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(54) **ASYMMETRIC UREA COMPOUNDS AND PROCESS FOR PRODUCING ASYMMETRIC COMPOUNDS BY ASYMMETRIC CONJUGATE ADDITION REACTION USING THE SAME AS CATALYST**

ASYMMETRISCHE HARNSTOFF-VERBINDUNGEN UND VERFAHREN ZUR HERSTELLUNG VON ASYMMETRISCHEN VERBINDUNGEN DURCH ASYMMETRISCHE KONJUGAT-ADDITIONSREAKTION UNTER VERWENDUNG DIESER VERBINDUNGEN ALS KATALYSATOR

COMPOSÉS D'URÉE ASYMÉTRIQUE ET PROCÉDÉ POUR LA PRÉPARATION DES COMPOSÉS ASYMÉTRIQUES PAR RÉACTION D'ADDITION DE CONJUGUE ASYMÉTRIQUE EN UTILISANT LESDITS COMPOSÉS COMME CATALYSEUR

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Description

Technical Field

[0001] The present invention relates to a novel asymmetric urea compound useful as a catalyst for asymmetric synthesis. Moreover, the present invention relates to a production method of asymmetric compounds, which comprises an asymmetric conjugate addition reaction using the asymmetric urea compound as a catalyst.

Background Art

[0002] Asymmetric compounds obtained by asymmetric conjugate addition reaction to electron-deficient olefin such as nitroolefin compound, α,β-unsaturated carbonyl compound and the like are useful as intermediates for synthesizing amines, amino acids, pharmaceutical agents, agricultural chemicals, food additives and the like (e.g., Journal of the American Chemical Society, vol. 124, No. 44, p. 13097-13105 (2002)), and various production methods have been reported so far.

[0003] However, many of them require a stoichiometric amount of an asymmetric reagent (Journal of the American Chemical Society, vol. 124, No. 39, p. 11689-11698 (2002)), and most of the catalytic asymmetric conjugate addition reactions require strict reaction conditions or involve use of a metal catalyst (Tetrahedron, vol. 58, No. 29, p. 5773-5778 (2002) and Synlett, special edition, p. 879-887 (2001)), which cause inefficient cost and operation, as well as environmental problems.

[0004] As a catalytic asymmetric conjugate addition reaction without using a metal catalyst, a Michael reaction to a nitroolefin compound using L-proline as a catalyst has been reported (Synlett, vol. 1, p. 26-28 (2002)). However, its stereoselectivity was unsatisfactorily low.

[0005] Furthermore, a Michael reaction to a nitroolefin compound using an asymmetric catalyst consisting of a magnesium salt and an asymmetric ligand has been reported (Journal of the American Chemical Society, vol. 121, No. 43, p. 10215-10216 (1999)). This method achieved high stereoselectivity, but is associated with limitations because it cannot be applied to bulky nucleophilic reagents having tertiary carbon etc., and the like.

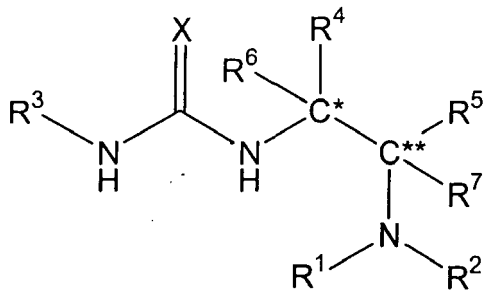
Disclosure of the Invention

[0006] The present invention has been made to solve the above-mentioned problems found in the conventional asymmetric conjugate addition reactions and aims at providing a non-metallic asymmetric catalyst capable of achieving a highly stereoselective asymmetric conjugate addition reaction in a high yield, and a production method of an asymmetric compound useful as an intermediate for synthesizing amines, amino acids, pharmaceutical agents, agricultural chemicals, food additives and the like, which is more advantageous than conventional methods, by developing an asymmetric conjugate addition reaction using the asymmetric catalyst.

[0007] To solve the above-mentioned problems, the present inventors took note of a compound wherein both of an acidic moiety that activates an electron-deficient olefin and a basic moiety that activates a nucleophilic reagent are bonded to optically active scaffolds, as a non-metallic asymmetric catalyst for a conjugate addition reaction, and conducted intensive studies. Consequently, they found a novel asymmetric urea compound, which resulted in the completion of the present invention.

[0008] Accordingly, the present invention provides the following.

(1) A compound represented by the formula (I):

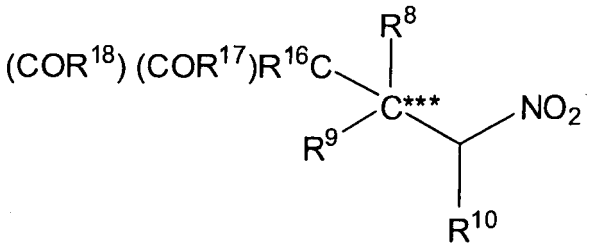


(I)

wherein

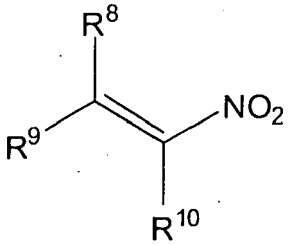
X is a sulfur atom;
C* and C** are each independently an asymmetric carbon, and the absolute configurations of C* and C** are both S-configurations or both R-configurations;
R^1 and R^2 are the same or different and each is methyl, ethyl or isopropyl, or form isoindoline together with the nitrogen atom they are bonded to;
R^3 is a phenyl group optionally having substituent(s) selected from C_{1-12} haloalkyl group(s), nitro group(s), cyano group(s) and -$COOR^{25}$ wherein R^{25} is a C_{1-12} alkyl group;
R^4 and R^5 form a cyclohexane together with the asymmetric carbons they are respectively bonded to; and
R^6 and R^7 are each a hydrogen atom,
or a salt thereof.
[hereinafter also referred to as asymmetric urea compound (I)], or a salt thereof.

(2) A method of producing a compound represented by the formula (IV):



(IV)

or a salt thereof,
which process comprises conjugately adding a nucleophilic reagent represented by the formula (III): H-$CR^{16}(COR^{17})(COR^{18})$ (III), to a compound represented by the formula (II):



(II)

or a salt thereof, in the presence of asymmetric urea compound (I) or a salt thereof
wherein

C*** is an asymmetric carbon;
R^8, R^9 and R^{10} are
the same or different and each is

(1) a hydrogen atom,
(2) a C_{1-12} alkyl group optionally having substituent(s),
(3) a C_{6-20} aryl-C_{1-12} alkyl group optionally having substituent(s),
(4) a C_{6-20} aryl group optionally having substituent(s),
(5) a heteroaryl group selected from (i) a 5- to 10-membered aromatic heterocyclic group containing, besides carbon atoms, 1 to 3 hetero atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom, and (ii) a fused heterocyclic group thereof, each of (i) and (ii) optionally having substituent(s),
(6) a hetero atom selected from a nitrogen atom, an oxygen atom and a sulfur atom, optionally having substituent(s) selected from

(a) a C_{1-12} alkyl group optionally having substituent(s),
(b) a C_{6-20} aryl-C_{1-12} alkyl group optionally having substituent(s),
(c) a C_{6-20} aryl group optionally having substituent(s), and
(d) a heteroaryl group selected from (i) a 5- to 10-membered aromatic heterocyclic group containing, besides carbon atoms, 1 to 3 hetero atoms selected from an oxygen atom, a sulfur atom and a nitrogen

atom, and (ii) a fused heterocyclic group thereof, each of (i) and (ii) optionally having substituent(s), or

(7) an electron withdrawing group, or

R^9 and R^{10} form, together with the carbon atoms they are respectively bonded to,

(1) a C_{3-7} homocyclic ring optionally having substituent(s), or
(2) a 5- to 10-membered heterocycle containing, besides carbon atoms, 1 to 3 hetero atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom and optionally having substituent(s),
provided that R^8 and R^9 are not the same groups;
R^{16} is

(1) a hydrogen atom,
(2) a halogen atom,
(3) a hetero atom selected from a nitrogen atom, an oxygen atom and a sulfur atom, having substituent(s) selected from

(a) a C_{1-12} alkyl group optionally having substituent(s),
(b) a C_{6-20} aryl-C_{1-12} alkyl group optionally having substituent(s),
(c) a C_{6-20} aryl group optionally having substituent(s),
(d) a heteroaryl group selected from (i) a 5- to 10-membered aromatic heterocyclic group containing, besides carbon atoms, 1 to 3 hetero atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom, and (ii) a fused heterocyclic group thereof, each of (i) and (ii) optionally having substituent(s),
(e) $-COOR^{26}$ wherein R^{26} is a C_{1-12} alkyl group,
(f) $-COR^{27}$ wherein R^{27} is a C_{1-12} alkyl group, and
(g) $-SO_2R^{28}$ wherein R^{28} is a C_{1-12} alkyl group,

(4) a C_{1-12} alkyl group optionally having substituent(s) or
(5) a C_{6-20} aryl group optionally having substituent(s); and
R^{17} and R^{18} are the same or different and each is a hydrogen atom, a C_{1-12} alkyl group, a C_{1-12} alkoxy group, a mono-C_{1-12} alkylamino group or a di-C_{1-12} alkylamino group; or
R^{16} and R^{17} optionally form, together with the carbon atoms they are respectively bonded to,

(1) a C_{3-7} homocyclic ring substituted by oxo, which is optionally condensed with an aromatic hydrocarbon and optionally has substituent(s), or
(2) a 5- to 10-membered heterocycle substituted by oxo, which is optionally condensed with an aromatic hydrocarbon and contains, besides carbon atoms, 1 to 3 hetero atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom, and optionally has substituent(s).

(3) The method of the above-mentioned (2), wherein
R^{16} is

(1) a hydrogen atom,
(2) a halogen atom,
(3) a C_{1-12} alkyl group optionally having substituent(s), or
(4) a C_{6-20} aryl group optionally having substituent(s); and
R^{17} and R^{18} are the same or different and each is a hydrogen atom, a C_{1-12} alkyl group, a C_{1-12} alkoxy group, a mono-C_{1-12} alkylamino group or a di-C_{1-12} alkylamino group.

(4) The method of any of the above-mentioned (2) or (3), wherein
R^8 and R^{10} are each a hydrogen atom, and
R^9 is

(1) a C_{1-12} alkyl group optionally having substituent(s),
(2) a C_{6-20} aryl group optionally having substituent(s), or
(3) a heteroaryl group selected from (i) a 5- to 10-membered aromatic heterocyclic group containing, besides carbon atoms, 1 to 3 hetero atoms selected from an oxygen atom, a sulfur atom and a nitrogen

atom, and (ii) a fused heterocyclic group thereof, each of (i) and (ii) optionally having substituent(s).

(5) The method of the above-mentioned (2), wherein
R^{16} is

(1) a hydrogen atom,
(2) a C_{1-12} alkyl group optionally having substituent(s),
(3) a halogen atom, or
(4) a hetero atom selected from a nitrogen atom, an oxygen atom and a sulfur atom having substituent(s) selected from

(a) a C_{1-12} alkyl group optionally having substituent(s),
(b) a C_{6-20} aryl-C_{1-12} alkyl group optionally having substituent(s),
(c) a C_{6-20} aryl group optionally having substituent(s),
(d) a heteroaryl group selected from (i) a 5- to 10-membered aromatic heterocyclic group containing, besides carbon atoms, 1 to 3 hetero atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom, and (ii) a fused heterocyclic group thereof, each of (i) and (ii) optionally having substituent(s),
(e) $-COOR^{26}$ wherein R^{26} is a C_{1-12} alkyl group,
(f) $-COR^{27}$ wherein R^{27} is a C_{1-12} alkyl group, and
(g) $-SO_2R^{28}$ wherein R^{28} is a C_{1-12} alkyl group, and

R^{17} and R^{18} are the same or different and each is a C_{1-12} alkyl group or a C_{1-12} alkoxy group.

(6) The method of the above-mentioned (5), wherein R^{16} is a hydrogen atom, methyl, a chlorine atom, methoxy or tert-butoxycarbonylamino, and R^{17} and R^{18} are each methoxy or ethoxy.
(7) The method of the above-mentioned (2), wherein R^{16} and R^{17} form, together with the carbon atoms they are respectively bonded to, a C_{3-7} homocyclic ring substituted by oxo, which is optionally condensed with an aromatic hydrocarbon and optionally has substituent(s).
(8) The method of the above-mentioned (7), wherein the homocyclic ring is 1,2,3,4-tetrahydronaphthalen-1-one.
(9) The method of any of the above-mentioned (2) to (8), which is performed in at least one solvent selected from toluene and methylene chloride.
(10) The method of any of the above-mentioned (2) to (8), which is performed without a solvent.

Detailed Description of the Invention

[0009] The present invention is described in detail in the following.
[0010] First, each symbol used in the present description is defined in the following.
[0011] The alkyl used in the present invention is linear when it is free of a prefix (e.g., iso, neo, sec-, tert- and the like). For example, a simple propyl means linear propyl.
[0012] The "halogen atom" for R^{16} is fluorine atom, chlorine atom, bromine atom or iodine atom, and preferred are chlorine atom and bromine atom.
[0013] The "lower alkyl group" for R^{17} or R^{18} is a straight chain or branched chain alkyl group having 1 to 12 carbon atoms, and, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl and the like can be mentioned. Preferred are methyl, ethyl and propyl.
[0014] The "lower alkoxy group" for R^{17} or R^{18} is an alkoxy group wherein the alkyl moiety is the "lower alkyl group" defined above, and, for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentoxy, isopentoxy, neopentoxy, hexyloxy, heptyloxy, octyloxy, nonyloxy, decyloxy, undecyloxy, dodecyloxy and the like can be mentioned. Preferred are methoxy and ethoxy.
[0015] The "mono-lower alkylamino group" for R^{17} or R^{18} is a mono-alkylamino group wherein the alkyl moiety is the "lower alkyl group" defined above, and, for example, N-methylamino, N-ethylamino, N-propylamino, N-isopropylamino, N-butylamino, N-isobutylamino, N-sec-butylamino, N-tert-butylamino, N-pentylamino, N-isopentylamino, N-neopentylamino, N-hexylamino, N-heptylamino, N-octylamino, N-nonylamino, N-decylamino, N-undecylamino, N-dodecylamino and the like can be mentioned.
[0016] The "di-lower alkylamino group" for R^{17} or R^{18} is a di-alkylamino group wherein the alkyl moieties are the same or different and each is the "lower alkyl group" defined above, and, for example, N,N-dimethylamino, N,N-diethylamino, N,N-dipropylamino, N,N-diisopropylamino, N,N-dibutylamino, N,N-diisobutylamino, N,N-di-sec-butylamino, N,N-di-tert-

butylamino, N,N-dipentylamino, N,N-diisopentylamino, N,N-dineopentylamino, N,N-dihexylamino, N,N-diheptylamino, N-methyl-N-ethylamino, N-methyl-N-propylamino, N-methyl-N-isopropylamino, N-methyl-N-butylamino, N-methyl-N-isobutylamino, N-methyl-N-sec-butylamino, N-methyl-N-tert-butylamino, N-methyl-N-pentylamino, N-methyl-N-isopentylamino, N-methyl-N-neopentylamino, N-methyl-N-hexylamino, N-methyl-N-heptylamino, N-methyl-N-octylamino, N-methyl-N-nonylamino, N-methyl-N-decylamino, N-methyl-N-undecylamino, N-methyl-N-dodecylamino and the like can be mentioned.

[0017] As the "lower alkyl group" of the "lower alkyl group optionally having substituent(s)" for R^8, R^9, R^{10}, R^{16}, R^{17} or R^{18}, alkyl groups same as the "lower alkyl group" defined above can be mentioned.

[0018] The lower alkyl group optionally has substituent(s) at substitutable position(s), and as such substituent(s), a lower alkoxy group (exemplified by those defined above), a mono-lower alkylamino group (exemplified by those defined above), a di-lower alkylamino group (exemplified by those defined above), a halogen atom (exemplified by those defined above), a nitro group, a cyano group, $-COOR^{25}$ wherein R^{25} is a lower alkyl group as defined above, and the like can be mentioned. The number of substituents is not particularly limited, but is preferably 1 to 3. When it is 2 or more, the substituents may be the same or different.

[0019] The "aryl group" of the "aryl group optionally having substituent (s)" for R^8, R^9, R^{10} or R^{16} is an aryl group having 6 to 20 carbon atoms, and, for example, phenyl, 1- or 2-naphthyl, biphenyl, binaphthyl and the like can be mentioned.

[0020] The aryl group optionally has substituent(s) at substitutable position(s), and as such substituent(s), a lower alkyl group (exemplified by those defined above), a lower alkoxy group (exemplified by those defined above), a mono-lower alkylamino group (exemplified by those defined above), a di-lower alkylamino group (exemplified by those defined above), a halogen atom (exemplified by those defined above), a haloalkyl group (lower alkyl group substituted by one or more halogen atoms, such as trifluoromethyl etc.), a nitro group, a cyano group, $-COOR^{25}$ wherein R^{25} is as defined above, and the like can be mentioned. The number of substituents is not particularly limited, but is preferably 1 to 3. When it is 2 or more, the substituents may be the same or different.

[0021] The "substituent" of the "aryl group optionally having substituent(s)" for R^3 is a haloalkyl group, a nitro group, a cyano group, $-COOR^{25}$ wherein R^{25} is a $C_{1\text{-}12}$ alkyl group, more preferably a haloalkyl group.

[0022] The "aralkyl group" of the "aralkyl group optionally having substituent(s)" for R^8, R^9, R^{10} or R^{16} is an aralkyl group wherein the "lower alkyl group" defined above is substituted by the "aryl group" defined above at optional position(s), and, for example, benzyl, 1- or 2-phenethyl, 1-, 2- or 3-phenylpropyl, 1- or 2-naphthylmethyl, benzhydryl, trityl and the like can be mentioned.

[0023] The aralkyl group optionally has substituent(s) at substitutable position(s), and as such substituent(s), the substituents recited for the above-mentioned "aryl group optionally having substituent(s)" can be mentioned. The number of substituents is not particularly limited, but is preferably 1 to 3. When it is 2 or more, the substituents may be the same or different.

[0024] As the "heteroaryl group" of the "heteroaryl group optionally having substituent(s)" for R^8, R^9, R^{10}, for example, a 5- to 10-membered aromatic heterocyclic group containing, besides carbon atoms, 1 to 3 hetero atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom, and a fused heterocyclic group thereof and the like can be mentioned. For example, 2-or 3-thienyl, 2- or 3-furyl, 1-, 2- or 3-pyrrolyl, 1-, 2-, 4-or 5-imidazolyl, 2-, 4- or 5-oxazolyl, 2-, 4- or 5-thiazolyl, 1-, 3-, 4- or 5-pyrazolyl, 3-, 4- or 5-isoxazolyl, 3-, 4- or 5-isothiazolyl, 1,2,4-triazol-1, 3, 4 or 5-yl, 1,2,3-triazol-1, 2 or 4-yl, 1H-tetrazol-1 or 5-yl, 2H-tetrazol-2 or 5-yl, 2-, 3-or 4-pyridyl, 2-, 4- or 5-pyrimidinyl, 1-, 2-, 3-, 4-, 5-, 6-or 7-indolyl, 2-, 3-, 4-, 5-, 6- or 7-benzofuryl, 2-, 3-, 4-, 5-, 6- or 7-benzothienyl, 1-, 2-, 4-, 5-, 6- or 7-benzimidazolyl, 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolyl, 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolyl and the like can be mentioned.

[0025] The heteroaryl group optionally has substituent(s) at substitutable position(s), and as such substituent(s), the substituents recited for the above-mentioned "aryl group optionally having substituent(s)" can be mentioned. The number of substituents is not particularly limited, but is preferably 1 to 3. When it is 2 or more, the substituents may be the same or different.

[0026] The "hetero atom" of the "hetero atom optionally having substituent(s)" for R^8, R^9 or R^{10} is a nitrogen atom, an oxygen atom or a sulfur atom.

[0027] As the substituents that the hetero atom may have, the "lower alkyl group optionally having substituent(s)", "aralkyl group optionally having substituent(s)", "aryl group optionally having substituent(s)" and "heteroaryl group optionally having substituent(s)" are mentioned.

[0028] The "hetero atom" of the "hetero atom having substituent(s)" for R^{16} is a nitrogen atom, an oxygen atom or a sulfur atom.

[0029] As the substituents that the hetero atom has, the "lower alkyl group optionally having substituent(s)", "aralkyl group optionally having substituent(s)", "aryl group optionally having substituent(s)" and "heteroaryl group optionally having substituent(s)", each defined above, $-COOR^{26}$, $-COR^{27}$, $-SO_2R^{28}$ wherein R^{26}, R^{27} and R^{28} are the same or different and each is a lower alkyl group as defined above, are mentioned.

[0030] The "homocyclic ring" and heterocycle optionally have substituent(s) at substitutable position(s), and as such

substituent(s), the substituents recited for the above-mentioned "aryl group optionally having substituent(s)" can be mentioned. The number of substituents is not particularly limited, but is preferably 1 to 3. When it is 2 or more, the substituents may be the same or different.

[0031] The "homocyclic ring" of the "homocyclic ring optionally having substituent(s)", which R^{16} and R^{17} optionally form together with the carbon atoms they are respectively bonded to, is a homocyclic ring substituted by oxo, for example, a cycloalkanone having 3 to 7 carbon atoms (e.g., cyclopropanone, cyclobutanone, cyclopentanone, cyclohexanone, cycloheptanone etc.), a cycloalkenone having 4 to 7 carbon atoms (e.g., cyclobutenone, cyclopentenone, cyclohexenone, cycloheptenone etc.). Preferred are cyclopropanone, cyclobutanone, cyclopentanone, cyclohexanone, and more preferred is cyclohexanone.

[0032] The "heterocycle" of the "heterocycle optionally having substituent (s) ", which R^{16} and R^{17} optionally form together with the carbon atoms they are respectively bonded to, is a 5- to 10-membered heterocycle substituted by oxo and containing, besides carbon atoms, 1 to 3 hetero atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom, (e.g., tetrahydropyranone, tetrahydrofuranone, pyrrolidone, piperidone).

[0033] The "homocyclic ring" and "heterocycle" are optionally further condensed with an aromatic hydrocarbon (e.g., benzene, naphthalene, biphenyl, binaphthyl etc.).

[0034] The "homocyclic ring" and "heterocycle" optionally have substituent(s) at substitutable position(s), and as such substituent(s), the substituents recited for the above-mentioned "aryl group optionally having substituent(s)" can be mentioned. The number of substituents is not particularly limited, but is preferably 1 to 3. When it is 2 or more, the substituents may be the same or different.

[0035] In compound (II), as the "homocyclic ring" of the "homocyclic ring optionally having substituent(s)", which R^9 and R^{10} optionally form together with the carbon atoms they are respectively bonded to, a homocyclic ring having the double bond in compound (II), for example, a cycloalkene having 3 to 7 carbon atoms (e.g., cyclopropene, cyclobutene, cyclopentene, cyclohexene, cycloheptene etc.) and the like can be mentioned.

[0036] In compound (II), as the "heterocycle" of the "heterocycle optionally having substituent(s)", which R^9 and R^{10} optionally form together with the carbon atoms they are respectively bonded to, a 5- to 10-membered heterocycle having the double bond in compound (II) and containing, besides carbon atoms, 1 to 3 hetero atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom, (e.g., 5,6-dihydro-2H-pyran, 3,4-dihydro-2H-pyran, 2,3- or 2,5-dihydrofuran, 2- or 3-pyrroline, 1,2,3,4- or 1,2,3,6-tetrahydropyridine and the like) can be mentioned.

[0037] The "homocyclic ring" and "heterocycle" are optionally further condensed with an aromatic hydrocarbon (e.g., benzene, naphthalene, biphenyl, binaphthyl etc.).

[0038] The "homocyclic ring" and "heterocycle" optionally have substituent(s) at substitutable position(s), and as such substituent(s), the substituents recited for the above-mentioned "aryl group optionally having substituent(s)" can be mentioned. The number of substituents is not particularly limited, but is preferably 1 to 3. When it is 2 or more, the substituents may be the same or different.

[0039] In compound (II), the "electron withdrawing group" for R^8, R^9, R^{10} is not particularly limited as long as it sufficiently absorbs the electron of the double bond in compound (II), so that the conjugate addition of nucleophilic reagent (III) to the double bond can be afforded, and, for example, a nitro group, a cyano group, $-COR^{11}$, $-SO_2R^{12}$, $-COOR^{13}$ and $-PO(OR^{14})(OR^{15})$

wherein

R^{11}, R^{12}, R^{13}, R^{14} and R^{15} are a hydrogen atom, a C1-12 alkyl group optionally having substituents, an aralkyl group optionally having substituents, an aryl group optionally having substituents, or a heteroaryl group optionally having substituents. R^{14} and R^{15} may be the same or different.

[0040] For R^8, R^9 or R^{10} a nitro group is preferable.

[0041] The "asymmetric carbon" of C*, C** or C*** each has an independent absolute configuration, and is not particularly limited. The absolute configurations of C* and C** in asymmetric thiourea compound (I) can be appropriately selected to obtain asymmetric compound (IV) having a desired configuration.

[0042] The asymmetric thiourea compound (I), compound (II) and asymmetric compound (IV) may be in the form of a salt. As such a salt, for example, inorganic acid salts (e.g., hydrochloride, sulfate, nitrate, phosphate etc.); organic acid salts (e.g., acetate, propionate, methanesulfonate, 4-toluenesulfonate, oxalate, maleate etc.); alkali metal salts (e.g., sodium salt, potassium salt etc.); alkaline earth metal salts (e.g., calcium salt, magnesium salt etc.); organic base salts (e.g., trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt etc.) and the like can be mentioned.

[0043] R^4 and R^5 form cyclohexane together with the asymmetric carbons they are respectively bonded to and R^6 and R^7 are each a hydrogen atom. The absolute configurations of C* and C** are both S-configurations or both R-configurations.

[0044] R^1 and R^2 in asymmetric urea compound (I) are methyl, ethyl or isopropyl, or form isoindoline together with the nitrogen atom they are bonded to, preferably methyl or isopropyl.

[0045] R^3 in asymmetric urea compound (I) is a phenyl group substituted by haloalkyl group(s), nitro group(s), cyano

group (s) or -$COOR^{25}$ wherein R^{25} is as defined above, preferably a phenyl group substituted by haloalkyl group(s), still more preferably a phenyl group substituted by trifluoromethyl.

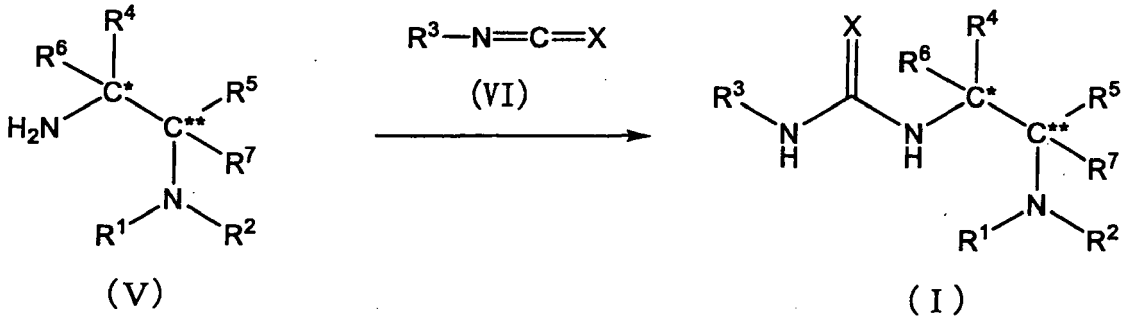
[0046] Since C*** in compound (IV) is an asymmetric carbon, R^8 and R^9 in compound (II) cannot be the same group simultaneously.

[0047] R^8, R^9 and R^{10} in compound (II) are each preferably an aryl group optionally having substituent(s) or a heteroaryl group optionally having substituent(s), more preferably R^8 and R^{10} are each a hydrogen atom, and R^9 is an aryl group optionally having substituent(s) or a hereroaryl group optionally having substituent(s).

[0048] In a preferable embodiment R^{16} is a hydrogen atom, a lower alkyl group optionally having substituent(s), a halogen atom or a hetero atom having substituent(s), more preferably a hydrogen atom, methyl, chlorine atom, methoxy or tert-butoxycarbonylamino, and R^{17} and R^{18} are each a lower alkyl group or a lower alkoxy group, more preferably a lower alkoxy group, still more preferably methoxy or ethoxy. In another preferable embodiment, R^{16} and R^{17} form, together with the carbon atoms they are respectively bonded to, a homocyclic ring optionally having substituent(s) (the homocyclic ring is optionally condensed with an aromatic hydrocarbon), more preferably 1,2,3,4-tetrahydronaphthalen-1-one.

[0049] The asymmetric thiourea compound (I) of the present invention can be produced according to Production Method 1 shown by the following reaction scheme.

Production Method 1



wherein each symbol is as defined above.

[0050] That is, asymmetric thiourea compound (I) can be synthesized, for example, by reacting a compound represented by the formula (V) [hereinafter to be also referred to as compound (V)] with an isocyanate compound or isothiocyanate compound represented by the formula (VI) [hereinafter to be also referred to as isocyanates (VI)] in a solvent.

[0051] In Production Method 1, the order of addition of compound (V) and isocyanates (VI) is not particularly limited, and they may be added to a solvent simultaneously or successively.

[0052] The amount of isocyanates (VI) to be used in Production Method 1 is preferably 0.5 mol to 5 mol, more preferably 0.9 mol to 1.5 mol, per 1 mol of compound (V).

[0053] As the solvent to be used in Production Method 1, any can be used as long as it does not inhibit the reaction and, for example, halogen solvents such as methylene chloride, chloroform, chlorobenzene, α, α, α-trifluorotoluene and the like; methyl-tert-butyl ether, 1,2-dimethoxyethane, tetrahydrofuran, 1,4-dioxane, ethyl acetate, isopropyl acetate, tert-butyl acetate, toluene, xylene, acetonitrile and the like can be used alone or in a mixture. When a mixed solvent is used, they can be admixed at any ratio.

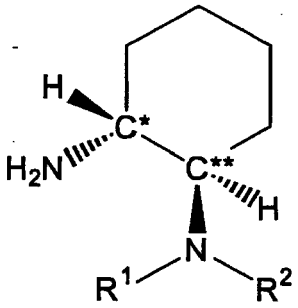
[0054] The amount of the solvent to be used is generally 1 L to 100 L, more preferably 10 L to 30 L, per 1 kg of compound (V).

[0055] The reaction temperature in Production Method 1 is generally -78°C to 100°C, preferably 0°C to 40°C.

[0056] While the reaction time varies depending on the reagent to be used and reaction temperature, it is generally 1 hr to 10 hr.

[0057] The asymmetric thiourea compound (I) produced according to Production Method 1 can be isolated and purified according to a conventional method. For example, asymmetric urea compound (I) can be isolated by pouring a reaction mixture into water to partition the mixture, and washing and concentrating the organic layer under reduced pressure; or by concentrating the reaction mixture. After isolation, the obtained product is purified, for example, by, but not limited to, silica gel column chromatography.

[0058] The compound (V), which is a starting material in Production Method 1, can be produced according a known method (e.g., a method described in Tetrahedron, 57, 1765-1769 (2001)). For example, a compound represented by the formula (Va), which is a preferable mode of the present invention:



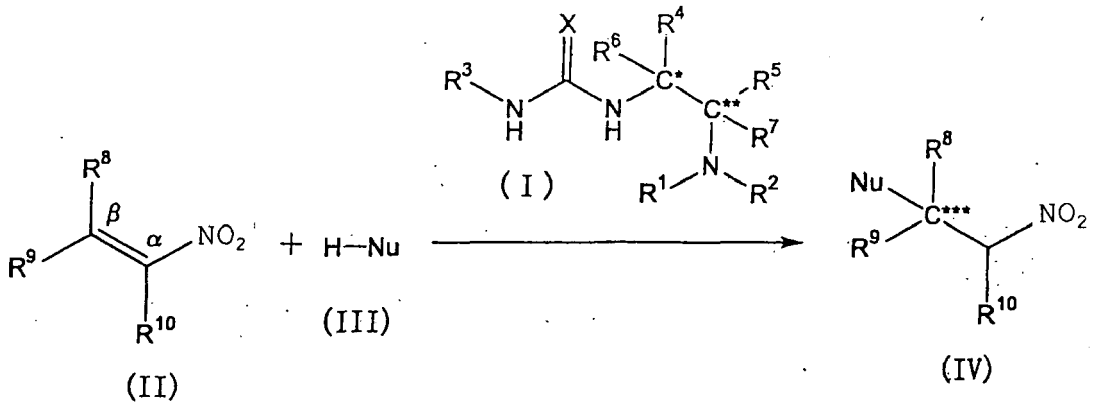
(V a)

wherein each symbol is as defined above, can be produced according a method described in Tetrahedron Letters, 41, 8431-8434(2000).

[0059] The isocyanates (VI), which is the other starting material in Production Method 1, can be synthesized from an amine represented by R^3-NH_2 wherein R^3 is as defined above according to a known method (e.g., a method described in Eur. J. Org. Chem., 3004-3014 (2002)), or a commercially available product can also be used.

[0060] Now, the production method of asymmetric compound (IV) of the present invention by an asymmetric conjugate addition reaction (hereinafter to be also simply referred to as the production method of the present invention) is explained.

[0061] The production method of the present invention is shown by the following reaction scheme:



wherein each symbol is as defined above, Nu is $-CR^{16}(COR^{17})(COR^{18})$

[0062] That is, according to the production method of the present invention, for example, asymmetric compound (IV) is produced by conjugately adding nucleophilic reagent (III) to compound (II) in the presence of asymmetric thiourea compound (I) in a solvent or without a solvent.

[0063] The asymmetric compound (IV) produced according to the production method of the present invention is optically active, wherein the optical purity is not particularly limited. As an enantiomer excess measured by HPLC chiral analysis, it is generally not less than 50% e.e., preferably not less than 90% e.e.

[0064] In the production method of the present invention, the conjugate addition means, in compound (II), an addition reaction of nucleophilic reagent (III) to a carbon not bonded to NO_2 (i.e., β-carbon) from the carbons of the double bond conjugate-bonded to the electron withdrawing group for NO_2.

[0065] In production method of the present invention, the order of addition of the reagents is not particularly limited, and asymmetric thiourea compound (I), compound (II) and nucleophilic reagent (III) can be added simultaneously or successively.

[0066] The amount of asymmetric thiourea compound (I) to be used in the production method of the present invention can be a catalytic amount and it is, for example, preferably 0.01 mol to 1.00 mol, more preferably 0.05 mol to 0.20 mol, per 1 mol of compound (II). When the amount of asymmetric thiourea compound (I) to be used is less than this range, the reaction tends to be slow and when it exceeds this range, the effect tends to be less than comparable to its amount of use, which is economically disadvantageous.

[0067] The amount of nucleophilic reagent (III) to be used in the production method of the present invention is preferably 1 mol to 10 mol, more preferably 1.2 mol to 3 mol, per 1 mol of compound (II). When the amount of nucleophilic reagent (III) to be used is less than the range, the reaction tends to be incomplete, and when it exceeds this range, the effect tends to be less than comparable to its amount of use, which is economically disadvantageous.

[0068] The production method of the present invention can be performed in a solvent or without a solvent. The production method performed without a solvent is economically advantageous because the solvent is not necessary, and is indus-

trially advantageous because the volume efficiency can be increased.

[0069] When a solvent is used for the production method of the present invention, the solvent may be any as long as it does not inhibit the reaction and, for example, halogen solvents such as methylene chloride, chloroform, chlorobenzene, α, α, α-trifluorotoluene and the like; methyl-tert-butyl ether, 1,2-dimethoxyethane, tetrahydrofuran, 1,4-dioxane, ethyl acetate, isopropyl acetate, tert-butyl acetate, toluene, xylene, acetonitrile and the like can be used alone or in a mixture. In view of superior yield and stereoselectivity, toluene or methylene chloride is preferably used.

[0070] When a mixed solvent is used, they may be mixed at any ratio.

[0071] The amount of the solvent to be used is generally 1 L to 100 L, more preferably 10 L to 30 L, per 1 kg of compound (II).

[0072] The reaction temperature in the production method of the present invention is generally -78°C to 100°C, preferably 0°C to 40°C.

[0073] While the reaction time varies depending on the reagent to be used and reaction temperature, it is generally 0.1 hr to 100 hr.

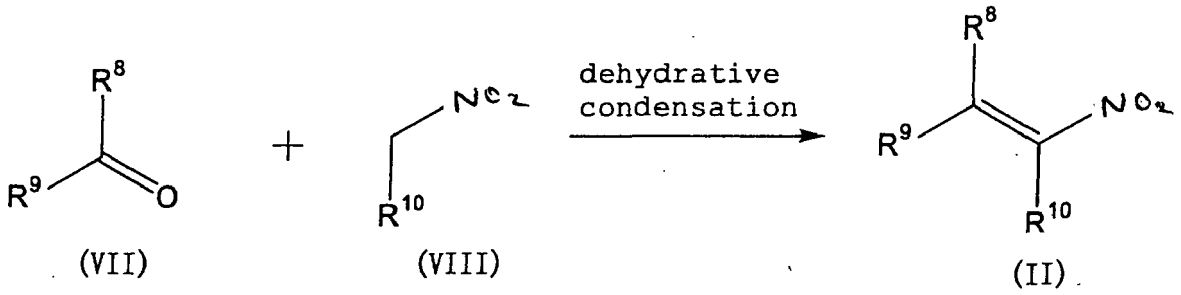
[0074] The asymmetric compound (IV) produced according the production method of the present invention can be isolated and purified according to a conventional method. For example, asymmetric compound (IV) can be isolated by pouring a reaction mixture into water to partition the mixture, and washing and concentrating the organic layer under reduced pressure; or by concentrating the reaction mixture. After isolation, the obtained product is purified, for example, by, but not limited to, silica gel column chromatography.

[0075] The asymmetric thiourea compound (I) can be easily separated and recovered during isolation and purification of asymmetric compound (IV). For example, since basic amine is present in asymmetric thiourea compound (I), compound (I) can be separated from asymmetric compound (IV) during extraction by transferring compound (I) in the form of a salt into the aqueous layer by treating the mixture with an aqueous acidic solution (e.g., hydrochloric acid, nitric acid, sulfuric acid etc.). After neutralization of the aqueous solution, it is extracted with an organic solvent (e.g., ethyl acetate, toluene, chloroform, methylene chloride etc.) to recover asymmetric thiourea compound (I). It may also be separated and recovered by silica gel column chromatography.

[0076] The asymmetric thiourea compound (I) separated and recovered in this manner can be re-used for the production method of the present invention. That is, since asymmetric thiourea compound (I) of the present invention is non-metal, degradation of catalytic activity as observed in metal catalysts etc. does not occur easily, and compound (I) can be re-used as many times as desired upon recovery, which is economically advantageous.

[0077] As asymmetric thiourea compound (I), which is a starting material in the production method of the present invention, for example, one produced according to the above-mentioned Production Method 1 can be used.

[0078] The compound (II), which is a starting material in the production method of the present invention, can be produced according a known method, such as dehydrative condensation of a carbonyl compound represented by the following formula (VII) and an active methylene compound represented by the following formula (VIII) :



wherein each symbol is as defined above.

[0079] As such a dehydrative condensation reaction, the Knoevenagel reaction, and modification of this method can be mentioned.

[0080] In addition, commercially available products may be used for trans-β-nitrostyrene and the like, which are preferable examples of compound (II).

[0081] The nucleophilic reagent (III), which is a starting material in the present invention, can be produced according a known method, such as the methods described in Tetrahedron Letters, 39, 8013-8016 (1998), Bull. Chem. Soc. Jpn., 61, 4029-4035 (1988) and the like. In addition, commercially available products may be used for diethyl malonate and the like, which are preferable examples of nucleophilic reagent (III).

[0082] The asymmetric compound (IV) produced according to the production method of the present invention is useful as an intermediate for synthesizing amines, amino acids, pharmaceutical agents, agricultural chemicals, food additives and the like. For example, ethyl (R)-3-(3-cyclopentyl-4-methoxyphenyl)-2-ethoxycarbonyl-4-nitrobutyrate, which is one

example of compound (IV), can be converted to (R)-Rolipram (antidepressant) according to a method described in Journal of the American Chemical Society, vol. 124, No. 44, p. 13097-13105 (2002).

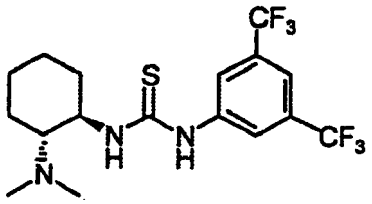
Examples

[0083] The present invention is explained more specifically in the following by referring to Examples.

Example 1A

(R,R)-trans-1-[3,5-bis (trifluoromethyl)phenyl]-3-[2-(N,N-dimethylamino)cyclohexyl]thiourea

[0084]

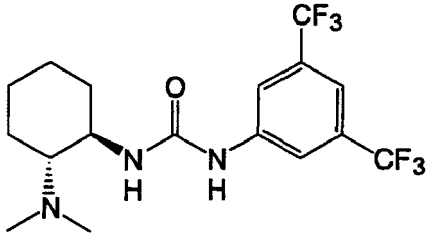


[0085] To a solution (1.0 ml) of 3,5-bis(trifluoromethyl)phenylisothiocyanate (605 mg, 2.23 mmol) in dry tetrahydrofuran was added (R,R)-trans-N,N-dimethyl-1,2-diaminocyclohexane (317 mg, 2.23 mmol) under an argon atmosphere. The reaction mixture was stirred at room temperature for 3 hr, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (elution solvent: chloroform/methanol/triethylamine=100/5/1) to give the title compound as a white amorphous solid (597 mg, yield 65 %).
$[\alpha]_D^{16}$ -32.7 (c 0.99, $CHCl_3$);
^{1}H-NMR (500MHz, DMSO-d_6) δ 10.0 (s, 1H), 8.21 (s, 1H), 8.17 (s, 2H), 7.66 (s, 1H), 4.09 (brs, 1H), 2.54 (brs, 1H), 2.21 (s, 7H), 1.82 (brs, 1H), 1.74 (brs, 1H), 1.63 (brd, J=11.0Hz, 1H), 1.31-1.01 (m, 4H) ppm;
^{13}C-NMR (126MHz, DMSO-d_6) δ 178.6, 142.0, 130.8, 130.5, 130.3, 130.0, 126.5, 124.3, 122.2, 120.9, 120.0, 115.3, 65.0, 55.3, 45.7, 31.6, 24.6, 24.5, 21.0 ppm;
IR ($CHCl_3$) ν 3402, 3200, 2942, 2865, 1528, 1469, 1383, 1278 cm^{-1};
MS (FAB^+) 414 (MH^+, 100);
Elemental analysis
Calculated (for $C_{17}H_{21}F_6N_3S$): C, 49.39; H, 5.12; N, 10.16; F, 27.57.
Found: C, 49.36; H, 5.28; N, 10.11; F, 27.71.

Example 1B

(R,R)-trans-1-[3,5-bis (trifluoromethyl)phenyl]-3-[2-(N,N-dimethylamino)cyclohexyl]urea

[0086]



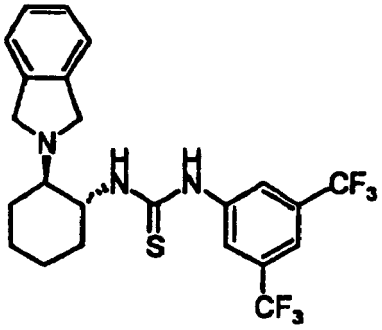
[0087] To a solution (0.60 ml) of 3,5-bis(trifluoromethyl)phenylisocyanate (0.26 ml, 1.5 mmol) in dry benzene was added (R,R)-trans-N,N-dimethyl-1,2-diaminocyclohexane (213 mg, 1.5 mmol) under an argon atmosphere. The reaction mixture was stirred at room temperature for 1 hr, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography ($CHCl_3$/MeOH=20/1-7/1) to give the title compound as a white amorphous solid.
$[\alpha]D^{25}$ -35.3 (c 0.93, $CHCl_3$) ;

^{1}H-NMR (500MHz, DMSO-d_6) δ 9.39 (s, 1H), 8.02 (s, 2H), 7.51 (s, 1H), 6.21 (d, J=5.5Hz, 1H), 3.35 (ddd, J=15.2, 10.5, 4.3Hz, 1H), 2.28 (dt, J=3.1, 10.2Hz, 1H), 2.18 (brs, 1H), 2.15 (s, 6H), 1.85-1.66 (m, 2H), 1.63-1.52 (m, 1H), 1.31-0.96 (m, 4H) ppm;
^{13}C-NMR (126MHz, DMSO-d_6) δ 154.9, 142.9, 131.3, 131.1, 130.8, 130.5, 126.9, 124.7, 122.5, 120.4, 117.12, 117.09, 113.4, 113.3, 65.6, 50.9, 39.9, 33.2, 24.9, 24.5, 21.4 ppm;
IR ($CHCl_3$) v 3424, 3332, 2939, 2864, 2792, 1695, 1549, 1473 cm^{-1};
MS (FAB$^+$) 398 (MH^+, 100) ;
Elemental analysis
Calculated (for $C_{17}H_{21}F_6N_3O$): C, 51.38; H, 5.33; N, 10.57; F, 28.69.
Found: C, 51.30; H, 5.22; N, 10.58; F, 28.46.

Example 2

(R,R)-trans-1-[3,5-bis(trifluoromethyl)phenyl]-3-[2-(isoindolin-2-yl)cyclohexyl]thiourea

[0088]

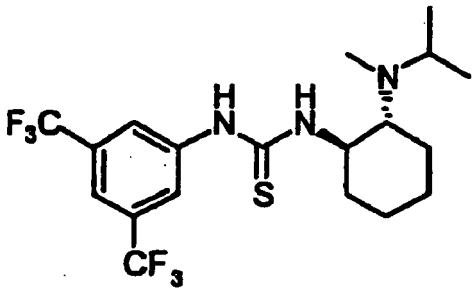


[0089] In the same manner as in Example 1A except that (R,R)-trans-N-[2-(isoindolin-2-yl)cyclohexyl]amine was used instead of (R,R)-trans-N,N-dimethyl-1,2-diaminocyclohexane, the title compound was obtained as colorless crystals (yield 21%). melting point: 154-156°C (n-hexane/ethyl acetate).
$[\alpha]_D^{17}$ -18.1 (c 1.01, $CHCl_3$) ;
^{1}H-NMR (500MHz, DMSO-d_6) δ 10.00 (s, 1H), 8.30 (d, J=7.0Hz, 1H), 8.15 (s, 2H), 7.67 (s, 1H), 7.24 (dd, J=3.4, 5.2Hz, 2H), 7.18 (dd, J= 3.2, 5.3Hz, 2H), 4.31 (brs, 1H), 4.04 (d, J=11.6Hz, 2H), 3.99 (d, J=11.9Hz, 2H), 2.87 (dt, J=2.7, 9.8Hz, 1H), 2.18 (brd, J=8.2Hz, 1H), 1.88 (brd, J=11.6Hz, 1H), 1.76 (brd, J=7.9Hz, 1H), 1.65 (m, 1H), 1.44 (m, 1H), 1.30 (m, 3H) ppm;
^{13}C-NMR (126MHz, DMSO-d_6) δ 184.1, 147.0, 144.9, 135.6, 135.3, 131.6, 129.5, 127.5, 127.3, 126.4, 120.8, 65.6, 60.5, 58.3, 29.0, 28.82, 28.77, 28.1 ppm;
IR ($CHCl_3$) ν 3402, 2941, 2862, 1539, 1495, 1470, 1382, 1279, 1179 ,1140 cm^{-1};
MS (FAB$^+$) 488 (MH^+, 100);
Elemental analysis
Calculated (for $C_{23}H_{23}F_6N_3S$) : C, 56.67; H, 4.76; N, 8.62; F, 23.38.
Found: C, 56.66; H, 4.74; N, 8.46; F, 23.45.

Example 3

(R,R)-trans-1-[3,5-bis(trifluoromethyl)phenyl]-3-[2-(N-isopropyl-N-methylamino)cyclohexyl]thiourea

[0090]

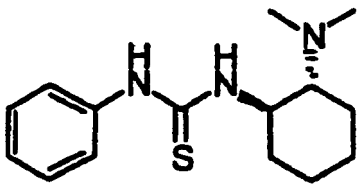


[0091] In the same manner as in Example 1A except that (R,R)-trans-N-isopropyl-N-methyl-1,2-diaminocyclohexane was used instead of (R,R)-trans-N,N-dimethyl-1,2-diaminocyclohexane, the title compound was obtained as a colorless amorphous solid (yield 64%).
$[\alpha]_D^{26}$ +51.3 (c 0.98, $CHCl_3$);
^{1}H-NMR (500MHz, DMSO-d_6) δ 10.10 (s, 1H), 8.21 (s, 2H), 7.87 (s, 1H), 7.69 (s, 1H), 4.08 (brs, 1H), 2.96-2.78 (m, 1H), 2.62 (brs, 1H), 2.37-2.07 (m, 4H), 1.82 (brd, J=10.7Hz, 1H), 1.71 (brd, J=6.7Hz, 1H), 1.61 (brd, J=7.7Hz, 1H), 1.31-1.07 (m, 4H), 0.98 (d, J=6.1Hz, 6H) ppm;
^{13}C-NMR (126MHz, DMSO-d_6) δ 179.2, 142.0, 130.7, 130.5, 130.2, 129.9, 126.6, 124.4, 122.2, 121.4, 120.1, 115.6, 63.6, 55.0, 31.8, 31.3, 25.6, 25.0, 24.5, 21.4, 20.1 ppm;
IR ($CHCl_3$) ν 3402, 2943, 2863, 1496, 1470, 1384, 1279, 1179, 1141 cm^{-1};
MS (FAB^+) 442 (MH^+, 100);
HRMS (FAB^+)
Calculated (for $[C_{19}H_{26}F_6N_3S]^+$): 442.1752;
Found: 442.1743.

Example 4

(R,R)-trans-1-[2-(N,N-dimethylamino)cyclohexyl]-3-phenylthiourea

[0092]

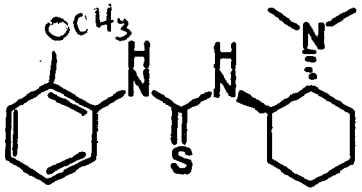


[0093] In the same manner as in Example 1A except that phenylisothiocyanate was used instead of 3,5-bis(trifluoromethyl)phenylisothiocyanate, the title compound was obtained as a colorless amorphous solid (yield 95%).
$[\alpha]D^{21}$-112 (c 0.98, $CHCl_3$);
^{1}H-NMR (500MHz, DMSO-d_6) δ 7.38 (t, J= 7.8Hz, 2H), 7.30-7.14 (m, 4H), 6.79 (s, 1H), 3.86 (brs, 1H), 2.73 (brs, 1H), 2.33 (dt, J=2.9, 11.1Hz, 1H), 2.24 (s, 6H), 1.93-1.75 (m, 2H), 1.70 (brd, J=13.7Hz, 1Hz), 1.42-1.28 (m, 1H), 1.28-1.11 (m, 2H), 1.10-0.96 (m, 1H) ppm;
^{13}C-NMR (126MHz, DMSO-d_6) δ 179.1, 137.4, 128.9, 125.5, 124.3, 66.0, 55.4, 39.4, 32.4, 24.6, 24.2, 21.0 ppm;
IR ($CHCl_3$) ν 3411, 2939, 2864, 2790, 1529, 1500 cm^{-1};
MS (FAB^+) 278 (MH^+, 100);
HRMS (FAB^+)
Calculated (for $[C_{15}H_{24}N_3S]^+$) : 278.1691;
Found: 278.1692.

Example 5

1-[(R,R)-2-(N,N-dimethylamino)cyclohexyl]-3-(2-methoxyphenyl)thiourea

[0094]



[0095] In the same manner as in Example 1A except that 2-methoxyphenylisothiocyanate was used instead of 3,5-bis(trifluoromethyl)phenylisothiocyanate, the title compound was obtained as a colorless amorphous solid (yield 100%).
$[\alpha]_D^{19}$-116 (c 1.10, $CHCl_3$) ;
^{1}H-NMR (500MHz, DMSO-d_6) δ 8.19 (s, 1H), 7.41 (d, J=7.3Hz, 1H), 7.15-6.92 (m, 2H), 6.89-6.69 (m, 2H), 3.79 (brs, 1H), 3.67 (s, 3H), 2.60 (d, J=10.7Hz, 1H), 2.35-2.22 (m, 1H), 2.09 (s, 6H), 1.83-1.60 (m, 2H), 1.54 (d, J=13.7Hz, 1H), 1.20 (q, J=13.0Hz, 1H), 1.15-0.97 (m, 2H), 0.96-0.81 (m, 1H) ppm;
^{13}C-NMR (126MHz, DMSO-d_6) δ 179.5, 151.5, 126.3, 125.0, 124.1, 120.2, 111.1, 66.3, 55.9, 55.3, 39.5, 32.3, 24.8, 24.3, 21.2 ppm;
IR ($CHCl_3$) ν 3406, 2939, 2863, 1600, 1512 cm^{-1};
MS (FAB^+) 308 (MH^+, 100);
HRMS (FAB^+)
Calculated (for $[C_{16}H_{26}N_3OS]^+$) : 308.1757;
Found: 308.1790

Comparative Example 1

(R,R)-trans-N-[2-(N',N'-dimethylamino)cyclohexyl]acetamide

[0096] In the same manner as in Example 1A except that acetic anhydride was used instead of 3,5-bis(trifluoromethyl)phenylisothiocyanate, the title compound was obtained as a colorless amorphous solid (yield 87%).

Comparative Example 2

1-[3,5-bis(trifluoromethyl)phenyl]-3-cyclohexylthiourea

[0097] In the same manner as in Example 1A except that cyclohexylamine was used instead of (R,R)-trans-N,N-dimethyl-1,2-diaminocyclohexane, the title compound was obtained as colorless crystals (yield 88%).

Example 6A

ethyl (S)-2-ethoxycarbonyl-4-nitro-3-phenylbutyrate

[0098] To a solution (0.40 ml) of trans-β-nitrostyrene (29.8 mg, 0.20 mmol) and diethyl malonate (0.061 ml, 0.40 mmol) in toluene was added, as an asymmetric catalyst, (R,R)-trans-1-[3,5-bis(trifluoromethyl)phenyl]-3-[2-(N,N-dimethylamino)cyclohexyl]thiourea (8.2 mg, 0.02 mmol) obtained in Example 1A at room temperature under an argon atmosphere. After 24 hr, the reaction mixture was concentrated under reduced pressure. The residue was purified by preparative TLC (elution solvent: n-hexane/diethyl ether) to give the title compound as colorless needle crystals (53.3 mg, yield 86%). The yield and optical purity are shown in Tables 1 - 3. melting point: 45-47°C (n-hexane/diethyl ether)
HPLC analysis conditions:

column: CHIRALCEL AD (manufactured by DAICEL CHEMICAL INDUSTRIES, LTD.),
mobile phase: n-hexane/ethanol=90/10,
flow rate: 1.0 ml/min,
detection: λ=254 nm,
retention time: (S)-isomer (main peak); 11.1 min, (R)-isomer; 13.9 min.

$[\alpha]_D^{30}$-6.00 (c 1.00, $CHCl_3$) ;
^{1}H-NMR (500MHz, DMSO-d_6) δ 7.42-7.10 (m, 5H), 4.93 (dd, J=4.6, 13.1Hz, 1H), 4.86 (dd, J=9.2, 13.1Hz, 1H), 4.33-4.15 (m, 3H), 4.00 (q, J=7.2Hz, 2H), 3.82 (d, J=9.5Hz, 1H), 1.25 (t, J=7.2Hz, 3H), 1.03 (t, J=7.2Hz, 3H) ppm;
^{13}C-NMR (126MHz, DMSO-d_6) δ 167.4, 166.7, 136.2, 128.8, 128.2, 127.9, 77.6, 62.0, 61.8, 54.9, 42.9, 13.9, 13.6 ppm;

IR ($CHCl_3$) ν 2989, 2938, 1731, 1557 cm^{-1};
MS (FAB^+) 310 (MH^+, 100);
Elemental analysis
Calculated (for $C_{15}H_{19}NO_6$) : C, 58.24; H, 6.19; N, 4.53.
Found: C, 58.43; H, 6.20; N, 4.56.

Example 6B

ethyl (S)-2-ethoxycarbonyl-4-nitro-3-phenylbutyrate

[0099] To a solution (0.40 ml) of trans-β-nitrostyrene (29.8 mg, 0.20 mmol) and diethyl malonate (0.061 ml, 0.40 mmol) in toluene was added, as an asymmetric catalyst, (R,R)-trans-1-[3,5-bis(trifluoromethyl)phenyl]-3-[2-(N,N-dimethylamino)cyclohexyl]urea (7.9 mg, 0.02 mmol) obtained in Example 1B at room temperature under an argon atmosphere. After 24 hr, the reaction mixture was concentrated under reduced pressure. The residue was purified by preparative TLC (elution solvent: n-hexane/ethyl acetate=5/1) to give the title compound as colorless needle crystals (53.8 mg, 87%, 91% ee). The yield and optical purity are shown in Table 1.

Example 7

ethyl (S)-2-ethoxycarbonyl-4-nitro-3-phenylbutyrate

[0100] In the same manner as in Example 6A except that 0.20 mmol of diethyl malonate was used, the title compound was obtained. The yield and optical purity are shown in Table 1.

Example 8

ethyl (S)-2-ethoxycarbonyl-4-nitro-3-phenylbutyrate

[0101] In the same manner as in Example 7 except that methylene chloride was used as a solvent instead of toluene, the title compound was obtained. The yield and optical purity are shown in Table 1.

Example 9

ethyl (S)-2-ethoxycarbonyl-4-nitro-3-phenylbutyrate

[0102] In the same manner as in Example 7 except that acetonitrile was used as a solvent instead of toluene, the title compound was obtained. The yield and optical purity are shown in Table 1.

Example 10

ethyl (S)-2-ethoxycarbonyl-4-nitro-3-phenylbutyrate

[0103] In the same manner as in Example 7 except that tetrahydrofuran was used as a solvent instead of toluene, the title compound was obtained. The yield and optical purity are shown in Table 1.

Table 1

Example	solvent	nucleophilic reagent equivalent	yield (%)	optical purity (% ee)
6A	toluene	2	86	93
6B	toluene	2	87	91
7	toluene	1	60	92
8	methylene chloride	1	53	90
9	acetonitrile	1	47	75
10	tetrahydrofuran	1	29	88

[0104] It is clear that the use of 2 equivalents of the nucleophilic reagent increased the yield. When toluene or methylene chloride was used, the yield and selectivity were superior to the use of acetonitrile or tetrahydrofuran.

Example 11

ethyl (S)-2-ethoxycarbonyl-4-nitro-3-phenylbutyrate

[0105] In the same manner as in Example 6A except that the reaction time was set to 48 hr and (R,R)-trans-1-[3,5-bis(trifluoromethyl)phenyl]-3-[2-(isoindolin-2-yl)cyclohexyl]thiourea obtained in Example 2 was used as an asymmetric catalyst, the title compound was obtained. The yield and optical purity are shown in Table 2.

Example 12

ethyl (S)-2-ethoxycarbonyl-4-nitro-3-phenylbutyrate

[0106] In the same manner as in Example 6A except that the reaction time was set to 48 hr and (R,R)-trans-1-[3,5-bis(trifluoromethyl)phenyl]-3-[2-(N-isopropyl-N-methylamino)cyclohexyl]thiourea obtained in Example 3 was used as an asymmetric catalyst, the title compound was obtained. The yield and optical purity are shown in Table 2.

Example 13

ethyl (S)-2-ethoxycarbonyl-4-nitro-3-phenylbutyrate

[0107] In the same manner as in Example 6A except that the reaction time was set to 48 hr and (R,R)-trans-1-[2-(N,N-dimethylamino)cyclohexyl]-3-phenylthiourea obtained in Example 4 was used as an asymmetric catalyst, the title compound was obtained. The yield and optical purity are shown in Table 2.

Example 14

ethyl (S)-2-ethoxycarbonyl-4-nitro-3-phenylbutyrate

[0108] In the same manner as in Example 6A except that the reaction time was set to 48 hr and 1-[(R,R)-2-(N,N-dimethylamino)cyclohexyl]-3-(2-methoxyphenyl)thiourea obtained in Example 5 was used as an asymmetric catalyst, the title compound was obtained. The yield and optical purity are shown in Table 2.

Comparative Example 3

ethyl (S)-2-ethoxycarbonyl-4-nitro-3-phenylbutyrate

[0109] In the same manner as in Example 6A except that triethylamine was used instead of the asymmetric catalyst, the title compound was obtained. The yield is shown in Table 2.

Comparative Example 4

ethyl (S)-2-ethoxycarbonyl-4-nitro-3-phenylbutyrate

[0110] In the same manner as in Example 6A except that (R,R)-trans-N-[2-(N',N'-dimethylamino) cyclohexyl]acetamide obtained in Comparative Example 1 was used as an asymmetric catalyst, the title compound was obtained. The yield and optical purity are shown in Table 2.

Comparative Example 5

ethyl (S)-2-ethoxycarbonyl-4-nitro-3-phenylbutyrate

[0111] In the same manner as in Example 6A except that 1-[3,5-bis(trifluoromethyl)phenyl]-3-cyclohexylthiourea obtained in Comparative Example 2 and 0.1 equivalent of triethylamine were used instead of the asymmetric catalyst, the title compound was obtained. The yield is shown in Table 2.

Table 2

Example	asymmetric catalyst	reaction time (hr)	yield (%)	optical purity (% ee)
6A	Example 1A	24	86	93
11	Example 2	48	29	91
12	Example 3	48	76	87
13	Example 4	48	58	80
14	Example 5	48	40	52
Comparative Example 3	TEA	24	17	-
Comparative Example 4	Comparative Example 1	24	14	35
Comparative Example 5	Comparative Example 2 + TEA	24	57	-

[0112] Introduction of bulky substituents into R^1 and R^2 of asymmetric urea compound (I) tends to result in a decreased yield. When R^3 is a substituted phenyl, the use of a compound wherein the phenyl is substituted by methoxy, which is electron-donative, tended to result in decreased yield and stereoselectivity.

[0113] A catalyst having an amine moiety or thiourea moiety alone caused a striking decrease in the yield, and when a catalyst having an amine moiety alone and a catalyst having thiourea moiety alone were added simultaneously, the yield was improved but only to a level not comparable to Example 6A and Example 6B.

Example 15

ethyl (S)-3-(2,6-dimethoxyphenyl)-2-ethoxycarbonyl-4-nitrobutyrate

[0114] In the same manner as in Example 6A except that the reaction time was set to 72 hr and trans-2,6-dimethoxy-β-nitrostyrene was used instead of trans-β-nitrostyrene, the title compound was obtained as a colorless oil. The yield and optical purity are shown in Table 3.
HPLC analysis conditions:

column: CHIRALCEL AD (manufactured by DAICEL CHEMICAL INDUSTRIES, LTD.),
mobile phase: n-hexane/2-propanol=95/5,
flow rate: 1.0 ml/min,
detection: λ=254 nm,
retention time: (S)-isomer (main peak); 12.8 min, (R)-isomer; 15.7 min.

$[\alpha]D^{24}$-11.4 (c 1.03, $CHCl_3$);
^{1}H-NMR (500MHz, DMSO-d_6) δ 7.18 (t, J=8.4Hz, 1H), 6.52 (d, J=8.2Hz, 2H), 5.08-4.99 (m, 1H), 4.93 (dd, J=12.1, 9.0Hz, 1H), 4.85 (dd, J=12.1, 4.7Hz, 1H), 4.32-4.15 (m, 3H), 3.92-3.80 (m, 2H), 3.82 (s, 6H), 1.29 (t, J=7.2Hz, 3H), 0.95 (t, J=7.0Hz, 3H) ppm;
^{13}C-NMR (126MHz, DMSO-d_6) δ 168.4, 167.3, 158.9, 129.6, 112.5, 104.3, 76.6, 61.8, 61.2, 52.8, 52.5, 33.2, 13.9, 13.5 ppm; IR ($CHCl_3$) ν 3030, 2985, 2842, 1730, 1555 cm^{-1};
MS (EI^+) 369 (M^+), 249 (MH^+, 100);
Elemental analysis
Calculated (for $C_{17}H_{23}NO_8$): C, 55.28; H, 6.28; N, 3.79.
Found: C, 55.31; H, 6.13; N, 3.55.

Example 16

ethyl (S)-2-ethoxycarbonyl-3-(1-fluorophenyl)-4-nitrobutyrate

[0115] In the same manner as in Example 6A except that the reaction time was set to 12 hr and trans-4-fluoro-β-nitrostyrene was used instead of trans-β-nitrostyrene, the title compound was obtained as a colorless oil. The yield and optical purity are shown in Table 3.
HPLC analysis conditions:

column: CHIRALCEL AD (manufactured by DAICEL CHEMICAL INDUSTRIES, LTD.),
mobile phase: n-hexane/ethanol=90/10,
flow rate: 1.0 ml/min,
detection: λ=254 nm,
retention time: (S)-isomer (main peak); 16.3 min, (R)-isomer; 23.9 min.

$[\alpha]_D^{28}$ -7.20 (c 1.00, $CHCl_3$);
^{1}H-NMR (500MHz, DMSO-d_6) δ 7.28-7.18 (m, 2H), 7.05-6.96 (m, 2H), 4.91 (dd, J=13.1, 4.6Hz, 1H), 4.83 (dd, J=13.1, 9.5Hz, 1H), 4.30-4.15 (m, 3H), 4.03 (q, J=7.0Hz, 2H), 3.78 (d, J=9.2Hz, 1H), 1.27 (t, J=7.2Hz, 3H), 1.08 (t, J=7.0Hz, 3H) ppm;
^{13}C-NMR (126MHz, DMSO-d_6) δ 167.4, 166.8, 163.6, 161.6, 132.02, 131.99, 129.9, 129.8, 116.0, 115.9, 77.6, 62.2, 61.9, 54.9, 42.2, 13.9, 13.7 ppm;
IR ($CHCl_3$) v 3031, 2987, 1733, 1558 cm^{-1};
MS (EI^+) 327 (M^+), 207 (100) ;
Elemental analysis
Calculated (for $C_{15}H_{18}FNO_6$): C, 55.04; H, 5.54; N, 4.28; F, 5.80.
Found: C, 55.24; H, 5.46; N, 4.15; F, 5.67.

Example 17

ethyl 2-ethoxycarbonyl-3-(1-naphthyl)-4-nitrobutyrate

[0116] In the same manner as in Example 6A except that trans-1-(2-nitrovinyl)naphthalene was used instead of trans-β-nitrostyrene, the title compound was obtained as a colorless oil. The yield and optical purity are shown in Table 3. The absolute configuration of the obtained compound was not identified.
HPLC analysis conditions:

column: CHIRALCEL OD (manufactured by DAICEL CHEMICAL INDUSTRIES, LTD.),
mobile phase: n-hexane/2-propanol=90/10,
flow rate: 1.0 ml/min,
detection: λ=254 nm,
retention time: isomer (main peak); 14.6 min, isomer; 16.7 min.

$[\alpha]_D^{32}$+1.60 (c 1.14, $CHCl_3$);
^{1}H-NMR (500MHz, DMSO-d_6) δ 8.19 (d, J=8.6 Hz, 1H), 7.87 (d, J=7.9Hz, 1H), 7.79 (d, J=7.3Hz, 1H), 7.65-7.56 (m, 1H), 7.52 (t, J=7.5Hz, 1H), 7.47-7.34 (m, 2H), 5.29-5.18 (m, 1H), 5.18-5.10 (m, 1H), 5.06 (dd, J=4.7, 13.3Hz, 1H), 4.28-4.12 (m, 2H), 4.07 (d, J=8.6Hz, 1H), 4.01-3.88 (m, 2H), 1.23 (t, J=7.2 Hz, 3H), 0.93 (t, J=7.0Hz, 3H) ppm;
^{13}C-NMR (126MHz, DMSO-d_6) δ 167.7, 167.0, 134.1, 132.4, 131.1, 129.2, 128.9, 127.0, 126.1, 125.1, 124.3, 122.4, 77.0, 62.0, 61.9, 54.7, 36.7, 13.8, 13.5 ppm;
IR ($CHCl_3$) v 3025, 2987, 1732, 1557 cm^{-1};
MS (EI^+) 359 (M^+), 152 (100);
Elemental analysis
Calculated (for $C_{19}H_{21}NO_6$): C, 63.50; H, 5.89; N, 3.90.
Found: C, 63.58; H, 5.96; N, 3.76.

Example 18

ethyl 2-ethoxycarbonyl-4-nitro-3-(2-thienyl)butyrate

[0117] In the same manner as in Example 6A except that the reaction time was set to 48 hr and trans-2-(2-nitrovinyl)thiophene was used instead of trans-β-nitrostyrene, the title compound was obtained as a colorless oil. The yield and optical purity are shown in Table 3. The absolute configuration of the obtained compound was not identified.
HPLC analysis conditions:

column: CHIRALCEL AD (manufactured by DAICEL CHEMICAL INDUSTRIES, LTD.),
mobile phase: n-hexane/2-propanol=90/10,
flow rate: 1.0 ml/min,
detection: λ=254 nm,

retention time: isomer (main peak); 12.0 min, isomer; 21.9 min.

$[\alpha]_D^{32}$ +4.28 (c 0.90, $CHCl_3$);
^{1}H-NMR (500MHz, DMSO-d_{16}) δ 7.22 (d, J=4.9Hz, 1H), 7.01-6.85 (m, 2H), 5.01-4.81 (m, 2H), 4.62-4.47 (m, 1H), 4.30-4.16 (m, 2H), 4.12 (q, J=7.1Hz, 2H), 3.87 (d, J=8.2Hz, 1H), 1.27 (t, J=7.2Hz, 3H), 1.15 (t, J=7.2Hz, 3H) ppm;
^{13}C-NMR (126MHz, DMSO-d_6) δ 167.3, 166.8, 138.6, 127.0, 126.8, 125.6, 78.0, 62.2, 62.1, 55.5, 38.3, 13.9, 13.7 ppm;
IR ($CHCl_3$) ν 3031, 2988, 1733, 1558 cm^{-1};
MS (EI^+) 315 (M^+), 195 (100);
Elemental analysis
Calculated (for $C_{13}H_{17}NO_6S$): C, 49.51; H, 5.43; N, 4.44.
Found: C, 49.67; H, 5.43; N, 4.23.

Example 19

ethyl (S)-2-ethoxycarbonyl-3-(nitromethyl)octanoate

[0118] In the same manner as in Example 6A except that the reaction time was set to 48 hr and trans-1-nitro-1-heptene was used instead of trans-β-nitrostyrene, the title compound was obtained as a colorless oil. The yield and optical purity are shown in Table 3.
HPLC analysis conditions:

column: CHIRALCEL OD (manufactured by DAICEL CHEMICAL INDUSTRIES, LTD.),
mobile phase: n-hexane/2-propanol=98/2,
flow rate: 0.5 ml/min,
detection: λ=210 nm,
retention time: (S)-isomer (main peak); 12.7 min, (R)-isomer; 16.3 min.

$[\alpha]_D^{30}$-4.87 (c 1.00, $CHCl_3$);
^{1}H-NMR (500MHz, DMSO-d_6) δ 4.71 (dd, J=13.4, 4.9Hz, 1H), 4.54 (dd, J=13.3, 6.9Hz, 1H), 4.30-4.10 (m, 4H), 3.63 (d, J=5.8Hz, 1H), 3.02-2.76 (m, 1H), 1.51-1.42 (m, 2H), 1.53-1.19 (m, 12H), 0.88 (t, J=6.9Hz, 3H) ppm;
^{13}C-NMR (126MHz, DMSO-d_6) δ 168.1, 167.9, 76.7, 61.9, 61.7, 52.6, 36.9, 31.4, 29.9, 26.2, 22.3, 14.0, 13.9, 13.8 ppm;
IR ($CHCl_3$) ν 3030, 2960, 2932, 2865, 1730, 1553 cm^{-1}; MS (FAB^+) 304 (MH^+, 100);
HRMS (FAB^+)
Calculated (for $[C_{14}H_{26}NO_6]^+$): 304.1760;
Found: 304.1762.

Example 20

ethyl (S)-2-ethoxycarbonyl-5-methyl-3-(nitromethyl)hexanoate

[0119] In the same manner as in Example 6A except that the reaction time was set to 48 hr and trans-4-methyl-1-nitro-1-pentene was used instead of trans-β-nitrostyrene, the title compound was obtained as a colorless oil. The yield and optical purity are shown in Table 3.
HPLC analysis conditions:

column: CHIRALCEL OD (manufactured by DAICEL CHEMICAL INDUSTRIES, LTD.),
mobile phase: n-hexane/2-propanol=98/2,
flow rate: 0.5 ml/min,
detection: λ=210 nm,
retention time: (R)-isomer; 12.1 min, (S)-isomer (main peak); 16.2 min.

$[\alpha]_D^{24}$ -6.92 (c 1.04, $CHCl_3$) ;
^{1}H-NMR (500MHz, DMSO-d_6) δ 4.71 (dd, J=13.3, 5.0Hz, 1H), 4.53 (dd, J=13.3, 6.6 Hz, 1H), 4.31-4.14 (m, 4H), 3.62 (d, J=5.5Hz, 1H), 3.07-2.82 (m, 1H), 1.73-1.57 (m, 1H), 1.36-1.25 (m, 8H), 0.95-0.89 (m, 6H) ppm;
^{13}C-NMR (126MHz, DMSO-d_6) δ 168.0, 167.9, 76.8, 61.8, 61.7, 52.6, 38.9, 34.8, 25.0, 22.3, 22.1, 13.93, 13.90 ppm;
IR ($CHCl_3$) ν 3030, 2962, 2873, 1730, 1553 cm^{-1};
MS (EI^+) 290 (MH^+), 160 (100);
Elemental analysis

Calculated (for $C_{13}H_{23}NO_6$) :C, 53.97; H, 8.01; N, 4.84.
Found: C, 54.20; H, 7.95; N, 4.85.

Table 3

Example	compound (II)				reaction time (hr)	yield (%)	optical purity (% ee)
	EWG	R^8	R^{10}	R^9			
6A	NO_2	H	H	Ph	24	86	93
15	NO_2	H	H	2,6-$(OMe)_2$Ph	72	87	93
16	NO_2	H	H	4-F-Ph	12	87	92
17	NO_2	H	H	1-naphthyl	24	95	92[1)]
18	NO_2	H	H	2-thienyl	48	74	90[1)]
19	NO_2	H	H	n-pentyl	48	78	81
20	NO_2	H	H	isobutyl	48	88	81
1) absolute configuration: not identified							

Example 21

methyl 2-methoxycarbonyl-2-methyl-4-nitro-3-phenylbutyrate

[0120] In the same manner as in Example 6A except that the reaction time was set to 36 hr and dimethyl methylmalonate was used instead of diethyl malonate, the title compound was obtained as colorless crystals (yield 82%, optical purity 93% ee). melting point: 130-132°C (n-hexane/ethyl acetate). The absolute configuration of the obtained compound was not identified.
HPLC analysis conditions:

column: CHIRALCEL OD (manufactured by DAICEL CHEMICAL INDUSTRIES, LTD.),
mobile phase: n-hexane/2-propanol=90/10,
flow rate: 1.0 ml/min,
detection: λ=254 nm,
retention time: (R)-isomer; 8.9 min, (S)-isomer (main peak); 13.9 min.

$[a]_D^{32}$ +32.3 (c 1.06, $CHCl_3$);
^{1}H-NMR (500MHz, DMSO-d_6) δ 7.39-7.23 (m, 3H), 7.21-7.09 (m, 2H), 5.12-4.95 (m, 2H), 4.18 (dd, J=9.9, 4.4Hz, 1H), 3.77 (s, 3H), 3.73 (s, 3H), 1.35 (s, 3H) ppm;
^{13}C-NMR (126MHz, DMSO-d_6) δ 171.4, 170.8, 135.0, 129.0, 128.8, 128.5, 77.5, 56.7, 53.0, 52.8, 48.3, 20.2 ppm;
IR ($CHCl_3$) v 3032, 2955, 1735, 1557 cm^{-1};
MS (EI^+) 295 (M^+), 189 (100);
MS (FAB^+) 310 (MH^+, 100) ;
Elemental analysis
Calculated (for $C_{14}H_{17}NO_6$): C, 56.94; H, 5.80; N, 4.74.
Found: C, 56.92; H, 5.82; N, 4.64.

Example 22

ethyl (S)-2-ethoxycarbonyl-4-nitro-3-phenylbutyrate (without solvent)

[0121] To a mixture of trans-β-nitrostyrene (149 mg, 1.0 mmol) and diethyl malonate (0.304 ml, 2.0 mmol) was added, as an asymmetric catalyst, (R,R)-trans-1-[3,5-bis(trifluoromethyl)phenyl]-3-[2-(N,N-dimethylamino)cyclohexyl]thiourea (20.7 mg, 0.05 mmol), obtained in Example 1A at room temperature under an argon atmosphere. After 12 hr, the reaction mixture was purified by preparative TLC (elution solvent: n-hexane/diethyl ether) to give the title compound as colorless needle crystals (257 mg, yield 83%, optical purity 88%).

Example 23

methyl (R)-2-methoxy-2-methoxycarbonyl-4-nitro-3-phenylbutyrate

[0122] In the same manner as in Example 6A except that dimethyl methoxymalonate was used instead of diethyl malonate, the title compound was obtained as a colorless oil. The yield and optical purity are shown in Table 4.
HPLC analysis conditions:

column: CHIRALCEL OD (manufactured by DAICEL CHEMICAL INDUSTRIES, LTD.),
mobile phase: n-hexane/2-propanol=90/10,
flow rate: 0.5 ml/min,
detection: λ=210 nm,
retention time: (R)-isomer (main peak); 16.3 min, (S)-isomer; 21.0 min.

$[\alpha]_D^{28}$ -4.69 (c 1.13, $CHCl_3$) ;
^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.35-7.18 (m, 5H), 5.24 (dd, J=13.7, 3.4Hz, 2H), 4.84 (dd, J=10.1, 13.7Hz, 1H), 4.28 (dd, J=9.9, 3.5Hz, 1H), 3.83 (S, 3H), 3.58 (S, 3H), 3.46 (S, 3H) ppm;
^{13}C-NMR (126MHz, DMSO-d_6) δ 168.0, 167.4, 135.1, 129.4, 128.5, 128.4, 86.0, 76.8, 56.0, 52.9, 52.2, 48.8 ppm;
IR ($CHCl_3$) ν 3032, 2954, 1742, 1556 cm^{-1};
MS (FAB^+) 311 (MH^+), 104 (100);
Elemental analysis
Calculated (for $C_{14}H_{17}NO_7$) : C, 54.02; H, 5.50; N, 4.50.
Found: C, 54.18; H, 5.49; N, 4.43.

Example 24

methyl (R)-2-tert-butoxycarbonylamino-2-methoxycarbonyl-4-nitro-3-phenylbutyrate

[0123] In the same manner as in Example 6A except that dimethyl tert-butoxycarbonylaminomalonate was used instead of diethyl malonate, the title compound was obtained as a colorless oil. The yield and optical purity are shown in Table 4.
HPLC analysis conditions:

column: CHIRALCEL AD (manufactured by DAICEL CHEMICAL INDUSTRIES, LTD.),
mobile phase: n-hexane/2-propanol=90/10,
flow rate: 1.0 ml/min,
detection: λ=210 nm,
retention time: (R)-isomer (main peak); 11.5 min, (S)-isomer; 17.5 min.

$[\alpha]_D^{24}$+27.1 (c 0.94, $CHCl_3$);
^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.36-7.17 (m, 5H), 5.94 (s, 1H), 5.50 (dd, J=13.1, 2.4Hz, 1H), 4.72 (t, J=12.5Hz, 1H), 4.62 (dd, J=11.9, 2.8Hz, 1H), 4.34-4.21 (m, 2H), 4.19-4.09 (m, 1H), 4.05-3.95 (m, 1H), 1.46 (s, 9H), 1.29 (t, J=7.2Hz, 3H), 1.19 (t, J=7.2Hz, 3H) ppm;
^{13}C-NMR (126MHz, DMSO-d_6) δ 166.4, 166.3, 154.8, 134.1, 129.0, 128.7, 128.7, 81.2, 77.0, 67.5, 63.4, 62.7, 48.2, 28.1, 13.8, 13.7 ppm;
IR ($CHCl_3$) ν 3396, 3027, 2985, 1743, 1715, 1555, 1485 cm^{-1};
MS (FAB^+) 425 (MH^+), 325(100);
HRMS (FAB^+)
Calculated (for $[C_{20}H_{29}N_2O_8]^+$): 424.1846;
Found: 425.1932.

Example 25

methyl (R)-2-chloro-2-methoxycarbonyl-4-nitro-3-phenylbutyrate

[0124] In the same manner as in Example 6A except that dimethyl chloromalonate was used instead of diethyl malonate, the title compound was obtained as colorless needle crystals. The yield and optical purity are shown in Table 4. melting point: 175-177°C (n-hexane/ethyl acetate).
HPLC analysis conditions:

column: CHIRALCEL OD (manufactured by DAICEL CHEMICAL INDUSTRIES, LTD.),
mobile phase: n-hexane/2-propanol=90/10,
flow rate: 0.5 ml/min,
detection: λ=210 nm,
retention time: (R)-isomer (main peak); 18.6 min, (S)-isomer; 23.3 min.

$[\alpha]_D^{20}$ -6.16 (c 0.85, $CHCl_3$);
^{1}H-NMR (500MHz, $CDCl_3$) δ 7.42-7.25 (m, 3H), 5.21 (dd, J=13.4, 3.3Hz, 1H), 5.00 (dd, J=13.4, 10.4Hz, 1H), 4.63 (dd, J=10.5, 3.2Hz, 1H), 3.84 (s, 3H), 3.59 (s, 3H) ppm;
^{13}C-NMR (126MHz, DMSO-d_6) δ 165.7, 164.5, 133.3, 129.4, 129.0, 128.6, 76.6, 72.3, 54.6, 54.3, 48.2 ppm;
IR ($CHCl_3$) ν 3029, 2957, 1750, 1560 cm^{-1};
MS (FAB^+) 316 (MH^+), 154(100);
Elemental analysis
Calculated (for $C_{13}H_{14}ClNO_6$): C, 49.46; H, 4.47; N, 4.44.
Found: C, 49.46; H, 4.44; N, 4.41.

Example 26

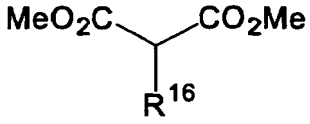
methyl 2-(2'-nitro-1'-phenylethyl)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate

[0125] In the same manner as in Example 6A except that methyl 1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate was used instead of diethyl malonate, the title compound (diastereomer mixture) (90% d.e., optical purity of the main diastereomer: 90% e.e., yield 97%) was obtained. The obtained diastereomer mixture was recrystallized from n-hexane/ethyl acetate to give the main diastereomer of the title compound as colorless plate crystals. The yield and optical purity are shown in Table 4. melting point: 101-103°C (n-hexane/ethyl acetate). The absolute configuration of the obtained compound was not identified.
HPLC analysis conditions:

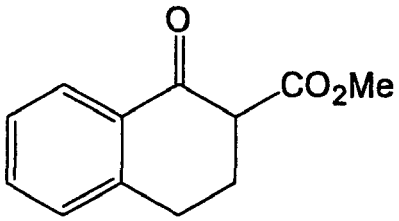
column: CHIRALCEL OD (manufactured by DAICEL CHEMICAL INDUSTRIES, LTD.),
mobile phase: n-hexane/2-propanol=90/10,
flow rate: 0.5 ml/min,
detection: λ=254 nm,
retention time: isomer (main peak); 27.9 min, isomer; 46.7 min.

$[\alpha]_D^{20}$ +51.0 (c 0.75, $CHCl_3$);
^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.03 (d, J=7.9Hz, 1H), 7.50 (t, J=7.5Hz, 1H), 7.41-7.23 (m, 6H), 7.19 (d, J=7.6Hz, 1H), 5.15 (dd, J=13.5, 3.5Hz, 1H), 5.05 (dd, J=13.5, 10.5Hz, 1H), 4.20 (dd, J=10.5, 3.5Hz, 1H), 3.65 (s, 3H), 3.05-2.89 (m, 2H), 2.47-2.39 (m, 1H), 2.10-1.98 (m, 1H) ppm;
^{13}C-NMR (126MHz, DMSO-d_6) δ 194.3, 170.3, 142.5, 135.9, 134.1, 131.6, 129.9, 128.8, 128.7, 128.5, 128.3, 127.1, 77.8, 59.7, 52.7, 47.1, 30.7, 25.5 ppm;
IR ($CHCl_3$) ν 3031, 2954, 1736, 1687, 1601 cm^{-1};
MS (FAB^+) 354 (MH^+), 189 (100) ;
Elemental analysis
Calculated (for $C_{20}H_{19}ClNO_5$): C, 67.98; H, 5.42; N, 3.96.
Found: C, 67.79; H, 5.43; N, 3.95.

Table 4

Example	nucleophilic reagent (III)		yield (%)	optical purity (% ee)
		R^{16}		
23		OMe	89	94
24		$NHCO_2t$-Bu	81	82
25		Cl	100	99[1)]

(continued)

Example	nucleophilic reagent (III)		yield (%)	optical purity (% ee)
		R^{16}		
26			97[2)]	90[3)4)]
1) after recrystallization 2) diastereomer mixture (90% d.e.) 3) main diastereomer 4) absolute configuration: not identified				

Industrial Applicability

[0126] According to the present invention, a novel asymmetric urea compound (I), which is a non-metallic asymmetric catalyst enabling an asymmetric conjugate addition reaction in a high yield and with high stereoselectivity, is provided, and using this compound for an asymmetric conjugate addition reaction, an advantageous production method of an asymmetric compound [asymmetric compound (IV)] is provided.

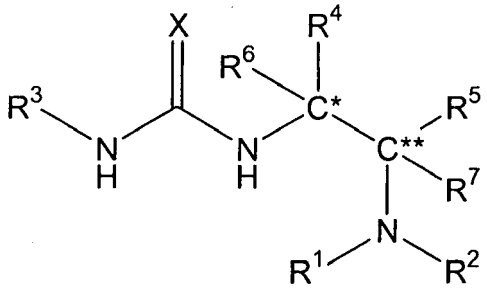
[0127] Since the asymmetric urea compound (I) of the present invention is non-metallic and does not require treatments of metal waste liquid and the like, it is an environmentally-friendly catalyst. Moreover, since it is non-metallic, the compound can be recovered and reused easily.

[0128] Since the production method of the present invention is applicable to bulky nucleophilic reagents such as tertiary carbon and the like, the method permits a broad range of application.

[0129] Furthermore, since the reaction conditions are mild and the method can also be performed without solvent, it is a highly practical method.

Claims

1. A compound represented by the formula (I):



(I)

wherein

X is a sulfur atom;

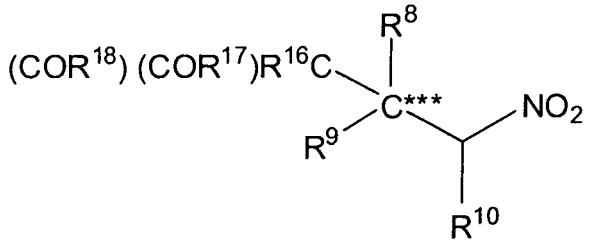
C* and C** are each independently an asymmetric carbon, and the absolute configurations of C* and C** are both S-configurations or both R-configurations;

R^1 and R^2 are the same or different and each is methyl, ethyl or isopropyl, or form isoindoline together with the nitrogen atom they are bonded to;

R^3 is a phenyl group optionally having substituent(s) selected from $C_{1\text{-}12}$ haloalkyl group (s), nitro group (s), cyano group(s) and -$COOR^{25}$ wherein R^{25} is a $C_{1\text{-}12}$ alkyl group;

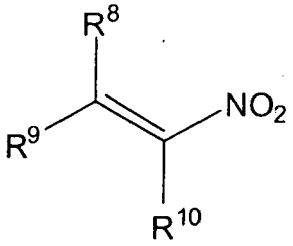
R^4 and R^5 form a cyclohexane together with the asymmetric carbons they are respectively bonded to; and
R^6 and R^7 are each a hydrogen atom,
or a salt thereof.

2. A method of producing a compound represented by the formula (IV) :



(IV)

or a salt thereof,
which process comprises conjugately adding a nucleophilic
reagent represented by the formula (III) : H-$CR^{16}(COR^{17})(COR^{18})$ (III), to a compound represented by the formula (II):



(II)

or a salt thereof, in the presence of a compound or a salt thereof of claim 1
wherein

C*** is an asymmetric carbon;
R^8, R^9 and R^{10} are
the same or different and each is

(1) a hydrogen atom,
(2) a $C_{1\text{-}12}$ alkyl group optionally having substituent(s),
(3) a $C_{6\text{-}20}$ aryl-$C_{1\text{-}12}$ alkyl group optionally having substituent(s),
(4) a $C_{6\text{-}20}$ aryl group optionally having substituent(s),
(5) a heteroaryl group selected from (i) a 5- to 10-membered aromatic heterocyclic group containing, besides carbon atoms, 1 to 3 hetero atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom, and (ii) a fused heterocyclic group thereof, each of (i) and (ii) optionally having substituent(s),
(6) a hetero atom selected from a nitrogen atom, an oxygen atom and a sulfur atom, optionally having substituent(s) selected from

(a) a $C_{1\text{-}12}$ alkyl group optionally having substituent(s),
(b) a $C_{6\text{-}20}$ aryl-$C_{1\text{-}12}$ alkyl group optionally having substituent(s),
(c) a $C_{6\text{-}20}$ aryl group optionally having substituent(s), and
(d) a heteroaryl group selected from (i) a 5- to 10-membered aromatic heterocyclic group containing, besides carbon atoms, 1 to 3 hetero atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom, and (ii) a fused heterocyclic group thereof, each of (i) and (ii) optionally having substituent(s), or

(7) an electron withdrawing group, or

R^9 and R^{10} form, together with the carbon atoms they are respectively bonded to,

(1) a C_{3-7} homocyclic ring optionally having substituent(s), or
(2) a 5- to 10-membered heterocycle containing, besides carbon atoms, 1 to 3 hetero atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom and optionally having substituent(s),
provided that R^8 and R^9 are not the same groups;
R^{16} is

(1) a hydrogen atom,
(2) a halogen atom,
(3) a hetero atom selected from a nitrogen atom, an oxygen atom and a sulfur atom, having substituent(s) selected from

(a) a C_{1-12} alkyl group optionally having substituent(s),
(b) a C_{6-20} aryl-C_{1-12} alkyl group optionally having substituent(s),
(c) a C_{6-20} aryl group optionally having substituent(s),
(d) a heteroaryl group selected from (i) a 5- to 10-membered aromatic heterocyclic group containing, besides carbon atoms, 1 to 3 hetero atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom, and (ii) a fused heterocyclic group thereof, each of (i) and (ii) optionally having substituent(s),
(e) $-COOR^{26}$ wherein R^{26} is a C_{1-12} alkyl group,
(f) $-COR^{27}$ wherein R^{27} is a C_{1-12} alkyl group, and
(g) $-SO_2R^{28}$ wherein R^{28} is a C_{1-12} alkyl group,

(4) a C_{1-12} alkyl group optionally having substituent(s) or
(5) a C_{6-20} aryl group optionally having substituent(s); and
R^{17} and R^{18} are the same or different and each is a hydrogen atom, a C_{1-12} alkyl group, a C_{1-12} alkoxy group, a mono-C_{1-12} alkylamino group or a di-C_{1-12} alkylamino group; or
R^{16} and R^{17} optionally form, together with the carbon atoms they are respectively bonded to,

(1) a C_{3-7} homocyclic ring substituted by oxo, which is optionally condensed with an aromatic hydrocarbon and optionally has substituent(s), or
(2) a 5- to 10-membered heterocycle substituted by oxo, which is optionally condensed with an aromatic hydrocarbon and contains, besides carbon atoms, 1 to 3 hetero atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom, and optionally has substituent(s).

3. The method of claim 2, wherein
R^{16} is

(1) a hydrogen atom,
(2) a halogen atom,
(3) a C_{1-12} alkyl group optionally having substituent(s), or
(4) a C_{6-20} aryl group optionally having substituent(s); and R^{17} and R^{18} are the same or different and each is a hydrogen atom, a C_{1-12} alkyl group, a C_{1-12} alkoxy group, a mono-C_{1-12} alkylamino group or a di-C_{1-12} alkylamino group.

4. The method of any of claims 2 or 3, wherein
R^8 and R^{10} are each a hydrogen atom, and
R^9 is

(1) a C_{1-12} alkyl group optionally having substituent(s),
(2) a C_{6-20} aryl group optionally having substituent(s), or
(3) a heteroaryl group selected from (i) a 5- to 10-membered aromatic heterocyclic group containing, besides carbon atoms, 1 to 3 hetero atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom, and (ii) a fused heterocyclic group thereof, each of (i) and (ii) optionally having substituent(s).

5. The method of claim 2, wherein
R^{16} is

(1) a hydrogen atom,

(2) a C_{1-12} alkyl group optionally having substituent(s),
(3) a halogen atom, or
(4) a hetero atom selected from a nitrogen atom, an oxygen atom and a sulfur atom having substituent(s) selected from

(a) a C_{1-12} alkyl group optionally having substituent(s),
(b) a C_{6-20} aryl-C_{1-12} alkyl group optionally having substituent(s),
(c) a C_{6-20} aryl group optionally having substituent(s),
(d) a heteroaryl group selected from (i) a 5- to 10-membered aromatic heterocyclic group containing, besides carbon atoms, 1 to 3 hetero atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom, and (ii) a fused heterocyclic group thereof, each of (i) and (ii) optionally having substituent(s),
(e) $-COOR^{26}$ wherein R^{26} is a C_{1-12} alkyl group,
(f) $-COR^{27}$ wherein R^{27} is a C_{1-12} alkyl group, and
(g) $-SO_2R^{28}$ wherein R^{28} is a C_{1-12} alkyl group, and

R^{17} and R^{18} are the same or different and each is a C_{1-12} alkyl group or a C_{1-12} alkoxy group.

6. The method of claim 5, wherein R^{16} is a hydrogen atom, methyl, a chlorine atom, methoxy or tert-butoxycarbonylamino, and R^{17} and R^{18} are each methoxy or ethoxy.

7. The method of claim 2, wherein R^{16} and R^{17} form, together with the carbon atoms they are respectively bonded to, a C_{3-7} homocyclic ring substituted by oxo, which is optionally condensed with an aromatic hydrocarbon and optionally has substituent(s).

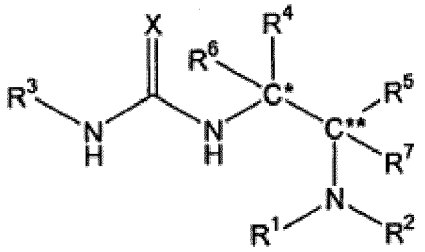
8. The method of claim 7, wherein the homocyclic ring is 1,2,3,4-tetrahydronaphthalen-1-one.

9. The method of any of claims 2 to 8, which is performed in at least one solvent selected from toluene and methylene chloride.

10. The method of any of claims 2 to 8, which is performed without a solvent.

Patentansprüche

1. Verbindung, die durch die Formel (I) dargestellt wird:



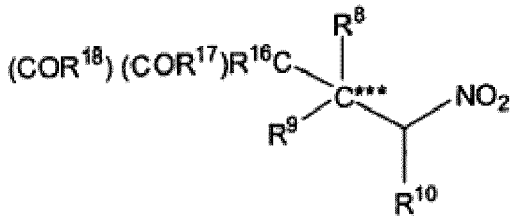
(I)

wobei

X ein Schwefelatom ist;
C* und C** jeweils unabhängig ein asymmetrisches Kohlenstoffatom sind und die absoluten Konfigurationen von C* und C** beides S-Konfigurationen oder beides R-Konfigurationen sind;
R^1 und R^2 gleich oder verschieden sind und jeweils Methyl, Ethyl oder Isopropyl sind oder zusammen mit dem Stickstoffatom, an das sie gebunden sind, Isoindolin bilden;
R^3 eine Phenylgruppe ist, die gegebenenfalls einen oder mehrere Substituenten aufweist, die aus C_{1-12}-Halogenalkylgruppen, Nitrogruppen, Cyanogruppen und $-COOR^{25}$, wobei R^{25} eine C_{1-12}-Alkylgruppe ist, ausgewählt sind;
R^4 und R^5 zusammen mit den asymmetrischen Kohlenstoffatomen, an die sie jeweils gebunden sind, ein Cyclohexan bilden; und

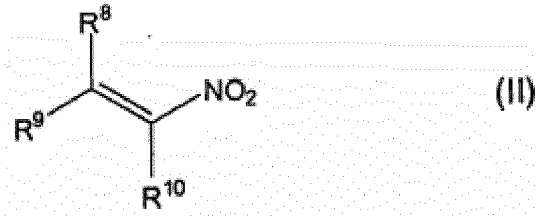
R^6 und R^7 jeweils ein Wasserstoffatom sind;
oder ein Salz davon.

2. Verfahren zur Herstellung einer Verbindung, die durch die Formel (IV) dargestellt wird:



(IV)

oder eines Salzes davon,
wobei das Verfahren das Addieren eines nucleophilen Reagens, das durch die Formel (III), H-$CR^{16}(COR^{17})(COR^{18})$ (III), dargestellt wird, an eine Verbindung, die durch die Formel (II) dargestellt wird:



(II)

oder ein Salz davon, in Gegenwart einer Verbindung oder eines Salzes davon gemäß Anspruch 1 umfasst;
wobei

C*** ein asymmetrisches Kohlenstoffatom ist;
R^8, R^9 und R^{10} gleich oder verschieden sind und jeweils Folgendes sind:

(1) ein Wasserstoffatom;
(2) eine C_1-C_{12}-Alkylgruppe, die gegebenenfalls einen oder mehrere Substituenten aufweist;
(3) eine C_{6-20}-Aryl-C_{1-12}-alkyl-Gruppe, die gegebenenfalls einen oder mehrere Substituenten aufweist;
(4) eine C_{6-20}-Arylgruppe, die gegebenenfalls einen oder mehrere Substituenten aufweist;
(5) eine Heteroarylgruppe, die aus (i) einer fünf- bis zehngliedrigen aromatischen heterocyclischen Gruppe, die neben Kohlenstoffatomen 1 bis 3 aus einem Sauerstoffatom, einem Schwefelatom und einem Stickstoffatom ausgewählte Heteroatome enthält, und (ii) einer diese umfassenden kondensierten heterocyclischen Gruppe ausgewählt ist, wobei (i) und (ii) jeweils gegebenenfalls einen oder mehrere Substituenten aufweisen;
(6) ein Heteroatom, das aus einem Stickstoffatom, einem Sauerstoffatom und einem Schwefelatom ausgewählt ist, die gegebenenfalls einen oder mehrere Substituenten aufweisen, die ausgewählt sind aus

(a) einer C_{1-12}-Alkylgruppe, die gegebenenfalls einen oder mehrere Substituenten aufweist;
(b) einer C_{6-20}-Aryl-C_{1-12}-alkyl-Gruppe, die gegebenenfalls einen oder mehrere Substituenten aufweist;
(c) einer C_{6-20}-Arylgruppe, die gegebenenfalls einen oder mehrere Substituenten aufweist; und
(d) einer Heteroarylgruppe, die aus (i) einer fünf- bis zehngliedrigen aromatischen heterocyclischen Gruppe, die neben Kohlenstoffatomen 1 bis 3 aus einem Sauerstoffatom, einem Schwefelatom und einem Stickstoffatom ausgewählte Heteroatome enthält, und (ii) einer diese umfassenden kondensierten heterocyclischen Gruppe ausgewählt ist, wobei (i) und (ii) jeweils gegebenenfalls einen oder mehrere Substituenten aufweisen; oder

(7) eine elektronenziehende Gruppe; oder

R^9 und R^{10} zusammen mit den Kohlenstoffatomen, an die sie jeweils gebunden sind, Folgendes bilden:

(1) einen homocyclischen C_{3-7}-Ring, der gegebenenfalls einen oder mehrere Substituenten aufweist; oder
(2) einen fünf- bis zehngliedrigen Heterocyclus, der neben Kohlenstoffatomen 1 bis 3 aus einem Sauerstoffatom, einem Schwefelatom und einem Stickstoffatom ausgewählte Heteroatome enthält und gegebenenfalls einen oder mehrere Substituenten aufweist;

mit der Maßgabe, dass R^8 und R^9 nicht dieselben Gruppen sind;
R^{16} Folgendes ist:

(1) ein Wasserstoffatom;
(2) ein Halogenatom;
(3) ein Heteroatom, das aus einem Stickstoffatom, einem Sauerstoffatom und einem Schwefelatom ausgewählt ist, die gegebenenfalls einen oder mehrere Substituenten aufweisen, die ausgewählt sind aus

(a) einer C_{1-12}-Alkylgruppe, die gegebenenfalls einen oder mehrere Substituenten aufweist;
(b) einer C_{6-20}-Aryl-C_{1-12}-alkyl-Gruppe, die gegebenenfalls einen oder mehrere Substituenten aufweist;
(c) einer C_{6-20}-Arylgruppe, die gegebenenfalls einen oder mehrere Substituenten aufweist;
(d) einer Heteroarylgruppe, die aus (i) einer fünf- bis zehngliedrigen aromatischen heterocyclischen Gruppe, die neben Kohlenstoffatomen 1 bis 3 aus einem Sauerstoffatom, einem Schwefelatom und einem Stickstoffatom ausgewählte Heteroatome enthält, und (ii) einer diese umfassenden kondensierten heterocyclischen Gruppe ausgewählt ist, wobei (i) und (ii) jeweils gegebenenfalls einen oder mehrere Substituenten aufweisen;
(e) $-COOR^{26}$, wobei R^{26} eine C_{1-12}-Alkylgruppe ist;
(f) $-COR^{27}$, wobei R^{27} eine C_{1-12}-Alkylgruppe ist; und
(g) $-SO_2R^{28}$, wobei R^{28} eine C_{1-12}-Alkylgruppe ist;

(4) eine C_{1-12}-Alkylgruppe, die gegebenenfalls einen oder mehrere Substituenten aufweist; oder
(5) eine C_{6-20}-Arylgruppe, die gegebenenfalls einen oder mehrere Substituenten aufweist; und

R^{17} und R^{18} gleich oder verschieden sind und jeweils ein Wasserstoffatom, eine C_{1-12}-Alkylgruppe, eine C_{1-12}-Alkoxygruppe, eine Mono-C_{1-12}-alkylamino-Gruppe oder eine Di-C_{1-12}-alkylamino-Gruppe sind; oder
R^{16} und R^{17} gegebenenfalls zusammen mit dem Kohlenstoffatom, an das sie jeweils gebunden sind, Folgendes bilden:

(1) einen homocyclischen C_{3-7}-Ring, der mit Oxo substituiert ist, gegebenenfalls mit einem aromatischen Kohlenwasserstoff kondensiert ist und gegebenenfalls einen oder mehrere Substituenten aufweist; oder
(2) einen fünf- bis zehngliedrigen Heterocyclus, der mit Oxo substituiert ist, gegebenenfalls mit einem aromatischen Kohlenwasserstoff kondensiert ist und neben Kohlenstoffatomen 1 bis 3 aus einem Sauerstoffatom, einem Schwefelatom und einem Stickstoffatom ausgewählte Heteroatome enthält und gegebenenfalls einen oder mehrere Substituenten aufweist.

3. Verfahren gemäß Anspruch 2, wobei
R^{16} Folgendes ist:

(1) ein Wasserstoffatom;
(2) ein Halogenatom;
(3) eine C_{1-12}-Alkylgruppe, die gegebenenfalls einen oder mehrere Substituenten aufweist; oder
(4) eine C_{6-20}-Arylgruppe, die gegebenenfalls einen oder mehrere Substituenten aufweist; und

R^{17} und R^{18} gleich oder verschieden sind und jeweils ein Wasserstoffatom, eine C_{1-12}-Alkylgruppe, eine C_{1-12}-Alkoxygruppe, eine Mono-C_{1-12}-alkylamino-Gruppe oder eine Di-C_{1-12}-alkylamino-Gruppe sind.

4. Verfahren gemäß einem der Ansprüche 2 oder 3, wobei
R^8 und R^{10} jeweils ein Wasserstoffatom sind; und
R^9 Folgendes ist:

(1) eine C_1-C_{12}-Alkylgruppe, die gegebenenfalls einen oder mehrere Substituenten aufweist;
(2) eine C_{6-20}-Arylgruppe, die gegebenenfalls einen oder mehrere Substituenten aufweist; oder
(3) eine Heteroarylgruppe, die aus (i) einer fünf- bis zehngliedrigen aromatischen heterocyclischen Gruppe, die

neben Kohlenstoffatomen 1 bis 3 aus einem Sauerstoffatom, einem Schwefelatom und einem Stickstoffatom ausgewählte Heteroatome enthält, und (ii) einer diese umfassenden kondensierten heterocyclischen Gruppe ausgewählt ist, wobei (i) und (ii) jeweils gegebenenfalls einen oder mehrere Substituenten aufweisen.

5. Verfahren gemäß Anspruch 2, wobei
R^{16} Folgendes ist:

(1) ein Wasserstoffatom;
(2) eine C_1-C_{12}-Alkylgruppe, die gegebenenfalls einen oder mehrere Substituenten aufweist;
(3) ein Halogenatom; oder
(4) ein Heteroatom, das aus einem Stickstoffatom, einem Sauerstoffatom und einem Schwefelatom ausgewählt ist, die gegebenenfalls einen oder mehrere Substituenten aufweisen, die ausgewählt sind aus

(a) einer C_{1-12}-Alkylgruppe, die gegebenenfalls einen oder mehrere Substituenten aufweist;
(b) einer C_{6-20}-Aryl-C_{1-12}-alkyl-Gruppe, die gegebenenfalls einen oder mehrere Substituenten aufweist;
(c) einer C_{6-20}-Arylgruppe, die gegebenenfalls einen oder mehrere Substituenten aufweist;
(d) einer Heteroarylgruppe, die aus (i) einer fünf- bis zehngliedrigen aromatischen heterocyclischen Gruppe, die neben Kohlenstoffatomen 1 bis 3 aus einem Sauerstoffatom, einem Schwefelatom und einem Stickstoffatom ausgewählte Heteroatome enthält, und (ii) einer diese umfassenden kondensierten heterocyclischen Gruppe ausgewählt ist, wobei (i) und (ii) jeweils gegebenenfalls einen oder mehrere Substituenten aufweisen;
(e) $-COOR^{26}$, wobei R^{26} eine C_{1-12}-Alkylgruppe ist;
(f) $-COR^{27}$, wobei R^{27} eine C_{1-12}-Alkylgruppe ist; und
(g) $-SO_2R^{28}$, wobei R^{28} eine C_{1-12}-Alkylgruppe ist; und

R^{17} und R^{18} gleich oder verschieden sind und jeweils eine C_{1-12}-Alkylgruppe oder eine C_{1-12}-Alkoxygruppe sind.

6. Verfahren gemäß Anspruch 5, wobei R^{16} ein Wasserstoffatom, Methyl, ein Chloratom, Methoxy oder tert-Butoxycarbonylamino ist und R^{17} und R^{18} jeweils Methoxy oder Ethoxy sind.

7. Verfahren gemäß Anspruch 2, wobei R^{16} und R^{17} zusammen mit dem Kohlenstoffatom, an das sie jeweils gebunden sind, einen homocyclischen C_{3-7}-Ring, der mit Oxo substituiert ist, gegebenenfalls mit einem aromatischen Kohlenwasserstoff kondensiert ist und gegebenenfalls einen oder mehrere Substituenten aufweist, bilden.

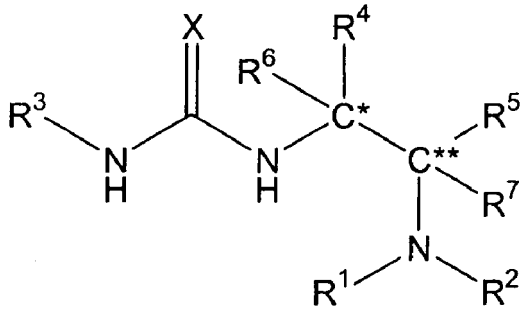
8. Verfahren gemäß Anspruch 7, wobei es sich bei dem homocyclischen Ring um 1,2,3,4-Tetrahydronaphthalin-1-on handelt.

9. Verfahren gemäß einem der Ansprüche 2 bis 8, das in wenigstens einem Lösungsmittel, welches aus Toluol und Methylenchlorid ausgewählt ist, durchgeführt wird.

10. Verfahren gemäß einem der Ansprüche 2 bis 8, das ohne Lösungsmittel durchgeführt wird.

Revendications

1. Composé représenté par la formule (I) :

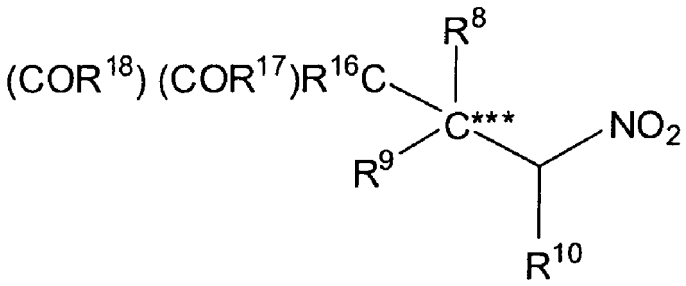


(I)

dans laquelle

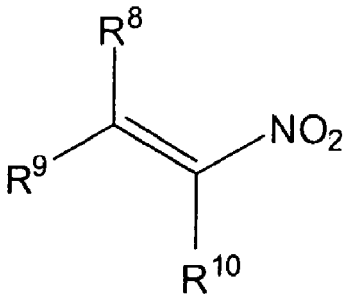
X est un atome de soufre ;
C* et C** sont chacun indépendamment un carbone asymétrique, et les configurations absolues de C* et C** sont toutes deux des configurations S ou toutes deux des configurations R ;
R^1 et R^2 sont identiques ou différents et sont chacun un méthyle, un éthyle ou un isopropyle, ou forment une isoindoline conjointement avec l'atome d'azote auquel ils sont liés ;
R^3 est un groupe phényle ayant facultativement un (des) substituant(s) sélectionné(s) parmi un (des) groupe(s) C_{1-12} halogénoalkyle, un (des) groupe (s) nitro, un (des) groupe(s) cyano et $-COOR^{25}$ dans lequel R^{25} est un groupe C_{1-12} alkyle ;
R^4 et R^5 forment un cyclohexane conjointement avec les carbones asymétriques auxquels ils sont respectivement liés ; et
R^6 et R^7 sont chacun un atome d'hydrogène,
ou un sel de celui-ci.

2. Méthode de production d'un composé représenté par la formule (IV) :



(IV)

ou d'un sel de celui-ci ;
lequel procédé comprend l'ajout de façon conjuguée d'un réactif nucléophile représenté par la formule (III) : $H-CR^{16}(COR^{17})(COR^{18})$ (III), à un composé représenté par la formule (II) :



(II)

ou un sel de celui-ci, en présence d'un composé ou d'un sel de celui-ci selon la revendication 1
dans laquelle

C*** est un carbone asymétrique ;
R^8, R^9 et R^{10} sont
identiques ou différents et sont chacun

(1) un atome d'hydrogène,
(2) un groupe C_{1-12} alkyle ayant facultativement un (des) substituant(s),
(3) un groupe C_{6-20} aryl-C_{1-12} alkyle ayant facultativement un (des) substituant(s),
(4) un groupe C_{6-20} aryle ayant facultativement un (des) substituant(s),
(5) un groupe hétéroaryle sélectionné parmi (i) un groupe hétérocyclique aromatique à 5 à 10 chainons comprenant, outre des atomes de carbone, 1 à 3 hétéroatomes sélectionnés parmi un atome d'oxygène, un atome de soufre et un atome d'azote, et (ii) un groupe hétérocyclique fusionné de celui-ci, chacun de (i) et (ii) ayant facultativement un (des) substituant(s),

(6) un hétéroatome sélectionné parmi un atome d'azote, un atome d'oxygène et un atome de soufre, ayant facultativement un (des) substituant(s) sélectionnés parmi

(a) un groupe C_{1-12} alkyle ayant facultativement un (des) substituant(s),
(b) un groupe C_{6-20} aryl-C_{1-12} alkyle ayant facultativement un (des) substituant(s),
(c) un groupe C_{6-20} aryle ayant facultativement un (des) substituant(s), et
(d) un groupe hétéroaryle sélectionné parmi (i) un groupe hétérocyclique aromatique à 5 à 10 chainons contenant, outre des atomes de carbone, 1 à 3 hétéroatomes sélectionnés parmi un atome d'oxygène, un atome de soufre et un atome d'azote, et (ii) un groupe hétérocyclique fusionné de celui-ci, chacun de (i) et (ii) ayant facultativement un (des) substituant(s), ou

(7) un groupe électroattracteur, ou

R^9 et R^{10} forment, conjointement avec les atomes de carbone auxquels ils sont respectivement liés,

(1) un cycle C_{3-7} homocyclique ayant facultativement un (des) substituant(s), ou
(2) un hétérocycle à 5 à 10 chainons contenant, outre des atomes de carbone, 1 à 3 hétéroatomes sélectionnés parmi un atome d'oxygène, un atome de soufre et un atome d'azote et ayant facultativement un (des) substituant(s),

à condition que R^8 et R^9 ne soient pas les mêmes groupes ;
R^{16} est

(1) un atome d'hydrogène,
(2) un atome d'halogène,
(3) un hétéroatome sélectionné parmi un atome d'azote, un atome d'oxygène et un atome de soufre, ayant un (des) substituant(s) sélectionnés parmi

(a) un groupe C_{1-12} alkyle ayant facultativement un (des) substituant(s),
(b) un groupe C_{6-20} aryl-C_{1-12} alkyle ayant facultativement un (des) substituant(s),
(c) un groupe C_{6-20} aryle ayant facultativement un (des) substituant(s),
(d) un groupe hétéroaryle sélectionné parmi (i) un groupe hétérocyclique aromatique à 5 à 10 chainons contenant, outre des atomes de carbone, 1 à 3 hétéroatomes sélectionnés parmi un atome d'oxygène, un atome de soufre et un atome d'azote, et (ii) un groupe hétérocyclique fusionné de celui-ci, chacun de (i) et (ii) ayant facultativement un (des) substituant(s),
(e) $-COOR^{26}$ dans lequel R^{26} est un groupe C_{1-12} alkyle,
(f) $-COR^{27}$ dans lequel R^{27} est un groupe C_{1-12} alkyle, et
(g) $-SO_2R^{28}$ dans lequel R^{28} est un groupe C_{1-12} alkyle,

(4) un groupe C_{1-12} alkyle, ayant facultativement un (des) substituant(s), ou
(5) un groupe C_{6-20} aryle ayant facultativement un (des) substituant(s), et

R^{17} et R^{18} sont identiques ou différents et sont chacun un atome d'hydrogène, un groupe C_{1-12} alkyle, un groupe C_{1-12} alcoxy, un groupe mono-C_{1-12} alkylamino ou un groupe di-C_{1-12} alkylamino ; ou
R^{16} et R^{17} forment facultativement, conjointement avec les atomes de carbone auxquels ils sont respectivement liés,

(1) un cycle C_{3-7} homocyclique substitué par oxo, qui est facultativement condensé avec un hydrocarbure aromatique et a facultativement un (des) substituant (s), ou
(2) un hétérocycle à 5 à 10 chainons substitué par oxo, lequel est facultativement condensé avec un hydrocarbure aromatique et contient, outre des atomes de carbone, 1 à 3 hétéroatomes sélectionnés parmi un atome d'oxygène, un atome de soufre et un atome d'azote, et a facultativement un (des) substituant(s).

3. Méthode selon la revendication 2, dans laquelle R^{16} est

(1) un atome d'hydrogène,
(2) un atome d'halogène,
(3) un groupe C_{1-12} alkyle ayant facultativement un (des) substituant(s), ou

(4) un groupe C_{6-20} aryle ayant facultativement un (des) substituant(s) ; et

R^{17} et R^{18} sont identiques ou différents et sont chacun un atome d'hydrogène, un groupe C_{1-12} alkyle, un groupe C_{1-12} alcoxy, un groupe mono-C_{1-12} alkylamino ou un groupe di-C_{1-12} alkylamino.

4. Méthode selon l'une quelconque des revendications 2 ou 3, dans laquelle
R^8 et R^{10} sont chacun un atome d'hydrogène, et
R^9 est

(1) un groupe C_{1-12} alkyle ayant facultativement un (des) substituant(s),
(2) un groupe C_{6-20} aryle ayant facultativement un (des) substituant(s), ou
(3) un groupe hétéroaryle sélectionné parmi (i) un groupe hétérocyclique aromatique à 5 à 10 chainons comprenant, outre des atomes de carbone, 1 à 3 hétéroatomes sélectionnés parmi un atome d'oxygène, un atome de soufre et un atome d'azote, et (ii) un groupe hétérocyclique fusionné de celui-ci, chacun de (i) et (ii) ayant facultativement un (des) substituant(s).

5. Méthode selon la revendication 2, dans laquelle
R^{16} est

(1) un atome d'hydrogène,
(2) un groupe C_{1-12} alkyle ayant facultativement un (des) substituant(s),
(3) un atome d'halogène, ou
(4) un hétéroatome sélectionné parmi un atome d'azote, un atome d'oxygène et un atome de soufre ayant un (des) substituant(s) sélectionnés parmi

(a) un groupe C_{1-12} alkyle ayant facultativement un (des) substituant(s),
(b) un groupe C_{6-20} aryl-C_{1-12} alkyle ayant facultativement un (des) substituant(s),
(c) un groupe C_{6-20} aryle ayant facultativement un (des) substituant(s),
(d) un groupe hétéroaryle sélectionné parmi (i) un groupe hétérocyclique aromatique à 5 à 10 chainons contenant, outre des atomes de carbone, 1 à 3 hétéroatomes sélectionnés parmi un atome d'oxygène, un atome de soufre et un atome d'azote, et (ii) un groupe hétérocyclique fusionné de celui-ci, chacun de (i) et (ii) ayant facultativement un (des) substituant(s),
(e) $-COOR^{26}$ dans lequel R^{26} est un groupe C_{1-12} alkyle,
(f) $-COR^{27}$ dans lequel R^{27} est un groupe C_{1-12} alkyle, et
(g) $-SO_2R^{28}$ dans lequel R^{28} est un groupe C_{1-12} alkyle, et

R^{17} et R^{18} sont identiques ou différents et sont chacun un groupe C_{1-12} alkyle ou un groupe C_{1-12} alcoxy.

6. Méthode selon la revendication 5, dans laquelle R^{16} est un atome d'hydrogène, un méthyle, un atome de chlore, un méthoxy ou un tert-butoxycarbonylamino, et R^{17} et R^{18} sont chacun un méthoxy ou un éthoxy.

7. Méthode selon la revendication 2, dans laquelle R^{16} et R^{17} forment, conjointement avec les atomes de carbone auxquels ils sont respectivement liés, un cycle C_{3-7} homocyclique substitué par oxo, qui est facultativement condensé avec un hydrocarbure aromatique et a facultativement un (des) substituant(s).

8. Méthode selon la revendication 7, dans laquelle, le cycle homocyclique est la 1,2,3,4-tétrahydronaphtalén-1-one.

9. Méthode selon l'une quelconque des revendications 2 à 8, qui est réalisée dans au moins un solvant sélectionné parmi le toluène et le chlorure de méthylène.

10. Méthode selon l'une quelconque des revendications 2 à 8, qui est réalisée sans solvant.

REFERENCES CITED IN THE DESCRIPTION

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