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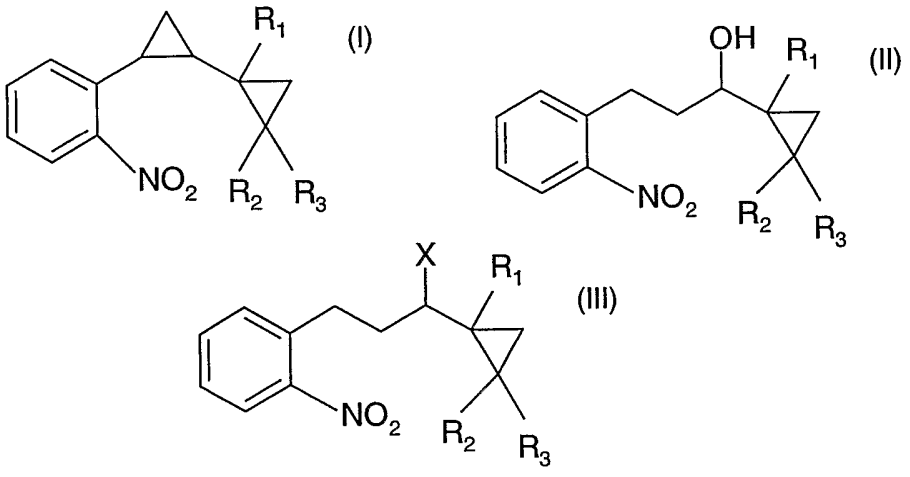
(54) Title: PROCESS FOR THE PRODUCTION OF NITROBENZOLES



(57) Abstract: The present invention relates to a process for the preparation of compounds of formula (I) wherein the substituents are as defined in claim 1, by reaction of a compound of formula (II) wherein the substituents are as defined in claim 1, either a1) with triphenylphosphine dibromide or triphenylphosphine dichloride or a2) with RSO_2CI, wherein R is C_1C_4alkyl, C_1-C_4 fluoroalkyl, benzyl, phenyl, nitrophenyl, halophenyl or C_1-C_6alkylphenyl, in the presence of a base, to form a compound of formula (III) wherein the substituents are as defined in claim 1 ; and conversion of that compound in the presence of a base into a compound of formula I, and also to novel nitrobenzene intermediates for use in that process.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Process for the production of nitrobenzoles

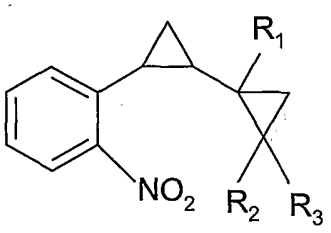
The present invention relates to a process for the preparation of 2-(2-nitrophenyl)-bicyclopropanes, and to novel nitrobenzene intermediates for use in that process.

2-(2-Aminophenyl)-bicyclopropanes, such as, for example, unsubstituted 2-(2-aminophenyl)-bicyclopropane, are valuable intermediates for the preparation of ortho-bicyclopropyl-carboxanilide fungicides, such as are described, for example, in WO 03/074491. 2-(2-Aminophenyl)-bicyclopropanes can be prepared in simple manner from the 2-(2-nitrophenyl)-bicyclopropanes on which they are based, for example by reduction under reaction conditions such as are described in WO 03/074491 for the reduction of 2-(2-nitrophenyl)-cyclopropanes.

The preparation of 2-(2-aminophenyl)-bicyclopropanes using 2-(2-nitrophenyl)-bicyclopropane intermediates is described in WO 03/074491 with reference to two possible routes. A first route is by way of nitration of bicyclopropyl-benzenes. It has been found, however, that the reaction is not workable in view of the fact that the cyclopropyl ring linked directly to the benzene ring has increased reactivity in bicyclopropyl-benzenes with respect to electrophiles. A second route is by way of application of the Simmons-Smith reaction (Zn/Cu, CH_2I_2 with ether as solvent) to 1-((E/Z)-2-cyclopropylvinyl)-2-nitrobenzenes. In that case, too, the reaction has been found to be unsuitable for the preparation of 2-(2-nitrophenyl)-bicyclopropanes, since the reactivity of the double bond is too low.

The aim of the present invention is therefore to provide a process for the preparation of 2-(2-nitrophenyl)-bicyclopropanes that allows such compounds to be prepared in an economically advantageous manner in high yields and in good quality.

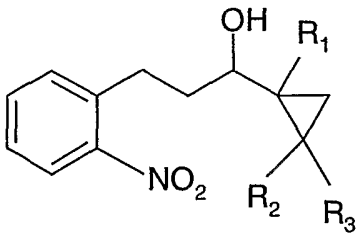
The present invention accordingly relates to a process for the preparation of compounds of formula I



(I),

wherein R_1, R_2 and R_3 are each independently of the others hydrogen or methyl, which comprises

a) reaction of a compound of formula II



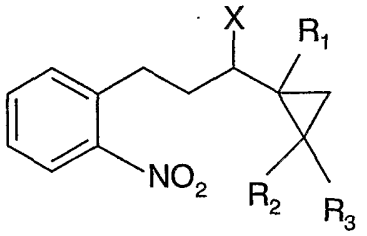
(II),

wherein R_1, R_2 and R_3 are as defined for formula I, either

a1) with triphenylphosphine dibromide or triphenylphosphine dichloride or

a2) with RSO_2Cl, wherein R is C_1-C_4alkyl, C_1-C_4fluoroalkyl, benzyl, phenyl, nitrophenyl, halophenyl or C_1-C_6alkylphenyl, in the presence of a base,

to form a compound of formula III



(III),

wherein X is bromine, chlorine or OSO_2R, wherein R is C_1-C_4alkyl, C_1-C_4fluoroalkyl, benzyl, phenyl, nitrophenyl, halophenyl or C_1-C_6alkylphenyl, and R_1, R_2 and R_3 are as defined for formula I; and

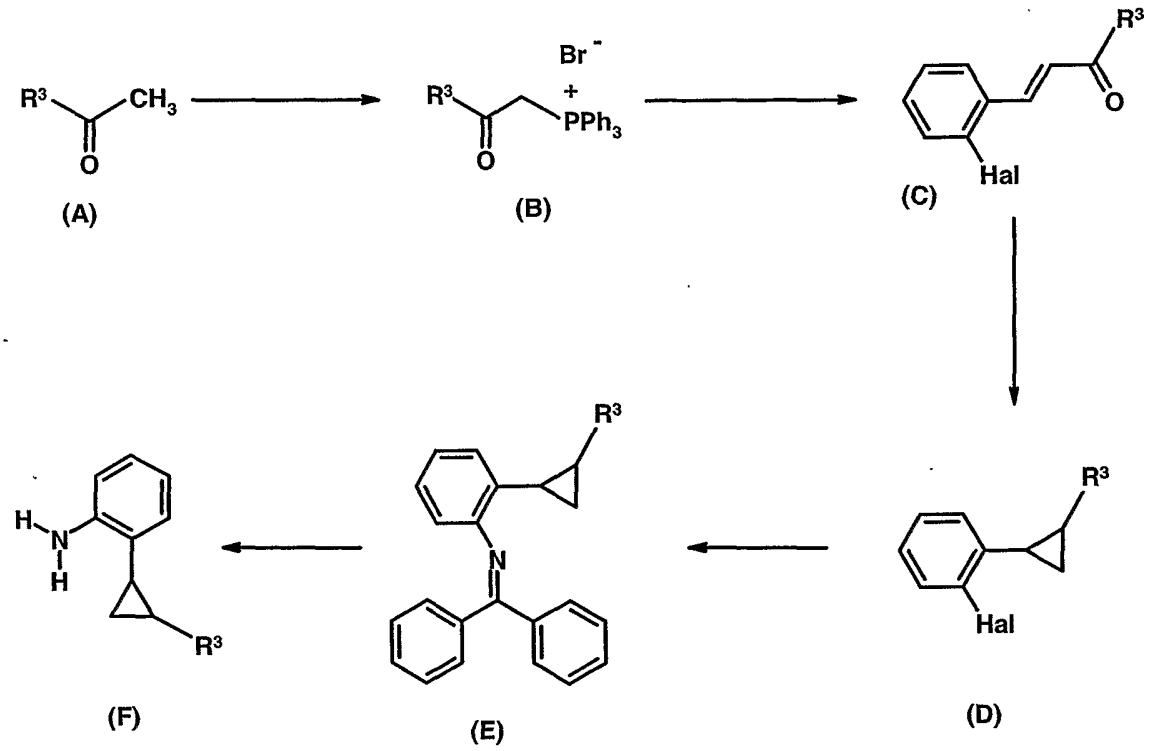
b) conversion of that compound in the presence of a base into a compound of formula I.

Ortho-bicyclopropylcarboxanilide fungicides are generally chiral molecules that occur in isomeric forms. Accordingly they exist as trans/cis isomers based on the substitution pattern of the cyclopropyl ring linked directly to the benzene ring. It is known that the fungicidal activity of compounds such as are described, for example, in WO 03/074491, can be influenced by the stereochemistry. It has been found in the case of the ortho-bicyclopropyl-carboxanilide fungicides described therein that the trans isomers generally have higher fungicidal activity. The development of a process that enables the production of a marked excess of trans ortho-bicyclopropylcarboxanilide fungicides is therefore extremely desirable.

It is known that ortho-bicyclopropylcarboxanilide fungicides can also be prepared without the use of 2-(2-nitrophenyl)-bicyclopropanes as intermediates. For example, in WO 03/074491 a

process for the preparation of 2-(2-aminophenyl)-bicyclopropane intermediates is described that uses 2-(2-halophenyl)-bicyclopropanes (see Scheme 1):

Scheme 1:



According to WO 03/074491, ketones of formula (A), wherein R^3 may be, *inter alia*, unsubstituted or substituted cyclopropyl, are reacted, for example, first with bromine and methanol and then with triphenylphosphine. The compounds of formula (B) obtained are converted in a two-step reaction into compounds of formula (C) wherein Hal is bromine or iodine (first, reaction with sodium hydride, then reaction with 2-bromobenzaldehyde or 2-iodobenzaldehyde, respectively). Compounds of formula (C) can be converted into the corresponding 2-(2-halophenyl)-bicyclopropanes (D) by Kishner cyclisation, which proceeds by way of a Δ^2-pyrazoline. For that purpose, compounds of formula (C) are reacted, with heating, with hydrazine, as a result of which the corresponding Δ^2-pyrazolines are formed. Subsequently, potassium hydroxide is added for isomerisation, and renewed heating is carried out to remove N_2. 2-(2-Halophenyl)-bicyclopropanes (D) can be aminated in a two-step reaction to form the corresponding 2-(2-aminophenyl)-bicyclopropanes (F). For that purpose, first of all benzophenone imine, sodium tert-butanolate, tris(dibenzylideneacetone)-dipalladium (Pd_2dba_3) and racemic 2,2'-bis(diphenylphosphine)-1,1'-binaphthyl (BINAP) are

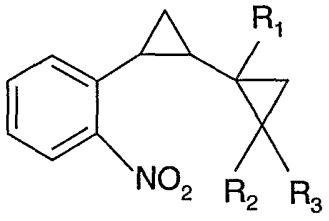
added. The resulting imines (E) are reacted in the second reaction step, for example with hydroxylamine and sodium acetate, to form the corresponding 2-(2-aminophenyl)-bicyclopropanes (F).

The reaction sequence described in WO 03/074491 (Scheme 1) yields a trans:cis ratio of the 2-(2-aminophenyl)-bicyclopropane isomers of about 2:1.

In the conversion of the 2-(2-nitrophenyl)-bicyclopropanes into 2-(2-aminophenyl)-bicyclopropanes by reduction, the ratio of those cis/trans isomers to one another is essentially unaffected.

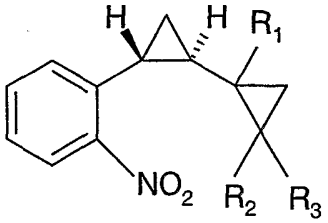
A further aim of the present invention is accordingly to provide a process for the preparation of 2-(2-nitrophenyl)-bicyclopropanes having a significantly higher proportion of trans isomers.

The process according to the invention allows compounds of formula I



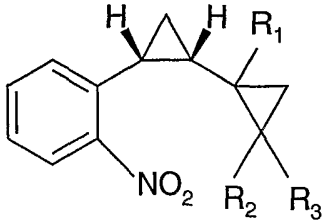
(I)

to be produced wherein R_1, R_2 and R_3 are each independently of the others hydrogen or methyl and wherein the ratio of compounds of formula Ia (trans)



(Ia, trans)

to compounds of formula Ib (cis)



(Ib, cis)

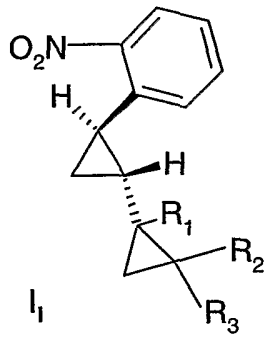
is more than 2:1.

The alkyl groups in the definitions of the substituents may be straight-chain or branched and are, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, pentyl and hexyl and branched isomers thereof.

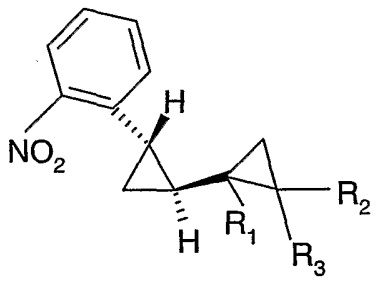
Halogen in the context of halophenyl is generally fluorine, chlorine, bromine or iodine.

Fluoroalkyl groups having a chain length of from 1 to 4 carbon atoms are, for example, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 1-fluoroethyl, 2-fluoroethyl, 2-fluoroprop-2-yl, pentafluoroethyl, 2,2,3,3-tetrafluoroethyl, pentafluoroethyl or heptafluoro-n-propyl; fluoroalkyl groups are preferably trichloromethyl, fluoromethyl, dichlorofluoromethyl, difluoromethyl, trifluoromethyl, pentafluoroethyl or heptafluoro-n-propyl.

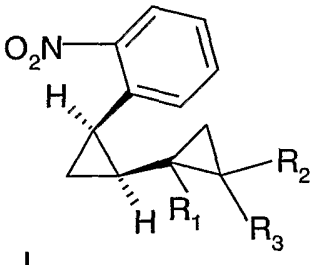
Compounds of formula I occur in various stereoisomeric forms, which are represented by formulae I_I, I_{II}, I_{III} and I_{IV}:



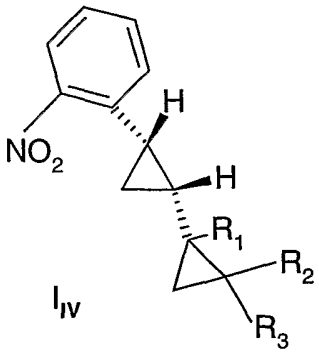
I_I



I_{II}



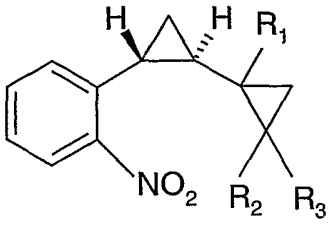
I_{III}



I_{IV}

The process according to the invention includes the preparation of those stereoisomeric forms of formulae I_I, I_{II}, I_{III} and I_{IV}, wherein R_1, R_2 and R_3 are as defined for formula I, and the preparation of mixtures of those stereoisomeric forms in any ratio.

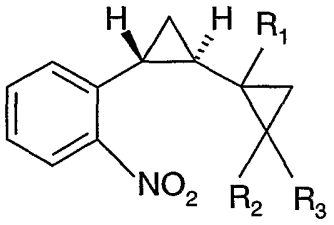
In the context of the present invention, compounds of formula Ia (trans)



(Ia, trans),

wherein R_1, R_2 and R_3 are as defined for formula I, are understood to be compounds of formula I_I, wherein R_1, R_2 and R_3 are as defined for formula I; compounds of formula I_{II}, wherein R_1, R_2 and R_3 are as defined for formula I; or a mixture, in any ratio, of compounds of formula I_I, wherein R_1, R_2 and R_3 are as defined for formula I, and compounds of formula I_{II}, wherein R_1, R_2 and R_3 are as defined for formula I.

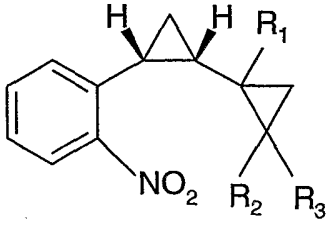
In the context of the present invention, compounds of formula Ia (trans)



(Ia, trans),

wherein R_1, R_2 and R_3 are as defined for formula I, are understood to be, preferably, a racemic mixture of compounds of formula I_I, wherein R_1, R_2 and R_3 are as defined for formula I, and compounds of formula I_{II}, wherein R_1, R_2 and R_3 are as defined for formula I.

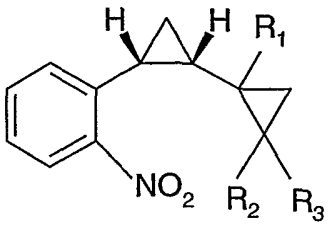
In the context of the present invention, compounds of formula Ib (cis)



(Ib, cis),

wherein R_1, R_2 and R_3 are as defined for formula I, are understood to be compounds of formula I_{III}, wherein R_1, R_2 and R_3 are as defined for formula I; compounds of formula I_{IV}, wherein R_1, R_2 and R_3 are as defined for formula I; or a mixture, in any ratio, of compounds of formula I_{III}, wherein R_1, R_2 and R_3 are as defined for formula I, and compounds of formula I_{IV}, wherein R_1, R_2 and R_3 are as defined for formula I.

In the context of the present invention, compounds of formula Ib (cis)



(Ib, cis),

wherein R_1, R_2 and R_3 are as defined for formula I, are understood to be, preferably, a racemic mixture of compounds of formula I_{III}, wherein R_1, R_2 and R_3 are as defined for formula I, and compounds of formula I_{IV}, wherein R_1, R_2 and R_3 are as defined for formula I.

In the context of the present invention, a "racemic mixture" of two enantiomers is understood to be a mixture of the two enantiomers in a ratio substantially equal to 1 :1.

The process according to the invention is suitable especially for the preparation of compounds of formula I wherein R_2 and R_3 are hydrogen.

The process according to the invention is suitable more especially for the preparation of compounds of formula I wherein R_1, R_2 and R_3 are hydrogen.

The process according to the invention is suitable more especially for the preparation of compounds of formula I wherein R_1 is methyl and R_2 and R_3 are hydrogen.

Process Step a):

In an embodiment (a1) of the process according to the invention, in Process Step a), a compound of formula II is reacted with triphenylphosphine dibromide or triphenylphosphine dichloride.

In that embodiment, either triphenylphosphine dibromide or triphenylphosphine dichloride is added directly to the compounds of formula II, or triphenylphosphine dibromide or triphenylphosphine dichloride is generated *in situ* in the reaction mixture by the addition of bromine or chlorine in the presence of triphenylphosphane.

Suitable amounts of triphenylphosphine dibromide or triphenylphosphine dichloride for that reaction are, for example, from 1 to 3 equivalents, especially from 1 to 1.5 equivalents.

When triphenylphosphine dibromide or triphenylphosphine dichloride is generated *in situ*, an amount, for example, of from 1 to 3 equivalents, especially from 1 to 1.5 equivalents, of bromine or chlorine is suitable. Suitable amounts of triphenylphosphane for that variant of the reaction are, for example, from 1 to 3 equivalents, especially from 1 to 1.5 equivalents.

In that embodiment, the reaction can be carried out in the presence of an inert solvent. Suitable solvents are, for example, ethers, for example tetrahydrofuran or dioxane, or CH_3CN, and mixtures thereof; CH_3CN is preferred.

Temperatures are generally from -20°C to 80°C, with a range from -20°C to 25°C being preferred; special preference is given to carrying out the reaction at ambient temperature.

The reaction time for that reaction is generally from 1 to 48 hours, preferably from 1 to 18 hours.

In a further embodiment (a2) of the process according to the invention, in Process Step a), a compound of formula II is reacted in the presence of a base with RSO_2Cl, wherein R is C_1-C_4alkyl, C_1-C_4fluoroalkyl, benzyl, phenyl, nitrophenyl, halophenyl or C_1-C_6alkylphenyl, especially C_1-C_4alkyl, more especially methyl.

For that reaction, suitable amounts of RSO_2Cl, wherein R is C_1-C_4alkyl, C_1-C_4fluoroalkyl, benzyl, phenyl, nitrophenyl, halophenyl or C_1-C_6alkylphenyl, are, for example, from 1 to 3 equivalents, especially from 1 to 1.2 equivalents.

Suitable bases are, for example, tertiary amines, such as trialkylamines, e.g. trimethylamine, triethylamine, diisopropylethylamine (Hünig's base), tri-n-butylamine, N,N-dimethylaniline or N-methylmorpholine, or inorganic bases, such as carbonates, e.g. K_2CO_3 or Na_2CO_3, or hydroxides, e.g. NaOH or KOH, with preference being given to trialkylamines and special preference being given to triethylamine.

Suitable amounts of base for that reaction are, for example, from 1 to 3 equivalents, especially from 1 to 1.3 equivalents.

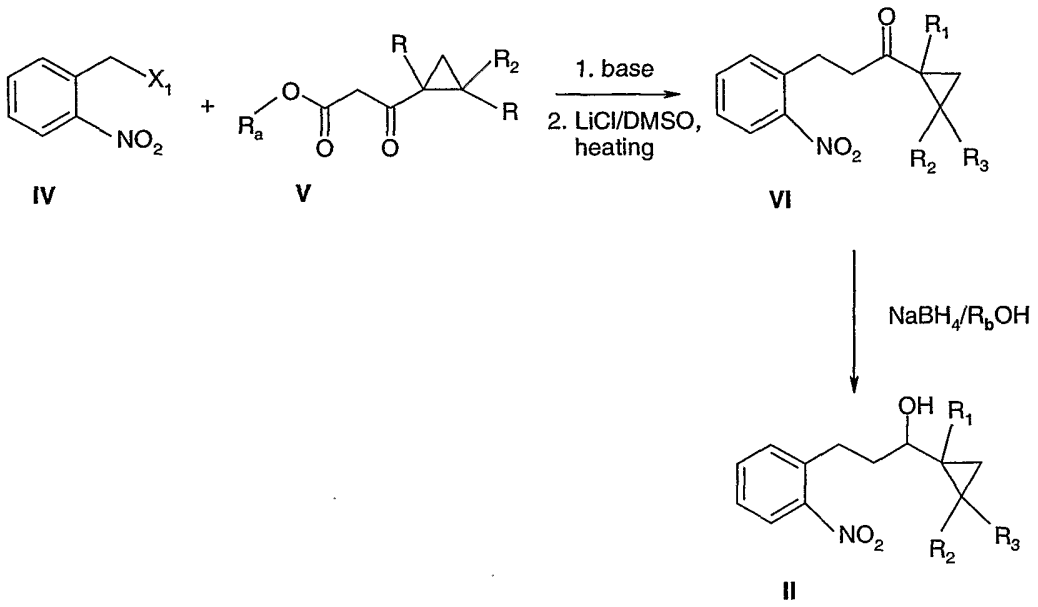
The reaction is preferably carried out in the presence of an inert solvent. Suitable solvents are, for example, dichloromethane, pyridine or ethers, for example tetrahydrofuran, and mixtures thereof, with preference being given to dichloromethane or pyridine, and special preference being given to dichloromethane.

Temperatures are generally from -20°C to 80°C, with a range from -20°C to 25°C being preferred; special preference is given to carrying out the reaction at ambient temperature.

The reaction time for that reaction is generally from 1 to 48 hours, preferably from 1 to 18 hours.

The starting compounds of formula II, wherein R_1, R_2 and R_3 are as defined for formula I, can be prepared, for example, in accordance with the following reaction sequence (see Scheme 2):

Scheme 2:



Compounds of formula IV, wherein X_1 is chlorine or bromine, are reacted with compounds of formula V, wherein R_1, R_2 and R_3 are as defined for formula I and R_a is C_1-C_6alkyl, in a two-step reaction sequence to form compounds of formula VI, wherein R_1, R_2 and R_3 are as defined for formula I. In the first reaction step, compounds of formula IV are reacted with compounds of formula V under basic conditions, for example obtained by addition of NaH,

NaOH or K_2CO_3. After isolation of the crude product, heating in dimethyl sulfoxide (DMSO) in the presence of LiCl is carried out in the second reaction step. The resulting compounds of formula VI can be reacted to form compounds of formula II by addition of sodium borohydride in a protic solvent R_bOH, wherein R_b is C_1-C_6alkyl, such as, for example, isopropanol. Compounds of formula IV, wherein X_1 is chlorine or bromine, are known and are obtainable commercially.

Some of the compounds of formula V, wherein R_1, R_2 and R_3 are as defined for formula I and R_a is C_1-C_6alkyl, are known and are obtainable commercially. The remaining compounds of formula V, wherein R_1, R_2 and R_3 are as defined for formula I and R_a is C_1-C_6alkyl, can be prepared in an analogous manner to preparation processes such as are described, for example, in Journal of Organic Chemistry 68(1), 27-34 (2003) and in Organic Preparations and Procedures International 10(5), 221-224 (1978).

Process Step b):

Suitable bases for Process Step b) are, for example, nitrogen-containing organic bases, such as, for example, tertiary amines, such as trialkylamines, e.g. trimethylamine, triethylamine, diisopropylethylamine (Hünig's Base), or tri-n-butylamine, N,N-dimethylaniline or N-methyl-morpholine, piperidine, pyrrolidine, alkali metal or alkaline earth metal alcoholates, such as, for example, lithium, sodium or potassium alcoholates, especially methanolates, ethanolates or butanolates, or inorganic bases, such as hydroxides, e.g. NaOH or KOH, or hydrides, such as, for example, NaH.

Bases to which preference is given are hydroxides, especially KOH, hydrides, especially NaH, or alkali metal alcoholates, especially potassium tert-butanolate.

Suitable amounts of base for that reaction are, for example, from 1 to 3 equivalents, especially from 1.1 to 1.8 equivalents.

The reaction is preferably carried out in the presence of an inert solvent. Suitable solvents are, for example, alcohols, such as methanol, ethanol, propanol or isopropanol, or aprotic solvents, such as tetrahydrofuran, dimethylformamide, dimethylacetamide, N-methyl-pyrrolidone or dimethyl sulfoxide, and also mixtures thereof; dimethyl sulfoxide or dimethylformamide is especially preferred.

Temperatures are generally from 0°C to 80°C, with a range from 0°C to 25°C being preferred; special preference is given to carrying out the reaction at ambient temperature.

The reaction time for the reaction is generally from 1 to 48 hours, preferably from 1 to 18 hours.

By selecting suitable reaction conditions, the compound of formula III obtained in Reaction Step a) can be converted directly to a compound of formula I without isolation of intermediates. That reaction procedure is a particular advantage of the process according to the invention.

The process according to the invention is suitable for the preparation of compounds of formula I, wherein R_1, R_2 and R_3 are each independently of the others hydrogen or methyl, very especially by

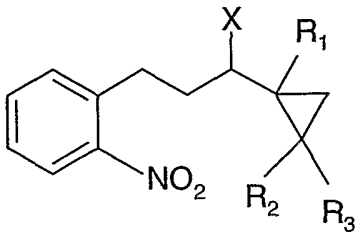
a) reaction of a compound of formula II, wherein R_1, R_2 and R_3 are each independently of the others hydrogen or methyl, with RSO_2Cl, wherein R is C_1-C_4alkyl, in the presence of triethylamine in a temperature range of from -20°C to 25°C, using dichloromethane as solvent, to form a compound of formula III, wherein X is OSO_2-C_1-C_4alkyl and R_1, R_2 and R_3 are as defined for formula I; and

b) conversion of that compound into a compound of formula I in the presence of a base selected from KOH, NaH and potassium tert-butanolate, in a temperature range of from -20°C to 25°C, using a solvent selected from dimethyl sulfoxide and dimethylformamide.

For that preferred embodiment there are especially suitable compounds of formula I wherein R_2 and R_3 are hydrogen.

For that preferred embodiment there are very especially suitable compounds of formula I wherein R_1, R_2 and R_3 are hydrogen.

The compounds of formula III



(III),

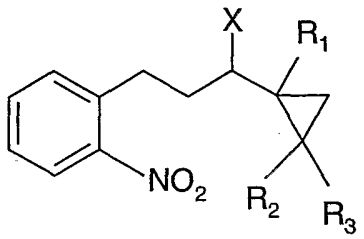
wherein X is bromine, chlorine or OSO_2R, wherein R is C_1-C_4alkyl, C_1-C_4fluoroalkyl, benzyl, phenyl, nitrophenyl, halophenyl or C_1-C_6alkylphenyl, and R_1, R_2 and R_3 are as defined for formula I, are valuable intermediates for the preparation of compounds of formula I and were developed specifically for the present process according to the invention. The present invention accordingly relates also to those compounds.

Especially valuable for the preparation of compounds of formula I are those compounds of formula III wherein X is OSO_2CH_3.

An intermediate especially suitable for the preparation of compounds of formula I is the compound of formula III wherein X is OSO_2CH_3 and R_1, R_2 and R_3 are hydrogen.

Preferred compounds of formula III are listed in the following Table. In the following Table, "Ph" denotes phenyl.

Table 1: Compounds of formula III



(III)

Comp. No.	R_1	R_2	R_3	X
Z1	H	H	H	OSO_2CH_3
Z2	CH_3	H	H	OSO_2CH_3
Z3	H	CH_3	H	OSO_2CH_3
Z4	H	H	CH_3	OSO_2CH_3
Z5	CH_3	CH_3	H	OSO_2CH_3
Z6	CH_3	H	CH_3	OSO_2CH_3
Z7	H	CH_3	CH_3	OSO_2CH_3

Comp. No.	R_1	R_2	R_3	X
Z8	CH_3	CH_3	CH_3	OSO_2CH_3
Z9	H	H	H	OSO_2CH_2Ph
Z10	CH_3	H	H	OSO_2CH_2Ph
Z11	H	CH_3	H	OSO_2CH_2Ph
Z12	H	H	CH_3	OSO_2CH_2Ph
Z13	CH_3	CH_3	H	OSO_2CH_2Ph
Z14	CH_3	H	CH_3	OSO_2CH_2Ph
Z15	H	CH_3	CH_3	OSO_2CH_2Ph
Z16	CH_3	CH_3	CH_3	OSO_2CH_2Ph
Z17	H	H	H	Br
Z18	CH_3	H	H	Br
Z19	H	CH_3	H	Br
Z20	H	H	CH_3	Br
Z21	CH_3	CH_3	H	Br
Z22	CH_3	H	CH_3	Br
Z23	H	CH_3	CH_3	Br
Z24	CH_3	CH_3	CH_3	Br
Z25	H	H	H	Cl
Z26	CH_3	H	H	Cl
Z27	H	CH_3	H	Cl
Z28	H	H	CH_3	Cl
Z29	CH_3	CH_3	H	Cl
Z30	CH_3	H	CH_3	Cl
Z31	H	CH_3	CH_3	Cl
Z32	CH_3	CH_3	CH_3	Cl

The present invention is explained in greater detail by way of the following Examples:

Example P1: Preparation of 2-(2-nitrophenyl)-bicyclopropane:

A mixture of 0.5 g of 1-cyclopropyl-3-(2-nitrophenyl)-propan-1-ol (2.26 mmol), 0.26 g of triethylamine (2.6 mmol) and 12 ml of dichloromethane is cooled to a temperature of 5°C and

0.28 g of methanesulfonic acid chloride, dissolved in 3 ml of dichloromethane, is added dropwise. The resulting mixture is stirred for 16 hours at ambient temperature. The organic phase is washed with ice-water and dried over sodium sulfate and concentrated by evaporation. 1-Cyclopropyl-3-(2-nitrophenyl)-propyl methanesulfonate is obtained in the form of a crude product, which is used directly in the cyclisation.

The 1-cyclopropyl-3-(2-nitrophenyl)-propyl methanesulfonate is dissolved in 15 ml of dimethyl sulfoxide and 0.17 g of potassium hydroxide (2.48 mmol) is added, and stirring is carried out for 5 hours at ambient temperature. The reaction mixture is added to ice-water. Extraction is carried out with ethyl acetate and the organic phase is dried over sodium sulfate and concentrated by evaporation. Chromatography on silica gel is carried out in order to remove by-products (eluant: ethyl acetate / hexane 1:15). After removal of the eluant, 0.28 g of 2-(2-nitrophenyl)-bicyclopropane (61 % of theory) is obtained in the form of a brownish liquid (trans:cis ratio: 4.5:1). ^{1}H-NMR of trans-2-(2-nitrophenyl)-bicyclopropane ($CDCl_3$ - ppm): 0.17/m/1H, 0.19/m/1H, 0.42/m/1H, 0.48/m/1H, 0.83/m/1H, 0.84/m/1H, 0.99/m/1H, 1.13/m/1H, 2.17/m/1H, 7.10/dd/1H, 7.25/m/1H, 7.45/m/1H, 7.78/dd/1H); ^{1}H-NMR of cis-2-(2-nitrophenyl)-bicyclopropane ($CDCl_3$ - ppm): -0.09/m/1H, 0.02/m/1H, 0.06/m/1H, 0.27/m/1H, 0.71/m/1H, 0.85/m/1H, 0.98/m/1H, 1.10/m/1H, 2.53/m/1H, 7.35/m/1H, 7.45/m/1H, 7.52/m/1H, 7.92/dd/1H.

Example P2: Preparation of 2-(2-nitrophenyl)-bicyclopropane:

A mixture of 0.5 g of 1-cyclopropyl-3-(2-nitrophenyl)-propan-1-ol (2.26 mmol), 0.26 g of triethylamine (2.6 mmol) and 12 ml of dichloromethane is cooled to a temperature of 5°C and 0.28 g of methanesulfonic acid chloride, dissolved in 3 ml of dichloromethane, is added dropwise. The resulting mixture is stirred for 16 hours at ambient temperature. The organic phase is washed with ice-water and dried over sodium sulfate and concentrated by evaporation. 1-Cyclopropyl-3-(2-nitrophenyl)-propyl methanesulfonate is obtained in the form of a crude product, which is used directly in the cyclisation.

The 1-cyclopropyl-3-(2-nitrophenyl)-propyl methanesulfonate is dissolved in 15 ml of dimethylformamide and 0.21 g of potassium hydroxide (3.2 mmol) is added, and stirring is carried out for 6 hours at ambient temperature. The reaction mixture is added to ice-water. Extraction is carried out with ethyl acetate, and the organic phase is dried over sodium sulfate and concentrated by evaporation. Chromatography on silica gel is carried out in order to remove by-products (eluant: ethyl acetate / hexane 1:15). After removal of the eluant,

0.28 g of 2-(2-nitrophenyl)-bicyclopropane (61 % of theory) is obtained in the form of a brownish liquid (trans:cis ratio: 4.4:1).

Example P3: Preparation of 2-(2-nitrophenyl)-bicyclopropane:

A mixture of 2.21 g of 1-cyclopropyl-3-(2-nitrophenyl)-propan-1-ol (10 mmol), 1.21 g of triethylamine (12 mmol) and 20 ml of dichloromethane is cooled to a temperature of 5°C and 1.26 g of methanesulfonic acid chloride (11 mmol), dissolved in 5 ml of dichloromethane, are added dropwise. The resulting mixture is stirred for 16 hours at ambient temperature. The organic phase is washed with ice-water and dried over sodium sulfate and concentrated by evaporation. 1-Cyclopropyl-3-(2-nitrophenyl)-propyl methanesulfonate is obtained in the form of a crude product, which is used directly in the cyclisation.

0.48 g of sodium hydride (12 mmol) is introduced into 10 ml of dimethyl sulfoxide and a solution consisting of the 1-cyclopropyl-3-(2-nitrophenyl)-propyl methanesulfonate and 15 ml of DMSO is added. Stirring is then carried out for 5 hours at ambient temperature. The reaction mixture is added to ice-water. Extraction is carried out with ethyl acetate, and the organic phase is dried over sodium sulfate and concentrated by evaporation. Chromatography on silica gel is carried out in order to remove by-products (eluant: ethyl acetate / hexane 1:15). After removal of the eluant, 0.28 g of 2-(2-nitrophenyl)-bicyclopropane (64 % of theory) is obtained in the form of a brownish liquid (trans:cis ratio: 4.1:1).

Example P4: Preparation of 2-(2-nitrophenyl)-bicyclopropane:

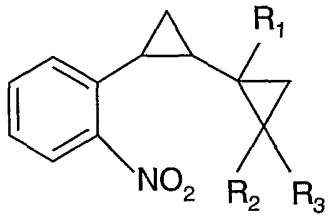
A mixture of 0.5 g of 1-cyclopropyl-3-(2-nitrophenyl)-propan-1-ol (2.26 mmol), 0.26 g of triethylamine (2.6 mmol) and 12 ml of dichloromethane is cooled to a temperature of 5°C and 0.28 g of methanesulfonic acid chloride, dissolved in 3 ml of dichloromethane, is added dropwise. The resulting mixture is stirred for 16 hours at ambient temperature. The organic phase is washed with ice-water and dried over sodium sulfate and concentrated by evaporation. 1-Cyclopropyl-3-(2-nitrophenyl)-propyl methanesulfonate is obtained in the form of a crude product, which is used directly in the cyclisation.

The 1-cyclopropyl-3-(2-nitrophenyl)-propyl methanesulfonate is dissolved in 15 ml of dimethyl sulfoxide and 0.28 g of potassium tert-butanolate (2.48 mmol) is added, and stirring is carried out for 3 hours at ambient temperature. The reaction mixture is added to ice-water. Extraction is carried out with ethyl acetate, and the organic phase is dried over sodium sulfate and concentrated by evaporation. Chromatography on silica gel is carried out in order to remove by-products (eluant: ethyl acetate / hexane 1:15). After removal of the eluant,

0.3 g of 2-(2-nitrophenyl)-bicyclopropane (65 % of theory) is obtained in the form of a brownish liquid (trans:cis ratio: 4.7:1).

The following compounds of formula I can be prepared according to the above Examples:

Table 2: Compounds of formula I



(I)

Comp. No.	R_1	R_2	R_3
A1	H	H	H
A2	CH_3	H	H
A3	H	CH_3	H
A4	H	H	CH_3
A5	CH_3	CH_3	H
A6	CH_3	H	CH_3
A7	H	CH_3	CH_3
A8	CH_3	CH_3	CH_3

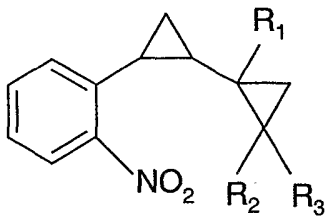
The starting materials for the process of the present invention are distinguished by ease of availability and good handling properties and are moreover reasonably priced.

A further advantage of the process is that the ratio of trans isomers of formula Ia to cis isomers of formula Ib at the 2-(2-nitrophenyl)-bicyclopropane Step is sufficiently high for 2-(2-aminophenyl)-bicyclopropanes having a trans:cis ratio significantly higher than described in the prior art to be prepared by simple subsequent conversion reactions, such as, for example, reduction reactions. Generally, trans:cis ratios of the prepared 2-(2-nitrophenyl)-bicyclopropanes of more than 3:1 are achieved.

In accordance with the present process, compounds of formula I can be prepared in simple manner wherein the ratio of compounds of formula Ia (trans) to compounds of formula Ib (cis) is from 3:1 to 5:1.

What is claimed is:

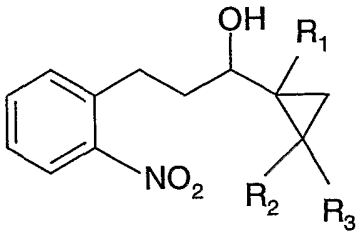
1. A process for the preparation of a compound of formula I



(I),

wherein R_1, R_2 and R_3 are each independently of the others hydrogen or methyl, which comprises

a) reaction of a compound of formula II



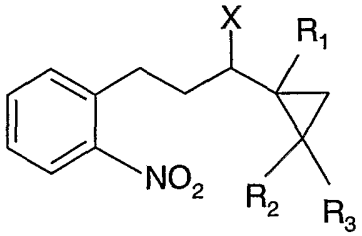
(II),

wherein R_1, R_2 and R_3 are as defined for formula I, either

a1) with triphenylphosphine dibromide or triphenylphosphine dichloride or

a2) with RSO_2Cl, wherein R is C_1-C_4alkyl, C_1-C_4fluoroalkyl, benzyl, phenyl, nitrophenyl, halophenyl or C_1-C_6alkylphenyl, in the presence of a base,

to form a compound of formula III

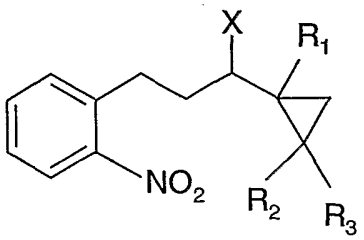


(III),

wherein X is OSO_2R wherein R is C_1-C_4alkyl, C_1-C_4fluoroalkyl, benzyl, phenyl, nitrophenyl, halophenyl or C_1-C_6alkylphenyl, or is bromine or chlorine and R_1, R_2 and R_3 are as defined for formula I; and

b) conversion of that compound in the presence of a base into a compound of formula I.

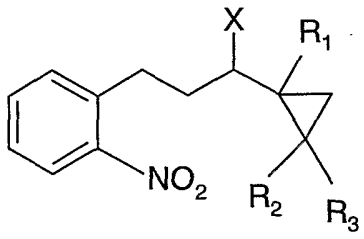
2. A compound of formula III



(III),

wherein R_1, R_2 and R_3 are as defined for formula I in claim 1 and X is as defined for formula III in claim 1.

3. Use of a compound of formula III



(III),

wherein R_1, R_2 and R_3 are as defined for formula I in claim 1 and X is as defined for formula III in claim 1, in the preparation of a compound of formula I according to claim 1.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/001506

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C201/12 C07C205/06 C07C205/19 C07C309/65 A01N33/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07C A01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 03/074491 A (SYNGENTA PARTICIPATIONS AG; EHRENFREUND, JOSEF; TOBLER, HANS; WALTER,) 12 September 2003 (2003-09-12) cited in the application page 20, Scheme 1B, "X -> XI"; page 21, line 20 - page 22, line 7; examples; claims	1-3

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 July 2006	28/07/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Sen, A

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/001506

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	TURNBULL M D: "Productivity in synthesis: a mixture protocol to raise compound output is demonstrated for asymmetric cyclopropanation of allyl alcohols" JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1, CHEMICAL SOCIETY. LETCHWORTH, GB, no. 8, 21 April 1997 (1997-04-21), pages 1241-1248, XP002175166 ISSN: 0300-922X page 1242, Scheme 1; page 1243, Table 2; pages 1244 - 1246, "Experimental"	1-3

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/001506

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		JP 2005532271 T	27-10-2005
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		US 2005221989 A1	06-10-2005