(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 724 251 A1

(12) **EUROPEAN PATENT APPLICATION**
published in accordance with Art. 158(3) EPC

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

(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)

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

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

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

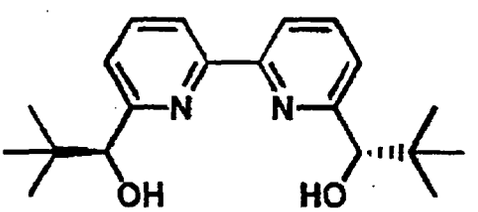
(72) Inventors:
- **KOBAYASHI, Shu**
  Chiyoda-ku, Tokyo 1010048 (JP)
- **MANABE, Kei**
  Bunkyo-ku, Tokyo 1130033 (JP)

(74) Representative: **Wilson Gunn**
Chancery House
Chancery Lane
GB-London WC2A 1QU (GB)

(54) PROCESS FOR PRODUCTION OF OPTICALLY ACTIVE HYDROXYMETHYLATED COMPOUNDS

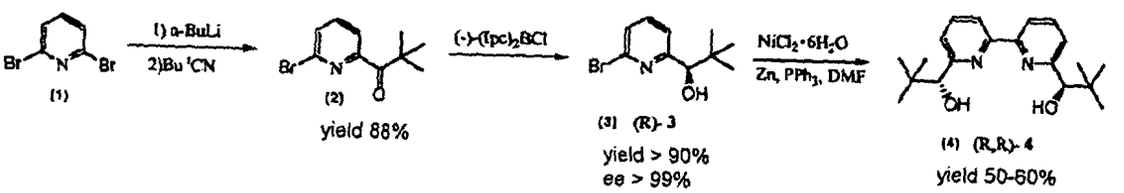
(57) The present invention presents a catalyst that allows asymmetric hydroxymethylation reactions to progress with excellent asymmetric selectivity and a production method for optically active hydroxymethylated compounds using the catalyst.

Optically active hydroxymethylated compounds are obtained with excellent asymmetric selectivity by using a catalyst obtained by mixing chiral ligands (for example, chemical formula 4)



with scandium triflate and the like.

Figure 1



EP 1 724 251 A1

Description

Field of the Invention

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

Prior Art

[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]

Reference 1:

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

Reference 2:

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

Reference 3:

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

Reference 4:

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

Reference 5:

Bolm, C.; Ewald, M.; Felder, M.; Schlingloff, G. Chem. Ber. 1992, 125, 1169.

Problems to be solved by the Invention

[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 hydroxymethlated compounds using the catalyst.

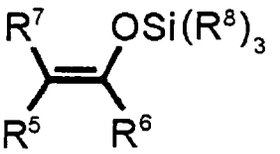
Means to solve the Problems

[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.

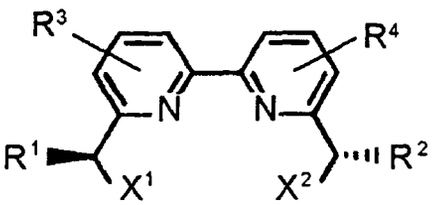
The catalytic system of the present invention is not only useful in the synthesis of optically active materials but also can provide an important direction for the development of catalytic asymmetric reactions in aqueous media.

[0006] 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,

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



wherein R^5 to R^7 are hydrogen atoms, aliphatic hydrocarbon groups, monocyclic or polycyclic alicyclic hydrocarbon groups, monocyclic or polycyclic aromatic hydrocarbon groups or heterocyclic groups where R^6 is not a hydrogen atom, R^5 and R^7 are not identical, R^5 and R^6 may together form a ring and R^8, may be identical or different, are hydrocarbon 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 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 $-OR^9$, $-SR^{10}$ or $-NHR^{11}$, wherein R^9 to R^{11} are hydrogen atoms or alkyl groups, 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.

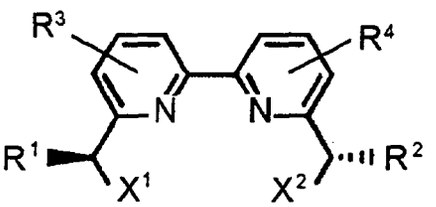
Brief Description of the Drawings

[0007]

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

Detailed Description of the Invention

[0008] The catalyst used in the present invention is obtained by mixing a ligand having the following structure (chemical formula 1):



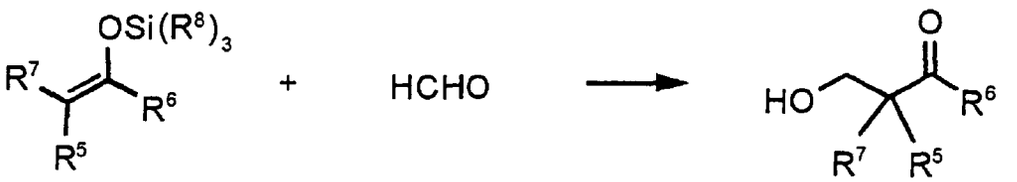
and a Lewis acid represented by MY_n.

[0009] R^1 and R^2 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 R^1 and R^2 needs to be bulky and, more specifically, needs to contain at least three carbon atoms.
R^3 and R^4 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.

[0010] X^1 and X^2 represent $-OR^9$, $-SR^{10}$ or $-NHR^{11}$, preferably -OH or -OMe, where R^9 to R^{11} represent hydrogen atoms or alkyl groups with hydrogen atoms preferred, and the number of carbon atoms in the alkyl groups is 1 to 3.
M represents Cu (divalent), Zn (divalent), Fe(divalent or trivalent), Sc (trivalent) or lanthanoid elements (^{57}La to ^{71}Lu) (trivalent) but preferably represents Sc.
n represents an integer corresponding to the valence of M and represents 2 or 3.
Y represents a halogen atom, OAc, $OCOCF_3$, ClO_4, SbF_6, PF_6 or OSO_2CF_3(OTf), preferably OTf.

[0011] 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.

[0012] In the present invention, this catalyst is used in asymmetric hydroxymethylation reactions of formaldehyde and a silicon enolate as described below (chemical formula 3):



R^5 to R^7 represent hydrogen atoms, aliphatic hydrocarbon groups, monocyclic or polycyclic alicyclic hydrocarbon groups, monocyclic or polycyclic aromatic hydrocarbon groups or heterocyclic groups. However, R^6 is not a hydrogen atom, and R^5 and R^7 are not the same. In addition R^5 and R^6 may together form a ring and they may also contain substituents. As this hydrocarbon group or the heterocyclic group, alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl and the like, cyclohexyl groups, phenyl groups, benzyl groups, phenyl ethyl groups, phenyl vinyl groups, naphthyl groups, furyl groups, thienyl groups, silyloxy groups and the like may be listed as examples. In addition, a variety of substituents such as halogen atoms, alkoxy groups, thio ether groups, hydrocarbon groups and the like may be listed as substituents that may be attached to these.
R^5 to R^7 are preferably as described below:
R^5 represents a hydrogen atom or an alkyl group, and R^6 represents an alkyl group, an alkyl aryl group, an aryl group or a sulfide group. However, R^5 and R^6 may together form a ring, the ring may optionally contain a hetero atom or a portion of an aromatic ring and the ring is preferably a five to seven membered ring comprising a hydrocarbon. R^7 represents a hydrogen atom, an alkyl group, an alkyl aryl group, an aryl group or a trialkyl silyloxy group.

[0013] R^8 represents a hydrocarbon group. They may each be identical or different, but the preference is for them to be identical. R^8 is preferably an alkyl group, more preferably an alkyl group containing one to three carbon atoms and most preferably a methyl group.

[0014] 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.

[0015] 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.

[0016] 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.
The reaction temperature is ordinarily from -40˚C to ambient temperature, more preferably from -20˚C to 0˚C.
The reaction time may be selected appropriately and from 0.5 hours to sixty hours, for example, is selected.

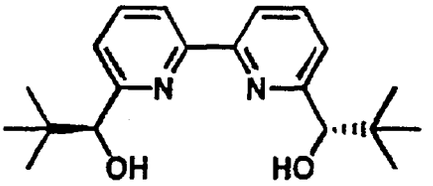
[0017] An optically active hydroxymethylated compound is formed by this reaction in excellent yield and selectivity.

[0018] The present invention is illustrated below by using the examples, but these are not intended to restrict the scope of the present invention.

Production Example 1

[0019] A ligand (henceforth referred to as "the ligand 1") having the structure shown by the formula below (chemical

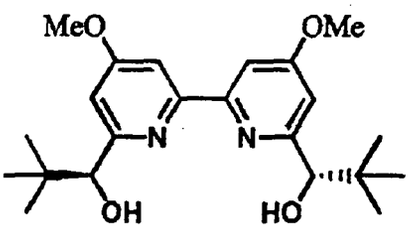
formula 4) was prepared according to the method described in Reference 5. The synthesis route is shown in Figure 1.



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

[0020] 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.



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 [$PdCl_2(PhCN)_2$-TDAE] to yield a pyridine isomer (9) (Chemical formula 5) in 36% yield (diastereomer ratio =>99.5/<0.5).

Example 1

[0021] 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 CH_2Cl_2. The organic layer was dried using Na_2SO_4, 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 ($CDCl_3$) 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, 1 H, J = 7.3), 7.97 (d, 2H, J = 8.5); ^{13}C NMR ($CDCl_3$) δ 14.5, 42.9, 64.5, 128.4, 128.7, 133.3, 13 6.1, 204.4; IR (neat) 3415, 2936, 1681, 1448, 974, 704 cm^{-1}; MS m/z 164 (M^+); Anal. Calcd fo r $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 72.87; H, 7.40; HPLC (Daicel Chiralpak AD-H, hexa ne/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

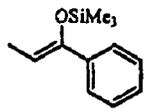
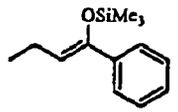
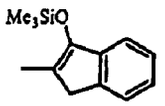
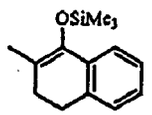
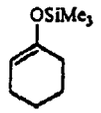
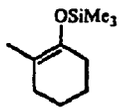
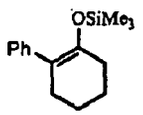
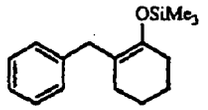
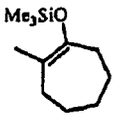
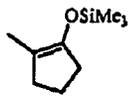
[0022] The same reaction conducted in Example 1 was executed using the ligand 2 synthesized in Production Example 2 in place of the ligand 1 synthesized in Production Example 1.

Examples 3-14

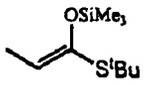
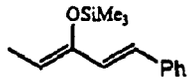
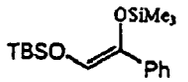
[0023] The silicon enolates shown in Table 1 were allowed to undergo the same reaction described in Example 1 using the reaction time described in the same table. However, the reaction was executed at a reaction temperature of -40˚C in Example 13 and a reaction temperature of -10˚C in Example 14.

[0024] 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(%)
1		24	80	80
2[a)]		30	60	87
3		30	66	88
4		14	90	90
5		20	80	94
6		29	22	62[b)]
7		20	68	91[b)]
8		21	63	60
9		19	77	67
10		2	62	90[b)]
11		10	50	85[b)]

(continued)

Example	Silicone Enolates	Time (h)	Yield (%)	ee(%)
12[c)]		24	31	93
13[d)]		65	73	92[b)]
14[e)]		8	61	77

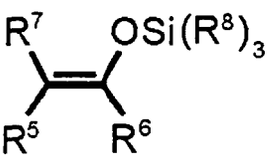
a) Used Ligand 2.
b) The ee was decided using chiral HPLC after converting the product into a benzoate.
c) HCHO (ten equivalent), H_2O/DME = 1/4
d) Reaction temperature -40˚C.
e) Reaction temperature -10˚C.

Potential Industrial Applicability

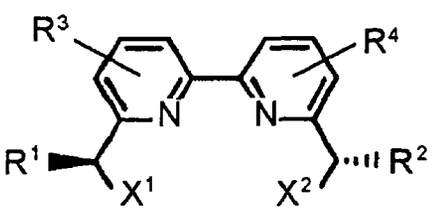
[0025] The optically active hydroxymethylated compounds formed according to the method of the present invention are useful as synthetic intermediates and the like for various chemical products.

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 to R^7 are hydrogen atoms, aliphatic hydrocarbon groups, monocyclic or polycyclic alicyclic hydrocarbon groups, monocyclic or polycyclic aromatic hydrocarbon groups or heterocyclic groups where R^6 is not a hydrogen atom, R^5 and R^7 are not identical, R^5 and R^6 may together form a ring and R^8, may be identical or different, are hydrocarbon 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):

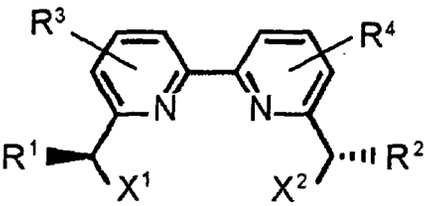


wherein R^1 and R^2, may be identical or different, are hydrogen atoms, alkyl groups or aryl groups, at least one of R^1 and R^2 contains at least three carbon atoms, R^3 and R^4, may be identical or different, are hydrogen atoms, alkyl

groups containing one to four carbon atoms or alkoxy groups, X^1 and X^2, may be identical or different, are represented by $-OR^9$, $-SR^{10}$ or $-NHR^{11}$, wherein R^9 to R^{11} are hydrogen atoms or alkyl groups, 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. The method as of claim 1, wherein R^5 is a hydrogen atom or an alkyl group, R^6 is an alkyl group, an alkyl aryl group, an aryl group or a sulfide group in which R^5 and R^6 may together form a five to six membered ring comprising carbon atoms and optional hetero atoms wherein sections of the ring may form an aromatic ring, R^7 is a hydrogen atom, an alkyl group, an alkyl aryl group or an aryl group and R^8, may be identical or different, are alkyl groups.

3. 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 $-OR^9$, $-SR^{10}$ or $-NHR^{11}$, wherein R^9 to R^{11} are hydrogen atoms or alkyl groups, 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.

Figure 1

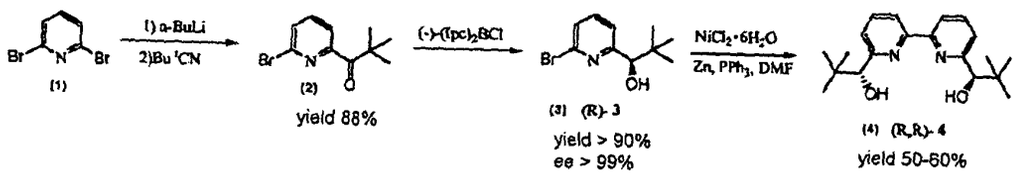
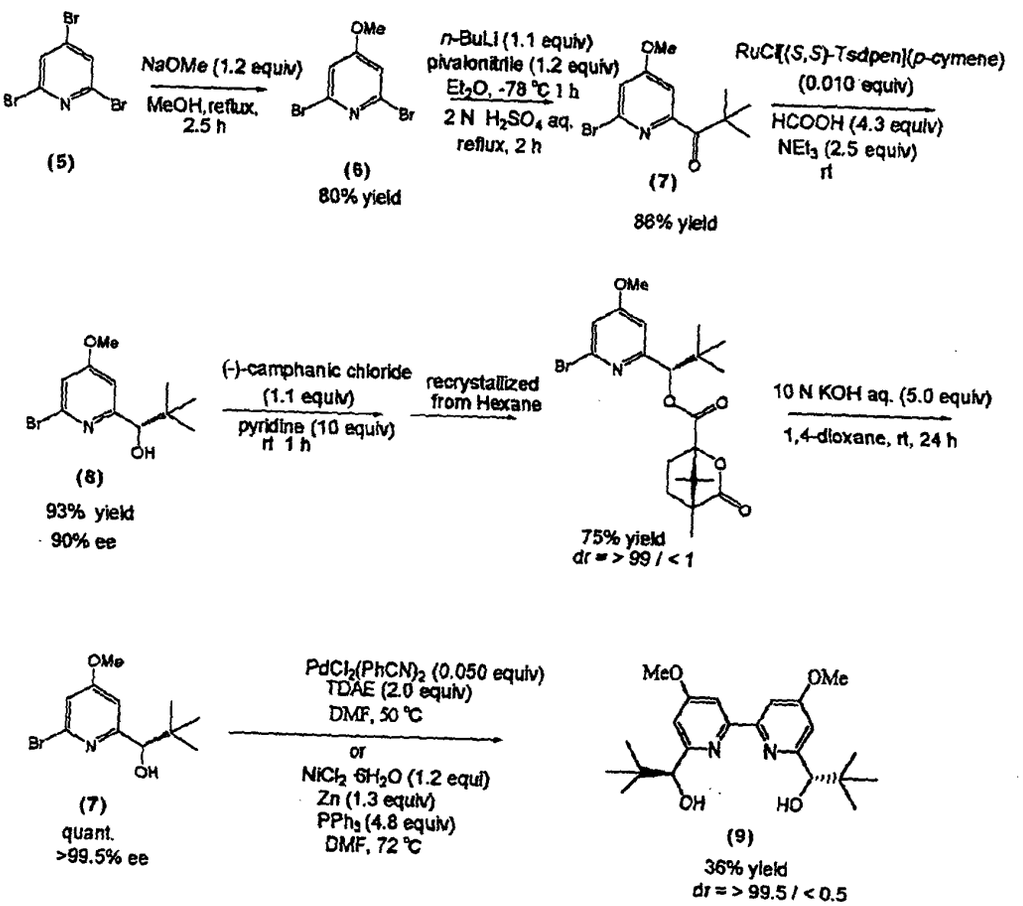


Figure 2



INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2005/001086

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[7] C07C45/00, B01J31/14, C07C45/75, 49/497, 49/733, 49/82, 327/22//C07B53/00, 61/00, C07M7:00

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)
Int.Cl[7] C07C45/00, 49/00, 327/00, C07B53/00

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)
CAPLUS(STN), REGISTRY(STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DENMARK, Scott E. et al., Catalytic, Enantioselective Aldol Additions to Ketones, Journal of the American Chemical Society, 2002, 124(16), pages 4233 to 4235	1-3
Y	JP 2001-252570 A (Japan Science and Technology Corp.), 18 September, 2001 (18.09.01), Pages 2 to 3 (Family: none)	1-3
Y	JP 6-166652 A (Nippon Steel Corp.), 14 June, 1994 (14.06.94), Pages 3 to 5 (Family: none)	1-3

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
06 April, 2005 (06.04.05)	26 April, 2005 (26.04.05)
Name and mailing address of the ISA/ Japanese Patent Office Facsimile No.	Authorized officer Telephone No.

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2005/001086

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JP 6-256248 A (Nippon Steel Corp.), 13 September, 1994 (13.09.94), Pages 3 to 5 (Family: none)	1-3

Form PCT/ISA/210 (continuation of second sheet) (January 2004)

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.

Non-patent literature cited in the description

- **MANABE, M ; ISHIKAWA, S. ; HAMADA, T. ; KOBAYASHI, S.** *Tetrahedron,* 2003, vol. 59, 10439 **[0003]**
- **OZASA, N. ; WADAMOTO, M. ; ISHIHARA, K. ; YAMAMOTO, H.** *Synlett,* 2003, vol. 2219 **[0003]**
- **KUWANO, R.** *Chem. Commun.,* 1998, vol. 71 **[0003]**
- **CASAS, J.** *Tetrahedron Lett.,* 2004, vol. 45, 6117 **[0003]**
- **BOLM, C. ; EWALD, M. ; FELDER, M. ; SCHLINGLOFF, G.** *Chem. Ber.,* 1992, vol. 125, 1169 **[0003]**