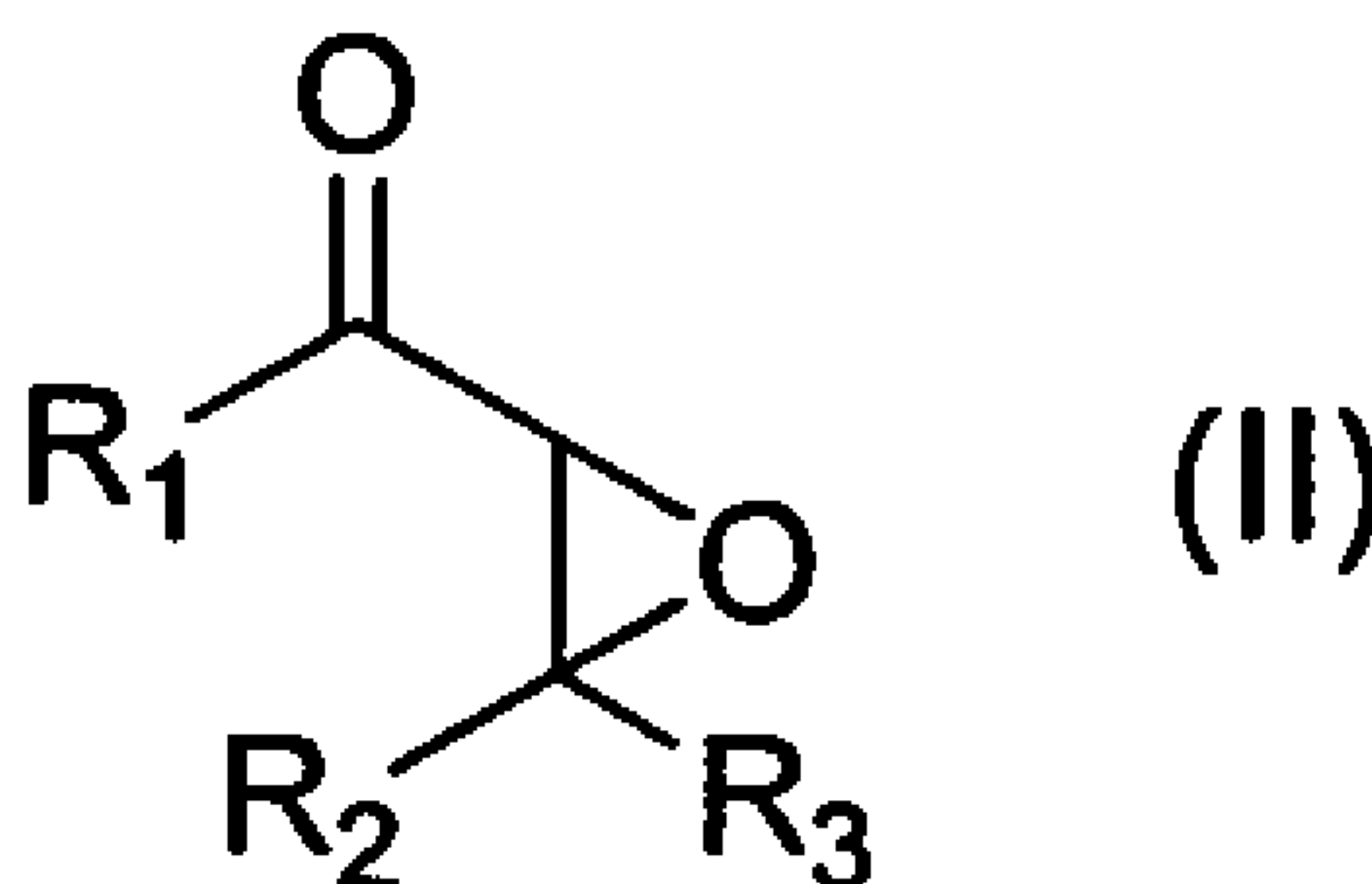
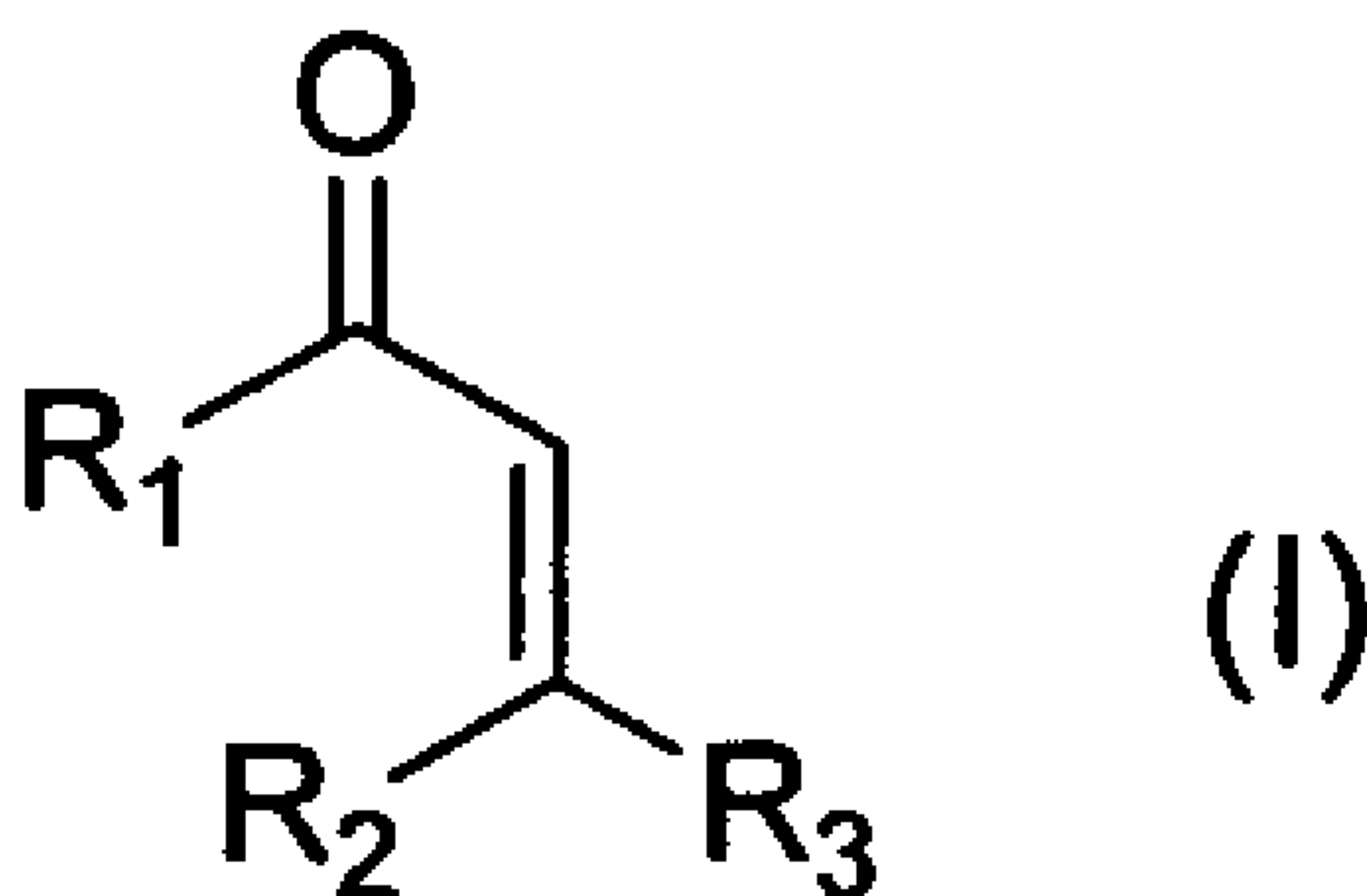




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(54) Titre : PROCÉDE DE FABRICATION D' α,β -EPOXYCETONES CHIRALES
(54) Title: METHOD FOR PRODUCING CHIRAL α,β -EPOXY KETONES



(57) Abrégé/Abstract:

The invention claims a method for the enantioselective epoxidation of α,β -unsaturated ketones, wherein a compound of the general formula (I) is reacted with an oxidation agent to form α,β -epoxy ketones of the general formula (II), in which R^1 , R^2 , R^3 are defined as above. The α,β -epoxy ketones of the general formula (II) can be obtained in good yields and excellent enantioselectivities from α,β -unsaturated ketones of the general formula (I) by epoxidation with hydrogen peroxide in the presence of a chiral catalyst, such as amino compounds and the acid addition salts thereof.

Abstract

A process is claimed for the enantioselective epoxidation of α,β -unsaturated ketones, in which a compound of the general formula I,



is reacted with an oxidizing agent to form α,β -epoxy ketones of the general formula II,



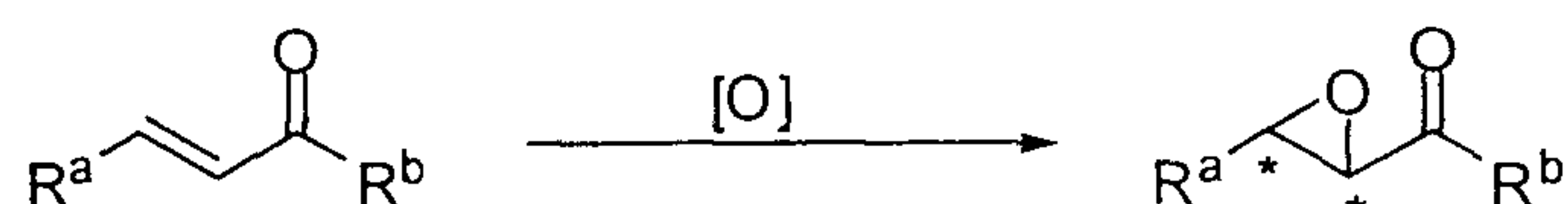
in which R^1 , R^2 , R^3 -are as defined above. The α,β -epoxy ketones of the general formula II can be obtained in good yields and outstanding enantioselectivities from α,β -unsaturated ketones of the general formula I by epoxidation with hydrogen peroxide in the presence of a chiral catalyst, such as amino compounds and their acid addition salts.

Method for producing chiral α,β -epoxy ketones

The present invention relates to a process for preparing chiral α,β -epoxy ketones.

Functionalized epoxides are very useful intermediates in the synthesis of industrially relevant compounds.

Possible routes to enantiomerically pure α,β -epoxy ketones include asymmetric epoxidations of the corresponding α,β -unsaturated ketones.



A series of examples of this type of reaction have been described in the literature. They include numerous examples of the enantioselective epoxidation of chalcone and chalcone derivatives. (Chem. Commun.) Highly enantioselective epoxidations of cyclic α,β -unsaturated ketones, however, are unknown. Neither with the aid of chiral reagents employed stoichiometrically, nor using chiral catalysts, has it been possible to achieve anything more than unsatisfactory enantioselectivities. Furthermore, there is no general method available for the highly enantioselective epoxidation of aliphatic α,β -unsaturated ketones.

It was an object of the present invention to provide a simple process for preparing enantiomerically enriched cyclic α,β -epoxy ketones.

The present invention provides a process for the enantioselective epoxidation of α,β -unsaturated ketones, in which a compound of the general formula I,



in which

R^1 is a branched or unbranched, saturated or unsaturated hydrocarbon radical having 1 to 30 carbon atoms, which may have suitable substituents and may have one or more heteroatoms in the chain,

R^2 is hydrogen, a branched or unbranched, saturated or unsaturated hydrocarbon radical having 1 to 30 carbon atoms, which may have suitable substituents and may have one or

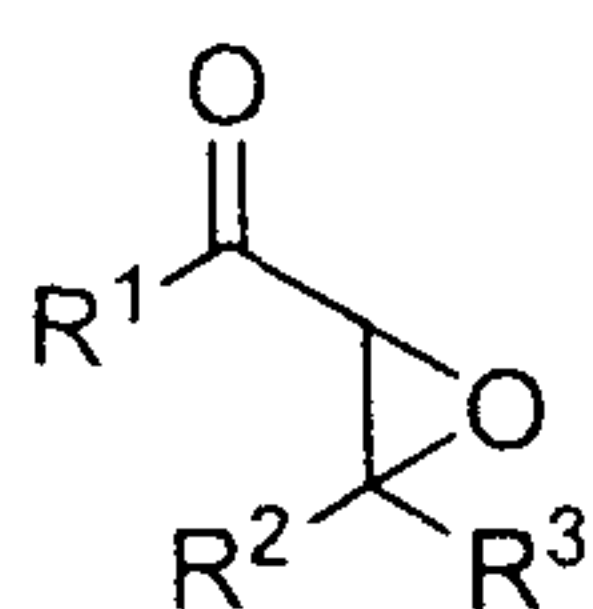
more heteroatoms in the chain, or an aryl group or heteroaryl group, which may have suitable substituents,

R^3 is hydrogen, a branched or unbranched, saturated or unsaturated hydrocarbon radical having 1 to 30 carbon atoms, which may have suitable substituents and may have one or more heteroatoms in the chain, or an aryl group or heteroaryl group, which may have suitable substituents,

R^1 , R^2 , and R^3 may be identical or different,

and the radical R^1 may, with the radicals R^2 and R^3 , form a ring, which may have 5 to 20 members, be saturated or unsaturated, alicyclic or heteroalicyclic, and may have suitable substituents,

is reacted with an oxidizing agent to form α,β -epoxy ketones of the general formula II,



(II)

in which R^1 , R^2 , R^3 are as defined above.

It has been found that α,β -epoxy ketones of the general formula II are obtained in good yields and outstanding enantioselectivities from α,β -unsaturated ketones of the general formula I by epoxidation with hydrogen peroxide in the presence of a chiral catalyst, such as amino compounds and their acid addition salts.

The process of the invention is implemented by reacting α,β -unsaturated ketones of the general formula I with a suitable oxidizing agent in the presence of a chiral catalyst. Any catalyst can be used that supports the reaction between the α,β -unsaturated ketone and the oxidizing agent. Organic bases, more particularly amines and their acid addition salts, have proven particularly suitable. The addition salts can be used per se or may form in the course of the reaction. Preferred amines have a structure of the general formula III,



in which

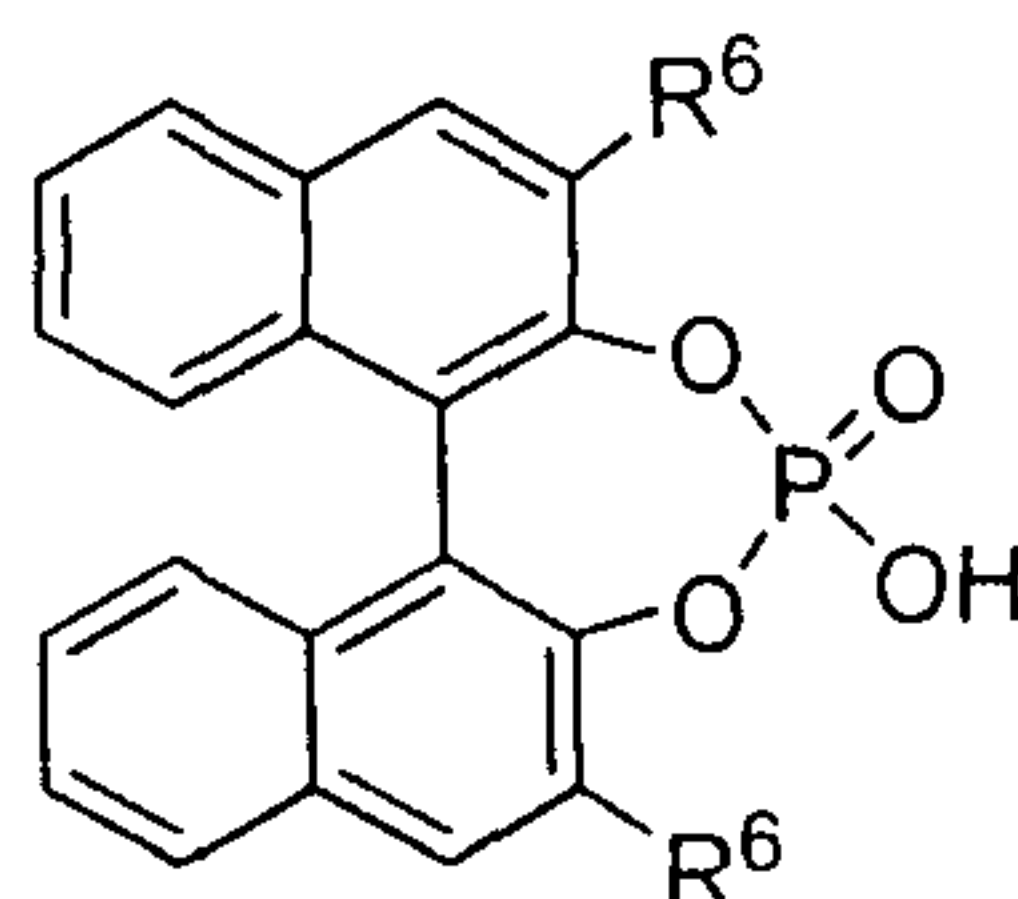
R^4 is a hydrocarbon group having 1 to 30 carbon atoms, such as a saturated or unsaturated, branched or linear alkyl group, alkenyl group, alkynyl group or aryl group, which may have suitable substituents including heteroatom substituents, or a heteroatom-containing hydrocarbon group, which may have suitable substituents, and their acid addition salts.

Preference is given to amines having the formula III, in which the radical R^4 has an additional basic functionality, such as an amino group.

The chiral catalyst is preferably selected from chiral amines of the general formula III, from addition salts of achiral amines of the general formula III with chiral acids, and from addition salts of chiral amines of the general formula III with achiral or chiral acids.

Examples of achiral acids which can be used in the process of the invention include halogenated carboxylic acids, such as halogenated acetic acids, e.g., trifluoroacetic acid, trichloroacetic acid, difluoroacetic acid and dichloroacetic acid, benzoic acid, substituted benzoic acids, etc.

Examples of suitable chiral acids are chiral organic phosphoric acids, phosphorimides, sulfuric acids, sulfonic acids, sulfonylimides, carboxylic acids, imides, etc. The chiral acids are preferably derived from binaphthol. In one possible embodiment, the chiral acid is selected from organic chiral phosphoric acids having the general formula IV,

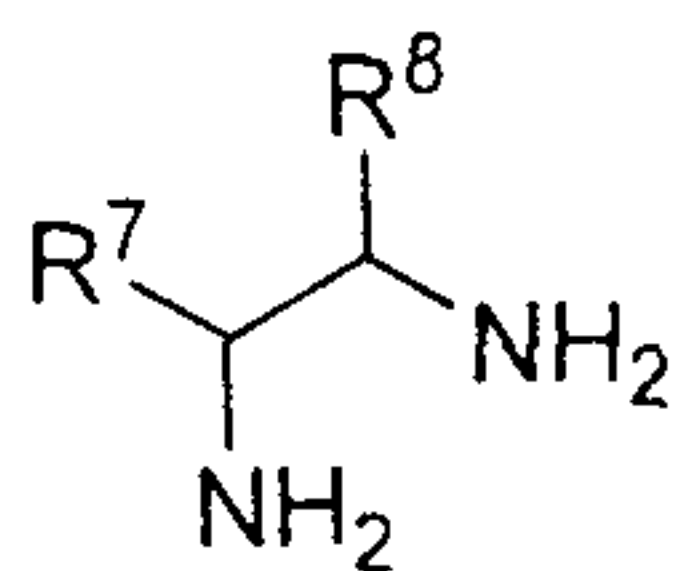


(IV)

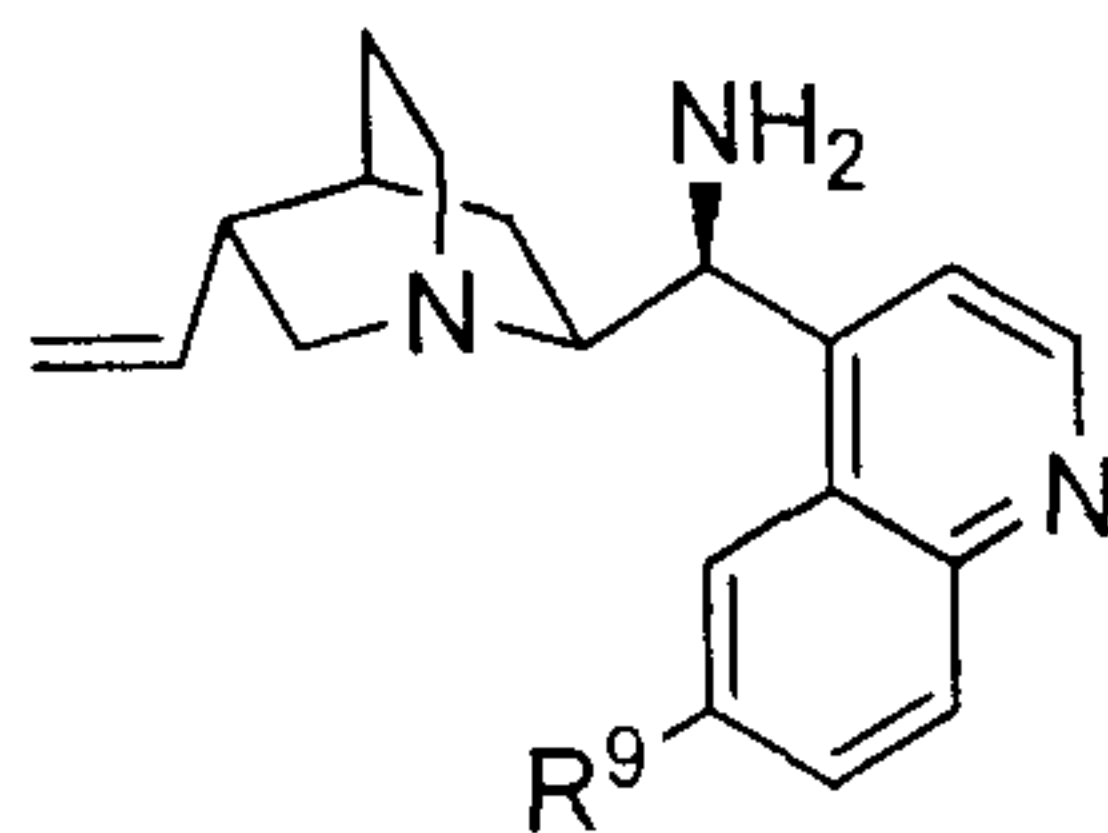
in which

R^6 is H, a hydrocarbon group, such as a saturated or unsaturated, branched or linear C_1 - C_{20} alkyl group, C_2 - C_{20} alkenyl group, C_2 - C_{20} alkynyl group or aryl group, which may have suitable substituents, including heteroatom substituents, or a heteroatom-containing hydrocarbon group, which may have suitable substituents.

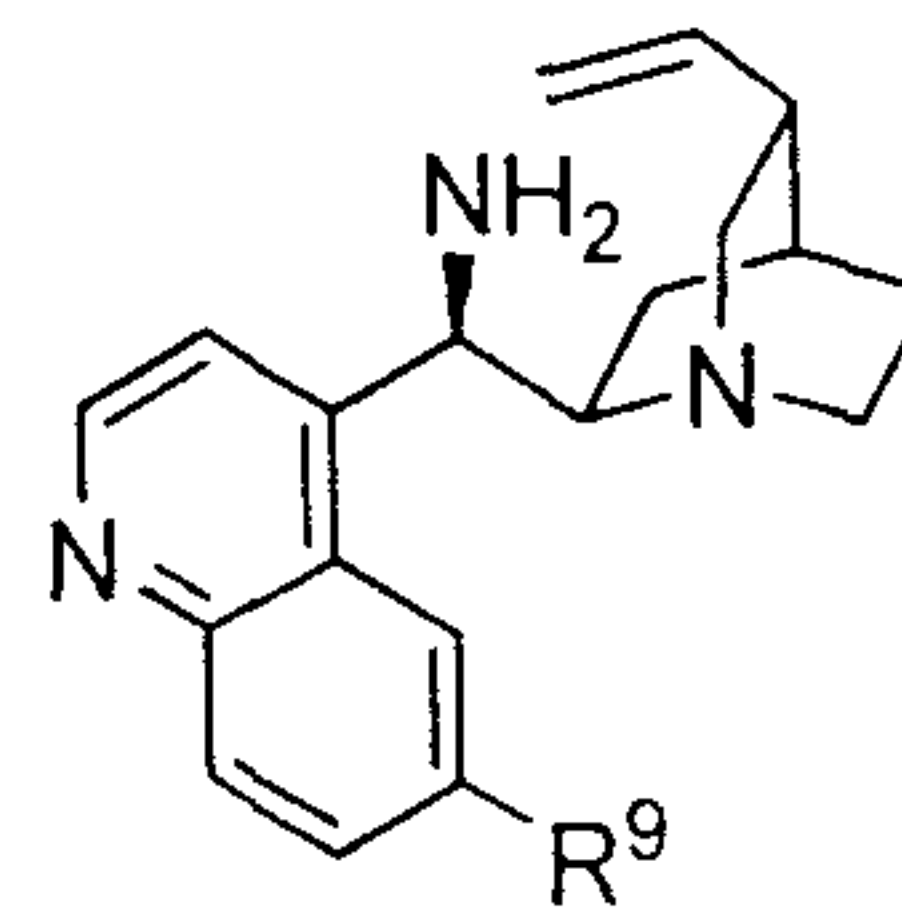
The amine having the general formula III is preferably a primary amine. Particularly good results are obtained with amines which are selected from the following compounds having the formulae V, VI, and VII



V



VI



VII

in which

R^7 is a hydrocarbon group, such as a saturated or unsaturated, branched or linear alkyl group, alkenyl group, alkynyl group or aryl group, which may have suitable substituents, including heteroatom substituents, or a heteroatom-containing hydrocarbon group, which may have suitable substituents, and

R^8 is a hydrocarbon group, such as a saturated or unsaturated, branched or linear alkyl group, alkenyl group, alkynyl group or aryl group, which may have suitable substituents, including heteroatom substituents, or a heteroatom-containing hydrocarbon group, which may have suitable substituents,

R^7 and R^8 may be identical or different,

and the radicals R^7 and R^8 may form a ring, which may have 4 to 20 members, be saturated or unsaturated, alicyclic or heteroalicyclic, and may have suitable substituents, and

R^9 is H, or a group $-OR^{10}$

in which R^{10} is hydrogen, a hydrocarbon group having 1 to 30 carbon atoms, such as a saturated or unsaturated, branched or linear alkyl group, alkenyl group, alkynyl group or aryl group, which may have suitable substituents, including heteroatom substituents, or a heteroatom-containing hydrocarbon group, which may have suitable substituents.

The catalyst is used typically in an amount of 0.1 to 200 mol%, preferably of 1 to 30 mol%, based on the starting compounds.

The oxidizing agent is more particularly H_2O_2 , which is used preferably in aqueous solution, more particularly in a concentration above 30% by weight, preferably between 30% and 50% by weight.

Hydrocarbon group in the context of the invention denotes a saturated or unsaturated, branched or linear alkyl group, alkenyl group, alkynyl group or aryl group, which may have suitable substituents, including heteroatom substituents, or a heteroatom-containing hydrocarbon group.

Alkyl may be unbranched (linear) or branched and has 1 to 30, preferably 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 carbon atoms. Alkyl is preferably methyl, but also ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or tert-butyl, and also pentyl, 1-, 2- or 3-methylpropyl, 1,1-, 1,2- or 2,2-dimethylpropyl, 1-ethylpropyl, hexyl, 1-, 2-, 3- or 4-methylpentyl, 1,1-, 1,2-, 1,3-, 2,2-, 2,3- or 3,3-dimethylbutyl, 1- or 2-ethylbutyl, 1-ethyl-1-methylpropyl, 1-ethyl-2-methylpropyl, 1,1,2- or 1,2,2-trimethylpropyl, but preferably also, e.g. trifluoromethyl.

Alkyl is more preferably an alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms, preferably methyl, ethyl, propyl, isopropyl, butyl, isopropyl, sec-butyl, tert-butyl, pentyl, hexyl, trifluoromethyl, pentafluoroethyl or 1,1,1-trifluoroethyl.

Cycloalkyl is preferably cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl. Alkylene is preferably methylene, ethylene, propylene, butylene, pentylene or hexylene, but also branched alkylene.

Alkylene is preferably vinyl.

Alkynyl is preferably $C\equiv CH$.

Halogen is F, Cl, Br or I.

Alkoxy is preferably methoxy, ethoxy, propoxy or butoxy.

C_3 - C_8 heterocycloalkyl having one or more heteroatoms selected from N, O and S is preferably 2,3-dihydro-2-, -3-, -4- or -5-furyl, 2,5-dihydro-2-, -3-, -4- or -5-furyl, tetrahydro-2- or -3-furyl, 1,3-dioxolan-4-yl, tetrahydro-2- or -3-thienyl, 2,3-dihydro-1-, -2-, -3-, -4- or -5-pyrrolyl, 2,5-dihydro-1-, -2-, -3-, -4- or -5-pyrrolyl, 1-, 2- or 3-pyrrolidiny, tetrahydro-1-, -2- or -4-imidazolyl, 2,3-dihydro-1-, -2-, -3-, -4- or -5-pyrazolyl, tetrahydro-1-, -3- or -4-pyrazolyl, 1,4-dihydro-1-, -2-, -3- or -4-pyridyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5- or -6-pyridyl, 1-, 2-, 3- or 4-piperidiny, 2-, 3- or 4-morpholiny, tetrahydro-2-, -3- or -4-pyranyl, 1,4-dioxanyl, 1,3-dioxan-2-, -4- or -5-yl, hexahydro-1-, -3- or -4-pyridaziny, hexahydro-1-, -2-, -4- or -5-pyrimidinyl, 1-, 2- or 3-piperaziny, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5-, -6-, -7- or -8-quinolyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5-, -6-, -7- or -8-isoquinolyl, 2-, 3-, 5-, 6-, 7- or 8-3,4-dihydro-2H-benzo-1,4-oxazinyl.

Optionally substituted means unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted.

Aryl is preferably phenyl, naphthyl or biphenyl.

Arylalkyl is preferably benzyl.

Heteroaryl having one or more heteroatoms selected from N, O and S is preferably 2- or 3-furyl, 2- or 3-thienyl, 1-, 2- or 3-pyrrolyl, 1-, 2-, 4- or 5-imidazolyl, 1-, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-isothiazolyl, 2-, 3- or

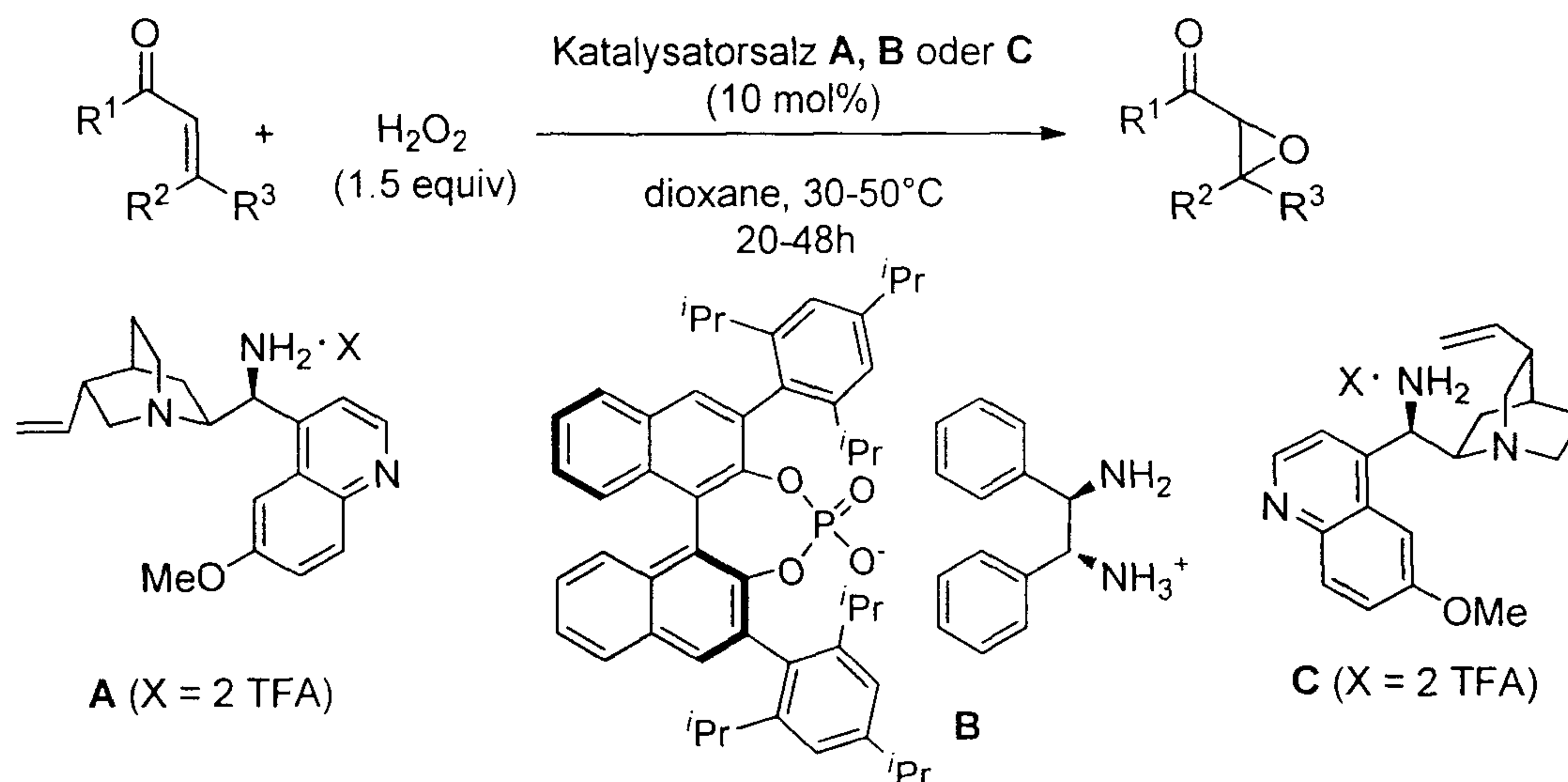
4-pyridyl, 2-, 4-, 5- or 6-pyrimidinyl, and also preferably 1,2,3-triazol-1-, -4- or -5-yl, 1,2,4-triazol-1-, -3- or -5-yl, 1- or 5-tetrazolyl, 1,2,3-oxadiazol-4- or -5-yl, 1,2,4-oxadiazol-3- or -5-yl, 1,3,4-thiadiazol-2- or -5-yl, 1,2,4-thiadiazol-3- or -5-yl, 1,2,3-thiadiazol-4- or -5-yl, 3- or 4-pyridazinyl, pyrazinyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 4- or 5-isoindolyl, 1-, 2-, 4- or 5-benzimidazolyl, 1-, 3-, 4-, 5-, 6- or 7-benzopyrazolyl, 2-, 4-, 5-, 6- or 7-benzoxazolyl, 3-, 4-, 5-, 6- or 7-benzisoxazolyl, 2-, 4-, 5-, 6- or 7-benzothiazolyl, 2-, 4-, 5-, 6- or 7-benzisothiazolyl, 4-, 5-, 6- or 7-benz-2,1,3-oxadiazolyl, 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolyl, 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolyl, 3-, 4-, 5-, 6-, 7- or 8-cinnolyl, 2-, 4-, 5-, 6-, 7- or 8-quinazolinyl, 5- or 6-quinoxalyl, 2-, 3-, 5-, 6-, 7- or 8-2H-benzo-1,4-oxazinyl, and also preferably 1,3-benzodioxol-5-yl, 1,4-benzodioxan-6-yl, 2,1,3-benzothiadiazol-4- or -5-yl or 2,1,3-benzoxadiazol-5-yl.

Examples of substituents are C₁-C₄ alk(en)yl, aryl, heteroaryl, halogen, such as F, Cl, Br, I, NO₂, amino, etc.

The reaction can be carried out in typical polar or nonpolar organic solvents.

Examples

A. General instructions:



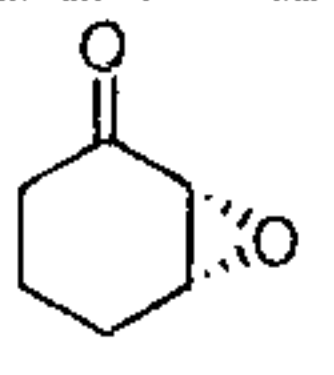
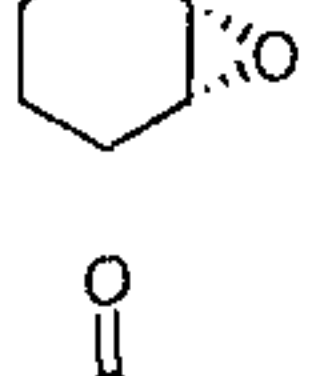
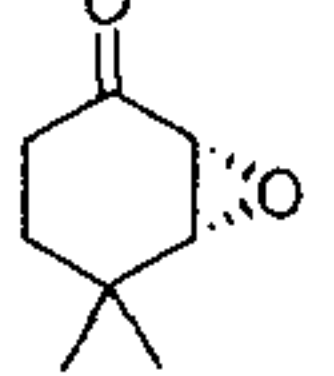
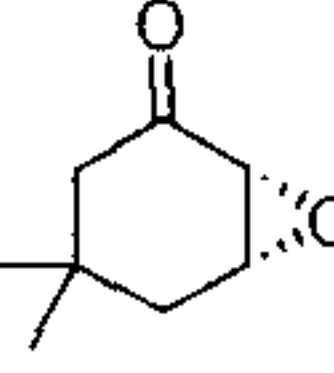
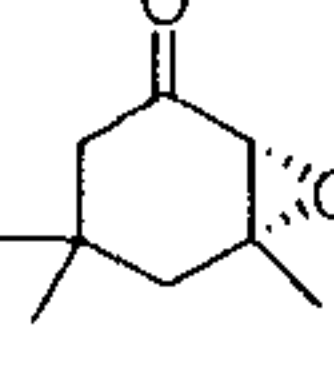
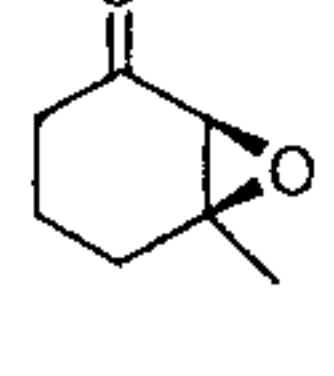
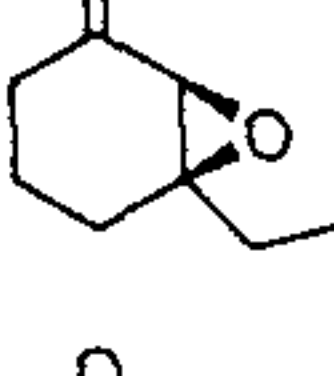
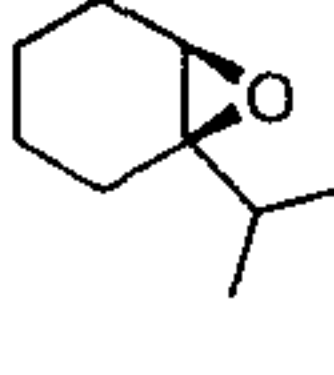
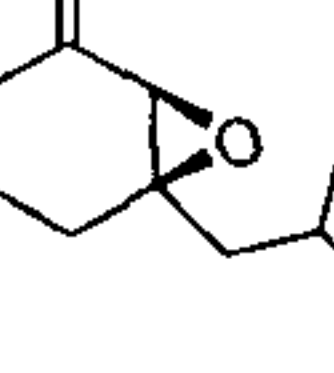
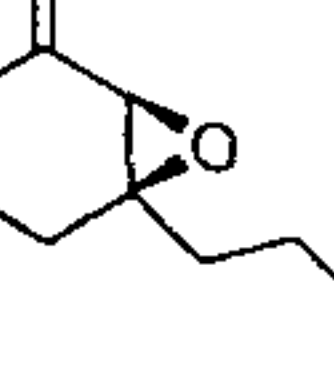
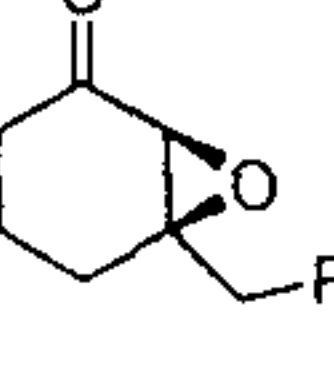
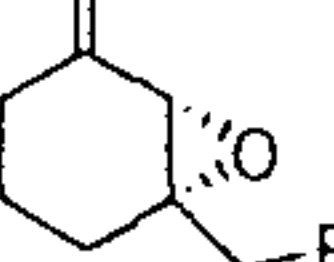
The catalyst salts **A-C** were prepared in situ in dioxane (2-4 ml) from the amine (10 mol%) and the respective acid (10-20 mol%). After 20 minutes of stirring the α,β -unsaturated ketones were added, and after a further 20 minutes, 1.5 equivalents of an aqueous hydrogen peroxide solution (50% w/w) were added. After a reaction time of 20-72 h at 30-50°C, the reaction mixture was cooled and water added. This was followed by extraction with ether, after which the combined organic phases were washed with saturated sodium chloride solution, dried (Na_2SO_4), filtered and concentrated on a rotary evaporator, to give the crude products which were purified by chromatography (SiO_2 , ether/pentane). In the case of the acyclic α,β -unsaturated ketone, the crude product obtained in this way was stirred optionally for 10 minutes to 1 hour in ether with one equivalent of 1 N NaOH solution. Thereafter the ether phase was washed with saturated sodium chloride solution, dried (Na_2SO_4), filtered and concentrated on a rotary evaporator. This was followed by purification by chromatography (SiO_2 , ether/pentane).

With catalyst A: 1.0 mmol scale based on the α,β -unsaturated ketone. The catalyst salt **A** was prepared from 9-amino-9-deoxyepiquinine (8.1 mg, 0.1 mmol, 10 mol%) and TFA (15.3 μl , 0.2 mmol, 20 mol%).

With catalyst B: 0.5 mmol scale based on the α,β -unsaturated ketone. The catalyst salt **B** was prepared from (*R,R*)-DPEN (10.6 mg, 0.05 mmol, 10 mol%) and *S*-TRIP (37.6 mg, 0.05 mmol, 10 mol%).

With catalyst C: 1.0 mmol scale based on the α,β -unsaturated ketone. The catalyst salt **C** was prepared from 9-amino-9-deoxyepiquinidine (8.1 mg, 0.1 mmol, 10 mol%) and TFA (15.3 μ l, 0.2 mmol, 20 mol%).

Table I: Preparation of cyclic epoxides

Example	Epoxide	Catalyst	Yield (%)	<i>er</i>
1		B	98	96:4
2		A	91	3:97
3		B	80	97:3
4		B	76	98:2
5		B	63	96:4
6		A	70	98:2
7		A	73	98.5:1.5
8		A	79	99:1
9		A	73	98:2
10		A	84	98.5:1.5
11		A	78	99:1
12		C	77	98.5:1.5

Continuation of Table I

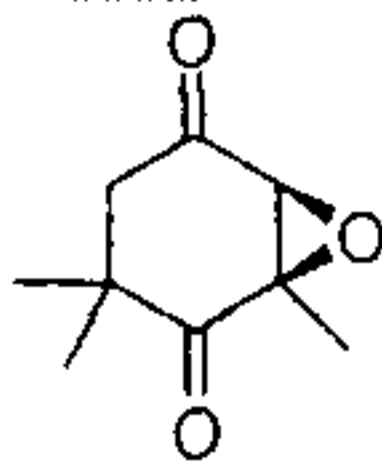
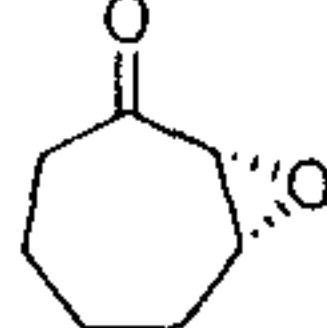
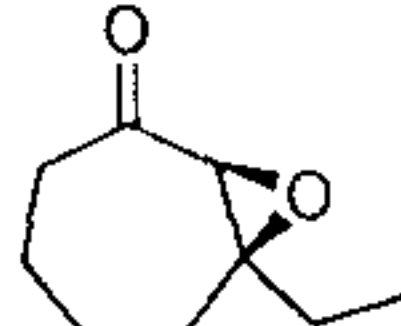
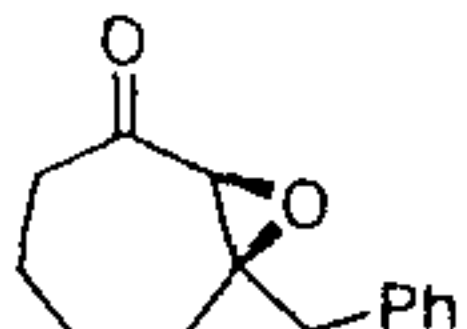
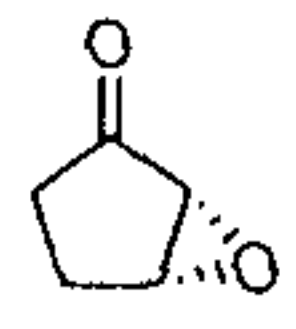
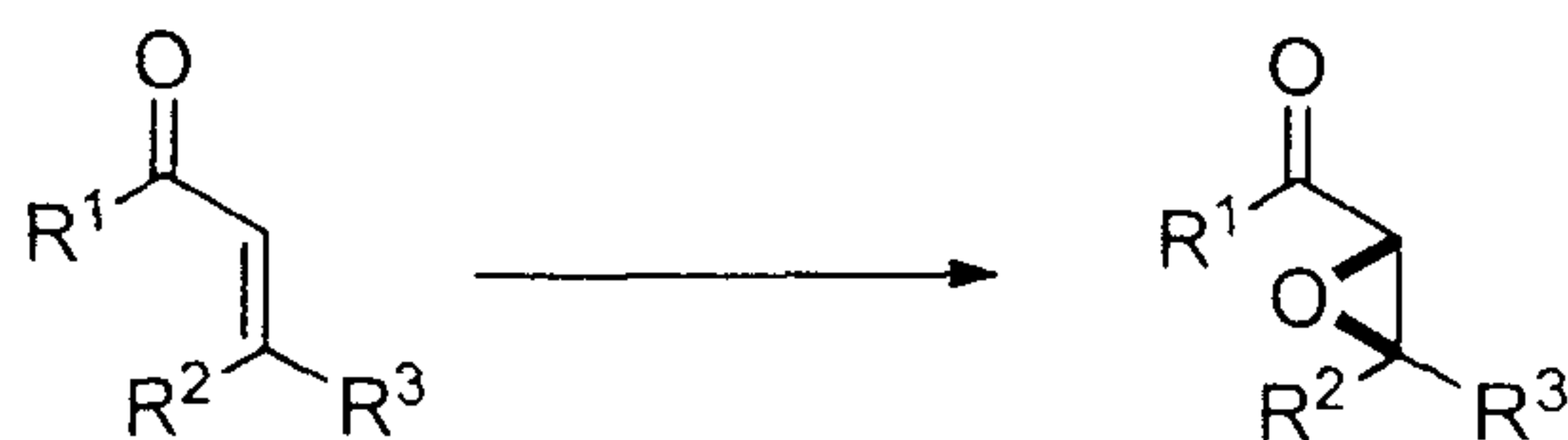
Example	Epoxide	Catalyst	Yield (%)	<i>er</i>
13		A	49	96:4
14		B	82	99:1
15		A	82	>99.5:0.5
16		A	85	>99.5:0.5
17		B	29	89:11

Table 2: Preparation of alicyclic epoxides

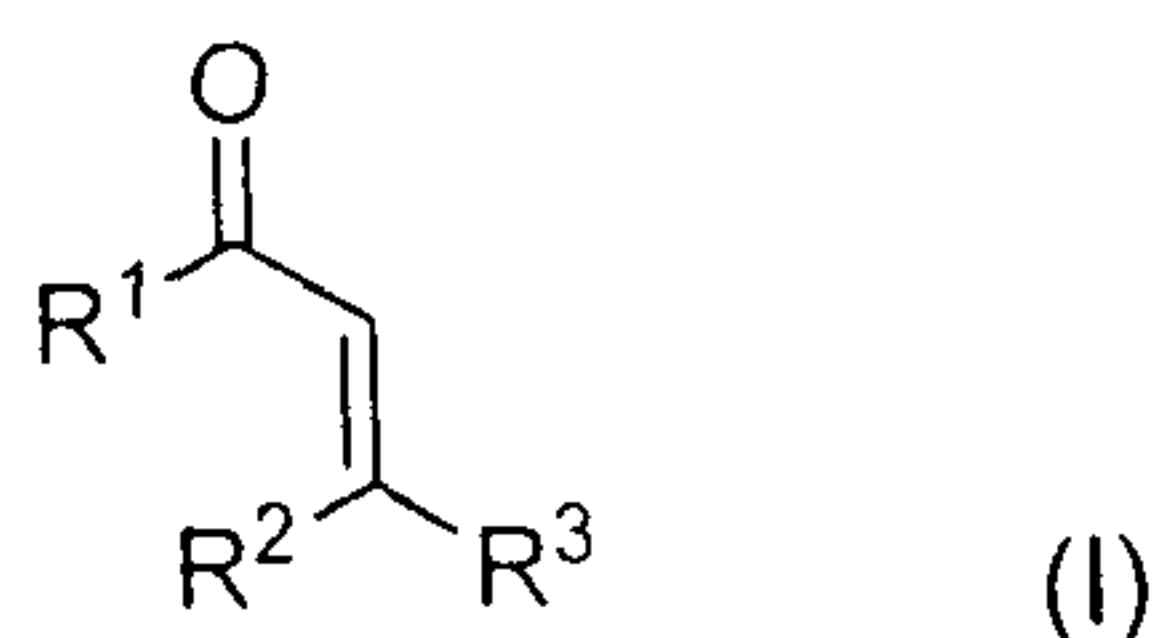


Example	R^1	R^2	R^3	Catalyst	Yield (%)	<i>er</i>
18	nC_6H_{13}	H	Me	A	72	98.5:1.5
19		H	Me	A	85	98.5:1.5
20		Me	H	A	82	97.5:2.5
21 ^a		H	Me	C	90	95:5
22		H	Me	A	76	98.5:1.5
23	<i>i</i> Bu	H	Me	A	77	98.5:1.5
24	Cy	H	Me	A	83	98.5:1.5
25		H	Me	A	81	>99.5:0.5
26	Me	H	Et	A	55	98.5:1.5
27	nC_9H_{19}	H	Et	A	82	99:1
28	nC_5H_{11}	H	nC_5H_{11} 1	A	76	99:1
29	nC_5H_{11}	H	<i>i</i> Bu	A	81	98.5:1.5

^a with catalyst C the opposite enantiomer is obtained.

Claims

1. The present invention provides a process for the enantioselective epoxidation of α,β -unsaturated ketones, in which a compound of the general formula I,



in which

R^1 is a branched or unbranched, saturated or unsaturated hydrocarbon radical having 1 to 30 carbon atoms, which may have suitable substituents and may have one or more heteroatoms in the chain,

R^2 is hydrogen, a branched or unbranched, saturated or unsaturated hydrocarbon radical having 1 to 30 carbon atoms, which may have suitable substituents and may have one or more heteroatoms in the chain, or an aryl group or heteroaryl group, which may have suitable substituents,

R^3 is hydrogen, a branched or unbranched, saturated or unsaturated hydrocarbon radical having 1 to 30 carbon atoms, which may have suitable substituents and may have one or more heteroatoms in the chain, or an aryl group or heteroaryl group, which may have suitable substituents,

R^1 , R^2 , and R^3 may be identical or different,

and the radical R^1 may, with the radicals R^2 and R^3 , form a ring, which may have 5 to 20 members, be saturated or unsaturated, alicyclic or heteroalicyclic, and may have suitable substituents,

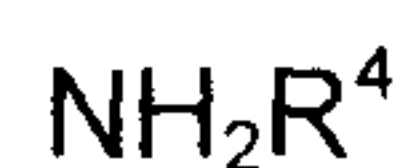
is reacted with an oxidizing agent to form α,β -epoxy ketones of the general formula II,



in which R^1 , R^2 , R^3 are as defined above.

2. The process as claimed in claim 1, characterized in that the oxidizing agent is selected from hydrogen peroxide and its formulations, alkyl peroxides and alkyl peroxide formulations, sodium hypochlorite, peracids, iodoso compounds and borates.

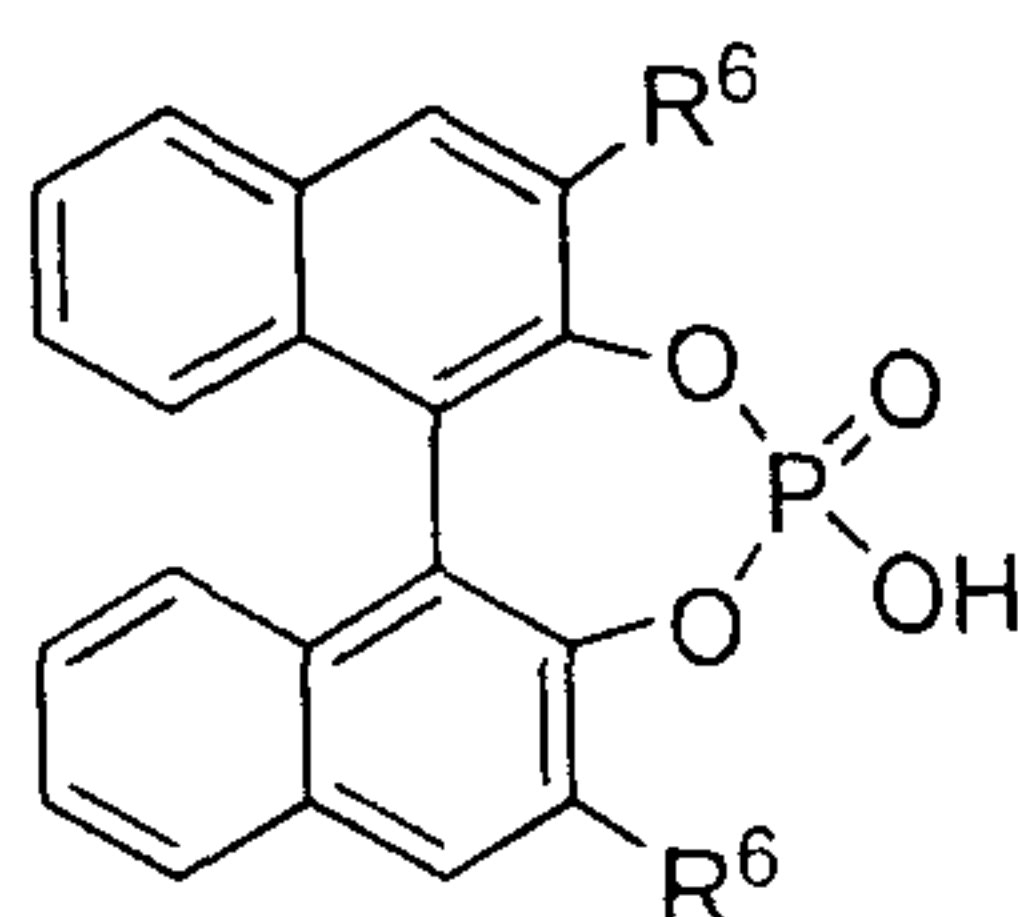
3. The process as claimed in claim 2, characterized in that an aqueous hydrogen peroxide solution is used as oxidizing agent.
4. The process as claimed in any of claims 1 to 3, characterized in that the reaction is carried out in the presence of a chiral catalyst.
5. The process as claimed in claim 4, characterized in that the chiral catalyst is selected from organic bases, more particularly amines and their acid addition salts.
6. The process as claimed in claim 5, characterized in that the chiral catalyst is selected from amines of the general formula III,



in which

R⁴ is a hydrocarbon group having 1 to 30 carbon atoms, such as a saturated or unsaturated, branched or linear alkyl group, alkenyl group, alkynyl group or aryl group, which may have suitable substituents including heteroatom substituents, or a heteroatom-containing hydrocarbon group, which may have suitable substituents, and their acid addition salts.

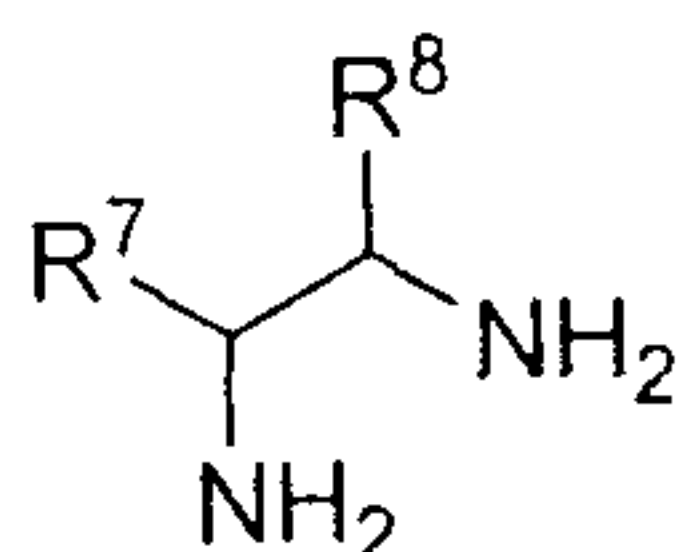
7. The process as claimed in claim 6, characterized in that the chiral catalyst is selected from chiral amines of the general formula III, from addition salts of achiral amines of the general formula III with chiral acids, and from addition salts of chiral amines of the general formula III with achiral or chiral acids.
8. The process as claimed in claim 7, characterized in that the chiral acids are selected from chiral organic phosphoric acids, phosphorimides, sulfuric acids, sulfonic acids, sulfonylimides, carboxylic acids, imides, etc.
9. The process as claimed in claim 8, characterized in that the chiral acid is derived from binaphthol.
10. The process as claimed in claim 9, characterized in that the chiral acid is selected from organic chiral phosphoric acids having the general formula IV,



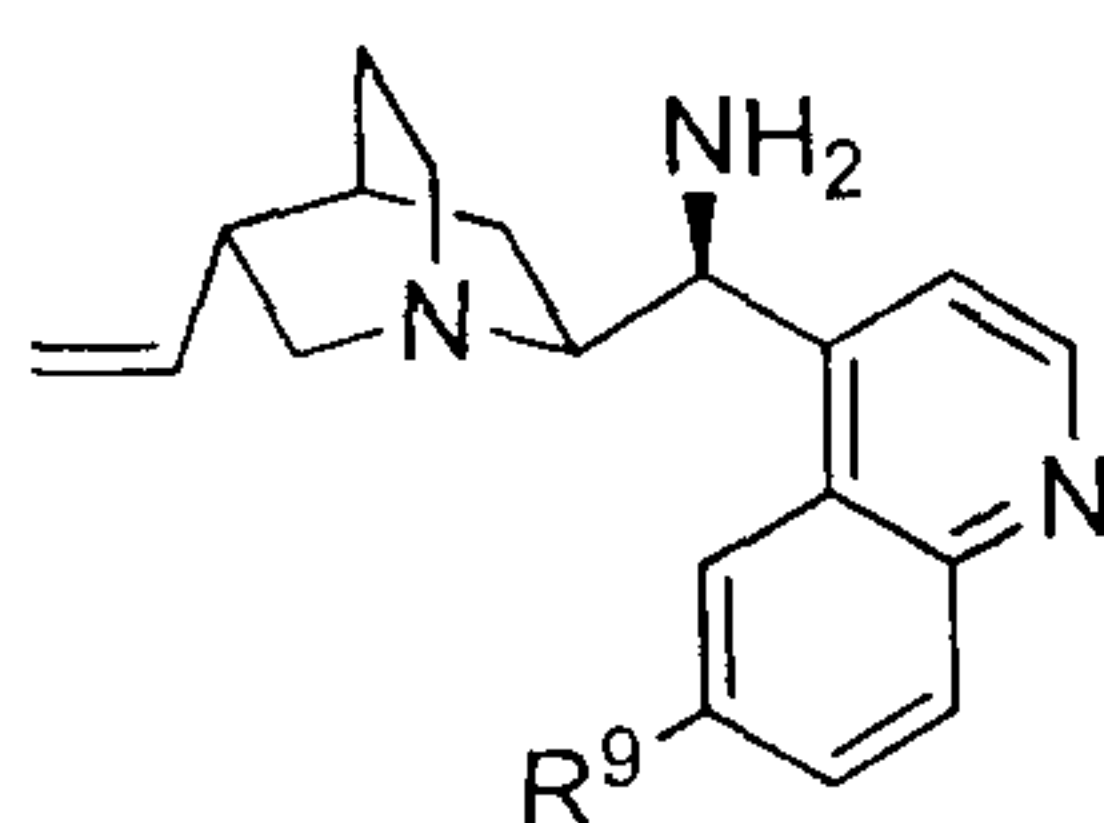
in which

R^6 is H, a hydrocarbon group, such as a saturated or unsaturated, branched or linear alkyl group, alkenyl group, alkynyl group or aryl group, which may have suitable substituents, including heteroatom substituents, or a heteroatom-containing hydrocarbon group, which may have suitable substituents.

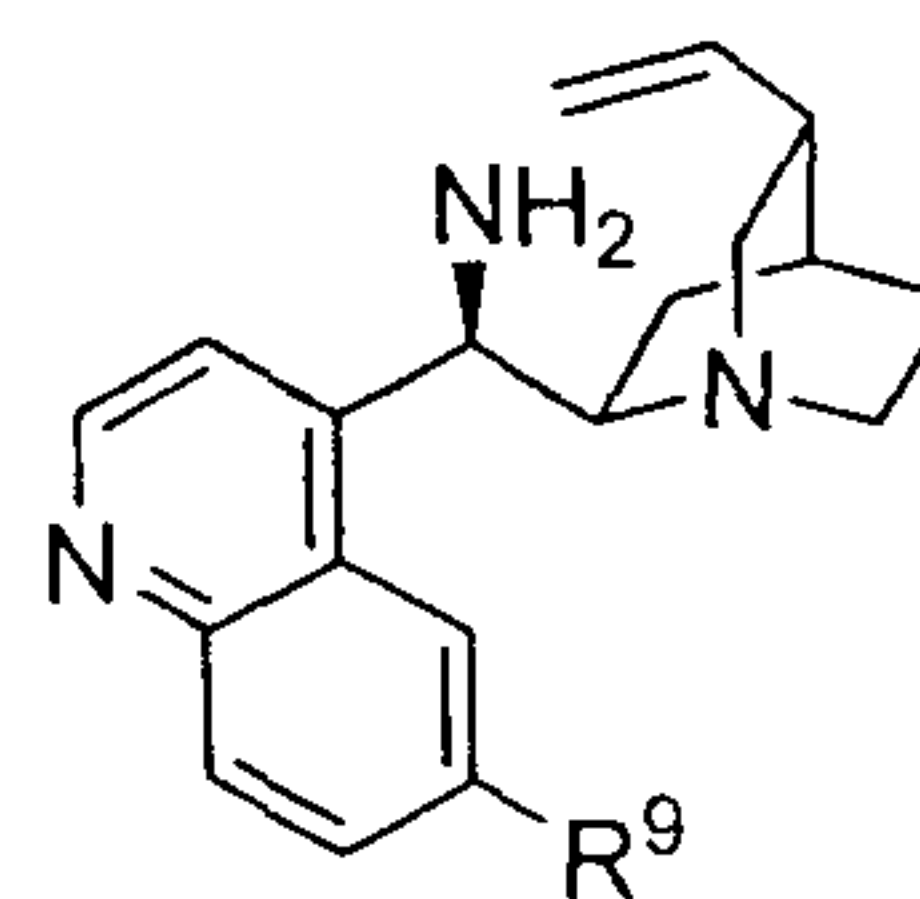
11. The process as claimed in claim 6 and 7, characterized in that the amine having the general formula III is preferably a primary amine.
12. The process as claimed in claim 11, characterized in that the primary amine is preferably selected from compounds having the formulae V, VI and/or VII



V



VI



VII

in which

R^7 is a hydrocarbon group, such as a saturated or unsaturated, branched or linear alkyl group, alkenyl group, alkynyl group or aryl group, which may have suitable substituents, including heteroatom substituents, or a heteroatom-containing hydrocarbon group, which may have suitable substituents, and

R^8 is a hydrocarbon group, such as a saturated or unsaturated, branched or linear alkyl group, alkenyl group, alkynyl group or aryl group, which may have suitable substituents, including heteroatom substituents, or a heteroatom-containing hydrocarbon group, which may have suitable substituents,

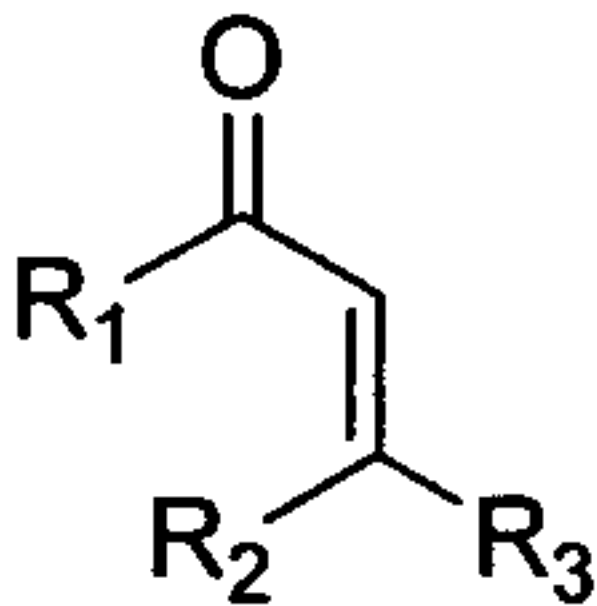
R^7 and R^8 may be identical or different,

and the radicals R^7 and R^8 may form a ring, which may have 4 to 20 members, be saturated or unsaturated, alicyclic or heteroalicyclic, and may have suitable substituents, and

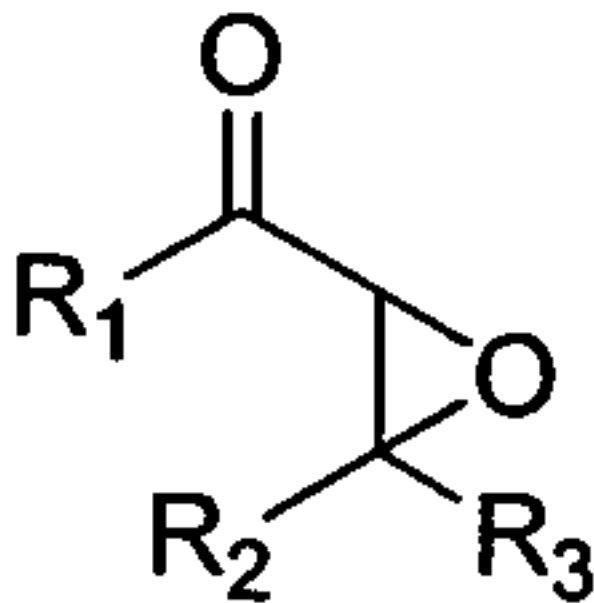
R^9 is H, or a group $-OR^{10}$

in which

R^{10} is hydrogen, a hydrocarbon group having 1 to 30 carbon atoms, such as a saturated or unsaturated, branched or linear alkyl group, alkenyl group, alkynyl group or aryl group, which may have suitable substituents, including heteroatom substituents, or a heteroatom-containing hydrocarbon group, which may have suitable substituents.



(I)



(II)