIP-chloride with $ee > 99\%$. A 2,2'-bipyridine isomer (4) (R,R) (Chemical formula 4), a C2 symmetric, was obtained by conducting a homo coupling reaction of the alcohol (3) using nickel.

Production Example 2

[0029] The ligand (henceforth referred to as "ligand 2") having the structure shown by the formula below (chemical formula 5) was prepared. The synthesis route is shown in Figure 2.



[0030] 2,6-Dibromo-4-methoxy pyridine (6) was obtained in 80% yield when 2,4,6-tribromopyridine (5) was allowed to react with sodium methoxide (1.2 eq) in refluxing methanol. The compound (6) was treated using n-butyl lithium (1.2 eq.), was allowed to react with pivalonitrile (1.2 eq.) for 150 minutes at -78°C and was refluxed for two hours in two normal sulfuric acid to yield ketone isomer (7) in 86% yield. An optically active alcohol (8) was obtained in 93% yield and in 90% ee optical purity from compound (7) through hydrogen transfer type asymmetric reduction of formic acid (4.3 eq.) and triethylamine (2.5 eq.) using the asymmetric ruthenium catalyst (RuCl[(S,S]-Tsdpen)(p-cumene), 0.01 eq.) as the catalyst. The compound (8) was converted to a camphor ester using the acid chloride, an optical resolution process was conducted using re-crystallization (75% yield, diastereomer ratio = >99/<1) and saponified again to obtain an almost optically pure alcohol (7, quant.). The compound (7) was subjected to homo coupling using a palladium catalyst [PdCl₂(PhCN)₂-TDAE] to yield a pyridine isomer (9) (Chemical formula 5) in 36% yield (diastereomer ratio =>99.5/<0.5).

Example 1

[0031] DME (0.50 ml) was added to Sc(OTf)₃ (0.9 mg, 0.020 mmole) that had been dried for an hour at 200°C under vacuum. The ligand 1 (7.9 mg, 0.024 mmole) synthesized in Production Example 1 was added to this solution, and the mixture was agitated at room temperature until it became clear. The solution was cooled to -20°C, and an aqueous HCHO solution (85.8 mg, 35% w/w, 1.0 mmole) and the silicon enolate (41 mg, 0.200 mmole) derived from propiophenone, the structure of which is shown in Table 1, were subsequently added. The mixture was agitated for twenty-four hours, and a saturated aqueous sodium bicarbonate solution was subsequently added. The aqueous layer was extracted three times using CH₂Cl₂. The organic layer was dried using Na₂SO₄, the solvent was removed by distillation under reduced pressure, and the residue was purified using silica gel thin layer chromatography (hexane:AcOEt = 2:1).

¹H NMR (CDCl₃) δ 1.24 (d, 3H, J = 7.1 Hz), 2.35 (brs), 3.68 (ddq, 1H, J = 4.3, 7.0, 7.1), 3.80 (dd, 1H, J = 4.3, 11.1 Hz), 3.94 (dd, 1H, J = 7.0, 11.1 Hz), 7.48 (dd, 2H, J = 7.3, 8.5), 7.58 (t, 1H, J = 7.3), 7.97 (d, 2H, J = 8.5); ¹³C NMR (CDCl₃) δ 14.5, 42.9, 64.5, 128.4, 128.7, 133.3, 136.1, 204.4; IR (neat) 3415, 2936, 1681, 1448, 974, 704 cm⁻¹; MS m/z 164 (M⁺); Anal. Calcd for C₁₀H₁₂O₂: C, 73.15; H, 7.37. Found: C, 72.87; H, 7.40; HPLC (Daicel Chiralpak AD-H, hexane/i-PrOH = 19/1, flow rate = 1.0 mL/min) R isomer: t_R = 20.0 min, S isomer: t_R = 17.2 min.

Example 2

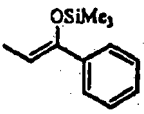
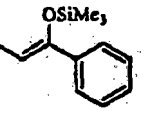
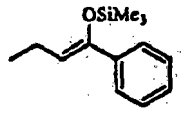
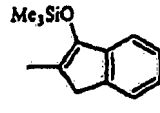
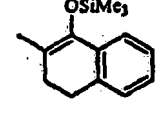
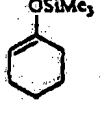
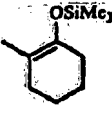
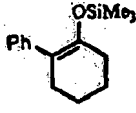
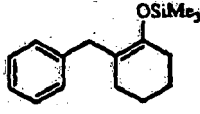

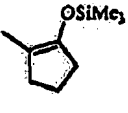
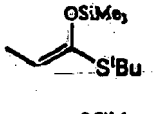
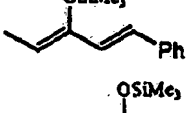
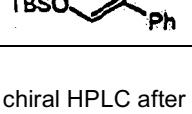
[0032] The same reaction conducted in Example 1 was executed using the ligand 2 synthesized in Production Example 2 in place of the ligand 1 synthesized in Production Example 1.

Examples 3-14

[0033] The silicon enolates shown in Table 1 were allowed to undergo the same reaction described in Example 1 using the reaction time described in the same table. However, the reaction was executed at a reaction temperature of -40°C in Example 13 and a reaction temperature of -10°C in Example 14. Examples 9, 10 and 12-14 are reference examples.

[0034] The yield and optical purity of the optically active hydroxymethylated compounds formed in Examples 1-14 are shown in Table 1. The data indicate that optically active hydroxymethylated compounds were formed in high yields.

[Table 1]

Example	Silicone Enolates	Time (h)	Yield (%)	ee(%)
5	1 	24	80	80
	2a) 	30	60	87
10	3 	30	66	88
15	4 	14	90	90
	5 	20	80	94
20	6 	29	22	62 ^{b)}
25	7 	20	68	91 ^{b)}
30	8 	21	63	60
35	9 	19	77	67
	10 	2	62	90 ^{b)}
40	11 	10	50	85 ^{b)}
45	12 ^{c)} 	24	31	93
	13 ^{d)} 	65	73	92 ^{b)}
50	14 ^{e)} 	8	61	77

a) Used Ligand 2.

b) The ee was decided using chiral HPLC after converting the product into a benzoate.

c) HCHO (ten equivalent), H₂O/DME = 1/4

d) Reaction temperature -40°C.

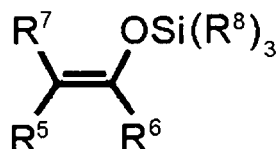
e) Reaction temperature -10°C.

Potential Industrial Applicability

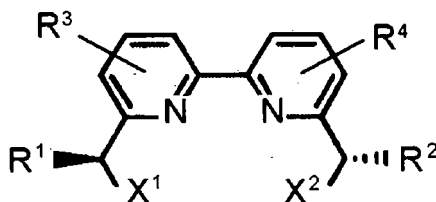
[0035] The optically active hydroxymethylated compounds formed according to the method of the present invention are useful as synthetic intermediates and the like for various chemical products.

Claims

1. A method for producing an optically active hydroxymethylated compound, comprising reacting a silicon enolate and formaldehyde, in the presence of a catalyst, in an aqueous solution or a mixed solvent of water and an organic solvent, wherein the silicon enolate is represented by the following formula (chemical formula 2):

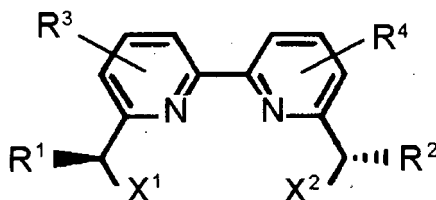


wherein R^5 is a hydrogen atom or an alkyl group, R^6 is an alkyl group, an alkyl aryl group or an aryl group, in which R^6 and R^6 may together form a five to six membered ring comprising carbon atoms and optional hetero atoms, R^7 is a hydrogen atom, an alkyl group, an alkyl aryl group or an aryl group and the groups R^8 , which may be identical or different, are each alkyl group, and the catalyst is obtained by mixing a ligand or its symmetric isomer and a Lewis acid, wherein the ligand is represented by the following formula (chemical formula 1):



wherein R^1 and R^2 , may be identical or different, are hydrogen atoms, alkyl groups or aryl groups, at least one of R^1 and R^2 contains at least three carbon atoms, R^3 and R^4 , may be identical or different, are hydrogen atoms, alkyl groups containing one to four carbon atoms or alkoxy groups, X^1 and X^2 , may be identical or different, are represented by $-\text{OH}$, $-\text{SH}$ or $-\text{NHR}^{11}$, wherein R^{11} is a hydrogen atom or an alkyl group, and the Lewis acid is represented by MY_n , wherein M is Cu , Zn , Fe , Sc or a lanthanoid element, Y is a halogen atom, OAc , OCOCF_3 , ClO_4 , SbF_6 , PF_6 or OSO_2CF_3 and n is 2 or 3.

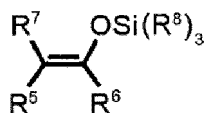
2. A catalyst obtained by mixing a ligand or its symmetric isomer and a Lewis acid, wherein the ligand is represented by the following formula (chemical formula 1):



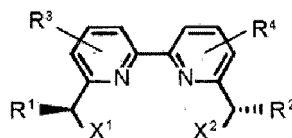
wherein R^1 and R^2 , may be identical or different, are hydrogen atoms, alkyl groups or aryl groups, at least one of R^1 and R^2 contains at least three carbon atoms, R^3 and R^4 , may be identical or different, are hydrogen atoms, alkyl groups containing one to four carbon atoms or alkoxy groups, X^1 and X^2 , may be identical or different, are represented by $-\text{OH}$, $-\text{SH}$ or $-\text{NHR}^{11}$, wherein R^{11} is a hydrogen atom or an alkyl group, and the Lewis acid is represented by MY_n , wherein M is Fe , Sc or a lanthanoid element, Y is a halogen atom, OAc , OCOCF_3 , ClO_4 , SbF_6 , PF_6 or OSO_2CF_3 and n is 2 or 3.

Patentansprüche

1. Verfahren zum Herstellen einer optisch aktiven hydroxymethylierten Verbindung, bei welchem ein Siliziumenolat und Formaldehyd in der Anwesenheit eines Katalysators in wässriger Lösung oder einem gemischten Lösemittel aus Wasser und einem organischen Lösemittel miteinander reagiert werden, wobei das Siliziumenolat durch die folgende Formel (chemische Formel 2) dargestellt ist:

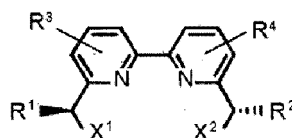


wobei R⁵ ein Wasserstoffatom oder eine Alkylgruppe ist, R⁶ eine Alkylgruppe, eine Alkylarylgruppe oder eine Arylgruppe ist, wobei R⁵ und R⁶ gemeinsam einen fünf- oder sechsgliedrigen Ring bilden können, welcher Kohlenstoffatome und wahlweise Heteroatome aufweist, R⁷ ein Wasserstoffatom, eine Alkylgruppe, eine Alkylarylgruppe oder eine Arylgruppe ist und die R⁸ Gruppen, welche identisch oder unterschiedlich sein können, jeweils Alkylgruppen sind und der Katalysator durch Mischen eines Liganden oder seines symmetrischen Isomers und einer Lewissäure erhalten wird, wobei der Ligand durch die folgende Formel (chemische Formel 1) dargestellt ist:



wobei R¹ und R², welche identisch oder unterschiedlich sein können, Wasserstoffatome, Alkylgruppen oder Arylgruppen sind, mindestens einer von R¹ oder R² mindestens drei Kohlenstoffatome enthält, R³ und R⁴, welche identisch oder unterschiedlich sein können, Wasserstoffatome, Alkylgruppen sind, welche ein bis vier Kohlenstoffatome oder Alkoxygruppen enthalten, X¹ und X², welche identisch oder unterschiedlich sein können, durch -OH, -SH oder -NHR¹¹ dargestellt sind, wobei R¹¹ ein Wasserstoffatom oder eine Alkylgruppe ist, und die Lewissäure durch MY_n dargestellt ist, wobei M Cu, Zn, Fe, Sc oder ein lanthanoides Element ist, Y ein Halogenatom, OAc, OCOCF₃, ClO₄, SbF₆, PF₆ oder OSO₂CF₃ ist und n 2 oder 3 ist.

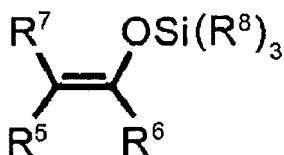
2. Katalysator, welcher durch Mischen eines Liganden oder seines symmetrischen Isomers und einer Lewissäure erhalten wird, wobei der Ligand durch die folgende Formel (chemische Formel 1) dargestellt ist:



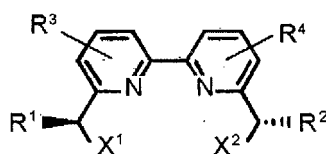
wobei R¹ und R², welche identisch oder unterschiedlich sein können, Wasserstoffatome, Alkylgruppen oder Arylgruppen sind, mindestens einer von R¹ oder R² mindestens drei Kohlenstoffatome enthält, R³ und R⁴, welche identisch oder unterschiedlich sein können, Wasserstoffatome, Alkylgruppen sind, welche ein bis vier Kohlenstoffatome oder Alkoxygruppen enthalten, X¹ und X², welche identisch oder unterschiedlich sein können, durch -OH, -SH oder -NHR¹¹ dargestellt sind, wobei R¹¹ ein Wasserstoffatom oder eine Alkylgruppe ist, und die Lewissäure durch MY_n dargestellt ist, wobei M Fe, Sc oder ein lanthanoides Element ist, Y ein Halogenatom, OAc, OCOCF₆, ClO₄, SbF₆, PF₆ oder OSO₂CF₃ ist und n 2 oder 3 ist.

Revendications

1. Procédé de production d'un composé hydroxyméthylé optiquement actif, comprenant la réaction d'un énoilate de silicium et de formaldéhyde, en présence d'un catalyseur, dans une solution aqueuse ou dans un solvant mélangé d'eau et d'un solvant organique, dans lequel l'énoilate de silicium est représenté par la formule suivante (formule chimique 2) :

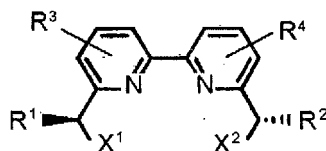


dans laquelle R⁵ est un atome d'hydrogène ou un groupe alkyle, R⁶ est un groupe alkyle, un groupe aryle-alkyle ou un groupe aryle, R⁵ et R⁶ pouvant former ensemble un cycle de cinq à six chaînons comprenant des atomes de carbone et des hétéroatomes éventuels, R⁷ est un atome d'hydrogène, un groupe alkyle, un groupe aryle-alkyle ou un groupe aryle et les groupes R⁸, qui peuvent être identiques ou différents, sont chacun un groupe alkyle, et le catalyseur est obtenu en mélangeant un ligand ou son isomère symétrique et un acide de Lewis, le ligand étant représenté par la formule suivante (formule chimique 1) :



dans laquelle R¹ et R², qui peuvent être identiques ou différents, sont des atomes d'hydrogène, des groupes alkyle ou des groupes aryle, au moins l'un parmi R¹ et R² contenant au moins trois atomes de carbone, R³ et R⁴, qui peuvent être identiques ou différents, sont des atomes d'hydrogène, des groupes alkyle contenant de un à quatre atomes de carbone ou des groupes alcoxy, X¹ et X², qui peuvent être identiques ou différents, sont représentés par -OH, -SH ou -NHR¹¹, R¹¹ étant un atome d'hydrogène ou un groupe alkyle, et l'acide de Lewis est représenté par MY_n, M étant du Cu, du Zn, du Fe, du Sc ou un élément lanthanide, Y étant un atome d'halogène, du OAc, du OCOF₃, du ClO₄, du SbF₆, du PF₆ ou du OSO₂CF₃ et n étant de 2 ou 3.

2. Catalyseur obtenu en mélangeant un ligand ou son isomère symétrique et un acide de Lewis, le ligand étant représenté par la formule suivante (formule chimique 1) :



dans laquelle R¹ et R², qui peuvent être identiques ou différents, sont des atomes d'hydrogène, des groupes alkyle ou des groupes aryle, au moins l'un parmi R¹ et R² contenant au moins trois atomes de carbone, R³ et R⁴, qui peuvent être identiques ou différents, sont des atomes d'hydrogène, des groupes alkyle contenant de un à quatre atomes de carbone ou des groupes alcoxy, X¹ et X², qui peuvent être identiques ou différents, sont représentés par -OH, -SH ou -NHR¹¹, dans lequel R¹¹ est un atome d'hydrogène ou un groupe alkyle, et l'acide de Lewis est représenté par MY_n, M étant du Fe, du Sc ou un élément lanthanide, Y étant un atome d'halogène, du OAc, du OCOF₃, du ClO₄, du SbF₆, du PF₆ ou du OSO₂CF₃ et n étant de 2 ou 3.

Figure 1

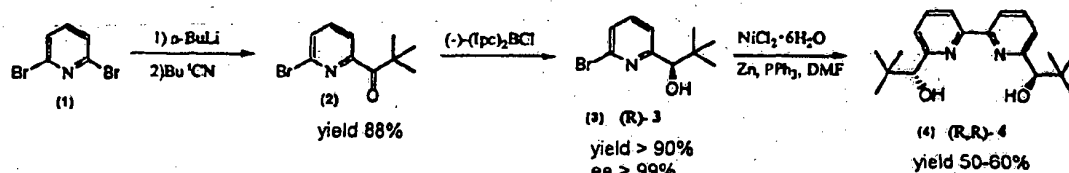
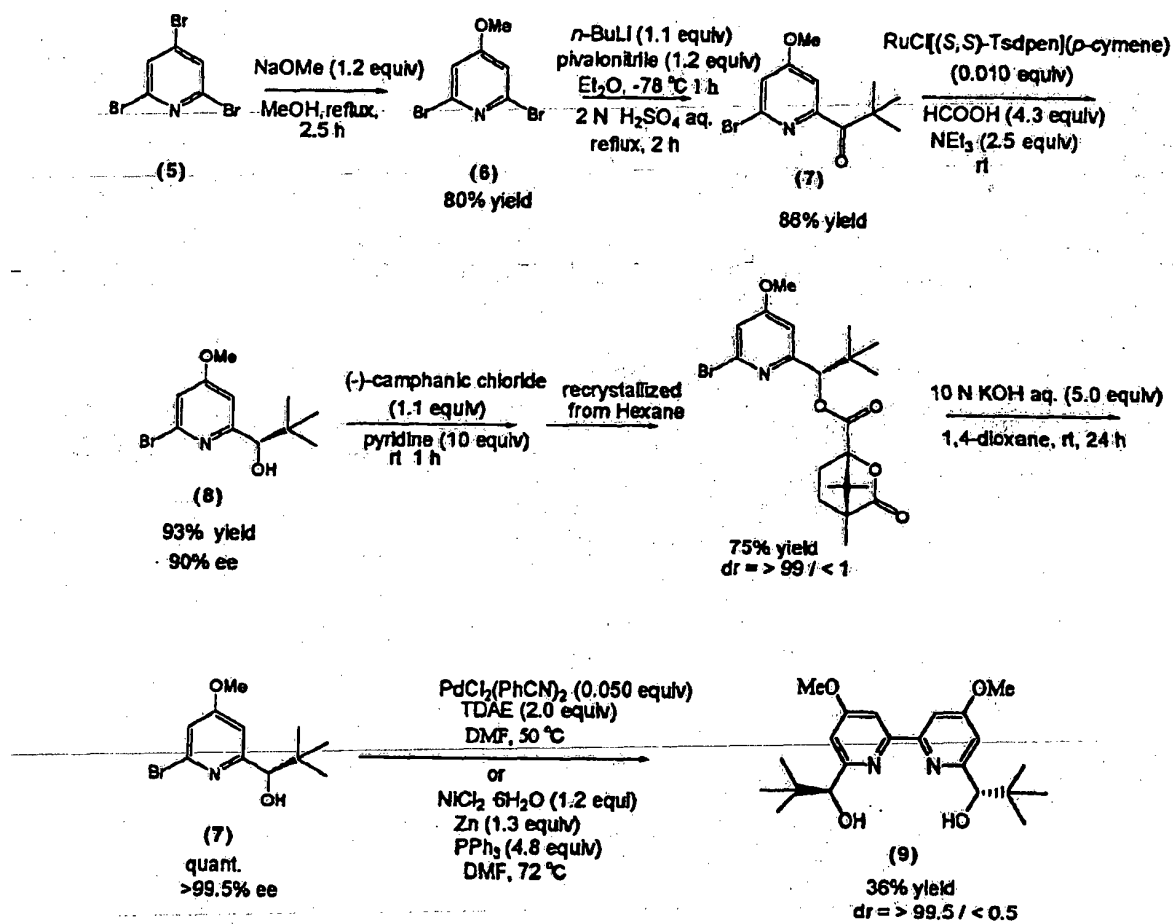


Figure 2



REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- JP 2001252570 A [0003]
- JP 6166652 A [0003]
- JP 6256248 A [0003]

Non-patent literature cited in the description

- **MANABE, K. ; ISHIKAWA, S. ; HAMADA, T. ; KOBAYASHI, S.** *Tetrahedron*, 2003, vol. 59, 10439 [0003]
- **OZASA, N. ; WADAMOTO, M. ; ISHIHARA, K. ; YAMAMOTO, H.** *Synlett*, 2003, 2219 [0003]
- **KUWANO, R. et al.** *Chem. Commun.*, 1998, 71 [0003]
- **CASAS, J. et al.** *Tetrahedron Lett.*, 2004, vol. 45, 6117 [0003]
- **BOLM, C. ; EWALD, M. ; FELDER, M. ; SCHLINGLOFF, G.** *Chem. Ber.*, 1992, vol. 125, 1169 [0003]
- Denmark and Fan have reported catalytic, enantioselective aldol additions to ketones. *J. Am. Chem. Soc.*, 2002, vol. 124, 4233-4235 [0003]