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(54) **ASYMMETRIC REACTION CATALYST AND PROCESS FOR PRODUCTION OF OPTICALLY ACTIVE COMPOUNDS WITH THE SAME**

KATALYSATOR FÜR ASYMMETRISCHE REAKTIONEN UND VERFAHREN ZUR HERSTELLUNG VON OPTISCH AKTIVEN VERBINDUNGEN DAMIT

CATALYSEUR DE REACTION ASYMETRIQUE ET PROCEDE POUR LA PRODUCTION DE COMPOSÉS ACTIFS OPTIQUEMENT

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Description

BACKGROUND OF THE INVENTION

1. Field of the Invention

[0001] The present invention relates to an asymmetric reaction catalyst used in nucleophilic addition and a method for preparing an optically active compound.

2. Description of the Related Art

[0002] Asymmetric nucleophilic addition reactions to the unsaturated carbon of a C=O bond or C=N bond (for example, imine (C=N) or hydrazone (C=N-N) compound) in the presence of a Lewis acid catalyst results in the formation of a new carbon-carbon bond. These reactions have been heavily examined because they can be used in the synthesis of various optically active compounds. Also, from the viewpoints of selectivity and stability, various metals and ligands are used as the above-mentioned catalyst.

[0003] The inventors of the present invention have already developed an asymmetric catalyst prepared from a zirconium alkoxide and a binaphthol derivative and have reported that asymmetric Diels-Alder reactions (for example, refer to Japanese Patent Laid-open Publication 2002-356454), aldol reactions (for example, refer to Japanese Patent Laid-open Publication 2000-67833 and Yamashita et al., J. Am. Chem. Soc., 2002, Vol. 124, page 3292) and imino aldol reactions (for example, refer to Japanese Patent Laid-open Publication H11-33407) can be carried out with high yields and high stereoselectivity.

[0004] Also, it is expected that niobium has a high Lewis acidity (for example refer to C. Andrade, Tetrahedron Lett., 2001, Vol. 42, page 6473) and an example of an asymmetric Diels-Alder reaction carried out using niobium in the catalyst has been reported (for example, refer to J. Howarth and K. Gillespie, Molecules, 2000, Vol. 5, page 993).

[0005] JP 2002/275112 reports a catalyst for asymmetric synthesis formed from a triol of a binaphthol and zirconium. Ishitani, Haruro et al. also report a zirconium catalyst formed from a triol of binaphthol this catalyst is used in Mannich-type reactions (Tetrahedron Letters, (1999), 40(:1), 2161 - 2164).

SUMMARY OF THE INVENTION

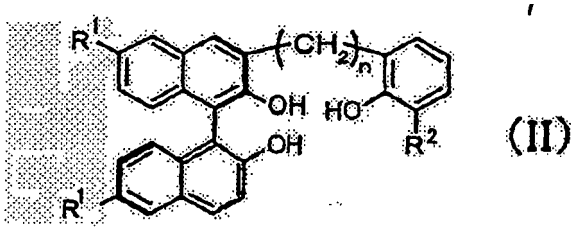
[0006] Effective catalysts are desired for the purpose of developing more effective reactions, in other words, reactions having chemical yields close to 100% and stereoselectivity close to 100%.

[0007] An object of the present invention is to solve the above-mentioned problem by providing an asymmetric reaction catalyst which achieves superior yields and superior stereoselectivity as well as being easy to handle and by also providing a method for preparing an optically active compound using the same.

[0008] The inventors have found that an asymmetric catalyst having niobium as the active central metal can be obtained by mixing a niobium compound and a triol having an optically active binaphthol structure as defined in claim 1. Also, the inventors have found that this catalyst is suitable for asymmetric nucleophilic addition reactions as defined in claim 3.

[0009] The asymmetric reaction catalyst of the present invention is obtained by mixing a pentavalent niobium compound and a triol of formula (II) having an optically active binaphthol structure of R or S configuration. Preferably, the above-mentioned niobium compound is represented by the formula NbX_5 (wherein, X represents an alkoxide or a halogen atom).

[0010] The above-mentioned triol is represented by the following



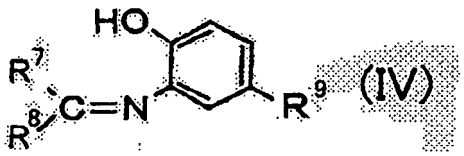
(II)

(wherein, R^1 represents a hydrogen atom, a halogen atom, a perfluoroalkyl group having at most 4 carbons, or an alkyl group or an alkoxy group having at most four carbons; R^2 represents a hydrogen atom or a hydrocarbon group having 1 to 10 carbons; and n is an integer from 0 to 2).

[0011] In the method for preparing a optically active compound of the present invention, a reaction substrate represented by R^5R^6C=N-Z (wherein R^5 and R^6, not being the same, are selected from the group consisting of a hydrogen atom, a

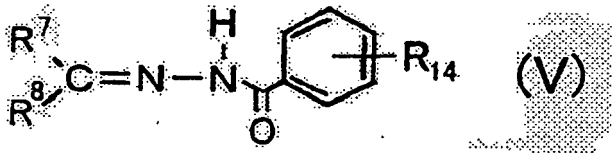
hydrocarbon group, and a hydrocarbon group having a functional group and Z represents an aryl group or an acylamino group) and a nucleophilic agent are reacted by nucleophilic addition using the above-mentioned asymmetric reaction catalyst.

[0012] Preferably, the above-mentioned reaction substrate is an imine represented by the following formula (IV):



(IV)

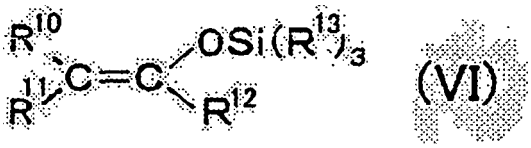
(wherein, R^7 and R^8, not being the same, are selected from the group consisting of a hydrogen atom, a hydrocarbon group, and a hydrocarbon group having a functional group and R^9 represents a hydrogen atom or a trifluoromethyl group) or the above-mentioned reaction substrate is a benzoylhydrazone represented by the following formula (V):



(V)

(wherein, R^7 and R^8, not being the same, are selected from the group consisting of a hydrogen atom, a hydrocarbon group, and a hydrocarbon group having a functional group and R^{14} represents a hydrogen atom or a substituent having an electron-withdrawing property).

[0013] Preferably, the above-mentioned nucleophilic agent is a silicon enolate represented by the following formula (VI):



(VI)

(wherein R^{10} and R^{11} are each independently one selected from the group consisting of a hydrogen atom, an aliphatic hydrocarbon group, an aromatic hydrocarbon group, an alkyloxy group, an aryloxy group, and an silyloxy group; R^{12} is one selected from the group consisting of a hydrogen atom, an aliphatic hydrocarbon group, an alkyloxy group, an aryloxy group, an arylthio group, and a alkylthio group; and each R^{13}, being the same or different, represents a hydrocarbon group).

[0014] Preferably, the above-mentioned method for preparing the optically active compound is carried out by adding an imidazole derivative and/or a synthetic crystalline zeolite to the reaction system.

[0015] In accordance with the present invention, an asymmetric reaction catalyst which achieves superior yields and superior stereoselectivity as well as being easy to handle can be obtained. Also, an optically active compound can be efficiently prepared by an asymmetric nucleophilic addition reaction using this catalyst. Furthermore, a selective reaction can be carried out without the occurrence of side reactions because the reaction is mild.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016]

Fig. 1 shows a reaction scheme in order to prepare a triol having a binaphthol structure.

DETAILED DESCRIPTION OF THE INVENTION

[0017] The embodiments of the present invention will now be explained.

<Niobium Compound>

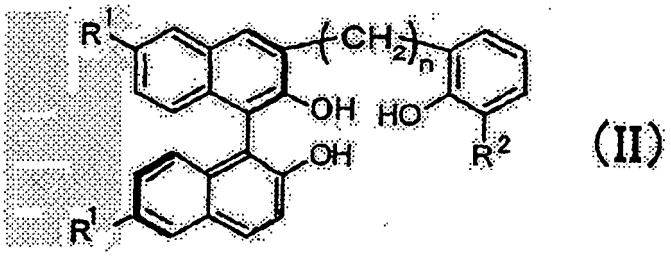
[0018] There are no particular limitations as to what can be used as the pentavalent niobium compound in the present

invention. Examples include compounds represented by the formula NbX_5 (wherein, X is an alkoxide or a halogen atom). Among these, from the viewpoint of ease of handling, Nb alkoxides (in particular, Nb methoxide or Nb ethoxide) are preferable.

<Triol Having a Binaphthol Structure>

[0019] The triol having a binaphthol structure used in the present invention includes an optically active binaphthol skeleton of R configuration or S configuration. By mixing this triol with the above-mentioned niobium compound, an asymmetric niobium catalyst is formed having a structure in which the optically active triol is bonded to an atom of niobium, which is the central metal, via an oxygen atom. Here, by finely adjusting the distance between the binaphthol ring and the phenol as well as by finely adjusting the substituent of the phenol, catalyst structures suitable for various nucleophilic addition reactions can be formed.

[0020] A compound represented by the following formula (II):



(II)

(wherein, R^1 represents a hydrogen atom, a halogen atom, a perfluoroalkyl group having at most 4 carbons, or an alkyl group or alkoxy group having at most 4 carbons; R^2 represents a hydrogen atom or a hydrocarbon group having 1 to 10 carbons; and n is an integer from 0 to 2) can be suitably used as the above-mentioned triol. Specific examples include triols wherein, R^2 is one selected from the group consisting of hydrogen, a methyl group, t-butyl, and an isopropyl group and n = 0 or 1.

[0021] Examples of the above-mentioned substituent R^1 on the naphthalene ring in the above-mentioned triol include a hydrogen atom, a halogen, an alkyl group, and a perfluoroalkyl group. Specific examples of a binaphthol structure having this type of substituent include 3,3'-dibromo-, 6,6'-dibromo-, 3,3'-dibromo-6,6'-diiodo-, 3,3'-methyl-, 6,6'-dimethyl-, and 3,3',6,6'-tetraiodo-1,1'-bi-2-naphthol.

[0022] The role of the substituent on the naphthalene ring is considered to mainly be an electronic effect. There is no influence merely by the ease of positioning.

<Preparation of the Catalyst>

[0023] The mixed ratio of the above-mentioned niobium compound and the above-mentioned triol is preferably 1/1 to 1/2 (niobium compound/triol or tetraol) and more preferably 1/1 to 1/1.3.

[0024] There are no particular limitations to the method for mixing the above-mentioned niobium compound and the above-mentioned triol. Normally, the above-mentioned compounds can be mixed in an organic solvent and arbitrarily stirred. Hydrocarbons and halogenated hydrocarbons can be suitably used as the organic solvent. In particular, methylene chloride, toluene, or their mixture is suitable. There are no particular limitations to the mixing temperature. It is easy to mix close to room temperature and then it is suitable to heat to a temperature between room temperature and the boiling point of toluene (preferably around 60°C) for aging. The heating time of the catalyst is normally in the range from 30 minutes to 24 hours and preferably in the range from 1 to 3 hours.

<Other Components>

[0025] If a nitrogen-containing compound is further added to asymmetric catalysts consisting of the above-mentioned niobium compound and the triol, the catalytic properties become better. Preferably, the nitrogen containing compound is a pyridine (for example, pyridine, 2,6-Lutidine, 2,4,6-Collindine, or the like), a quinoline (for example, quinoline or isoquinoline), ^{i}Pr2NEt, or an imidazoles (for example, N-methylimidazole). It is preferable that the amount of these nitrogen-containing compounds added is approximately the same number of moles as the above-mentioned niobium compound. There are no particular limitations to the timing when these nitrogen-containing compounds are added to the reaction system. Normally, it is preferable that these nitrogen-containing compounds are either mixed with the triol before addition of the niobium compound or are added between the mixing of the triol with the niobium compound and

the addition of the nucleophilic agent.

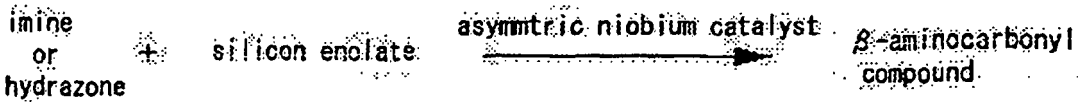
[0026] Also, the catalytic properties of asymmetric catalysts consisting of the above-mentioned niobium compound and the above-mentioned triol can be improved by further adding a synthetic crystalline zeolite such as molecular sieves. Normally, 3A or 4A are suitable as the molecular sieves.

<Reaction Substrate>

[0027] The catalyst of the present invention which has been prepared as above has a catalytic action for various asymmetric reactions. Examples include asymmetric Mannich reactions, epoxide asymmetric ring opening reactions, asymmetric allylation reactions, asymmetric Michael reactions, asymmetric cyanation reactions, and asymmetric alkylation reactions. In particular, the target product can be obtained in high yield and high stereoselectivity when the catalyst of the present invention is used in asymmetric Mannich reactions and epoxide asymmetric ring opening reactions.

<Mannich Reaction>

[0028] The catalyst of the present invention is particularly effective in a Mannich reaction where the electrophilic agent (reaction substrate) is an imine or an acylhydrazone and the nucleophilic agent is silicon enolate. An optically active nitrogen-containing compound is formed by this asymmetric reaction.



(Reaction Substrate)

[0029] The reaction substrates are compounds represented by $R^5R^6C=N-Z$ (wherein, R^5, R^6, and Z have the same definition as above and $R^5 \neq R^6$). These compounds are collectively termed imines and acylhydrazones.

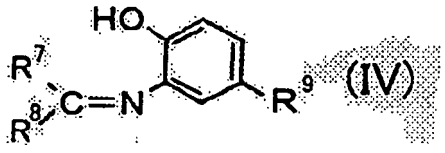
[0030] When these compounds are used, the substituents R^5 and R^6 in the above-mentioned formula are each independently one selected from the group consisting of a saturated or an unsaturated aliphatic hydrocarbon group, an aromatic hydrocarbon group, and an alkoxycarbonyl group. These substituents may have a heteroatom or a functional group which does not inhibit the addition reaction. Each type of imine compound can be easily synthesized by the corresponding carbonyl compound and amine following an already known method. Similarly, each type of acylhydrazone compound can be easily synthesized from the corresponding carbonyl compound and acylhydrazine following an already known method.

(Nucleophilic Agent)

[0031] A silicon enolate can be suitably used as the nucleophilic agent. When the above-mentioned compound ($R^5R^6C=N-Z$) is the reaction substrate and a silicon enolate is used as the nucleophilic agent, an optically active β-aminocarbonyl compound or an optically active β-amino acid derivative can be obtained.

(Imine)

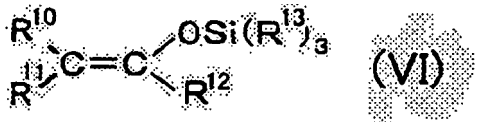
[0032] The imine used has been obtained by a dehydration reaction between an aldehyde or ketone and a primary amine. For example, an imine represented by the following formula (IV):



(wherein, R^7 and R^8, not being the same, are selected from the group consisting of a hydrogen atom, a hydrocarbon group, and a hydrocarbon group having a functional group and R^9 represents a hydrogen atom or a trifluoromethyl group) can be suitably used. An imine where either R^7 or R^8 is a hydrogen atom is particularly suitable.

(Silicon Enolate)

[0033] Examples include a silicon enolate represented by the following formula (VI):

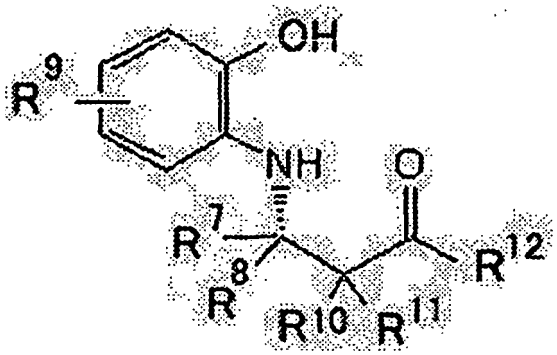


(VI)

(wherein R^{10} and R^{11} are each independently one selected from the group consisting of a hydrogen atom, an aliphatic hydrocarbon group, an aromatic hydrocarbon group, an alkyloxy group, an aryloxy group, and an silyloxy group; R^{12} is one selected from the group consisting of a hydrogen atom, an aliphatic hydrocarbon group, an alkyloxy group, an aryloxy group, an arylthio group, and a alkylthio group; and each R^{13}, being the same or different, represents a hydrocarbon group).

[0034] In particular, a silicon enolate is preferable wherein, at least one of the R^{13}, which may be same or different, is selected from the group consisting of a methyl group, an ethyl group, an isopropyl group, a phenyl group, and a tertiary butyl group.

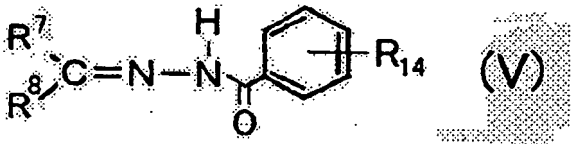
[0035] A β-aminocarbonyl compound having, for example, the following structure:



can be obtained by using the asymmetric niobium catalyst of the present invention when the above-mentioned imine and the above-mentioned enolate are used. When R^{12} represents a hydrocarbon group, this product is a β-amino ester and when R^{12} represents a thioalkoxy group, this product is a β-amino thioester. Also, the 2-hydroxyphenylamino group in the product can be converted to a primary amino group by removing the aryl group with a method using CAN (ceric ammonium nitrate).

(Hydrazone)

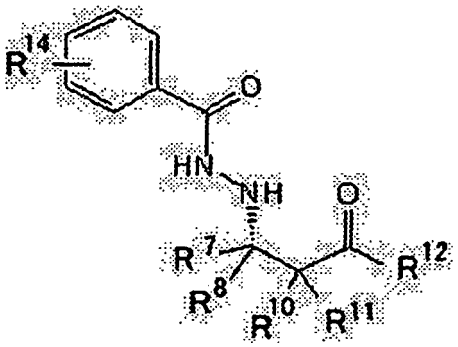
[0036] Instead of the above-mentioned imine, a benzoylhydrazone represented by the following formula (V):



(V)

(wherein, R^7 and R^8, not being the same, are selected from the group consisting of a hydrogen atom, a hydrocarbon group, and a hydrocarbon group having a functional group and R^{14} represents a hydrogen atom or a substituent having an electron-withdrawing property) may be used as the reaction substrate. In this situation, it is preferable that either R^7 or R^8 is a hydrogen atom. Also, examples of substituents having an electron-withdrawing property which are used as R^{14} include halogens, perfluoroalkyl groups having at most 4 hydrocarbons, and nitro groups.

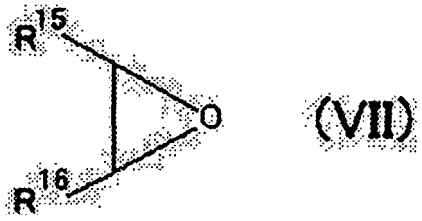
[0037] A β-hydrazinocarbonyl compound having, for example, the following structure:



can be obtained by using the asymmetric niobium catalyst of the present invention when the above-mentioned benzoylhydrazone and the above-mentioned silicon enolate are used. This product can be converted to a primary amino group by breaking the N-N bond using samarium oxide or Raney nickel.

<Epoxide Ring-opening Reaction Using a Nucleophilic Agent>

[0038] The catalyst of the present invention can be applied to an epoxide ring opening reaction using a nucleophilic agent in which the epoxide is an electrophilic agent. There are no particular limitations to the structure of the epoxide. Examples include a compound represented by the following formula (VII):



(VII)

(wherein R^{15} and R^{16} are selected from the group consisting of a hydrogen atom, a aliphatic hydrocarbon group, an aromatic hydrocarbon group, and a hydrocarbon group having a substituent, with the proviso that either R^{15} or R^{16} is not a hydrogen atom and R^{15} and R^{16} may form at least a 5-membered ring structure).

[0039] Examples of the nucleophilic agent include azides, primary amines, secondary amines, thiols, cyano compounds, and halides. Among these, nitrogen-containing compounds are preferable. In particular, primary and secondary amines are preferable.

<Other Nucleophilic Addition Reactions>

[0040] The asymmetric reaction catalyst of the present invention can be used in a nucleophilic addition reaction by a nucleophilic agent other than a silicon enolate for the above-mentioned imine or the above-mentioned acylhydrazone. For example, asymmetric allylation reactions by an allylation agent such as allyltrichlorosilane and asymmetric cyanation reactions by trialkyl tin cyanide or the like can be carried out.

<Reaction Method>

[0041] There are no particular limitations to the method for adding the reaction substrate to the above-mentioned catalyst.

[0042] Generally, the imine or the like, which has been dissolved in a solvent, is added dropwise to a solution including the above-mentioned catalyst and a solution including the nucleophilic agent may then be added dropwise. The reaction temperature can by arbitrarily selected according to the type of reaction substrate. Normally, the temperature is -78°C to room temperature and preferably -40°C to 0°C. The reaction time is generally 1 to 72 hours. The concentration of the reaction substrate in the reaction system including the above-mentioned catalyst and solvent is preferably 0.05 to 1.0 mol/l and more preferably 0.1 to 0.5 mol/l.

[0043] For example, after an imine compound or the like dissolved in a halogen hydrocarbon such as methylene chloride is added dropwise to the solution containing the above-mentioned catalyst, the nucleophilic agent may then be added dropwise.

[0044] When the catalyst of the present invention is used in an asymmetric reaction in which the above-mentioned

nucleophilic agent is nucleophilically added to the above-mentioned reaction substrate, very high enantioselectivity is shown and various amine compounds can be obtained in high optical purity. For example, a β-aminoketone (right-hand side formula (VI)) in the above-mentioned formula) with at least 70% chemical yield and at least 90% optical yield can be obtained in most situations by the Mannich reaction. The compounds of formula (III) and (IV) in the left-hand side of the above-mentioned formula are an imine compound and a silicon enolate, respectively, already shown by chemical formulas. The contents represented by reference symbols such as R^3 are as already mentioned.

[0045] Below, the present invention will be specifically explained using examples and comparative examples. However, these do not limit the present invention.

[0046] The NMR spectra (^{1}H-NMR, ^{13}C-NMR) were measured using JEOL-LA300, JEOL-LA400, or JEOL-LA500 (NMR (nuclear magnetic resonance) spectrometers manufactured by JEOL Ltd.). Optical rotation was measured using JASCO P-1010 (polarimeter manufactured by JASCO Corporation). The IR spectra were measured using FT/IR-610 (Fourier transform IR spectrometer manufactured by JASCO Corporation).

1. Experiment 1

[Example 1]

<Preparation of Triol Having Binapthol Structure>

[0047] A triol was prepared in accordance with the reaction formula shown in Fig. 1.

[0048] Firstly, sodium hydride (275 mmol) was suspended in tetrahydrofuran (THF) (120 ml) and to this, 2-isopropyl-phenol (111 mmol, reference symbol A1 in Fig. 1) dissolved in THF (30 ml) was added dropwise at 0°C. After 30 minutes, chloromethyl methyl ether (221 mmol) was added to this solution and after heating to room temperature, the reaction was stopped by adding methanol and then water. The aqueous phase was extracted with ether. The organic phases were combined and washed with water and a saturated sodium chloride solution in that order and then dried using anhydrous sodium sulfate. After removing the drying agent by filtering, the solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography to obtain 1-isopropyl-2-methoxy methoxybenzene (17.5 g, 87% yield, reference symbol A2 in Fig. 1).

[0049] At -78°C, a hexane solution of n-butyl lithium (100 mmol/64 ml) was added dropwise to a THF (200 ml) solution including 15.0 g (83 mmol) of the above-mentioned compound A2 and 15 ml (100 mmol) of tetramethylethylenediamine (TMEDA). After 30 min, the solution was heated to 0°C, stirred for 1 hour, and again cooled to -78°C. Dimethylformamide (DMF) (15.9 ml) was then added dropwise. After the reaction solution was slowly heated to room temperature, the reaction solution was poured into a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted with ether. The organic phases were combined and washed with water and a saturated sodium chloride solution in that order and then dried using anhydrous sodium sulfate. After removing the drying agent by filtering, the solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography to obtain 3-isopropyl-2-methoxy methoxybenzaldehyde (12.9 g, 74% yield, reference symbol A3 in Fig. 1).

[0050] ^{1}H-NMR δ(ppm): 1.25 (d, 6H, *J* = 7.1 Hz), 3.40 (sept, 1H, *J* = 7.1 Hz), 3.60 (s, 3H), 5.06 (s, 1H), 7.25 (dd, 1H, *J* = 7.6, 7.6 Hz), 7.55 (dd, *J* = 1.7, 7.6 Hz), 7.70 (dd, 2H, *J* = 1.7, 7.6 Hz), 10.3 (s, 1H)

[0051] Next, after a hexane solution of n-butyl lithium (45.4 mmol/28.9 ml) was added dropwise at room temperature to an ether (450 ml) solution containing (R)-2,2'-bis(methoxymethoxy)-[1,1']binaphthalene (37.9 mmol, reference symbol A4 in Fig. 1) and TMEDA (45.1 mmol), the solution was stirred for 1.5 hours. After the mixed solution was cooled to -78°C, an ether (50 ml) solution of the above-mentioned product A3 (22.9 mmol) was added dropwise. After the reaction solution was slowly heated to room temperature, the reaction solution was poured into a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted with ether. The organic phases were combined and washed with water and a saturated sodium chloride solution in that order and then dried using anhydrous sodium sulfate. After removing the drying agent by filtering, the solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography to give approximately a 1:1 diastereomeric ratio of (R)-(2,2'-dimethoxy-methoxy-[1,1']binaphthyl-3-yl)-(3-isopropyl-2-methoxymethoxyphenyl)methanol (12.2 g, 92% yield, reference symbol A5 in Fig. 1).

[0052] Under ice-cooling, hydrogen chloride-saturated methanol (35 ml) was added to a dichloromethane (35 ml) solution of the above-mentioned product A5 (21 mmol) and stirred for 2 hours. The mixed solution was neutralized by the addition of a saturated aqueous solution of sodium hydrogen carbonate and the organic phase was separated. The aqueous phase was extracted with methylene chloride. The organic phases were combined and washed with water and a saturated sodium chloride solution in that order and dried using anhydrous sodium sulfate. After removing the drying agent by filtering, the solvent was distilled off under reduced pressure. At 0°C, triethylsilane (67.2 mmol) was added to a methylene chloride (100 ml) solution of the obtained crude alcohol (A6 in Fig. 1). Next, a boron trifluoride-ether complex (65.1 mmol) was added dropwise. After the reaction solution was stirred overnight, the reaction solution was neutralized by adding a saturated aqueous solution of sodium hydrogen carbonate. The organic phase was separated. The remaining

aqueous phase was extracted with methylene chloride. The organic phases were combined and washed with water and a saturated sodium chloride solution in that order and then dried with anhydrous sodium sulfate. After removing the drying agent by filtering, the solvent was distilled off under reduced pressure. The residue was purified by silica gel chromatography to give the final product [(R)-3-(2-hydroxy-3-isopropylbenzyl)-[1,1']binaphthalene 2,2'-diol] (6.2 g, 68% yield, 2 steps, reference symbol A7 in Fig. 1).

[0053] ^{1}H-NMR δ (ppm): 1.20 (d, 3H, *J* = 6.8 Hz), 1.21 (d, 3H, *J* = 6.8 Hz), 3.25 (sept, 1H, *J* = 6.8 Hz), 4.17 (d, 1H, *J* = 14.9 Hz), 4.23 (d, 1H, *J* = 14.9 Hz), 4.99 (s, 1H), 5.63 (s, 1H), 6.51 (s, 1H), 6.90 (ddd, 1H, *J* = 1.5, 7.5, 7.5 Hz), 7.08-7.11 (m, 3H), 7.22-7.39 (m, 6H), 7.82 (d, 1H, *J* = 7.9 Hz), 7.88 (d, 1H, *J* = 8.1 Hz), 7.93 (s, 1H), 7.97 (d, 1H, *J* = 9.0 Hz)

[0054] ^{13}C-NMR ($CDCl_3$) δ (ppm): 22.5, 22.8, 27.1, 31.5, 108.9, 110.6, 111.5, 117.8, 120.6, 124.1, 124.2, 124.5, 124.9, 125.9, 127.1, 127.6, 128.0, 128.1, 128.5, 128.8, 129.5, 129.9, 131.2, 131.7, 132.2, 133.2, 135.8, 149.8, 151.1, 152.8.
[α] D^{30}: +63.6 (c 1.03, THF)
Mp: 205-206°C
IR (KBr): 3505, 3425, 1592, 1463, 820, 751 cm^{-1}

<Asymmetric Nucleophilic Addition Reaction of a Ketene Silyl Acetal to an Aldimine Using an Asymmetric Reaction Catalyst> 1. Preparation of Reaction Substrate and Nucleophilic Agent

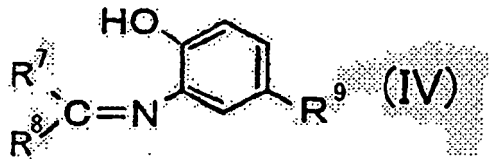
[0055] The imine (aldimine) prepared by recrystallizing the product prepared from the corresponding aldehyde and phenol derivative in dichloromethane and DMF and also in the presence of molecular sieves was used as the reaction substrate. The silyl enolate (silyl enol ether) was synthesized according to the method disclosed by S. Kobayashi et al. in "Silyl Enol Ethers", in Science of Synthesis: Houben-weyl Methods of Molecular Transformations, George Thieme Verlag, Stuttgart, 2002, Vol. 4, p. 317. The other chemicals used in the reaction were all purchased commercial products and were purified according to necessity. The reaction was completely performed under an argon atmosphere.

2. Preparation of Catalyst

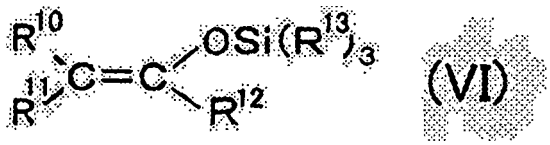
[0056] The above-mentioned product A7 (72 μmol) was dissolved in toluene (0.3 ml). To this solution was added a toluene (0.6 ml) solution of N-methylimidazole (NMI) (60 μmol) at room temperature and stirred. After this mixed solution was stirred for 10 min, a toluene (0.6 ml) solution of $Nb(OMe)_5$ (60 μmol) was added. After heating to 60°C and stirring for 3 hours, the mixed solution was then returned to room temperature. This mixed solution was transferred to a flask having molecular sieves 3A (100 mg) and after being washed with methylene chloride (0.5 ml), was stirred for 30 minutes.

3. Asymmetric Reaction

[0057] The above-mentioned solution was cooled to -20°C and a methylene chloride (0.7 ml) solution of the imine represented by the following formula IV:

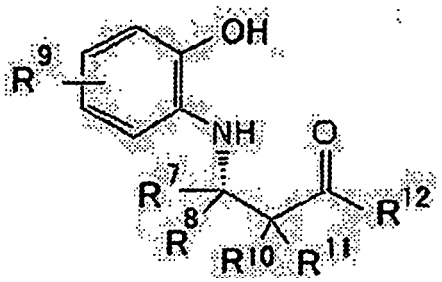


(0.6 mmol, R^7 = Ph, R^8 = H, R^9 = H)and then a methylene chloride (0.3 ml) solution of the silyl enol ether represented by the following formula VI:



(0.72 mmol, R^{10} = R^{11} = R^{13} = Me, R^{12} = OMe) were added. After stirring for 48 hours, the reaction was stopped by pouring the reaction solution into a saturated aqueous solution of sodium hydrogen carbonate. The aqueous phase was extracted with methylene chloride. The above-mentioned aqueous phase and organic phase were combined, washed with water and a saturated sodium chloride solution in that order, and then dried with anhydrous sodium sulfate. After removing the drying agent by filtering, the solvent was distilled off under reduced pressure. The obtained crude product

was purified using preparation thin layer chromatography (benzene/ethyl acetate = 9/1) and an aminoketone derivative (product) represented by the following formula:



was obtained (yield 86%, R^7 to R^{10} = same as in the above-mentioned formulas IV and V, a hydroxyl group and not a methoxy group is connected to the benzene). The asymmetric yield (99% ee) of the product was determined by HPLC (high-performance liquid chromatography) using a chiral column.

Various Properties of Products

[0058] Name: (S)-methyl 2,2'-dimethyl-3-(2-hydroxyphenyl)amino-3-phenylpropionate

[0059] IR (KBr): 3401, 1709, 1611, 1514, 1453, 1391 cm^{-1}.

[0060] ^{1}H-NMR ($CDCl_3$): δ (ppm): 1.21 (s, 3H), 1.24 (s, 3H) 3.68 (s, 3H), 4.57 (s, 1H), 6.36-6.76 (m, 4H), 7.21-7.28 (m, 5H).

[0061] ^{13}C-NMR ($CDCl_3$) : δ 19.9, 24.2, 47.3, 52.1, 64.3, 113.2, 114.1, 117.6, 120.8, 127.3, 127.9, 128.3, 135.6, 138.9, 144.0, 178.0.

[0062] HPLC (Daicel Chiralpak AD, hexane/^{i}PrOH = 9/1, flow rate = 1.0 ml/min, t_R = 9.3 min (3R), t_R = 16.0 min (3S). Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. found: C, 72.28; H, 7.20; N, 4.62.

[0063] HRMS: Calcd for $C_{18}H_{21}NO_3$ (M^+) 299.1522, found 299.1497.

[0064] Absolute configuration of S-configuration of product: determined by X-ray crystal structure analysis of the corresponding camphor acid ester.

<Examples 2 to 10>

[0065] In each of the compounds in the above-mentioned formulas IV and VI, apart from R^7 to R^{13} being changed to the products shown in Table 1, the reactions were performed the same as in Example 1. The chemical yields and asymmetric yields of the compounds are shown in Table 1.

Table 1

	Formula (III) Imine			Formula (IV) Ketene Silyl Acetal				Reaction Product Yields (%)	
	R^7	R^8	R^9	R^{10}	R^{11}	R^{12}	R^{13}	Chemical Yield	Asymmetric Yield
Example 1	H	Ph	H	Me	Me	OMe	Me	86	99% ee
Example 2	H	(4-Cl)C_6H_4	H	Me	Me	OMe	Me	82	98% ee
Example 3	H	(4-OMe)C_6H_4	H	Me	Me	OMe	Me	79	96% ee
Example 4	H	1-Naphthyl	H	Me	Me	OMe	Me	40	95% ee
Example 5	H	2-Naphthyl	H	Me	Me	OMe	Me	77	98% ee
Example 6	H	3-Thienyl	H	Me	Me	OMe	Me	85	93% ee
Example 7	H	Ph	CF_3	Me	Me	OMe	Me	75	91% ee
Example 8	H	Ph	H	H	H	SEt	Me	69	84% ee
Example 9	H	(4-Cl)C_6H_4	H	H	H	SEt	Me	44	88% ee
Example 10	H	2-Furyl	H	H	H	SEt	Me	70	87% ee

[0066] As shown in Table 1, when an imine was used in the reaction substrate of each of the Examples, a high

asymmetric yield of approximately 90% of the corresponding β-aminoketone derivative was obtained by a nucleophilic addition reaction using silyl enolate as the nucleophilic agent. Thus, it was understood that a nucleophilic reaction having high enantioselectivity to an imine is possible.

[0067] The properties of the reaction products (aminoketone derivatives) obtained in Examples 2 to 10 are shown below.

<Example 2>

(S)-methyl 3-(4-chlorophenyl)-2,2'-dimethyl-(2-hydroxyphenyl)aminopropionate

[0068] IR (KBr) 3359, 1709, 1610, 1513, 1490, 1450, 738 cm^{-1}.

[0069] ^{1}H-NMR ($CDCl_3$) : δ (ppm) 1.19 (s, 3H), 1.24 (s, 3H) 3.67 (s, 3H), 4.55 (s, 1H), 6.31-6.90 (m, 4H), 7.22 (s, 2H), 7.35 (s, 2H).

[0070] ^{13}C-NMR ($CDCl_3$): δ (ppm) 20.2, 24.7, 47.3, 52.4, 64.0, 113.3, 114.3, 117.9, 121.1, 128.2, 128.3, 129.7, 133.2, 135.4, 137.7, 144.0, 177.5.

[0071] HPLC: measuring conditions same as Example 1, t_R = 8.3 min (3R), t_R= 16.7 min (3S). Anal. Calcd for $C_{18}H_{20}NO_3Cl$: C, 64.77; H, 6.04; N, 4.20. found: C, 64.47; H, 6.18; N, 4.01.

[0072] HRMS: Calcd for $C_{18}H_{20}NO_3Cl$ (M^+) 333.1133, found 333.1109.

<Example 3>

Methyl 2,2'-dimethyl-3-(2'-hydroxyphenylamino)-3-(4'-methoxyphenyl)propionate

[0073] IR (neat): 3420, 2979, 1715, 1612, 1510, 1252 cm^{-1}.

[0074] ^{1}H-NMR ($CDCl_3$): δ (ppm) 1.20 (s, 3H), 1.22 (s, 3H), 3.68 (s, 3H), 3.76 (s, 3H), 4.50 (s, 1H), 6.39 (d, 1H, *J* = 7.9 Hz), 6.35 (dd, 1H, *J* = 7.6, 7.6 Hz) , 6.62 (dd, 1H, *J* = 7.6, 7.6 Hz), 6.68 (d, 1H, *J* = 7.9 Hz), 6.81 (d, 1H, *J* = 8.5 Hz), 7.19 (d, 1H, *J* = 8.5 Hz).

[0075] ^{13}C-NMR ($CDCl_3$): δ (ppm) 20.1, 24.4, 47.5, 52.2, 55.2, 64.2, 113.4, 114.3, 115.3, 117.2, 118.1, 119.7, 121.1, 129.4, 131.0, 135.6, 144.4, 158.8, 177.8.

[0076] HPLC: measuring conditions same as Example 1, t_R = 11.1 min (3R), t_R = 28.0 min (3S).

[0077] HRMS: Calcd for $C_{19}H_{23}NO_4$ (M^+) 329.1627, found 329.1638.

<Example 4>

(S)-methyl 2,2'-dimethyl-3-(2-hydroxyphenyl)amino 3-(1'-naphthyl)-propionate

[0078] ^{1}H-NMR ($CDCl_3$) : δ (ppm) 1.18 (s, 3H), 1.25 (s, 3H) 3.66 (s, 3H), 5.62 (s, 3H), 6.28-6.62 (m, 4H), 7.22-8.00 (m, 7H).

[0079] ^{13}C-NMR ($CDCl_3$): δ (ppm) 19.9, 25.1, 48.4, 52.4, 57.8, 113.4, 114.2, 117.9, 121.2, 122.1, 123.2, 125.2, 125.3, 125.4, 126.1, 128.1, 129.1, 133.6, 135.3, 144.1, 177.9.

[0080] HPLC: apart from using chiralcel AD in the column, measuring conditions same as Example 1, t_R = 14.6 min (3s), t_R = 10.6 min (3R).

[0081] Anal. Calcd for $C_{22}H_{23}NO_3$: C, 75.62; H, 6.63; N, 4.01. found: C, 75.48; H, 6.49; N, 3.94.

[0082] HRMS: Calcd for $C_{18}H_{20}NO_3Cl$ (M^+) 349.1678, found 349.1668.

<Example 5>

Methyl 2,2'-dimethyl-3-(2'-hydroxyphenyl)amino-3-(2'-naphthyl)propionate

[0083] IR (KBr) 3418, 1710, 1610, 1510, 1270, 736 cm^{-1}.

[0084] ^{1}H-NMR ($CDCl_3$) : δ (ppm) 1.26 (s, 3H), 1.29 (s, 3H), 3.70 (s, 3H), 4.71 (s, 1H), 6.40-6.70 (m, 4H) 7.41-7.46 (m, 3H), 7.75-7.81 (m, 4H).

[0085] ^{13}C-NMR ($CDCl_3$) : δ (ppm) 20.2, 24.5, 47.6, 52.3, 64.8, 114.0, 114.3, 118.0, 121.1, 125.8, 126.2, 127.5, 127.6, 127.6, 127.9, 132.9, 133.0, 135.5, 136.7, 144.3, 177.7.

[0086] HPLC: apart from the flow rate being 0.8 ml/min, measuring conditions same as Example 1, t_R = 12.2 min (3R), t_R = 26.0 min (3S).

[0087] HRMS: Calcd for $C_{22}H_{23}NO_3$ (M^+) 349.1678, found 349.1671.

<Example 6>

(R)-methyl 3-(2-hydroxyphenyl)amino-2,2'-dimethyl-3-(3'-thienyl)propionate

[0088] IR (neat) 3413, 2978, 1708, 1608, 1513, 1446, 1267, 1192, 1140, 741 cm^{-1}.
[0089] ^{1}H-NMR ($CDCl_3$) : δ (ppm) 1.25(s, 3H), 1.28(s, 3H), 3.69(s, 3H), 4.66(s, 1H), 6.46-6.71 (m, 4H), 6.98(d, 1H *J* = 5.6 Hz), 7.06(s, 1H), 7.21(s, 1H).
[0090] ^{13}C-NMR ($CDCl_3$): δ (ppm) 20.4, 24.1, 47.2, 52.2, 61.2, 114.5, 115.1, 118.9, 121.1, 122.9, 125.2, 127.3, 135.3, 140.7, 145.0, 177.7.
[0091] HPLC: measuring conditions same as Example 1, t_R = 9.2 min (3S), t_R = 14.3 min (3R).

<Example 7>

(S)-methyl 3-(2-hydroxy-5-trifluoromethylphenyl)amino-2,2'-dimethyl-3-phenylpropionate

[0092] IR (neat) 1707, 1612, 1531, 1442, 1336, 1277, 1115 cm-1.
[0093] ^{1}H-NMR ($CDCl_3$): δ (ppm) 1.22 (s, 3H), 1.26 (s, 3H), 3.70 (s, 3H), 4.54 (s, 1H), 6.58 (s, 1H), 6.75 (d, 2H, *J* = 7.6 Hz), 7.23-7.32 (m, 5H).
[0094] ^{13}C-NMR ($CDCl_3$): δ (ppm) 20.2, 24.7, 47.3, 52.4, 64.5, 109.9, 113.6, 115.0, 123.2, 123.5, 127.8, 128.2, 135.7, 138.3, 137.0, 146.6, 177.9.
[0095] HPLC: measuring conditions same as Example 1, t_R = 5.4min (3R), t_R = 7.3 min (3S).
[0096] Anal. Calcd for $C_{19}H_{20}F_3NO_3$: C, 62.12; H, 5.49; F, 15.11; N, 3.81; O, 13.07. found: C, H, N.

<Example 8>

(S)-S-ethyl 3-(2-hydroxyphenyl)amino-3-phenylpropanthioic acid

[0097] IR (KBr) 3396, 1647, 1608, 1520, 1449, 1362 cm^{-1}.
[0098] ^{1}H-NMR ($CDCl_3$) : δ (ppm) 1.67 (t, 3H, *J* = 7.3 Hz), 2.83 (q, 2H, *J* = 7.3 Hz), 2.97 (dd, 1H, *J* = 5.4, 14.9 Hz), 3.07 (dd, 1H, *J* = 8.1, 14.9 Hz), 4.81 (dd, 1H, *J* = 5.4, 8.1 Hz), 6.44-6.71 (m, 4H), 7.20-7.33 (m, 5H).
[0099] ^{13}C-NMR ($CDCl_3$) : δ (ppm) 14.4, 23. 6, 51.4, 56.1, 114.4, 114.6, 118.8, 121.1, 126.3, 127.4, 128.6, 134.9, 141.7, 144.7, 198.4.
[0100] HPLC: apart from using chiralpak AS in the column and hexane/^{i}PrOH = 19/1, measuring conditions same as Example 1, t_R = 26.6 min (3S), t_R = 38.2 min (3R). Anal. Calcd for $C_{17}H_{19}NO_2S$: C, 67.74; H, 6.35; N, 4.65. found: C, 68.00; H, 6.54; N, 4.54.
[0101] HRMS: Calcd for $C_{17}H_{19}NO_2S$ (M^+) 301.1138, found 301.1102.

<Example 9>

(S)-S-ethyl 3-(4'chlorophenyl)-3-(2-hydroxyphenyl)amino-phenylpropanthioic acid

[0102] IR (neat) 3412, 1665, 1516, 1447, 742 cm^{-1}.
[0103] ^{1}H-NMR ($CDCl_3$) : δ (ppm) 1.21 (t, 2H *J* = 7.4 Hz), 2.83 (q, 2H *J* = 7.4 Hz), 2.96 (dd, 1H, *J* = 5.1, 14.9 Hz), 3.05 (dd, 1H, *J* = 8.3, 14.9 Hz), 4.78 (dd, 1H, *J* = 5.1, 8.3 Hz), 6.39-6.78 (m, 4H), 7.22-7.28 (m, 5H).
[0104] ^{13}C-NMR ($CDCl_3$): δ (ppm) 14.5, 23.7, 51.2, 55.6, 114.5, 115.0, 119.3, 121.2, 127.8, 128.9, 133.2, 134.6, 140.3, 144.7, 197.8.
[0105] HPLC: measuring conditions same as Example 1, t_R = 19.5 min (3S), t_R = 24.3 min (3R). Anal. Calcd for $C_{17}H_{18}NO_2ClS$: C, 60.80; H, 5.40; N, 4.17. found: C, 60.85; H, 5.60; N, 3.99.
[0106] HRMS: Calcd for $C_{17}H_{18}NO_2ClS$ (M^+) 335.0747, found 335.9758.

<Example 10>

(S)-S-ethyl 3-(2'-furyl)-3-(2-hydroxyphenyl)amino-phenylpropanthioic acid

[0107] IR (neat) 3414, 1674, 1608, 1513, 1448, 1349, 740 cm^{-1}.
[0108] ^{1}H-NMR ($CDCl_3$) : δ (ppm) 1.32 (t, 3H, *J* = 7.3 Hz), 2.90 (q, 2H, *J* = 7.3 Hz), 3.06 (dd, 1H, *J* = 5.4, 15.6 Hz), 3.19 (dd, 1H *J* = 8.3, 15.6 Hz), 4.81 (dd, 1H *J* = 5.4, 8.3 Hz), 6.11 (d, 1H *J* = 3.2 Hz), 6.26 (dd, 1H *J* = 2.0, 3.2 Hz), 6.60-6.81 (m, 4H), 7.35 (d, 1H *J* = 2.0 Hz).

[0109] ^{13}C-NMR ($CDCl_3$) : δ (ppm) 14.5, 23. 6, 48.0, 50.8, 106.8, 110.2, 115.0, 118.0, 120.7, 121.5, 133.8, 142.0, 147.1, 153.8, 198.2.

[0110] HPLC: measuring conditions same as Example 4, t_R = 15.4 min (3S), t_R = 8.9 min (3R).

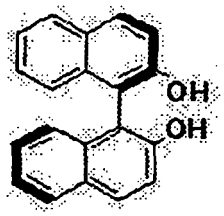
[0111] Anal. Calcd for $C_{15}H_{17}NO_3S$: C, 61.83; H, 5.88; N, 4.81. found: C, 61.86; H, 5.72; N, 4.80.

[0112] HRMS: Calcd for $C_{15}H_{17}NO_3S$ (M^+) 291.0932, found 291.0931.

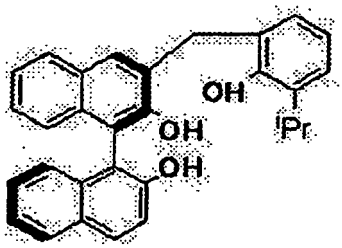
2. Experiment 2

<Epoxide Aminolysis Reaction According to Type of Binaphthol Structure>

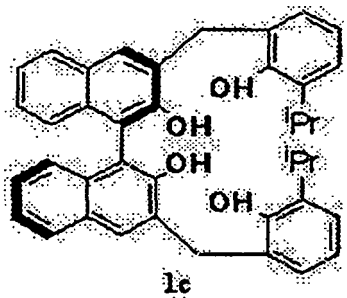
[0113] Under an argon atmosphere, a methylene chloride solution (0.60 ml) of the below niobium alkoxide (0.040 mmol) was added to a toluene solution (0.40 ml) of the below binaphthol structures 1a to 1c at room temperature (a toluene solution only was used for the binaphthol structure 1c) and then stirred for 3 hours at 60°C. The solution was then returned to room temperature and became a toluene solution of a chiral niobium complex.



1a



1b

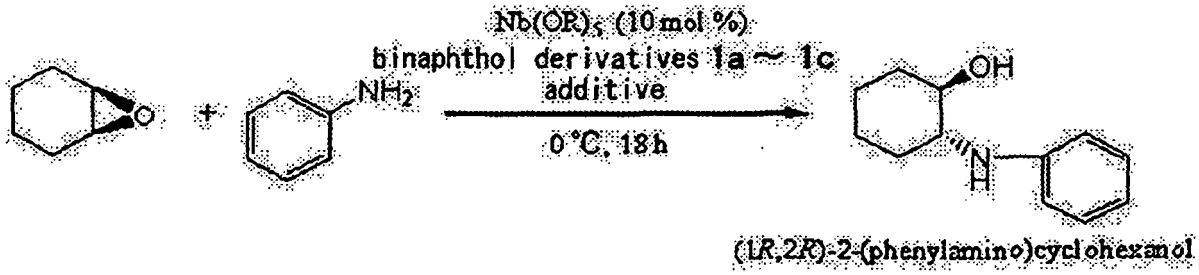


1c

[0114] Compounds 1a and 1c are illustrative and not of the invention.

[0115] To a different reaction vessel was added a given additive and after making the atmosphere a argon atmosphere, the chiral niobium complex methylene chloride (toluene) solution prepared above was transferred to this reaction vessel using a cannula and washed with methylene chloride (toluene for the binaphthol structure 1c) (0.50 ml). This was stirred for 30 minutes at room temperature and cooled to 0°C. A methylene chloride solution (0.50 ml) of an epoxide (cyclohexene oxide) (0.40 mmol) and a methylene chloride solution (0.50 ml) of an amine (aniline) (0.48 mmol) were added in that order and then stirred for 18 hours. An additive was not used with the binaphthol structure 1a and dried molecular sieves 4A (100mg) were used as the additive for the binaphthol structure 1c.

[0116] The reaction was stopped by adding a saturated aqueous sodium hydrogen carbonate solution (10 ml) and the aqueous phase was extracted with methylene chloride (10 ml x 3). The organic phases were combined and dried using anhydrous sodium sulfate. The solvent was distilled off under reduced pressure and the residue was purified using silica gel thin layer chromatography (Hexane: AcOEt = 4:1) to obtain the corresponding α-amino alcohol ((1R,2R)-2-(phenylamino)cyclohexanol. The optical purity of this product was determined by HPLC using an enantiomer separation column (Daicel Chiralpak AD).



(1*R*,2*R*)-2-(phenylamino)cyclohexanol

[0117] The results obtained are shown in Table 2. In the table, R represents the alkyl group of niobium alkoxide.

Table 2

Binaphthol Derivative 1	R	Additive	Solvent	Yield (%)	ee (%)
1a (22 mol%)	-$CH(CH_3)_2$	none	CH_2Cl_2	69	48
1b (11 mol%)	-$CH(CH_3)_2$	2,2'-biphenol (11 mol%)	CH_2Cl_2	55	48

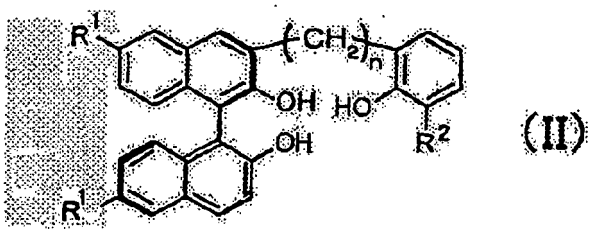
(continued)

Binaphthol Derivative 1	R	Additive	Solvent	Yield (%)	ee (%)
1c (11 mol%)	-Me	2,6-lutidine (12 mol%) MS 4A	CH_2Cl_2-toluene	quant	70
The reaction conditions were suitable conditions for each of the optically active binaphthol derivatives					

[0118] As is clear from Table 2, when a tetraol (not of the invention) is used as the binaphthol structure, the chemical yield and stereoselectivity of the epoxide asymmetric ring opening are the highest.

Claims

1. An asymmetric reaction catalyst obtained by mixing a pentavalent niobium compound and a triol having an optically active binaphtol structure of R or S configuration, wherein the triol is represented by the following formula (II):



(II)

wherein, R^1 represents a hydrogen atom, a halogen atom, a perfluoroalkyl group having at most 4 carbons, or an alkyl group or an alkoxy group having at most four carbons; R^2 represents a hydrogen atom or a hydrocarbon group having 1 to 10 carbons; and n is an integer from 0 to 2.

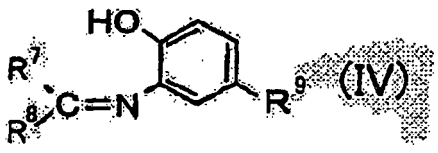
2. An asymmetric reaction catalyst according to claim 1, wherein the niobium compound is represented by the following formula:

$$NbX_5$$

wherein, X is an alkoxide or a halogen atom.

3. A method for preparing an optically active compound, wherein a reaction substrate represented by $R^5R^6C=N-Z$ wherein R^5 and R^6, not being the same, are selected from the group consisting of a hydrogen atom, a hydrocarbon group, and a hydrocarbon group having a functional group and Z represents an aryl group or an acylamino group and a nucleophilic agent are reacted by nucleophilic addition using an asymmetric reaction catalyst according to any one of claims 1 or 2.

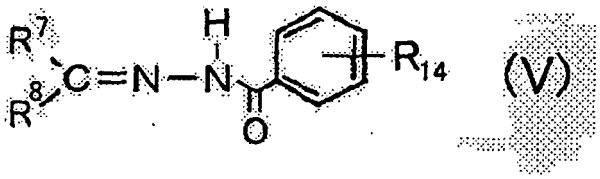
4. A method for preparing an optically active compound according to claim 3, wherein the above-mentioned reaction substrate is an imine represented by the following formula (IV) :



(IV)

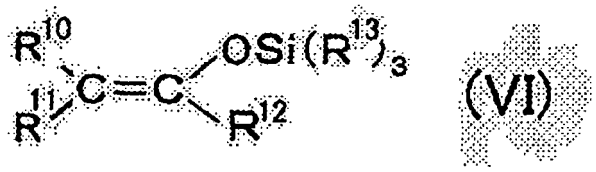
wherein, R^7 and R^8, not being the same, are selected from the group consisting of a hydrogen atom, a hydrocarbon group, and a hydrocarbon group having a functional group and R^9 represents a hydrogen atom or a trifluoromethyl group.

5. A method for preparing an optically active compound according to claim 3, wherein the above-mentioned reaction substrate is a benzoylhydrazone represented by the following formula (V):



wherein, R^7 and R^8, not being the same, are selected from the group consisting of a hydrogen atom, a hydrocarbon group, and a hydrocarbon group having a functional group and R^{14} represents a hydrogen atom or a substituent having an electron-withdrawing property.

6. A method for preparing an optically active compound according to any one of claims 3 to 5, wherein the above-mentioned nucleophilic agent is a silicon enolate represented by the following formula (VI):



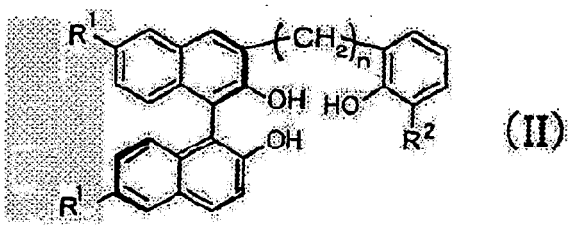
wherein R^{10} and R^{11} are each independently one selected from the group consisting of a hydrogen atom, an aliphatic hydrocarbon group, an aromatic hydrocarbon group, an alkyloxy group, an aryloxy group, and an silyloxy group; R^{12} is one selected from the group consisting of a hydrogen atom, an aliphatic hydrocarbon group, an alkyloxy group, an aryloxy group, an arylthio group, and a alkylthio group; and each R^{13}, being the same or different, represents a hydrocarbon group.

7. A method for preparing an optically active compound according to any one of claims 3 to 6, wherein an imidazole derivative is added to the reaction system.

8. A method for preparing an optically active compound system according to any one of claims 3 to 7, wherein a synthetic crystalline zeolite is added to the reaction system.

Patentansprüche

1. Ein asymmetrischer Reaktionskatalysator, welcher durch Mischen einer fünfwertigen Niobiumverbindung und eines Triols mit optisch aktiver Binaphtol Struktur mit R oder S Konfiguration erhalten wird, wobei das Triol durch folgende Formel (II) dargestellt wird:



wobei R^1 ein Wasserstoffatom, ein Halogenatom, eine Perfluoroalkylgruppe mit höchstens 4 Kohlenstoffen, oder eine Alkylgruppe oder eine Alkoxygruppe mit höchstens 4 Kohlenstoffen darstellt; R^2 ein Wasserstoffatom oder eine Kohlenwasserstoffgruppe mit 1 bis 10 Kohlenstoffen darstellt; und n eine ganze Zahl von 0 bis 2 ist.

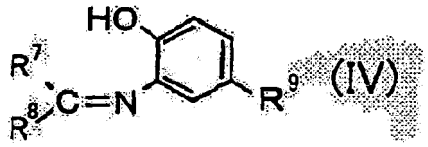
2. Ein asymmetrischer Reaktionskatalysator nach Anspruch 1, wobei die Niobiumverbindung durch folgende Formel dargestellt wird:

$$NbX_5,$$

wobei X ein Alkoxid oder ein Halogenatom ist.

3. Verfahren zum Herstellen einer optisch aktiven Verbindung, worin ein Reaktionssubstrat, dargestellt durch R^5R^6C=N-Z, worin R^5 und R^6 nicht gleich sind, aus der Gruppe bestehend aus einem Wasserstoffatom, einer Kohlenwasserstoffgruppe und einer Kohlenwasserstoffgruppe mit einer funktionellen Gruppe ausgewählt werden und Z eine Arylgruppe oder eine Acylaminogruppe darstellt, und ein nucleophiles Reagenz mittels eines asymmetrischen Reaktionskatalysators nach einem der Ansprüche 1 oder 2 eine nucleophile Additionsreaktion eingehen.

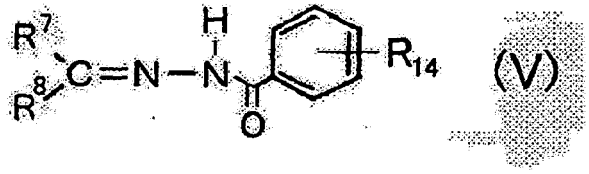
4. Verfahren zur Herstellung einer optisch aktiven Verbindung nach Anspruch 3,
wobei das oben genannte Reaktionssubstrat ein Imin ist, welches durch die folgende Formel (IV) dargestellt wird:



(IV)

wobei R^7 und R^8, welche nicht gleich sind, aus der Gruppe bestehend aus einem Wasserstoffatom, einer Kohlenwasserstoffgruppe und einer Kohlenwasserstoffgruppe mit einer funktionellen Gruppe ausgewählt werden, und R^9 ein Wasserstoffatom oder eine Trifluoromethylgruppe darstellt.

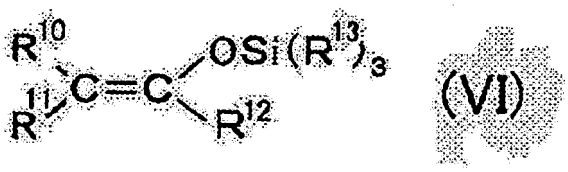
5. Verfahren zur Herstellung einer optisch aktiven Verbindung nach Anspruch 3, wobei das oben genannte Reaktionssubstrat ein Benzoylhydrazon ist, welches durch die folgende Formel (V) dargestellt wird:



(V)

wobei R^7 und R^8, welche nicht gleich sind, aus der Gruppe bestehend aus einem Wasserstoffatom, einer Kohlenwasserstoffgruppe und einer Kohlenwasserstoffgruppe mit einer funktionellen Gruppe ausgewählt werden, und R^{14} ein Wasserstoffatom oder einen Substituenten mit einer elektronenziehenden Eigenschaft darstellt.

6. Verfahren zum Herstellen einer optisch aktiven Verbindung nach einem der Ansprüche 3 bis 5,
wobei das oben beschriebene nucleophile Reagenz ein Silylenolether ist, welches durch die folgende Formel (VI) dargestellt wird:



(VI)

worin R^{10} und R^{11} jeweils unabhängig aus der Gruppe bestehend aus einem Wasserstoffatom, einer aliphatischen Kohlenwasserstoffgruppe, einer aromatischen Kohlenwasserstoffgruppe, einer Alkoxygruppe, einer Aryloxygruppe und einer Silyloxygruppe ausgewählt werden; R^{12} aus der Gruppe bestehend aus einem Wasserstoffatom, einer aliphatischen Kohlenwasserstoffgruppe, einer Alkoxygruppe, einer Aryloxygruppe, einer Arylthiogruppe, und einer Alkylthiogruppe ausgewählt werden; und jedes der R^{13}, welche gleich oder unterschiedlich sind, eine Kohlenwasserstoffgruppe darstellt.

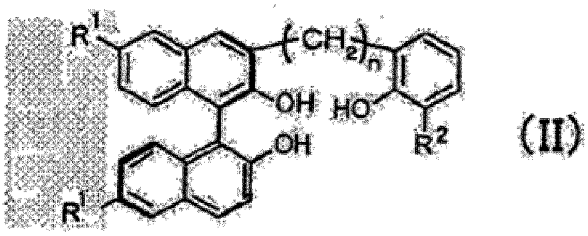
7. Verfahren zum Herstellen einer optisch aktiven Substanz nach einem der Ansprüche 3 bis 6,
wobei ein Imidazolderivat zum Reaktionssystem hinzugegeben wird.

8. Verfahren zum Herstellen eines optisch aktiven Verbindungssystems nach einem der Ansprüche 3 bis 7,

wobei ein synthetisches, kristallines Zeolith zum Reaktionssystem hinzugegeben wird.

Revendications

1. Une réaction de catalyse asymétrique obtenue en mélangeant un composé de niobium pentavalent et un triol ayant une structure de binaphtol optiquement active de configuration R ou S, dans laquelle le triol est représenté par la formule suivante (II):



(II)

dans laquelle, R^1 représente un atome d'hydrogène, un atome d'halogène un groupe perfluoroalkyle ayant au plus quatre carbones ; R^2 représente un atome d'hydrogène ou un groupe hydrocarbure ayant 1 à 10 carbones ; et n est un nombre entier entre 0 et 2.

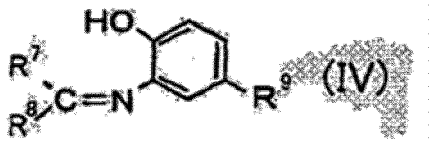
2. Une réaction de catalyse asymétrique selon la revendication 1, dans laquelle le composé niobium est représenté par la formule suivante :

$$NbX_5$$

dans laquelle X est un alcoxide ou un atome d'halogène.

3. Un procédé pour préparer un composé optiquement actif, dans lequel un substrat réactif, représenté par $R^5R^6C=N-Z$, dans lequel R^5 et R^6, n'étant pas les mêmes, sont sélectionnés dans un groupe consistant en un atome d'hydrogène, un groupe hydrocarbure, et un groupe hydrocarbure ayant un groupe fonctionnel, et Z représente un groupe aryle ou un groupe acylamino, et un agent nucléophile sont mis en réaction par addition nucléophile utilisant une réaction de catalyse asymétrique selon l'une quelconque des revendications 1 et 2.

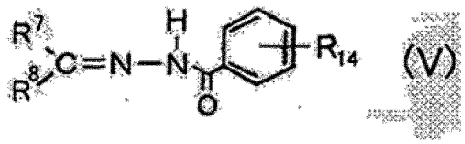
4. Un procédé pour préparer un composé optiquement actif selon la revendication 3, dans lequel le substrat réactif mentionné ci-dessus est un imine représenté par la formule suivante (IV) :



(IV)

dans lequel R^7 et R^8, n'étant pas les mêmes, sont sélectionnés dans le groupe consistant en un atome hydrogène, un groupe hydrocarbure, et un groupe hydrocarbure ayant un groupe fonctionnel et R^9 représente un atome d'hydrogène ou un groupe trifluorométhyle.

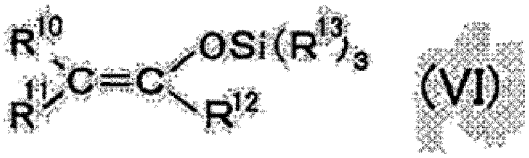
5. Un procédé pour préparer un composé optiquement actif selon la revendication 3, dans lequel le substrat réactif mentionné ci-dessus est un benzoylhydrazone représenté par la formule suivante (V) :



(V)

dans lequel R^7 et R^8, n'étant pas les mêmes, sont sélectionnés dans le groupe consistant en un atome hydrogène, un groupe hydrocarbure, et un groupe hydrocarbure ayant un groupe fonctionnel et R^{15} représente un atome d'hydrogène ou un substituant ayant une propriété électro-attractive.

6. Un procédé pour préparer un composé optiquement actif selon l'une quelconque des revendications 3 à 5, dans lequel l'agent nucléophile mentionné ci-dessus est un enolate représenté par la formule suivante (VI) :



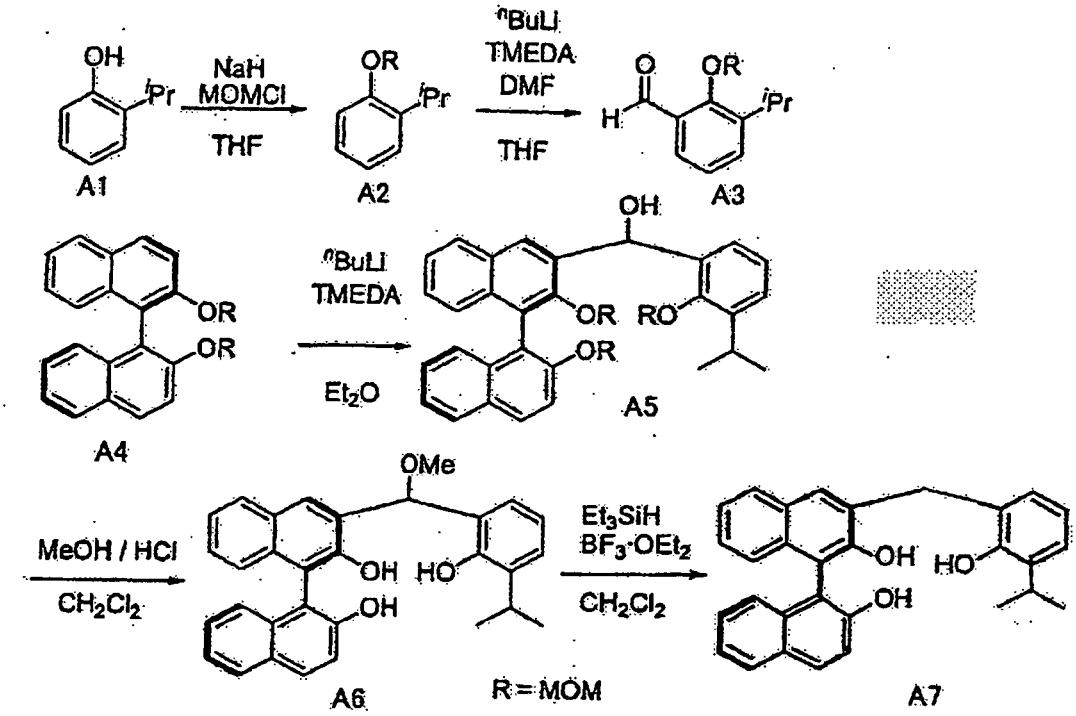
(VI)

dans lequel R^{10} et R^{11} sont chacun indépendamment sélectionnées dans le groupe consistant en un atome d'hydrogène, un groupe hydrocarbure aliphatique, un groupe hydrocarbure aromatique, un groupe alkyloxy, un groupe aryloxy, et un groupe silyloxy ; R^{12} est sélectionné sélectionnées dans le groupe consistant en un atome d'hydrogène, un groupe hydrocarbure aliphatique, un groupe alkyloxy, un groupe aryloxy, un groupe groupe arylthio, et un groupe alkylthio ; et chaque R^{13}, étant les mêmes ou étant différents, représente un groupe hydrocarbure.

7. Un procédé pour préparer un composé optiquement actif selon l'une quelconque des revendications 3 à 6, dans lequel un dérivé imidazole est ajouté au système réactionnel.

8. Un procédé pour préparer un composé optiquement actif selon l'une quelconque des revendications 3 à 7, dans lequel une zéolithe cristalline synthétique est ajoutée au système réactionnel.

Fig.1


OH
iPr
NaH
MOMCl
THF
OR
iPr
nBuLi
TMEDA
DMF
THF
O
H
OR
iPr
A1
A2
A3
OR
OR
nBuLi
TMEDA
Et2O
OH
OR
RO
OR
A4
A5
OMe
MeOH / HCl
CH2Cl2
OH
HO
OH
Et3SiH
BF3·OEt2
CH2Cl2
OH
HO
OH
A6
R = MOM
A7

REFERENCES CITED IN THE DESCRIPTION

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