

DESCRIPTION

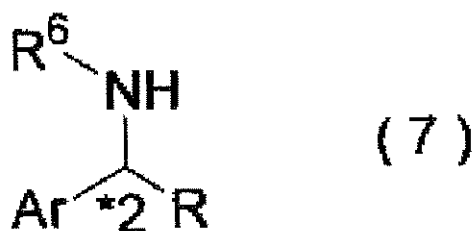
METHOD FOR PRODUCING OPTICALLY ACTIVE BENZYLAMINE DERIVATIVE

TECHNICAL FIELD

5 The present invention relates to an optically active benzylamine derivative which is an important intermediate in production in the pharmaceutical and agrochemical fields, and a method for producing the same. In more detail, it relates to a method for converting an optically active benzylalcohol
10 derivative to an optically active benzylamine derivative.

BACKGROUND ART

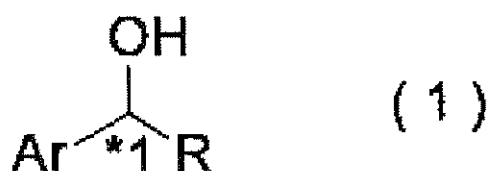
As a method for producing an optically active benzylamine derivative represented by a general formula (7):



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wherein Ar represents a substituted or unsubstituted aryl group having 6 to 20 carbon atoms or a substituted or unsubstituted heteroaromatic group having 4 to 20 carbon atoms, R represents a substituted or unsubstituted alkyl group having 1 to 18 carbon
20 atoms, a substituted or unsubstituted aryl group having 6 to 20 carbon atoms, or a substituted or unsubstituted aralkyl group

having 7 to 20 carbon atoms, R⁶ represents hydrogen, a substituted or unsubstituted alkyl group having 1 to 18 carbon atoms, a substituted or unsubstituted aryl group having 6 to 20 carbon atoms, or a substituted or unsubstituted aralkyl group having 5 7 to 20 carbon atoms, and *2 represents an asymmetric carbon atom, from an optically active benzylalcohol derivative represented by a general formula (1):



wherein Ar and R are as defined above, and *1 represents an asymmetric carbon atom, the following methods are reported:

10 1) a method for producing an optically active benzylamine derivative, in which a hydroxy group in an optically active benzylalcohol derivative is substituted with halogen such as chlorine and then the halogenated benzylalcohol derivative is

15 reacted with a nitrogen nucleophile (Non-Patent Document 1);

2) a method for producing an optically active benzylamine derivative, in which an optically active benzylalcohol derivative is reacted with diphenylphosphoryl azide and then the reactant is reduced (Non-Patent Documents 2 and 3);

20 3) a method for producing an optically active benzylamine

derivative, in which an optically active benzylalcohol derivative is sulfonylated and then the resulting compound is reacted with a nitrogen nucleophile (Patent Document 1);

4) a method for producing an optically active benzylamine

derivative, in which an optically active benzylalcohol derivative is reacted with a nitrogen nucleophile in the presence of an azodicarbonyl compound (Non-Patent Document 4); and the like.

Patent Document 1: Japanese Patent Application Laid-Open

(JP-A) No. 2002-30048

Non-Patent Document 1: Journal of Organic Chemistry, 1998,

63, 6273

Non-Patent Document 2: Journal of Organic Chemistry, 1996,

61, 3561

Non-Patent Document 3: Tetrahedron Asymmetry, 1996, 7,

2809

Non-Patent Document 4: Journal of Organic Chemistry, 1990,

55, 215

DISCLOSURE OF THE INVENTION

PROBLEMS TO BE SOLVED BY THE INVENTION

However, in the method 1), it has been known that a partial racemization takes place in the nucleophilic substitution reaction at a benzylic position because a SN1 type substitution reaction competes with a SN2 type substitution reaction due to

an involvement of a stabilized benzyl cation. Therefore, it is difficult to produce an optically active benzylamine derivative with high optical purity.

In the method 2), because a nitrogen nucleophilic species
5 is azide even though a substitution reaction proceeds in a high asymmetric transfer ratio, in order to produce optically active N-alkylbenzylamine, optically active N-arylbenzylamine, or optically active N-aralkylbenzylamine, it is necessary to perform N-alkylation, N-arylation, or N-aralkylation after
10 reduction of the obtained optically active azide compound. Therefore, the number of steps increases and the operation becomes complicated. Further, it is difficult to obtain an intended substance in a high yield by a monoalkylation reaction of amine because of the generation of byproducts of tertiary
15 amine and/or a quaternary ammonium salt, which is a general problem of the reaction. Furthermore, a handling of an azide compound with an explosion risk is a problematic procedure in terms of both safety and facility in industrial production.

Also, in the method 3), because of nucleophilic
20 substitution at a benzylic position, it is difficult to obtain an optically active benzylamine derivative with high optical purity. The racemization is relatively suppressed in the production method described in Patent Document 1. However, amine that can be produced by the substitution reaction and then
25 deprotection is limited to primary amine because a nitrogen

nucleophile that can be used is limited to benzylamine, allylamine, benzylcarbamate, hydroxylamine, phthalimide potassium, sodium azide, and the like. Therefore, in order to synthesize secondary amine, there is a problem that the number of processes increases and the operation becomes complicated, since it is necessary to perform the substitution reaction, a deprotection operation, and then N-alkylation, N-arylation, or N-aralkylation. Further, in the monoalkylation reaction of amine, tertiary amine and/or a quaternary ammonium salt are generally produced as byproducts, and it is difficult to obtain an intended substance in high yield.

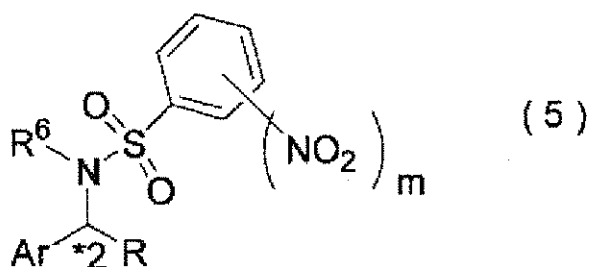
In the method 4), it is generally known that a reaction proceeds in a very high asymmetric transfer ratio. However, a nitrogen nucleophile that can be used is limited, and only compounds with low acidity, such as imide, e.g., phthalimide, and diacylamine, can be generally used. In the case of using imide or diacylamine as a nitrogen nucleophile, since the direct synthesis of N-alkyl, N-aryl, or N-aralkylamine is impossible, it is necessary to perform N-alkylation, N-arylation, or N-aralkylation after deprotection, and thus the number of processes increases and the operation becomes complicated. Further, a method of using hydrazine with a high toxicity, or a method of heating under a severe acid condition or alkaline condition is known as a deprotection condition. However, the former has a problem of toxicity, and the latter has a problem

of decomposition of a substrate in the case that the substrate has other functional groups.

MEANS FOR SOLVING THE PROBLEMS

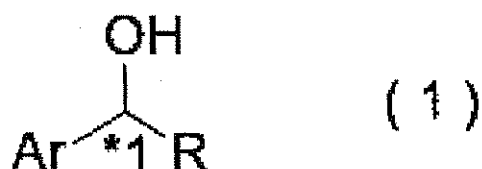
5 In view of the above circumstances, as a result of eager investigation of the reaction of an optically active benzylalcohol derivative with a nitrogen nucleophile with regard to a method for producing an optically active benzylamine, a production method as described below has been found.

10 That is, the present invention relates to a method for producing an optically active benzylsulfonylamide derivative represented by a general formula (5):

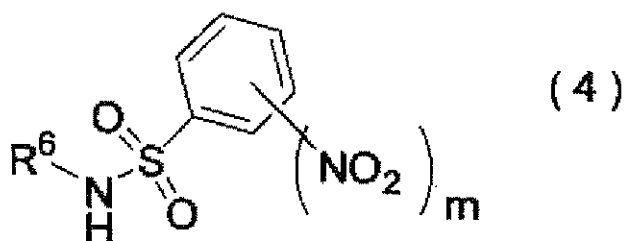


wherein Ar represents a substituted or unsubstituted aryl group
15 having 6 to 20 carbon atoms or a substituted or unsubstituted heteroaromatic group having 4 to 20 carbon atoms, R represents a substituted or unsubstituted alkyl group having 1 to 18 carbon atoms, a substituted or unsubstituted aryl group having 6 to 20 carbon atoms, or a substituted or unsubstituted aralkyl group
20 having 7 to 20 carbon atoms, R^6 represents hydrogen, a substituted

or unsubstituted alkyl group having 1 to 18 carbon atoms, a substituted or unsubstituted aryl group having 6 to 20 carbon atoms, or a substituted or unsubstituted aralkyl group having 7 to 20 carbon atoms, m represents an integer of 1 to 3, and *2 represents an asymmetric carbon atom, characterized by reacting an optically active benzylalcohol derivative represented by a general formula (1):

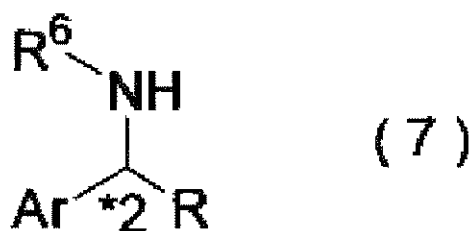


wherein Ar and R are as defined above, and *1 represents an asymmetric carbon atom, with a sulfonylamide derivative represented by a general formula (4):



wherein R⁶ is as defined above, and m is as defined above.

Further, the present invention relates to a method for producing an optically active benzylamine derivative represented by a general formula (7):



wherein Ar represents a substituted or unsubstituted aryl group having 6 to 20 carbon atoms or a substituted or unsubstituted heteroaromatic group having 4 to 20 carbon atoms, R represents
 5 a substituted or unsubstituted alkyl group having 1 to 18 carbon atoms, a substituted or unsubstituted aryl group having 6 to 20 carbon atoms, or a substituted or unsubstituted aralkyl group having 7 to 20 carbon atoms, R^6 represents hydrogen, a substituted or unsubstituted alkyl group having 1 to 18 carbon atoms, a
 10 substituted or unsubstituted aryl group having 6 to 20 carbon atoms, or a substituted or unsubstituted aralkyl group having 7 to 20 carbon atoms, and *2 represents an asymmetric carbon atom, characterized by reacting the optically active
 benzylsulfonylamide derivative represented by the general
 15 formula (5) with a thiol derivative represented by a general formula (6):

R^7SM (6)

20 wherein R^7 represents hydrogen, a substituted or unsubstituted alkyl group having 1 to 18 carbon atoms, a substituted or

unsubstituted aryl group having 6 to 20 carbon atoms, or a substituted or unsubstituted aralkyl group having 7 to 20 carbon atoms, and M represents hydrogen, an alkali metal or an alkaline earth metal.

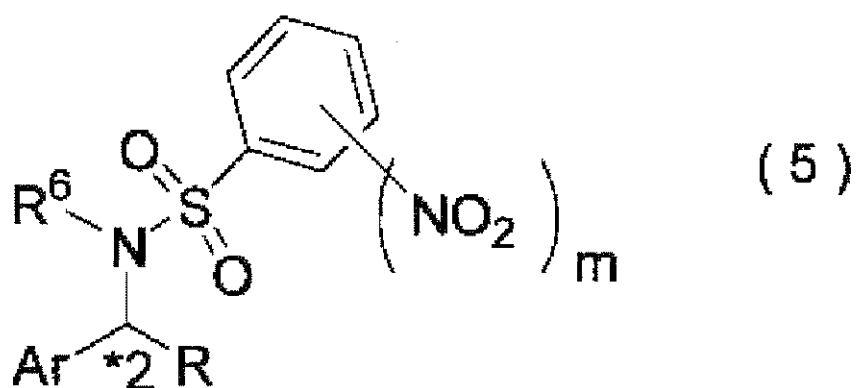
5 Further, the present invention relates to the optically active benzylsulfonylamide derivative represented by the general formula (5).

EFFECT OF THE INVENTION

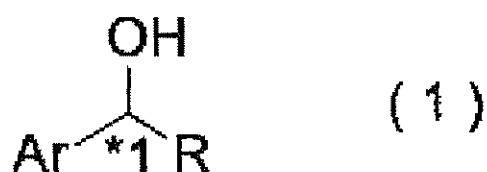
10 According to the present invention, the production of an optically active benzylamine derivative in a very high asymmetric transfer ratio becomes possible. Further, according to the present invention, optically active N-alkylbenzylamine, optically active N-arylbenzylamine, and optically active
15 N-aralkylbenzylamine are easily prepared by a simple and short process.

BEST MODE FOR CARRYING OUT THE INVENTION

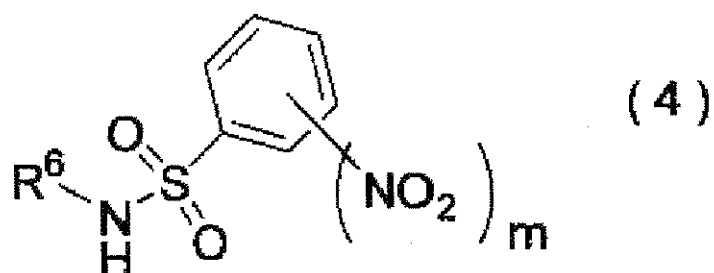
 First, a step for producing an optically active
20 benzylsulfonylamide derivative represented by the general formula (5):



by reacting an optically active benzylalcohol derivative represented by the general formula (1):



5 with an optically active benzylsulfonylamide derivative represented by the general formula (4):



is described.

In the present description, the number of carbon atoms
 10 does not include the number of carbon atoms in substitutional

groups. Examples of the substituents of an alkyl group, an aryl group, an aralkyl group, an alkoxy group, an aryloxy group, and an aralkyloxy group, as described below, include an alkyl group, an aryl group, an aralkyl group, an oxy group, an alkoxy group, a nitro group, a thio group, an amino group, a carbonyl group, a nitrile group, a sulfonyl group, halogen, and the like. Further, "2-, 3-, or 4-methyl substituted phenyl group" in the present description represents, for example, a 2-methylphenyl group, a 3-methylphenyl group, or a 4-methylphenyl group.

In the general formulae (1) and (5), Ar represents a substituted or unsubstituted aryl group having 6 to 20 carbon atoms or a substituted or unsubstituted heteroaromatic group having 4 to 20 carbon atoms.

Specific examples of the substituted or unsubstituted aryl group having 6 to 20 carbon atoms include alkyl substituted phenyl groups such as a phenyl group, a 2-, 3-, or 4-methyl substituted phenyl group, a 2,3-, 2,4-, 2,5-, 2,6-, 3,4-, or 3,5-dimethyl substituted phenyl group, a 2,3,4-, 2,3,5-, 2,3,6-, 2,4,5-, 2,4,6-, or 3,4,5-trimethyl substituted phenyl group, a 2-, 3-, or 4-ethyl substituted phenyl group, a 2,3-, 2,4-, 2,5-, 2,6-, 3,4-, or 3,5-diethyl substituted phenyl group, a 2,3,4-, 2,3,5-, 2,3,6-, 2,4,5-, 2,4,6-, or 3,4,5-triethyl substituted phenyl group, a 2-, 3-, or 4-propyl substituted phenyl group, a 2,3-, 2,4-, 2,5-, 2,6-, 3,4-, or 3,5-dipropyl substituted phenyl group, a 2,3,4-, 2,3,5-, 2,3,6-, 2,4,5-, 2,4,6-, or 3,4,5-tripropyl

substituted phenyl group, a 2-, 3-, or 4-isopropyl substituted phenyl group, a 2,3-, 2,4-, 2,5-, 2,6-, 3,4-, or 3,5-diisopropyl substituted phenyl group, a 2,3,4-, 2,3,5-, 2,3,6-, 2,4,5-, 2,4,6-, or 3,4,5-triisopropyl substituted phenyl group, a 2-, 3-, or 4-butyl substituted phenyl group, a 2,3-, 2,4-, 2,5-, 2,6-, 3,4-, or 3,5-dibutyl substituted phenyl group, a 2,3,4-, 2,3,5-, 2,3,6-, 2,4,5-, 2,4,6-, or 3,4,5-tributyl substituted phenyl group, a 2-, 3-, or 4-isobutyl substituted phenyl group, a 2,3-, 2,4-, 2,5-, 2,6-, 3,4-, or 3,5-diisobutyl substituted phenyl group, a 2,3,4-, 2,3,5-, 2,3,6-, 2,4,5-, 2,4,6-, or 3,4,5-triisobutyl substituted phenyl group, a 2-, 3-, or 4-octyl substituted phenyl group, a 2,3-, 2,4-, 2,5-, 2,6-, 3,4-, or 3,5-dioctyl substituted phenyl group, a 2,3,4-, 2,3,5-, 2,3,6-, 2,4,5-, 2,4,6-, or 3,4,5-trioctyl substituted phenyl group, a 2-, 3-, or 4-dodecyl substituted phenyl group, a 2,3-, 2,4-, 2,5-, 2,6-, 3,4-, or 3,5-didodecyl substituted phenyl group, a 2,3,4-, 2,3,5-, 2,3,6-, 2,4,5-, 2,4,6-, or 3,4,5-tridodecyl substituted phenyl group, a 2-, 3-, or 4-trifluoromethyl substituted phenyl group, a 2,3-bis(trifluoromethyl) phenyl group, a 2,4-, 2,5-, 2,6-, 3,4-, or 3,5-bis(trifluoromethyl) substituted phenyl group, a 2,3,4-tris(trifluoromethyl) phenyl group, a 2,3,5-, 2,3,6-, 2,4,5-, 2,4,6-, or 3,4,5-tris(trifluoromethyl) substituted phenyl group, a 2-, 3-, or 4-trifluoroethyl substituted phenyl group, a 2,3-, 2,4-, 2,5-, 2,6-, 3,4-, or 3,5-bis(trifluoroethyl) substituted phenyl group,

and a 2,3,4-, 2,3,5-, 2,3,6-, 2,4,5-, 2,4,6-, or
3,4,5-tris(trifluoroethyl) substituted phenyl group; an oxygen
atom substituted phenyl group such as a 2-, 3-, or 4-hydroxy
substituted phenyl group, a 2,3-, 2,4-, 2,5-, 2,6-, 3,4-, or
5 3,5-dihydroxy substituted phenyl group, and a 2,3,4-, 2,3,5-,
2,3,6-, 2,4,5-, 2,4,6-, or 3,4,5-trihydroxy substituted phenyl
group, a 2-, 3-, or 4-methoxy substituted phenyl group, a
2,3-dimethoxy phenyl group, a 2,4-, 2,5-, 2,6-, 3,4-, or
3,5-dimethoxy substituted phenyl group, and a 2,3,4-, 2,3,5-,
10 2,3,6-, 2,4,5-, 2,4,6-, or 3,4,5-trimethoxy substituted phenyl
group, a 2-, 3-, or 4-ethoxy substituted phenyl group, a 2,3-,
2,4-, 2,5-, 2,6-, 3,4-, or 3,5-diethoxy substituted phenyl group,
and a 2,3,4-, 2,3,5-, 2,3,6-, 2,4,5-, 2,4,6-, or 3,4,5-triethoxy
substituted phenyl group, a 2-, 3-, or 4-butoxy substituted
15 phenyl group, a 2,3-, 2,4-, 2,5-, 2,6-, 3,4-, or 3,5-dibutoxy
substituted phenyl group, and a 2,3,4-, 2,3,5-, 2,3,6-, 2,4,5-,
2,4,6-, or 3,4,5-tributoxy substituted phenyl group, a 2-, 3-,
or 4-octoxy substituted phenyl group, a 2,3-, 2,4-, 2,5-, 2,6-,
3,4-, or 3,5-dioctoxy substituted phenyl group, and a 2,3,4-,
20 2,3,5-, 2,3,6-, 2,4,5-, 2,4,6-, or 3,4,5-trioctoxy substituted
phenyl group, a 2-, 3-, or 4-trifluoromethoxy substituted phenyl
group, a 2,3-, 2,4-, 2,5-, 2,6-, 3,4-, or
3,5-bis(trifluoromethoxy) substituted phenyl group, and a
2,3,4-, 2,3,5-, 2,3,6-, 2,4,5-, 2,4,6-, or
25 3,4,5-tris(trifluoromethoxy) substituted phenyl group;

a sulfur substituted phenyl group such as a 2-, 3-, or 4-(methylthio) substituted phenyl group, a 2,3-, 2,4-, 2,5-, 2,6-, 3,4-, or 3,5-bis(methylthio) substituted phenyl group, and a 2,3,4-, 2,3,5-, 2,3,6-, 2,4,5-, 2,4,6-, or 3,4,5-tris(methylthio) substituted phenyl group, a 2-, 3-, or 4-(ethylthio) substituted phenyl group, a 2,3-, 2,4-, 2,5-, 2,6-, 3,4-, or 3,5-bis(ethylthio) substituted phenyl group, and a 2,3,4-, 2,3,5-, 2,3,6-, 2,4,5-, 2,4,6-, or 3,4,5-tris(ethylthio) substituted phenyl group, a 2-, 3-, or 4-(octylthio) substituted phenyl group, a 2,3-, 2,4-, 2,5-, 2,6-, 3,4-, or 3,5-bis(octylthio) substituted phenyl group, and a 2,3,4-, 2,3,5-, 2,3,6-, 2,4,5-, 2,4,6-, or 3,4,5-tris(octylthio) substituted phenyl group; an amino substituted phenyl group such as a 2-, 3-, or 4-amino substituted phenyl group, a 2,3-, 2,4-, 2,5-, 2,6-, 3,4-, or 3,5-diamino substituted phenyl group, and a 2,3,4-, 2,3,5-, 2,3,6-, 2,4,5-, 2,4,6-, or 3,4,5-triamino substituted phenyl group, a 2-, 3-, or 4-(N-methylamino) substituted phenyl group, a 2,3-, 2,4-, 2,5-, 2,6-, 3,4-, or 3,5-bis(N-methylamino) substituted phenyl group, and a 2,3,4-, 2,3,5-, 2,3,6-, 2,4,5-, 2,4,6-, or 3,4,5-tris(N-methylamino) substituted phenyl group, a 2-, 3-, or 4-(N-ethylamino) substituted phenyl group, a 2,3-, 2,4-, 2,5-, 2,6-, 3,4-, or 3,5-bis(N-ethylamino) substituted phenyl group, and a 2,3,4-, 2,3,5-, 2,3,6-, 2,4,5-, 2,4,6-, or 3,4,5-tris(N-ethylamino) substituted phenyl group, a 2-, 3-,

or 4-(N,N-dimethylamino) substituted phenyl group, a 2,3-, 2,4-, 2,5-, 2,6-, 3,4-, or 3,5-bis(N,N-dimethylamino) substituted phenyl group, and a 2,3,4-, 2,3,5-, 2,3,6-, 2,4,5-, 2,4,6-, or 3,4,5-tris(N,N-dimethylamino) substituted phenyl group, a 2-, 3-, or 4-(N,N-dibutylamino) substituted phenyl group, a 2,3-, 2,4-, 2,5-, 2,6-, 3,4-, or 3,5-bis(N,N-dibutylamino) substituted phenyl group, and a 2,3,4-, 2,3,5-, 2,3,6-, 2,4,5-, 2,4,6-, or 3,4,5-tris(N,N-dibutylamino) substituted phenyl group; a halogen substituted phenyl group such as a 2-, 3-, or 4-chloro-substituted phenyl group, a 2,3-, 2,4-, 2,5-, 2,6-, 3,4-, or 3,5-dichloro-substituted phenyl group, and a 2,3,4-, 2,3,5-, 2,3,6-, 2,4,5-, 2,4,6-, or 3,4,5-trichloro-substituted phenyl group, a 2-, 3-, or 4-bromo-substituted phenyl group, a 2,3-, 2,4-, 2,5-, 2,6-, 3,4-, or 3,5-dibromo-substituted phenyl group, and a 2,3,4-, 2,3,5-, 2,3,6-, 2,4,5-, 2,4,6-, or 3,4,5-tribromo-substituted phenyl group, a 2-, 3-, or 4-fluoro-substituted phenyl group, a 2,3-, 2,4-, 2,5-, 2,6-, 3,4-, or 3,5-difluoro-substituted phenyl group, and a 2,3,4-, 2,3,5-, 2,3,6-, 2,4,5-, 2,4,6-, or 3,4,5-trifluoro-substituted phenyl group; and an aryl substituted phenyl group such as a 2-, 3-, or 4-phenyl substituted phenyl group, a 2,3-, 2,4-, 2,5-, 2,6-, 3,4-, or 3,5-diphenyl substituted phenyl group, and a 2,3,4-, 2,3,5-, 2,3,6-, 2,4,5-, 2,4,6-, or 3,4,5-triphenyl substituted phenyl group, a 2-, 3-, or 4-(2-chlorophenyl) substituted phenyl group, a 2,3-, 2,4-, 2,5-, 2,6-, 3,4-, or

3,5-bis(2-chlorophenyl) substituted phenyl group, and a 2,3,4-, 2,3,5-, 2,3,6-, 2,4,5-, 2,4,6-, or 3,4,5-tris(2-chlorophenyl) substituted phenyl group.

Specific examples of the substituted or unsubstituted
5 heteroaromatic group include a 2-furyl group, a 3-furyl group, a 3-, 4-, or 5-methyl substituted-2-furyl group, a 2-, 4-, or 5-methyl substituted-3-furyl group, a 3-, or 5-ethyl substituted-2-furyl group, a 3-, or 5-phenyl substituted-2-furyl group, a 2-thienyl group, a 3-thienyl group,
10 a 3-, 4-, or 5-methyl substituted-2-thienyl group, a 2-, 4-, or 5-methyl substituted-3-thienyl group, a 3-, or 5-ethyl substituted-2-thienyl group, a 3-, or 5-phenyl substituted-2-thienyl group, a 2-pyrrolyl group, a 3-pyrrolyl group, a 3-, 4-, or 5-methyl substituted-2-pyrrolyl group, a
15 2-, 4-, or 5-methyl substituted-3-pyrrolyl group, a 3-, or 5-ethyl substituted-2-pyrrolyl group, a 3-, or 5-phenyl substituted-2-pyrrolyl group, a 2-pyridyl group, a 3-pyridyl group, a 4-pyridyl group, a 3-, 4-, 5- or 6-methyl substituted-2-pyridyl group, a 2-, 4-, 5-, or 6-methyl
20 substituted-3-pyridyl group, a 3-, or 5-ethyl substituted-2-pyridyl group, a 3-, or 5-phenyl substituted-2-pyridyl group, a 2-imidazole group, a 4- or 5-methyl substituted-2-imidazole group, a 3-isothiazolyl group, a 4-isothiazolyl group, a 5-isothiazolyl group, a 4- or 5-methyl
25 substituted-3-isothiazolyl group, a 3-methyl-4-isothiazolyl

group, a 5-phenyl-3-isothiazolyl group, a 2-indoyl group, a 3-indoyl group, a 4-methyl-2-indoyl group, and a 7-methyl-4-indoyl group.

Among these, Ar is preferably a substituted or
5 unsubstituted aryl group having 6 to 20 carbon atoms, more preferably a phenyl group substituted with one to three trifluoromethyl groups, fluoro groups, or trifluoromethoxy groups, and especially preferably a phenyl group substituted with one to three trifluoromethyl groups. Specific examples
10 include a 2-, 3-, or 4-trifluoromethyl substituted phenyl group, a 2,3-, 2,4-, 2,5-, 2,6-, 3,4-, or 3,5-bis(trifluoromethyl) substituted phenyl group, and a 2,3,4-, 2,3,5-, 2,3,6-, 2,4,5-, 2,4,6-, or 3,4,5-tris(trifluoromethyl) substituted phenyl group, and more preferably a 3,5-bis(trifluoromethyl) phenyl
15 group.

In the general formulae (1) and (5), R represents a substituted or unsubstituted alkyl group having 1 to 18 carbon atoms, a substituted or unsubstituted aryl group having 6 to 20 carbon atoms, or a substituted or unsubstituted aralkyl group
20 having 7 to 20 carbon atoms.

Examples of the substituted or unsubstituted alkyl group having 1 to 18 carbon atoms include a linear alkyl group such as a methyl group, an ethyl group, an n-propyl group, an isopropyl group, an n-butyl group, an isobutyl group, an s-butyl group,
25 a t-butyl group, an n-pentyl group, an isopentyl group, an

n-hexyl group, an n-octyl group, an n-dodecyl group, and a t-dodecyl group, and a cyclic alkyl group such as a cyclopropyl group, a cyclobutyl group, a cyclopentyl group, and a cyclohexyl group.

5 Examples of the substituted or unsubstituted aryl group having 6 to 20 carbon atoms include, for example, a phenyl group, a 1-naphthyl group, a 2-naphthyl group, a 2-methylphenyl group, a 3-methylphenyl group, a 4-methylphenyl group, a 2-ethylphenyl group, a 3-ethylphenyl group, a 4-ethylphenyl group, a
10 2-methoxyphenyl group, a 3-methoxyphenyl group, a 4-methoxyphenyl group, a 2-nitrophenyl group, a 4-phenylphenyl group, a 4-chlorophenyl group, a 4-bromophenyl group, a 4-fluorophenyl group, and the like.

 Examples of the substituted or unsubstituted aralkyl group
15 having 7 to 20 carbon atoms include, for example, a benzyl group, a 2-methylbenzyl group, a 3-methylbenzyl group, a 4-methylbenzyl group, a 2-methoxybenzyl group, a 3-ethoxybenzyl group, an 1-phenylethyl group, a 2-phenyl ethyl group, a 1-(4-methylphenyl)ethyl group, a 1-(4-methoxyphenyl)ethyl
20 group, a 3-phenylpropyl group, and a 2-phenylpropyl group.

Among these groups, an unsubstituted alkyl group is preferable, and a methyl group is more preferable.

*1 represents an asymmetric carbon atom. Its absolute configuration is not especially limited, and may be a (R)-isomer
25 or an (S)-isomer. However, the absolute configuration is

preferably an (S)-isomer. Further, *2 represents an asymmetric carbon atom. Its absolute configuration is not especially limited, and may be a (R)-isomer or an (S)-isomer. However, the absolute configuration is preferably a (R)-isomer. Because
5 the reaction in the present step proceeds with a stereo-inversion, a benzylsulfonylamide derivative of an (S)-isomer is produced from a benzylalcohol derivative of a (R)-isomer, and a benzylsulfonylamide derivative of a (R)-isomer is produced from a benzylalcohol derivative of an (S)-isomer.

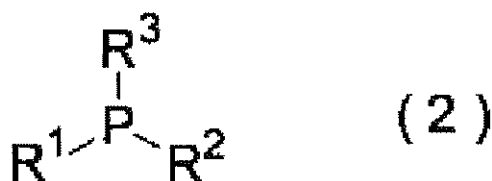
10 In the general formulae (4) and (5), R^6 represents hydrogen, a substituted or unsubstituted alkyl group having 1 to 18 carbon atoms, a substituted or unsubstituted aryl group having 6 to 20 carbon atoms, or a substituted or unsubstituted aralkyl group having 7 to 20 carbon atoms. Specific examples of the substituted
15 or unsubstituted alkyl group having 1 to 18 carbon atoms, the substituted or unsubstituted aryl group having 6 to 20 carbon atoms, or the substituted or unsubstituted aralkyl group having 7 to 20 carbon atoms include the groups described above. Among these groups, an unsubstituted alkyl group having 1 to 18 carbon
20 atoms is preferable as R^6 , and a methyl group and an ethyl group are more preferable.

In the general formulae (4) and (5), m represents an integer of 1 to 3. The substituted position by the nitro group is not especially limited. However, mono substitution at the
25 2-position, mono substitution at the 3-position, mono

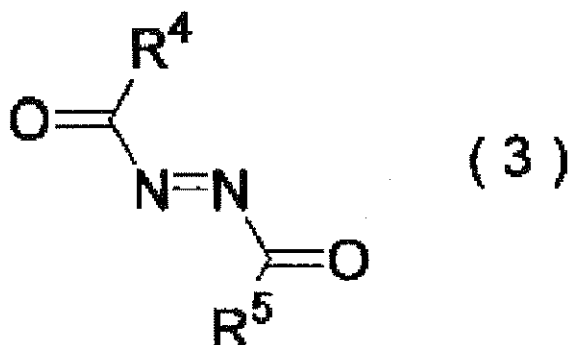
substitution at the 4-position, or di substitutions at the 2,4-positions is preferable. Specific examples of nitro group substituted phenyl group are a 2-nitrophenyl group, a 3-nitrophenyl group, a 4-nitrophenyl group, and a 2,4-dinitrophenyl group. More preferably, m is 1 and the nitro group substituted phenyl group is a 2-nitrophenyl group, a 3-nitrophenyl group, or a 4-nitrophenyl group.

The optically active benzylalcohol derivative (1) can be synthesized easily by asymmetric hydrogenation of the corresponding ketone according to Tetrahedron Asymmetry, 2003, 14, 3581 for example.

A conversion from the optically active benzylalcohol derivative (1) to the optically active benzylsulfonylamide derivative (5) can be performed in the presence of a phosphine derivative represented by a general formula (2):



and an azodicarbonyl compound represented by a general formula (3):



In the general formula (2), R^1 , R^2 , and R^3 are independent from each other, and may be the same or different. They represent a substituted or unsubstituted alkyl group having 1 to 18 carbon atoms, a substituted or unsubstituted aryl group having 6 to 20 carbon atoms, or a substituted or unsubstituted aralkyl group having 7 to 20 carbon atoms. Specific examples include the same groups as those exemplified by R. The derivative where all of R^1 , R^2 , and R^3 are a phenyl group or an n-butyl group is less expensive, low in toxicity, and more preferable.

In a general formula (3), R^4 and R^5 are independent from each other, and may be the same or different. They represent a substituted or unsubstituted alkoxy group having 1 to 18 carbon atoms, a substituted or unsubstituted aryloxy group having 6 to 20 carbon atoms, a substituted or unsubstituted aralkyloxy group having 7 to 20 carbon atoms, or a substituted or unsubstituted amino group.

Examples of the substituted or unsubstituted alkoxy group having 1 to 18 carbon atoms include a methoxy group, an ethoxy

group, an n-propoxy group, an isopropoxy group, an n-butoxy group, an isobutoxy group, an s-butoxy group, a t-butoxy group, an n-pentyloxy group, an isopentyloxy group, an n-hexyloxy group, an n-octyloxy group, an n-dodecyloxy group, a t-dodecyloxy group, and the like.

Examples of the substituted or unsubstituted aryloxy group having 6 to 20 carbon atoms include a phenyloxy group, an 1-naphthyloxy group, a 2-naphthyloxy group, a 2-methylphenyloxy group, a 3-methylphenyloxy group, a 4-methylphenyloxy group, a 2-ethylphenyloxy group, a 3-ethylphenyloxy group, a 4-ethylphenyloxy group, a 2-methoxyphenyloxy group, a 3-methoxyphenyloxy group, a 4-methoxyphenyloxy group, a 2-nitrophenyloxy group, a 4-phenylphenyloxy group, a 4-chlorophenyloxy group, a 4-bromophenyloxy group, a 4-fluorophenyloxy group, and the like.

Example of the substituted or unsubstituted aralkyloxy group having 7 to 20 carbon atoms include a benzyloxy group, a 2-methylbenzyloxy group, a 3-methylbenzyloxy group, a 4-methylbenzyloxy group, a 2-methoxybenzyloxy group, a 3-ethoxybenzyloxy group, a 1-phenylethyloxy group, a 2-phenylethyloxy group, a 1-(4-methylphenyl)ethyloxy group, a 1-(4-methoxyphenyl)ethyloxy group, a 3-phenylpropyloxy group, a 2-phenylpropyloxy group, and the like.

Examples of the substituted amino group include an amino group in which any of a substituted or unsubstituted alkyl group

having 1 to 18 carbon atoms, a substituted or unsubstituted aryl group having 6 to 20 carbon atoms, or a substituted or unsubstituted aralkyl group having 7 to 20 carbon atoms is mono-substituted or di-substituted independently. Specific
5 examples of these substituents of the amino group include the same groups exemplified by R.

Among these, compounds in which both R^4 and R^5 are preferably a methoxy group, an ethoxy group, an isopropyl group, or a benzyloxy group are preferable because they are industrially
10 easily available. Compound in which both R^4 and R^5 are an isopropoxy group are more preferable.

The used amount of the phosphine derivative (2) in the present step may be normally 1 equivalent or more to the optically active benzylalcohol derivative (1), preferably 1 to 10
15 equivalents, and more preferably 1 to 3 equivalents.

The used amount of the azodicarbonyl compound (3) in the present step may be normally 1 equivalent or more to the optically active benzylalcohol derivative (1), preferably 1 to 10
equivalents, and more preferably 1 to 3 equivalents.

20 The used amount of the sulfonylamide derivative (4) in the present step may be normally 1 equivalent or more to the optically active benzylalcohol derivative (1), preferably 1 to 10 equivalents, and more preferably 1 to 3 equivalents.

In the present step, the solvent used is not particularly
25 limited, and examples thereof include a non-protonic polar

solvent such as N,N-dimethylformamide (DMF), dimethylsulfoxide (DMSO), N-methylpyrrolidone, and hexamethylphosphoric triamide; a hydrocarbon solvent such as hexamethylbenzene, toluene, n-hexane, and cyclohexane; an ether solvent such as diethylether, tetrahydrofuran (THF), diisopropylether, methyltert-butylether, and dimethoxyethane; a halogen solvent such as chlorobenzene, methylene chloride, chloroform, and 1,1,1-trichloroethane; an ester solvent such as ethyl acetate and butyl acetate; a nitrile solvent such as acetonitrile and butyronitrile; alcohol such as methanol, ethanol, isopropanol, butanol, and octanol; water, and the like. These may be used alone or two or more kinds may be used in combination. Among these, tetrahydrofuran, toluene, and ethyl acetate are preferable, and toluene is more preferable.

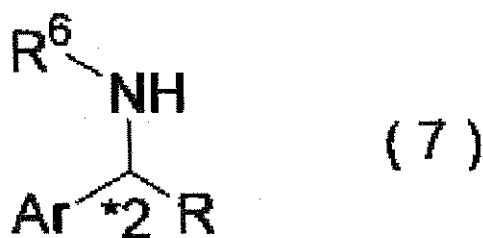
The reaction temperature is normally in the range of -50 to 110°C, and preferably -20 to 50°C.

In the present reaction, the addition order of the benzylalcohol derivative (1), the phosphine derivative (2), the azodicarbonyl compound (3), and the solvent is not especially limited.

A general work-up process may be performed in order to obtain a product from a reaction mixture after the reaction. For example, water is added to the reaction mixture after the reaction and an extraction operation is performed using a general extraction solvent such as ethyl acetate, diethylether,

methylene chloride, toluene, and hexane. The reaction solvent
 and the extraction solvent are distilled off from the obtained
 extraction liquid by an operation such as heating under reduced
 pressure, to obtain an intended compound. Further, the reaction
 5 solvent is distilled off by an operation such as heating under
 reduced pressure after the reaction, and then, the similar
 operation may be performed. In addition, a method, in which
 a hydrocarbon solvent such as hexane and heptane is added to
 the reaction mixture, in order to precipitate phosphine oxide
 10 produced as a byproduct, and then the precipitated solid is
 filtered off and the solvent is distilled off, may be performed.
 The intended compound obtained in such way is nearly pure.
 However, purity may be increased further by performing a general
 purification method such as crystallization purification,
 15 fractional distillation, and column chromatography.

Next, a step for producing an optically active benzylamine
 derivative represented by the general formula (7):



by reacting the optically active benzylsulfonylamide derivative
 20 represented by the general formula (5) with a thiol derivative
 represented by the general formula (6):

R⁷SM (6)

is described.

5 In the general formula (7), Ar, R, R⁶, and *2 are as defined above.

 In the general formula (6), R⁷ represents hydrogen, a substituted or unsubstituted alkyl group having 1 to 18 carbon atoms, a substituted or unsubstituted aryl group having 6 to
10 20 carbon atoms, or a substituted or unsubstituted aralkyl group having 7 to 20 carbon atoms. Specific examples include the same groups exemplified by R. Among these groups, unsubstituted alkyl group and a phenyl group is preferable, and a dodecyl group is more preferable.

15 Further, M represents hydrogen, an alkali metal such as lithium, sodium, potassium, and cesium, or an alkaline earth metal such as beryllium, magnesium, and calcium. Among these, hydrogen and an alkaline metal are preferable, and hydrogen, sodium, and potassium are more preferable.

20 The optically active benzylsulfonylamide derivative (5) may be used in a form of the reaction mixture obtained in the above-described process or in an isolated or purified form.

 The used amount of the thiol derivative (6) in the present step may be normally 1 equivalent or more to the optically active
25 benzylsulfonylamide derivative (5), preferably 1 to 10

equivalents, and more preferably 1 to 3 equivalents.

In the present step, a base may coexist. In the case that
Minthethiol derivative (6) is hydrogen, the reaction is promoted
by the coexistence of the base. Examples of the base used include
5 a metal hydroxide such as sodium hydroxide, potassium hydroxide,
lithium hydroxide, cesium hydroxide, magnesium hydroxide, and
calcium hydroxide, and carbonate such as sodium hydrogen
carbonate, sodium carbonate, potassium carbonate, calcium
carbonate, and magnesium carbonate. Among these bases, sodium
10 hydroxide, potassium hydroxide, cesium hydroxide, sodium
carbonate, and potassium carbonate are preferable, and sodium
hydroxide and potassium hydroxide are especially preferable.

These bases may be used without being modified. However,
especially in the case of using sodium hydroxide or potassium
15 hydroxide, an aqueous solution of 1 to 50% by weight is preferable,
and an aqueous solution of 5 to 30% by weight is more preferable.

The amount of the base used may be normally 1 equivalent
or more to the optically active benzylsulfonylamide derivative
(5), preferably 1 to 10 equivalents, and more preferably 1 to
20 5 equivalents.

The reaction temperature is normally in the range of -50
to 110°C, and preferably 0 to 110°C.

In the present step, the solvent used is not especially
limited, and specific examples thereof are the same solvents
25 given in the step for producing the optically active

benzylsulfonylamide derivative. Among these solvents, dimethylsulfoxide, N,N-dimethylformamide, acetonitrile, water, and toluene are preferable, and a two-layer system of water-toluene is more preferable.

5 In the present step, it is preferable that a phase transfer catalyst coexists because a reaction may be promoted. Examples of the phase transfer catalyst used include quaternary ammonium salts such as tetrabutylammonium chloride, tetrabutylammonium bromide, benzyltriethylammonium chloride,
10 benzyltriethylammonium bromide, trioctylmethylammonium chloride, and trioctylmethylammonium bromide, phosphonates such as tetrabutylphosphonium chloride, tetrabutylphosphonium bromide, tetraphenylphosphonium chloride, and tetraphenylphosphonium bromide, crown ether such as 15-crown-5
15 and 18-crown-6, and polyether such as polyethylene glycol. It is preferably quaternary ammonium salts, and more preferably tetrabutylammonium bromide.

The used amount of the phase transfer catalyst, when it coexists, is preferably 0.001 to 200 mol% to the optically active
20 benzylsulfonylamide derivative, and more preferably 0.01 to 100 mol%.

The addition order of the substrate, the catalyst, and the solvent in the present reaction is not especially limited.

After the reaction, a general work-up process may be
25 performed in order to obtain a product from the reaction mixture.

For example, water is added to the reaction mixture after the reaction and an extraction operation is performed using a general extraction solvent such as ethylacetate, diethylether, methylene chloride, toluene, and hexane. The reaction solvent and the extraction solvent are distilled off from the obtained extraction liquid by an operation such as a heating under reduced pressure, to obtain an intended compound. Further, the reaction solvent is distilled off by an operation such as a heating under reduced pressure after the reaction, and then, the same operation may be performed. The intended compound obtained in such way is nearly pure. However, purity may be increased further by performing purification by a general method such as crystallization purification, fractional distillation, and column chromatography.

Further, the optically active benzylsulfonylamide derivative (5) that can be produced effectively according to the present invention is a novel compound that has not been described in any documents as an optically active compound. The compound is invented with the above-described production method, and is developed to use as a pharmaceutical intermediate, as a result of the present inventors' investigation.

Ar, R, R⁶, m, and *2 in the optically active benzylsulfonylamide derivative (5) that is the compound in the present invention are as defined above.

Ar is preferably a phenyl group substituted with one to

three trifluoromethyl groups, fluoro groups, or trifluoromethoxy groups, and more preferably a phenyl group substituted with one to three trifluoromethyl groups. Specifically, it is a 2-, 3-, or 4-trifluoromethyl substituted phenyl group, 2,3-, 2,4-, 2,5-, 2,6-, 3,4-, or 3,5-bis(trifluoromethyl) substituted phenyl group, a 2,3,4-, 2,3,5-, 2,3,6-, 2,4,5-, 2,4,6-, or 3,4,5-tris(trifluoromethyl) substituted phenyl group. More preferably, it is a 3,5-bis(trifluoromethyl) phenyl group.

10 R is preferably unsubstituted alkyl group, and more preferably a methyl group.

R⁶ is preferably unsubstituted alkyl group, and more preferably, a methyl group and an ethyl group.

mispreferably 1 or 2. Monosubstitution at the 2-position, 15 mono substitution at the 3-position, mono substitution at the 4-position, and di substitutions at the 2,4-positions are more preferable. Specific examples of the nitro-substituted phenyl group are a 2-nitrophenyl group, a 3-nitrophenyl group, a 4-nitrophenyl group, and a 2,4-dinitrophenyl group. More 20 preferably, m is 1, and nitro-substituted phenyl group is a 2-nitrophenyl group, a 3-nitrophenyl group, or a 4-nitrophenyl group.

*2 may be an (R)-isomer or an (S)-isomer. However, it is preferably an (R)-isomer.

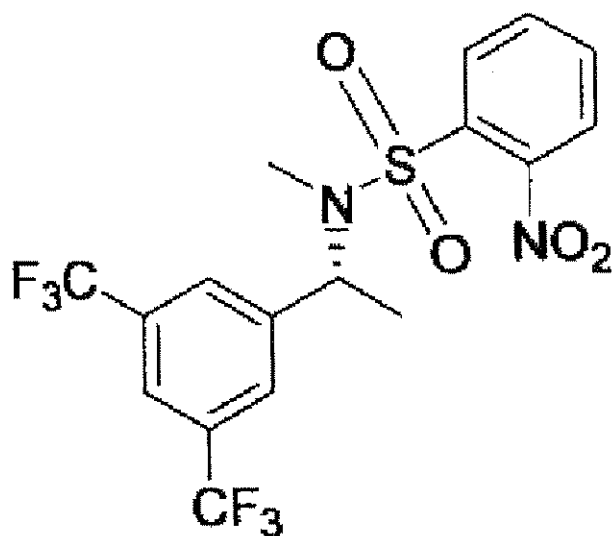
Examples

Hereinafter, the present invention is explained further in detail with reference to Examples. However, the present invention is not limited to these Examples.

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(Example 1)

A solution of diisopropylazodicarboxylate (4.64 mmol) in toluene (1.7 mL) was dropwise added to a suspension of α -methyl-3,5-bis(trifluoromethyl)benzylalcohol (3.87 mmol),
10 N-methyl-2-nitrobenzenesulfonylamide (3.87 mmol), and triphenylphosphine (4.64 mmol) in toluene (6 mL) at an internal temperature of 10 to 19°C. After completion of the dropwise addition, the resulting solution was stirred for 1 hour, hexane (3 mL) was added thereto, and then the mixture was stirred for
15 1 hour. The precipitated solid was filtered and a mother liquid was concentrated under reduced pressure, to obtain a crude product. As a result of comparison analysis to a standard with an HPLC, it was confirmed that 1.57 g of
(R)-N-methyl-N-[α -methyl-3,5-bis(trifluoromethyl)benzyl]-2-
20 nitrobenzenesulfonylamide represented by the following formula:



was contained (yield 89%). The obtained crude product was used in the next step without being purified further.

$^1\text{H-NMR}$ (400MHz, CDCl_3) δ 1.60 (3H, d), 2.73 (3H, s), 5.37-5.42 (1H, q),
 5 7.66-7.79 (6H, m), 8.05-8.07 (1H, m)

(Example 2)

A 3M aqueous sodium hydroxide solution (38.58 mmol, 12.9 mL) was added to a toluene (20 mL) mixture containing
 10 (R)-N-methyl-N-[α -methyl-3,5-bis(trifluoromethyl)benzyl]-2-nitrobenzenesulfonamide (12.95 mmol) obtained in Example 1, tetrabutylammonium bromide (1.30 mmol), and n-dodecanethiol (14.25 mmol), while controlling the internal temperature below
 25°C. After completion of the addition, the resulting solution
 15 was stirred for 1 hour at an internal temperature 20 to 25°C. Water (10 mL) was added to the reaction mixture, and an organic

phase was obtained with a liquid separation operation. pH in the system was adjusted to be 1.8 (at an internal temperature of 25°C) by adding water (30 mL) and adding concentrated hydrochloric acid to the obtained organic phase, and an aqueous phase was obtained with a liquid separation operation. pH in the system was adjusted to be 8.0 (at an internal temperature of 23°C) by adding ethyl acetate (30 mL) into the obtained aqueous phase and further adding a 30 wt% aqueous sodium hydroxide solution, and an organic phase was obtained with a liquid separation operation. The obtained organic phase was heated and concentrated under reduced pressure, to obtain 2.76 g of (R)-N-methyl-1-[3,5-bis(trifluoromethyl)phenyl]ethylamine. The yield was 79%. The optical purity of the crude product was 99.7%ee, the asymmetric transfer ratio by the 2 steps was 99.7%, and the substitution reaction with a nitrogen nucleophile proceeded with an inversion.

The asymmetric transfer ratio can be calculated with the following formula.

Asymmetric transfer ratio (%) = (Optical Purity (%ee) of Reaction Product / Optical Purity (%ee) of Reaction Substrate (Raw Material)) X 100

(Example 3)

A suspension containing (R)-N-methyl-N-[α-methyl-3,5-bis(trifluoromethyl)benzyl]-2-

nitrobenzenesulfonylamide (0.66 mmol) obtained in Example 1, benzenethiol (0.79 mmol), potassium carbonate (1.98 mmol), and dimethylformamide (DMF) (3 mL) was stirred for 2 hours at an internal temperature of 24°C. Toluene (15 mL) and water (5 mL) were added to the reaction mixture, and an organic phase was obtained with a liquid separation operation. pH in the system was adjusted to be 1.7 (at an internal temperature of 23°C) by adding water (10 mL) and adding concentrated hydrochloric acid to the obtained organic phase, and then an aqueous phase was obtained with a liquid separation operation. As a result of comparison analysis of the obtained aqueous phase to a standard with an HPLC, it was confirmed that 158 mg of (R)-N-methyl-1-[3,5-bis(trifluoromethyl)phenyl]ethylamine was obtained. The yield was 89%. The optical purity of the crude product was 99.5%ee, the asymmetric transfer ratio in the 2 steps was 99.5%, and the substitution reaction with a nitrogen nucleophile proceeded with an inversion.

(Example 4)

A solution of n-dodecanethiol (3.86 mmol) in DMSO (1 mL) was added to a suspension containing (R)-N-methyl-N-[α -methyl-3,5-bis(trifluoromethyl)benzyl]-2-nitrobenzenesulfonylamide (3.51 mmol) obtained in Example 1, lithium hydroxide-hydrate (10.52 mmol), and dimethylsulfoxide (DMSO) (3 mL) at an internal temperature of 27 to 31°C. After

completion of the addition, the resulting mixture was stirred for 3 hours. Toluene (21 mL) and water (13 mL) were added to the reaction mixture, and an organic phase was obtained with a liquid separation operation. pH in the system was adjusted to be 1.9 (at an internal temperature of 23°C) by adding water (20 mL) and adding concentrated hydrochloric acid to the obtained organic phase, and then an aqueous phase was obtained with a liquid separation operation. As a result of comparison analysis of the obtained aqueous phase to a standard with an HPLC, it was confirmed that 857 mg of (R)-N-methyl-1-[3,5-bis(trifluoromethyl)phenyl]ethylamine was contained. The yield was 90%. The optical purity of the crude product was 99.5%ee, the asymmetric transfer ratio in the 2 steps was 99.5%, and the substitution reaction with a nitrogen nucleophile proceeded with an inversion.

(Example 5)

A solution of diisopropylazodicarboxylate (6.06 mmol) in toluene (1.0 mL) was dropwise added to a suspension of (S)-1-phenyl-1-propanol (4.04 mmol) (96.3%ee), N-benzyl-2-nitrobenzenesulfonamide (4.45 mmol), and triphenylphosphine (6.06 mmol) in toluene (5 mL) while the internal temperature was kept at -3°C. After completion of the dropwise addition, the resulting mixture was stirred for 1 hour, hexane (2.5 mL) was added to the mixture, and the mixture was

stirred further for 1 hour. The precipitated solid was filtered off and a mother liquid was concentrated under reduced pressure, to obtain a crude product. As a result of comparison analysis to a standard with an HPLC, it was confirmed that 1.55 g of
5 (R)-N-benzyl-N-(1-phenylpropyl)-2-nitrobenzenesulfoneamide was contained (yield 94%). The obtained crude product was used in the next step without being purified further.

$^1\text{H-NMR}$ (400MHz, CDCl_3) δ 0.78 (3H, t), 1.88-1.95 (2H, m), 4.37 (2H, dd), 4.97-5.00 (1H, m), 7.12-7.62 (14H, m)

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(Example 6)

(R)-N-benzyl-N-(1-phenylpropyl)-2-nitrobenzenesulfone amide (3.79 mmol) obtained in Example 5, tetrabutylammonium bromide (0.38 mmol), a 1M aqueous sodium hydroxide solution
15 (11.37 mmol, 11.4 mL), and toluene (12 mL) were mixed, and n-dodecanethiol (5.68 mmol) was added to the mixture at an internal temperature of 30 to 35°C. After completion of the addition, the resulting mixture was stirred for 4 hours at the same temperature, and an organic phase was obtained with a liquid
20 separation operation. pH in the system was adjusted to be 1.7 (at an internal temperature of 27°C) by adding water (15 mL) and adding concentrated hydrochloric acid to the obtained organic phase, and an aqueous phase was obtained with a liquid separation operation. pH in the system was adjusted to be 9.7 (at an internal
25 temperature of 23°C) by adding a 30wt% aqueous sodium hydroxide

solution to the obtained aqueous phase. Then, after the addition of ethyl acetate (20 mL), an organic phase was obtained with a liquid separation operation. The obtained organic phase was heated and concentrated under reduced pressure, to obtain 0.62 g of (R)-N-benzyl-1-phenylpropylamine. The yield was 64%. The optical purity of the product was 90.0%ee, the asymmetric transfer ratio in the 2 steps was 93.5%, and the substitution reaction by a nitrogen nucleophile proceeded with an inversion.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 0.80 (3H, t), 1.59–1.80 (3H, m),

3.46–3.66 (3H, m), 7.21–7.36 (10H, m)

(Example 7)

A solution of diisopropylazocarboxylate (6.06 mmol) in toluene (1.0 mL) was dropwise added to a toluene (5 mL) suspension containing (S)-1,2-diphenylethanol (4.04 mmol) (96.6%ee), N-ethyl-2-nitrobenzenesulfonamide (4.45 mmol), and triphenylphosphine (6.06 mmol), while the internal temperature was kept at -3°C . After completion of the dropwise addition, the resulting mixture was stirred for 19 hours, and then water (10.0 mL) was added to the mixture. The reaction mixture was extracted with toluene (20.0 mL), and then was washed with a saturated sodium chloride solution. The obtained extraction liquid was used in the next step without being purified further. As a result of comparison analysis to a standard with an HPLC, it was confirmed that 0.61 g of

(R)-N-ethyl-N-(1,2-diphenylethyl)-2-nitrobenzenesulfonamide was contained (yield 37%).

¹H-NMR (400 MHz, CDCl₃) δ 0.97 (3H, t), 3.26-3.47 (4H, m), 5.37-5.41 (1H, m), 7.05-7.64 (14H, m)

5

(Example 8)

n-dodecanethiol (2.23 mmol) was added to a suspension containing a toluene mixture (18 mL) of (R)-N-ethyl-N-(1,2-diphenylethyl)-2-nitrobenzenesulfonamide (1.49 mmol) obtained in Example 7, tetrabutylammonium bromide (0.15 mmol), and a 1M aqueous sodium hydroxide solution (4.47 mmol, 4.5 mL) at an internal temperature of 30 to 35°C. After completion of the addition, the resulting mixture was stirred for 18 hours at the same temperature, and an organic phase was obtained with a liquid separation operation. pH in the system was adjusted to be 0.6 (at an internal temperature of 27°C) by adding water (15 mL) and adding concentrated hydrochloric acid to the obtained organic phase. Thereafter, an aqueous phase was obtained with a liquid separation operation. pH in the system was adjusted to be 9.7 (at an internal temperature of 23°C) by adding a 30wt% aqueous sodium hydroxide solution to the obtained aqueous phase. Then, after the addition of ethyl acetate (20 mL), an organic phase was obtained with a liquid separation operation. The obtained organic phase was heated and concentrated under reduced pressure, to obtain 0.33 g of

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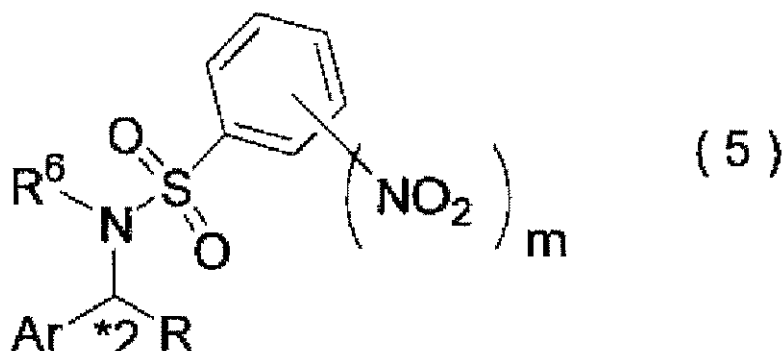
(R)-N-ethyl-1,2-diphenylethylamine. The yield was 83%. The optical purity of the product was 93.6%ee, the asymmetric transfer ratio in the 2 steps was 96.9%, and the substitution reaction by a nitrogen nucleophile proceeded with an inversion.

5 $^1\text{H-NMR}$ (400MHz, CDCl_3) δ 0.97 (3H, d), 1.51 (1H, br), 2.35-2.50 (2H, m), 2.87-2.96 (2H, m), 3.83-3.87 (1H, m), 7.16-7.32 (10H, m)

CLAIMS

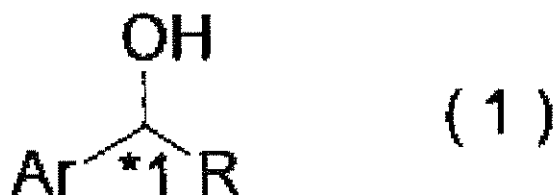
1. A method for producing an optically active
benzylsulfonylamide derivative represented by a general formula

5 (5):

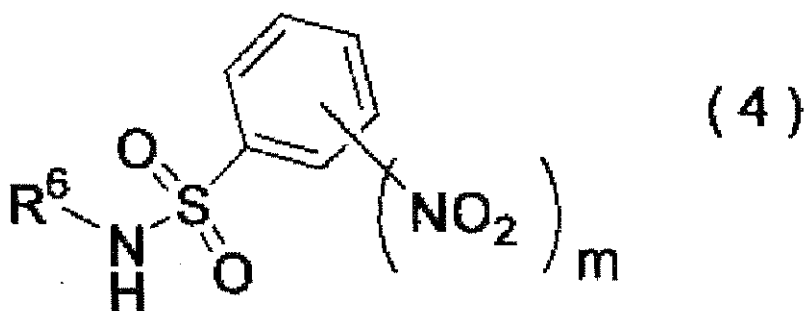


wherein Ar represents a substituted or unsubstituted aryl group
having 6 to 20 carbon atoms or a substituted or unsubstituted
heteroaromatic group having 4 to 20 carbon atoms, R represents
10 a substituted or unsubstituted alkyl group having 1 to 18 carbon
atoms, a substituted or unsubstituted aryl group having 6 to
20 carbon atoms, or a substituted or unsubstituted aralkyl group
having 7 to 20 carbon atoms, R^6 represents hydrogen, a substituted
or unsubstituted alkyl group having 1 to 18 carbon atoms, a
15 substituted or unsubstituted aryl group having 6 to 20 carbon
atoms, or a substituted or unsubstituted aralkyl group having
7 to 20 carbon atoms, m represents an integer of 1 to 3, and
*2 represents an asymmetric carbon atom,
comprising reacting an optically active benzylalcohol

derivative represented by a general formula (1):

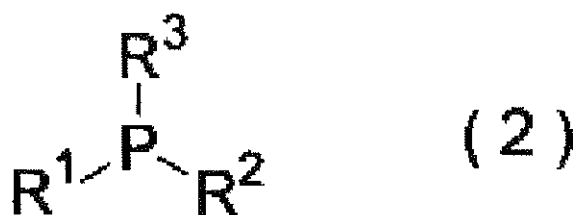


wherein Ar and R are as defined above, and *1 represents an
asymmetric carbon atom, with a sulfonylamide derivative
5 represented by a general formula (4):

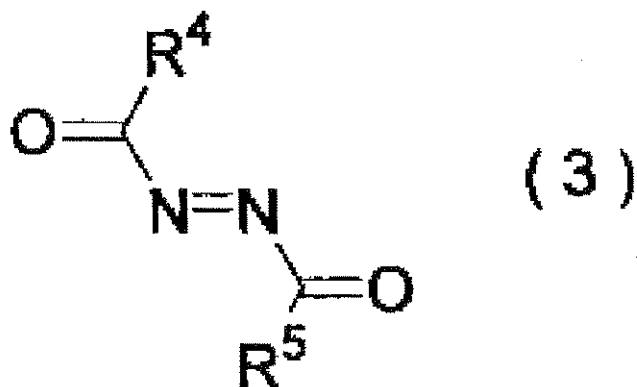


wherein R^6 and m are as defined above.

2. The production method according to Claim 1, wherein
10 the reaction is performed in the presence of a phosphine
derivative represented by a general formula (2):



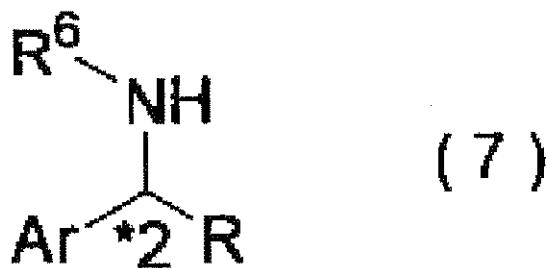
wherein R^1 , R^2 , and R^3 each independently represent a substituted or unsubstituted alkyl group having 1 to 18 carbon atoms, a substituted or unsubstituted aryl group having 6 to 20 carbon atoms, or a substituted or unsubstituted aralkyl group having 7 to 20 carbon atoms, and an azodicarbonyl compound represented by a general formula (3):



wherein R^4 and R^5 each independently represent a substituted or unsubstituted alkoxy group having 1 to 18 carbon atoms, a substituted or unsubstituted aryloxy group having 6 to 20 carbon atoms, or a substituted or unsubstituted aralkyloxy group having 7 to 20 carbon atoms.

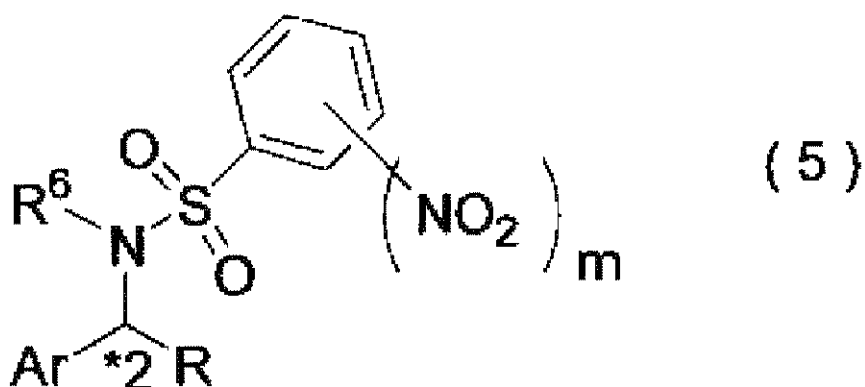
3. A method for producing an optically active benzylamine

derivative represented by a general formula (7):



wherein Ar represents a substituted or unsubstituted aryl group having 6 to 20 carbon atoms or a substituted or unsubstituted heteroaromatic group having 4 to 20 carbon atoms, R represents a substituted or unsubstituted alkyl group having 1 to 18 carbon atoms, a substituted or unsubstituted aryl group having 6 to 20 carbon atoms, or a substituted or unsubstituted aralkyl group having 7 to 20 carbon atoms, R⁶ represents hydrogen, a substituted or unsubstituted alkyl group having 1 to 18 carbon atoms, a substituted or unsubstituted aryl group having 6 to 20 carbon atoms, or a substituted or unsubstituted aralkyl group having 7 to 20 carbon atoms, and *2 represents an asymmetric carbon atom,

comprising reacting an optically active benzylsulfonylamide derivative represented by a general formula (5):



wherein Ar, R, R⁶, and *2 are as defined above, and m represents an integer of 1 to 3, with a thiol derivative represented by a general formula (6):

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R⁷SM (6),

wherein R⁷ represents hydrogen, a substituted or unsubstituted alkyl group having 1 to 18 carbon atoms, a substituted or unsubstituted aryl group having 6 to 20 carbon atoms, or a substituted or unsubstituted aralkyl group having 7 to 20 carbon atoms, and M represents hydrogen, an alkali metal, or an alkaline earth metal.

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4. The production method according to Claim 3, wherein the reaction is performed under the coexistence of a base and/or a phase transfer catalyst.

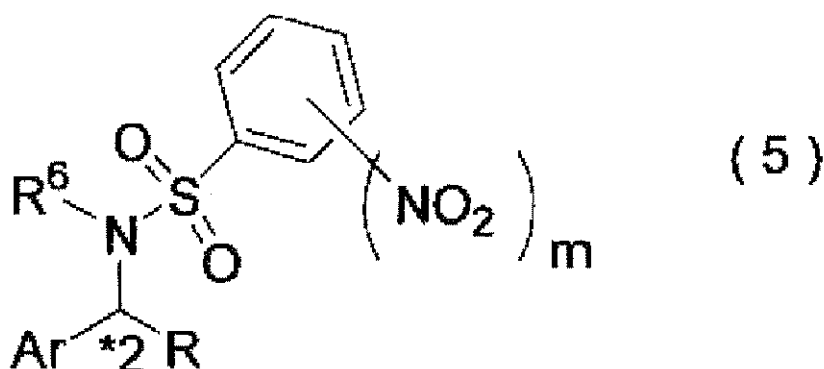
5. The production method according to Claim 3 or 4, wherein the optically active benzylsulfonylamide derivative

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represented by the formula (5) produced by the production method according to Claim 1 or 2 is used.

6. The production method according to any one of Claims 1 to 5, wherein Ar is a substituted or unsubstituted aryl group having 6 to 20 carbon atoms.

7. An optically active benzylsulfonylamide derivative represented by a general formula (5):



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wherein Ar represents a substituted or unsubstituted aryl group having 6 to 20 carbon atoms or a substituted or unsubstituted heteroaromatic group having 4 to 20 carbon atoms, R represents a substituted or unsubstituted alkyl group having 1 to 18 carbon atoms, a substituted or unsubstituted aryl group having 6 to 20 carbon atoms, or a substituted or unsubstituted aralkyl group having 7 to 20 carbon atoms, R^6 represents hydrogen, a substituted or unsubstituted alkyl group having 1 to 18 carbon atoms, a substituted or unsubstituted aryl group having 6 to 20 carbon atoms, or a substituted or unsubstituted aralkyl group having

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20

7 to 20 carbon atoms, m represents an integer of 1 to 3, and
*2 represents an asymmetric carbon atom.