The present invention relates to a process for providing substituted aryl ketones. Furthermore, the invention relates to intermediates of said process and the use of substituted aryl ketones obtained by the inventive process for the preparation of triazole compound of formula (I).
PROCESS FOR THE PREPARATION OF SUBSTITUTED ARYL KETONES

FIELD OF THE INVENTION

The present invention relates to a process for providing substituted aryl ketones. Furthermore, the invention relates to intermediates of said process and the use of substituted aryl ketones obtained by the inventive process for the preparation of triazole compound of formula (I).

BACKGROUND OF THE INVENTION

The aryl ketones provided by the process according to the present invention are valuable intermediate compounds for the synthesis of triazole compounds having pesticidal, in particular fungicidal activity. Triazole compounds that are accessible via aryl ketone intermediate are, for example, described in WO 2013/007767 (PCT/EP2012/063626) and WO 2014/108286 (PCT/EP2013/077083) that are directed to fungicidal substituted 2-[2-halogenoalkyl-4-phenoxyphenyl]-1-[1,2,4]triazole-yl-ethanol compounds.


The known art describes the use of stoichiometric amounts of organometallic reagents, that too frequently, in the presence of transition metal catalyst. For example, the use of a stoichiometric amount of magnesium leads to a high waste stream which requires extensive solvent recovery, waste throughput and waste treatment. Another disadvantage associated with the prior art is the use of a semi-batch process, which requires maintenance of variable temperature range at different reaction stages and, thus, the constant monitoring of the reaction becomes necessary.

Further, the processes known in the literature to prepare a compound analogous to the compound of formula V and/or Va are either disadvantageous in terms of the reaction conditions, the yields, and/or the work-up requirements or suffer from several limitations rendering them hardly suitable for industrial scale production. Substituted aryl ketones compounds, particularly compounds of formula V and/or Va can be used as versatile intermediates in the preparation of several heterocyclic derivatives. Consequently, the methods known in the art are sometimes not suitable for the efficient synthesis of substituted aryl ketones compounds, particularly compounds of formula V and/or Va.

An object of the present invention was to provide an improved process for the synthesis of substituted aryl ketones that are valuable intermediates for the preparation of fungicidal active triazole compounds. The invention also relates to intermediates of said process. Furthermore, the object underlying the present invention was to optimize the synthesis of triazole compounds using said aryl ketones. The present invention includes several advantages, for example, more efficient process having minimal waste throughput and waste treatment. The presently claimed process is shown to avoid the need for carefully controlled reaction conditions, tedious multiple purification techniques, and the use of stoichiometric amounts of organometallic reagents.
Description

This object is achieved by the processes described in detail hereafter.

A first aspect of the present invention relates to a process for the preparation of a compound of the general formula (I) or its salts

\[
\text{R}^2
\]

wherein

\( R^2 \) is hydrogen, C1-C6-alkyl, C2-C6-alkenyl, C2-C6-alkynyl, Cs-Cs-cycloalkyl, Cs-Cs-cycloalkyl-Ci-C6-alkyl, phenyl, phenyl-Ci-C4-alkyl, phenyl-C2-C4-alkenyl or phenyl-C2-C4-alkynyl; whereby the aliphatic moieties of \( R^2 \) are unsubstituted or further substituted by 1, 2 or 3 identical or different groups \( R^{12a} \) which are independently selected from the group consisting of halogen, OH, CN, nitro, Ci-C4-alkoxy, Cs-Cs-cycloalkyl, Cs-Cs-halocycloalkyl, C1-C4-halogenalkoxy and phenyl moieties or \( R^2 \) are unsubstituted or further substituted by 1, 2, 3, 4 or 5 identical or different groups \( R^{12b} \) which are independently selected from halogen, OH, CN, nitro, Ci-C4-alkoxy, Cs-Cs-cycloalkyl, Cs-Cs-halocycloalkyl and C1-C4-halogenalkoxy; and

\( R^4 \) is F or Cl; comprising at least the steps of:

(A) reacting a compound of formula (II)

\[
\text{R}^2
\]

wherein

\( R^3 \) is F and \( X \) is Br, Cl, I or Ci-C4-alkoxy; or

\( R^3 \) is Cl and \( X \) is Br, I, SO3-CF3, SO3-C4H6-CH3, S03-CH3 or Ci-C4-alkoxy; or

\( R^3 \) is

\[
\text{R}^4
\]

wherein \( R^4 \) is F or Cl, and \( X \) is Br, I, SO3-CF3, SO3-C4H6-CH3, SO3-CH3 or Ci-C4-alkoxy; with a compound of general formula (III)

\[
\text{R}^1
\]

wherein

\( R^1 \) is OR5 or NR6R7, wherein \( R^5 \) is d-Ce-alkyl or Cs-Cs-cycloalkyl, and \( R^6 \) and \( R^7 \), identical or different, are hydrogen, Ci-C6-alkyl, Cs-Cs-cycloalkyl, or C(=0)-Ci-C6-alkyl.
in the presence of at least one metal, at least one base and at least one phosphine compound,

to obtain a compound of general formula (IV),

\[ R^3 - CF_3 \]

\[ R^1 \]

(IV)

wherein

\[ R^3 \] is F, Cl or

\[ \text{phenyl} \]

10

wherein \[ R^4 \] is \text{F or Cl};

\[ R^1 \] is \text{OR}^5 \text{ or } \text{NR}^6 \text{R}^7, \text{wherein } \text{R}^5 \text{ is } \text{d-Ce-alkyl or C}_3\text{-C}_8\text{-cycloalkyl, and R}^6 \text{ and R}^7 \text{, identical or different, are hydrogen, C}i\text{-C6-alkyl, Cs-Cs-cycloalkyl;}

15 (B) converting a compound of general formula (IV) in the presence of at least one acid or at least one base or at least one buffer into a compound of general formula (V) or (Va),

\[ R^3 - CF_3 \]

\[ R^1 \]

(V) or (Va),

wherein

in a compound of formula (V) \[ R^3 \] is F or Cl and

in a compound of formula (Va) \[ R^3 \] is

wherein \[ R^4 \] is F or Cl.

25

The process of preparing compound of formula (I) further comprising the step of

(C) converting the compound of general formula (V) in the presence of at least one base into a compound of general formula (Va)

\[ R^4 - \text{phenyl} - \text{CF}_3 \]

(Va)

wherein

\[ R^4 \] is F or Cl.

The process of preparing compound of formula (I) further comprising the steps of
(D) converting the compound of formula (Va) in the presence of trimethylsulf(ox)onium halide ((CH$_3$)$_3$S $\cdot$ (O)Hah) (VII), wherein Hal is halogen, or in the presence of trimethylsulfonium methylsulfate of the formula (VIII) (CH$_3$)$_3$S$^+$ CH$_3$SO$_4^- $, into a compound of general formula (VI),

\[
\begin{array}{c}
\text{R}^4
\end{array}
\]

wherein

R$^4$ is F or Cl,

(E) reacting the compound of formula (VI) with 1H-1,2,4-triazole in the presence of at least one base to obtain compounds of formula (I), wherein R$^2$ is hydrogen, and

(F) optionally reacting a compound of formula (I), wherein R$^2$ is hydrogen, in the presence of at least one base with at least one compound of formula R$^2$-LG; wherein LG is a leaving group and R$^2$ is Ci-C6-alkyl, C2-C6-alkenyl, C2-C6-alkynyl, Cs-Cs-cycloalkyl, C3-Cs-cycloalkyl-Ci-C6-alkyl, phenyl, phenyl-Ci-C4-alkyl, phenyl-C2-C4-alkenyl or phenyl-C2-C4-alkynyl; whereby the aliphatic moieties of R$^2$ are unsubstituted or further substituted by 1, 2 or 3 identical or different groups R$_{12a}$ which are independently selected from the group consisting of halogen, OH, CN, nitro, Ci-C4-alkoxy, Cs-Cs-cycloalkyl, Cs-Cs-halocycloalkyl and Ci-C4-halogenalkoxy and the cycloalkyi and phenyl moieties or R$^2$ are unsubstituted or further substituted by 1, 2, 3, 4 or 5 identical or different groups R$_{12b}$ which are independently selected from halogen, OH, CN, nitro, Ci-C4-alkoxy, Cs-Cs-cycloalkyl, Cs-Cs-halocycloalkyl and Ci-C4-halogenalkoxy;

10 to obtain a compound of general formula (I),

wherein R$^2$ is Ci-C6-alkyl, C2-C6-alkenyl, C2-C6-alkynyl, Cs-Cs-cycloalkyl, C3-Cs-cycloalkyl-Ci-C6-alkyl, phenyl, phenyl-Ci-C4-alkyl, phenyl-C2-C4-alkenyl or phenyl-C2-C4-alkynyl; whereby the aliphatic moieties of R$^2$ are unsubstituted or further substituted by 1, 2 or 3 identical or different groups R$_{12a}$ which are independently selected from the group consisting of halogen, OH, CN, nitro, Ci-C4-alkoxy, Cs-Cs-cycloalkyl, Cs-Cs-halocycloalkyl and Ci-C4-halogenalkoxy and the cycloalkyi and phenyl moieties or R$^2$ are unsubstituted or further substituted by 1, 2, 3, 4 or 5 identical or different groups R$_{12b}$ which are independently selected from halogen, OH, CN, nitro, Ci-C4-alkoxy, Cs-Cs-cycloalkyl, Cs-Cs-halocycloalkyl and Ci-C4-halogenalkoxy.

Further aspect of the present invention relates to a process for the preparation of a compound of the general formula (I) or its salts according to following reaction sequence:
The $R^1$, $R^2$, $R^3$ and $R^4$ are as defined above.

Starting materials used in the process are commercially available or can be prepared by methods known in the literature.

The "present invention", "invention" or "process of the present invention" refers to one or more of the steps (A), (B), (C), (D), (E) and (F).

Salts of the compounds according to the invention can be formed in a customary manner, for example, by reacting the compound with an acid of the anion in question if the compounds according to the invention have a basic functionality or by reacting acidic compounds according to the invention with a suitable base. Salts of the compounds prepared according to the invention are preferably agriculturally and/or veterinary acceptable salts, preferably agriculturally acceptable salts.

The organic moieties or groups mentioned in the above definitions of the variables are - like the term halogen - collective terms for individual listings of the individual group members. The term "Cv-Cw" indicates the number of carbon atom possible in each case.

The term "halogen" refers to fluoro, chloro, bromo and iodo.

The term "Ci-C6-alkyl" refers to a straight-chained or branched saturated hydrocarbon group having 1 to 6 carbon atoms, for example, methyl, ethyl, propyl, 1-methylethyl, butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 2,2-dimethylpropyl, 1-ethylpropyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, hexyl, 1-methyloctyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylethyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-ethylbutyl, 2-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-1-methylpropyl and 1-ethyl-2-methylpropyl. Likewise, the term "Ci-Ci2-alkyl" refers to a straight-chained or branched alkyl group having 1 to 12 carbon atoms, such as ethyl, n-propyl, 1-methylethyl, octyl, 1-methylpropyl, 2-methylethyl and 1,1-dimethylethyl.

The term "Ci-C6-haloalkyl" refers to an alkyl group having 1 or 6 carbon atoms as defined above, wherein some or all of the hydrogen atoms in these groups may be replaced by halogen atoms as mentioned above. Examples are "Ci-C2-haloalkyl" groups such as chloromethyl, bromomethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, chlorofluoromethyl, dichlorofluoromethyl, chlorodifluoromethyl, 1-chloroethyl, 1-bromoethyl, 1-fluoroethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 2-chloro-2-fluoroethyl, 2-chloro-2,2-difluoroethyl, 2,2-dichloro-2-fluoroethyl, 2,2,2-trichloroethyl or pentafluoroethyl.
The term "C2-C6-alkenyl" refers to a straight-chain or branched unsaturated hydrocarbon radical having 2 to 6 carbon atoms and a double bond in any position. Examples are "C2-C4-alkenyl" groups, such as ethenyl, 1-propenyl, 2-propenyl, 1-methylethenyl, 1-butanyl, 2-butenyl, 3-butenyl, 1-methyl-1-propenyl, 2-methyl-1-propenyl, 1-methyl-2-propenyl, 2-methyl-2-propenyl. The term "C2-C6-alkynyl" refers to a straight-chain or branched unsaturated hydrocarbon radical having 2 to 6 carbon atoms and containing at least one triple bond. Examples are "C2-C4-alkynyl" groups, such as ethynyl, prop-1-ynyl, prop-2-ynyl, but-1-ynyl, but-2-ynyl, but-3-ynyl, 1-methyl-prop-2-ynyl.

The term "Cs-Cs-cycloalkyl" refers to monocyclic saturated hydrocarbon radicals having 3 to 8 carbon ring members, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl.

The term "C3-C8-cycloalkyl-C4-alkyl" refers to alkyl having 1 to 4 carbon atoms (as defined above), wherein one hydrogen atom of the alkyl radical is replaced by a cycloalkyl radical having 3 to 8 carbon atoms (as defined above).

The term "Cs-Cs-halocycloalkyl" refers to monocyclic saturated hydrocarbon radicals having 3 to 8 carbon ring members (as defined above), wherein one hydrogen atom is replaced by halogen, such as halocyclopropyl, in particular 1-fluorocyclopropyl or 1-chlorocyclopropyl.

The term "Ci-C4-alkoxy" refers to a straight-chain or branched alkyl group having 1 to 4 carbon atoms which is bonded via an oxygen, at any position in the alkyl group. Examples are "C1-C4-alkoxy" groups, such as methoxy, ethoxy, n-propoxy, 1-methylethoxy, butoxy, 1-methylpropoxy, 2-methylpropoxy or 1,1-dimethylethoxy.

The term "Ci-C4-haloalkoxy" refers to a Ci-C4-alkoxy radical as defined above, wherein some or all of the hydrogen atoms in these groups may be replaced by halogen atoms as mentioned above. Examples are "Ci-C4-haloalkoxy" groups, such as OCH2F, OCHF2, OCF3, OCH2Cl, OCHCl2, OCCI3, chlorofluoromethoxy, dichlorofluoromethoxy, chlorodifluoromethoxy, 2-fluoroethoxy, 2-chloroethoxy, 2-bromoethoxy, 2-iodoethoxy, 2,2-difluoroethoxy, 2,2,2-trifluoroethoxy, 2-chloro-2-fluoroethoxy, 2-chloro-2,2-difluoroethoxy, 2,2-dichloro-2-fluoroethoxy, 2,2,2-trichloroethoxy, OC2F5, 2-fluoroproxy, 3-fluoroproxy, 2,2-difluoroproxy, 2-chloropropoxy, 3-chloropropoxy, 2,3-dichloroproxy, 2-bromo-propoxy, 3-bromopropoxy, 3,3,3-trifluoroproxy, 3,3,3-trichloroproxy, OCH2-C2F5, OCF2-C2F5, 1-fluoromethyl-2-fluoroethoxy, 1-chloromethyl-2-chloroethoxy, 1-bromomethyl-2-bromoethoxy, 4-fluorobutoxy, 4-chlorobutoxy, 4-bromobutoxy or nonafluorobutoxy.

The term "phenyl-Ci-C4-alkyl" refers to alkyl having 1 to 6 carbon atoms (as defined above), wherein one hydrogen atom of the alkyl radical is replaced by a phenyl radical. Likewise, the terms "phenyl-C2-C4-alkenyl" and "phenyl-C2-C4-alkynyl" refer to alkenyl and alkynyl, respectively, wherein one hydrogen atom of the aforementioned radicals is replaced by a phenyl radical.

The term "C5-Ci4-aryl" refers to represents Cs-Cu-aryl radicals, for example phenyl or naphthyl.

The term "C5-Ci2-heteroaryl" means an aryl group where at least one carbon atom on the hydrocarbon chain normally carrying 5 to 12 carbon atoms is substituted by another atom selected from N, O, or S, for example, pyridyl, pyrimidyl, pyrazinyl, pyridaziny, triazinyl, thiényl, furanyl, pyrrolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, triazolyl, thiazadiazolyl, oxadiazolyl, and tetrazolyl rings, and the fused bicyclic moieties formed by fusing one of these monocyclic groups with a phenyl ring or any of the heteroaromatic monocyclic groups to form a Cs-C10 bicyclic group such as indolyl, benzimidazolyl, indazolyl, benzotriazolyl, isoquino-
linyl, quinolinyl, benzothiazolyl, benzofuranyl, benzothienyl, benzisoxazolyl, pyrazolopyridyl, quinazolinyl, quinoxaliny1, cinnolinyl, and the like. Any monocyclic or fused ring bicyclic system which has the characteristics of aromaticity in terms of electron distribution throughout the ring system is included in this definition.

The term "Cs-Cs-cycloalkenyl" refers to monocyclic unsaturated hydrocarbon radical having 3 to 8 carbon ring members and a double bond in any position, for example cyclobut enyl, cyclopentenyl, cyclohexenyl or cyclooctenyl.

The term "C5-C12-membered heterocycloalkyl" refers to saturated 5 to 12 membered, hydrocarbon cycle having one free valence wherein one or more of the carbon atoms of the saturated cycle is replaced, independently from each other, by a heteroatom selected from N, S, O and P.

For examples C3-C6-membered heterocycloalkyl are cyclopropyl, oxiranyl, cyclopentyl, pyrro lidyl, cyclohexyl, piperidyl and morpholinyl.

The term "C5-C14-membered heterocycloalkenyl" refers to monovalent or bivalent nonaromatic 5 to 8 membered monocyclic, 8 to 12 membered bicyclic, or 11 to 14 membered tricyclic ring system having one or more heteroatoms, such as O, N, S, P or Se and one or more double bonds.

The term "buffer" refers to that resists change in pH and contains either a weak acid and a soluble ionic salt of the acid or a weak base and a soluble ionic salt of the base.

The term "substituted" if not specified otherwise refers to substituted with 1, 2 or maximum possible number of substituents. If substituents are more than one, then they are independently from each other are same or different, if not mentioned other-wise.

Meaning of the terms that are not defined herein are generally known to a person skilled in the art or in the literature.

Preferred embodiments of the present invention are described below.

Step (A) of the present invention for the preparation of formula (I) is particularly as follows.

(A) Reacting a compound of formula (II)

\[
\begin{align*}
&\text{CF}_3 \\
&\quad \text{X} \\
&\quad (\text{II}) \\
&\text{R}^3 \\
&\quad \text{is } F \text{ and } X \text{ is } Br, Cl, I \text{ or } C_4\text{-alkoxy;} \text{ or} \\
&\text{R}^3 \\
&\quad \text{is } Cl \text{ and } X \text{ is } Br, I, SO_3\text{-CF}_3, SO_3\text{-C}_4\text{H}_6\text{-CH}_3, SO_3\text{-CH}_3 \text{ or } C_4\text{-alkoxy;} \text{ or} \\
&\text{R}^3 \\
&\quad \text{is } \\
&\quad \begin{aligned}
&\text{R}^4 \\
&\quad \text{is } F \text{ or } Cl, \text{ and } X \text{ is } Br, I, SO_3\text{-CF}_3, \\
&\quad \text{SO}_3\text{-C}_4\text{H}_6\text{-CH}_3, \text{ SO}_3\text{-CH}_3 \text{ or } C_4\text{-alkoxy;} \\
&\quad \text{with a compound of general formula (III)} \\
&\quad (\text{III}) \\
&\text{R}^1 \\
&\quad \text{is } OR^5 \text{ or } NR^6R^7, \text{ wherein } R^5 \text{ is } d\text{-Ce-alkyl or } C_2\text{-C}_8\text{-cycloalkyl, and } R^6 \text{ and}
\end{aligned}
\end{align*}
\]
R^7 are, identical or different, are hydrogen, C_{1-6}-alkyl, C_{6-8}-cycloalkyl, or C(=0)-C_{1-6}-alkyl in the presence of at least one metal, at least one base and at least one phosphine compound, to obtain a compound of general formula (IV),

![Chemical Structure](image)

(IV)

wherein
R^3 is F, Cl or

10 wherein R^4 is F or Cl;

R^1 is OR^6 or NR^6R^7, wherein R^5 is C_{1-6}-alkyl or C_{3-8}-cycloalkyl, and R^6 and R^7, identical or different, are hydrogen, C_{1-6}-alkyl, C_{6-8}-cycloalkyl.

In one embodiment of the invention, R^1 is OR^6 or NR^6R^7, wherein R^5 is C_{1-6}-alkyl or C_{3-8}-cycloalkyl, and R^6 and R^7 are, identical or different, are hydrogen, C_{1-6}-alkyl, C_{6-8}-cycloalkyl, or C(=0)-C_{1-6}-alkyl.

In another embodiment, R^1 is OR^6 wherein R^5 is C_{1-4}-alkyl or C_{6-8}-cycloalkyl.

In another embodiment, R^5 is ethyl, n-propyl, iso-butyl or n-butyl.

In another embodiment, R^5 is n-butyl or iso-butyl.

20 In another embodiment, R^1 is NR^6R^7 wherein R^6 and R^7 are, identical or different, are hydrogen, C_{1-6}-alkyl, C_{6-8}-cycloalkyl, or C(=0)-C_{1-6}-alkyl.

In one embodiment of the invention, R^2 is hydrogen, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-6}-cycloalkyl, C_{3-6}-cycloalkyl-C_{1-6}-alkyl, phenyl, phenyl-C_{1-4}-alkyl, phenyl-C_{2-4}-alkenyl or phenyl-C_{2-4}-alkynyl; whereby the aliphatic moieties of R^2 are unsubstituted or further substituted by 1, 2 or 3 identical or different groups R^{12}_{a} which are independently selected from the group consisting of halogen, OH, CN, nitro, C_{1-4}-alkoxy, C_{6-8}-cycloalkyl, C_{6-8}-halocycloalkyl, C_{1-4}-halogenalkoxy and phenyl moieties of R^2 are unsubstituted or further substituted by 1, 2, 3, 4 or 5 identical or different groups R^{12}_{b} which are independently selected from halogen, OH, CN, nitro, C_{1-4}-alkoxy, C_{6-8}-cycloalkyl, C_{6-8}-halocycloalkyl and C_{1-4}-halogenalkoxy.

30 In another embodiment, R^2 is hydrogen, C_{1-6}-alkyl, C_{6-8}-cycloalkyl, allyl, propargyl or benzyl.

In another preferred embodiment, R^2 is hydrogen, methyl, ethyl, n-propyl, n-butyl or benzyl.

In yet another preferred embodiment, R^2 is hydrogen.

35 In another preferred embodiment R^3 is F, Cl or, more preferably R^3 is F.

In one embodiment in step (A), X is BR, CI, I, SO3-CF3, SO3-C4H6-CH3, SO_{3}-CH_{3} or C_{1-6}-alkoxy.

In yet another embodiment X is BR, CI, I, SO3-CF3, SO_{3}-H_{e} -CH{3} or SO{3}-CH{3}.

39 In another preferred embodiment R^3 is F or Cl and X is C_{1-6}-alkoxy.

In another preferred embodiment R^3 is C_{1-6}-alkoxy.
In another preferred embodiment, R³ is F and X is Cl.

In yet another preferred embodiment, R³ is

and X is Br, Cl, l, SO₃-CF₃, SO₃-C₄H₆-CH₃, SO₃CH₃ or C₁-C₆-alkoxy.

In more preferred embodiment, R³ is F and X is Br.

In one embodiment, R⁴ is F or Cl.

In preferred embodiment, R⁴ is Cl.

The temperatures and the duration times of the reactions may be varied in broad ranges, which

the person skilled in the art knows from analogous reactions. The temperatures often depend

on the reflux temperature of the solvents or at higher temperature under pressure. Other reac-
tions are preferably performed at room temperature, for example, at about 25°C, or under ice

cooling, for example, at about 0°C. The end of the reaction can be monitored by methods

known to a person skilled in the art, for example, thin layer chromatography or HPLC or GC.

In an embodiment, the volume ratio of reactants to solvent is in the range of 1:40 to 1:0.

In another embodiment, the volume ratio of reactants to solvent is in the range of 1:40 to 1:5.

If not otherwise indicated, the reactants can in principle be contacted with one another in any

desired sequence.

The person skilled in the art knows when the reactants or reagents are moisture sensitive, so

that the reaction should be carried out under inert gases such as under a nitrogen atmosphere,

and dried solvents should be used.

The person skilled in the art also knows the best work-up of the reaction mixture after the end of

the reaction.

In the present invention, step (A) takes place in the presence of at least one metal, at least one

base and at least one phosphine compound and optionally at least one solvent, wherein the at

least one metal is preferably in a form of a free state of formula M or in a form of a metal com-

plex of formula M(L)_n.

In the present invention, step (A) takes preferably place in the presence of at least one metal, at

least one base, at least one phosphine compound and at least one solvent, wherein the at least

one metal is preferably in a form of a free state of formula M or in a form of a metal complex of

formula M(L)_n.

In the following, preferred embodiments regarding step (A) of the invention are provided. It is to

be understood that the preferred embodiments mentioned above and those still to be illustrated

below of step (A) of the invention are to be understood as preferred alone or in combination with

each other.

In one embodiment, the at least one metal (M) is selected from the group consisting of nickel

(Ni), cobalt (Co), iron (Fe), ruthenium (Ru), rhodium (Rh), palladium (Pd), iridium (Ir), platinum

(Pt), silver (Ag), copper (Cu), zinc (Zn), molybdenum (Mo) and tungsten (W).

In preferred embodiment, at least one metal (M) selected from the group consisting of palladi-

um (Pd), nickel (Ni), copper (Cu) and iron (Fe).

In one embodiment L, identical or different, is Cl, Br, i, P(C₅-C₂₆-aryl)m, P(C₅-C₂₆-heteroaryl)m,

P(C₅-C₂₆-heteroaryl)(C₅-C₂₆-aryl)₃-n, CN, C₁-C₆-alkyl, C₁-C₆-alkyl-0-C₁-C₆-alkyl, -CO-C₁-C₆-alkyl,

OH, nitro, -O-C₁-C₆-alkyl, C₁-C₆-haloalkoxy, C₃-C₆-cycloalkyl, C₃-C₆-cycloalkyl, C₃-C₆-cycloalkenyl,

C₁-C₆-aryl, C₅-C₂₆-aryl-(CH₂)ₙ-Q(CH₂)ₚ-Q(C₅-C₂₆-aryl and 1.1'-b(s(diphenyl phos-
phino)ferrocene; whereby Q represents a bridging group selected from the group consisting of -CR\textsuperscript{6}R\textsuperscript{9}, -0-, -S-, -NR\textsuperscript{10}R\textsuperscript{11}, -SiR\textsuperscript{12}R\textsuperscript{13} and -CO-, wherein R\textsuperscript{6} and R\textsuperscript{9}, identical or different, are hydrogen, C\textsubscript{1}-C\textsubscript{12} alkyl, Cs-C\textsubscript{u}-aryl or Cs-C\textsubscript{2}-heteroaryl; wherein R\textsuperscript{10}, R\textsuperscript{11}, R\textsuperscript{12} and R\textsuperscript{13}, identical or different, are hydrogen or C\textsubscript{1}-C\textsubscript{4} alkyl or R\textsuperscript{10} together with R\textsuperscript{11} forms Cs-C\textsubscript{2}-membered heterocycloalkyl, Cs-C\textsubscript{2}-membered heterocycloalkenyl or Cs-C\textsubscript{2}-membered heteroaryl and L is unsubstituted or further substituted by 1, 2, 3, 4 or 5 identical or different groups selected from the group consisting of Cl; F; Br; I; CN; -NO\textsubscript{2}; -NR\textsuperscript{10}R\textsuperscript{11}; -P(phenyl)\textsubscript{2}; -OH, unsubstituted or substituted Ci-C\textsubscript{2}-alkyl, C\textsubscript{2}-C\textsubscript{6}-alkenyl, C\textsubscript{2}-C\textsubscript{6}-alkynyl, unsubstituted or substituted Cs-C\textsubscript{u}-aryl, unsubstituted or substituted Cs-C\textsubscript{2}-heteroaryl, Cs-C\textsubscript{2}-membered heterocycloalkyl, Cs-C\textsubscript{2}-membered heterocycloalkenyl, -0-(CH\textsubscript{2})\textsubscript{r}-0-, -C(=0)R\textsuperscript{14}, -C(=0)-0-R\textsuperscript{15}, -C=N-R\textsuperscript{16}, -SO\textsubscript{3}H, -O-C\textsubscript{1}-C\textsubscript{6}-alkyl and -0-Si-C\textsubscript{4}-alkyl; wherein R\textsuperscript{14} is hydrogen or Ci-C\textsubscript{4}-alkyl; R\textsuperscript{15} is hydrogen or Ci-C\textsubscript{4}-alkyl; R\textsuperscript{16} is hydrogen, Ci-C\textsubscript{2}-alkyl, C\textsubscript{2}-C\textsubscript{6}-alkenyl, C\textsubscript{2}-C\textsubscript{6}-alkynyl, Cs-C\textsubscript{u}-aryl, Cs-C\textsubscript{2}-heteroaryl or C\textsubscript{5}-C\textsubscript{2}-cycloalkyl; n is 0, 1, 2, 3, 4, 5 or 6; m is 1.2 or 3; o is 0.1 or 2; p is 0.1 or 2 and r is 1, 2, 3, 4 or 5.

In yet another embodiment, L is, identical or different, Cl, Br, I, P(Cs-C\textsubscript{4}-aryl)\textsubscript{m}, CN, unsubstituted or substituted Ci-C\textsubscript{2}-alkyl, Ci-C\textsubscript{4}-alkoxy, Cs-Cs-cycloalkenyl, -0-CO-Ci-C\textsubscript{6}-alkyl, Cs-C\textsubscript{u}-aryl, 1,1'-b/s(diphenyl phosphino)ferrocene and Cs-C\textsubscript{4}-aryl-(CH\textsubscript{2})\textsubscript{o}-(Q)p-(CH\textsubscript{2})\textsubscript{o}Cs-C\textsubscript{4}-aryl; wherein m is 1.2 or 3; o is 0.1 or 2; p is 0.1 or 2.

In more preferred embodiment L is Cl, -OC\textsubscript{3}CH\textsubscript{3}, P(Phenyl)\textsubscript{3}, P(o-tolyl)\textsubscript{3}, CN, dibenzylic acetone, -CH\textsubscript{3}CN, 1,5-cyclooctadiene or 1,1'-b/s(diphenyl phosphino) ferrocene.

In another embodiment Ln is supported on silica gel, dendrimers, polystyrenes or mesoporous siliceous foam, for example as described in Vivek et al., Tetrahedron, 63, 2007, 6949-6976.

In another embodiment R\textsuperscript{8} is hydrogen, C\textsubscript{1}-C\textsubscript{12} alkyl, Cs-C\textsubscript{u}-aryl or Cs-C\textsubscript{2}-heteroaryl.

In another embodiment R\textsuperscript{8} is hydrogen, methyl or ethyl.

In another embodiment R\textsuperscript{9} is hydrogen, C\textsubscript{1}-C\textsubscript{12} alkyl, Cs-C\textsubscript{u}-aryl or Cs-C\textsubscript{2}-heteroaryl.

In more preferred embodiment R\textsuperscript{9} is hydrogen.

In another embodiment R\textsuperscript{10} is hydrogen, methyl, ethyl, propyl or n-butyl.

In another embodiment R\textsuperscript{11} is hydrogen, methyl, ethyl, propyl or butyl.

In another embodiment R\textsuperscript{12} is hydrogen, methyl, ethyl, propyl or butyl.

In another embodiment R\textsuperscript{13} is hydrogen, methyl, ethyl, propyl or butyl.

In another preferred embodiment R\textsuperscript{13} is hydrogen, methyl or ethyl.

In yet another embodiment R\textsuperscript{10} together with R\textsuperscript{11} forms Cs-C\textsubscript{2}-membered heterocycloalkyl, Cs-C\textsubscript{2}-membered heterocycloalkenyl or Cs-C\textsubscript{2}-membered heteroaryl.

In another embodiment R\textsuperscript{14} is hydrogen or Ci-C\textsubscript{4}-alkyl.

In yet another embodiment R\textsuperscript{14} is hydrogen, methyl, ethyl, propyl or butyl.
In another embodiment R is hydrogen, methyl, ethyl, propyl or butyl.
In another embodiment R is hydrogen, C1-C2-alkyl, C2-C6-alkenyl, C2-C6-alkynyl, C5-C14-aryl, C5-C12-heteroary or C3-C12-cycloalkyl.
In another embodiment n is 0.1, 2, 3, 4 or 5.

In yet another preferred embodiment n is 0.1 or 2.
In yet another preferred embodiment n is 3, 4, 5 or 6.
In more preferred embodiment n is 2, 3 or 4.
In another embodiment m is 1, 2 or 3.
In another embodiment o is 0.1 or 2

In another embodiment p is 0.1 or 2 and
In another embodiment r is 1, 2, 3, 4 or 5.
In more preferred embodiment, M, L and n are as follows in Table 1:

<table>
<thead>
<tr>
<th>Metal (M)</th>
<th>L</th>
<th>n</th>
<th>MLn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pd</td>
<td>OCOCH3</td>
<td>2</td>
<td>Pd(OCOCH3)2</td>
</tr>
<tr>
<td>Pd</td>
<td>Cl</td>
<td>2</td>
<td>Pd(Cl)2</td>
</tr>
<tr>
<td>Pd</td>
<td>Cl; CH3CN</td>
<td>4</td>
<td>PdCl2(CH3CN)2</td>
</tr>
<tr>
<td>Pd</td>
<td>Cl; 1,1'- bis(diphenyl phosphino)ferrocene</td>
<td>3</td>
<td>Pd(1,1'-bis(diphenyl phosphino)ferrocene)Cl2</td>
</tr>
<tr>
<td>Pd</td>
<td>dibenzylideneacetone</td>
<td>3</td>
<td>Pd2(dibenzylideneacetone)3</td>
</tr>
<tr>
<td>Pd</td>
<td>dibenzylideneacetone</td>
<td>2</td>
<td>Pd(dibenzylideneacetone)2</td>
</tr>
<tr>
<td>Ni</td>
<td>Cl; P(phenyl)3</td>
<td>4</td>
<td>Ni(Cl)2(P(phenyl)3)2</td>
</tr>
<tr>
<td>Ni</td>
<td>1,5-cyclooctadiene</td>
<td>2</td>
<td>Ni(1,5-cyclooctadiene)2</td>
</tr>
</tbody>
</table>

The amount of at least one M and/or MLn is in the range of 1:0.0001 to 1:0.07 equivalent, in particular less than 0.05 equivalent, more preferably 1:0.005 to 1:0.0005 equivalent per 1 equivalent of the compound of formula (II).

In one embodiment the phosphine compound is PX1X2X3 or (PX1X2)2(B)q, whereby X1, X2 and X3, identical or different, are F, Cl, Br, I, -NR17R18, hydrogen, -O-C1-C6-alkyl, -O-C1-C6-alkyl, C1-C2-alkyl, C2-C6-alkenyl, C2-C6-alkynyl, C5-C14-aryl, C5-C12-heteroary, C3-C12-cycloalkenyl, C3-C12-cycloalkyl, C3-C12-heterocycloalkenyl or -Si-(Cl-C2-alkyl)3, wherein B is CR19R20, -O-, -phenyl-O-phenyl, -S-, -NR17R18, -SiR21R22 or -C(=0)-, wherein R19 and R20, identical or different, are hydrogen, C1-C2-alkyl, C5-C14-aryl or C5-C12-heteroary, wherein R17, R18, R21 and R22, identical or different, are hydrogen or C1-C4-alkyl or R17 together with R18 forms heterocycloalkenyl, heterocycloalkenyl or C5-C14-heteroary, whereby X1, X2 and X3, identical or different, are unsubstituted or substituted by 1, 2, 3, 4 or 5 identical or different groups selected from the group consisting of Cl, F, Br, I, CN, -NO2, -NR17R18, -P(phenyl)2, -OH, unsubstituted or substituted C1-C2-alkyl, C2-C6-alkenyl, C2-C6-alkynyl, unsubstituted or substituted C5-C14-aryl, unsubstituted or substituted C5-C12-heteroary, -O-(CH2)7-O-, -C(=0)R23, -C(=0)R23, -C=N=NR25, -SO3H, -O-C1-C6-alkyl and -Si-C1-C6-alkyl, C5-C12-membered heterocycloalkenyl, C5-C12-membered heterocycloalkenyl and C5-C12-heteroary, wherein q is 1, 2, 3, 4 or 5; r is 1, 2, 3, 4 or 5;
R² is hydrogen or C₁-C₄-alkyl;
R²⁴ is hydrogen or C₁-C₄-alkyl; and
R²⁵ is hydrogen, C₁-C₂-alkyl, C₂₆-alkenyl, C₂₆-alkynyl, C₁-C₄-aryl, C₅-C₁₂-heteroaryl or C₃-C₁₂-cycloalkyl;
5 or their acceptable salts thereof.

In another embodiment X₁, X₂ and X₃, identical or different, are C₁-C₂-alkyl, C₁-C₄-aryl or C₅-C₁₂-heteroaryl.

In more preferred embodiment X₁, X₂ and X₃, identical or different, are methyl, ethyl, propyl, 1-methylethyl, butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 2,2-dimethylpropyl, 1-ethylpropyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, hexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-ethylbutyl, 2-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-1-methylpropyl and 1-ethyl-2-methylpropyl, n-octyl, 1-methylpropyl, 2-methylheptyl or 1,1-dimethylheptyl.

In yet another preferred embodiment X₁, X₂ and X₃, identical or different, are phenyl or naphthyl.

In another embodiment R¹⁷ is hydrogen or C₁-C₄ alkyl.

In another embodiment R¹⁷ is hydrogen, methyl, ethyl, propyl or butyl.

In another embodiment R¹⁸ is hydrogen, methyl, ethyl, propyl or butyl.

In another preferred embodiment R¹⁸ is hydrogen.

In yet another embodiment R¹⁷ together with R¹⁸ forms C₁-C₁₀-membered heterocycloalkyl, C₅-C₁₄-membered heterocycloalkenyl or C₅-C₁₂-heteroaryl.

In another embodiment R¹⁹ is hydrogen, C₁-C₂-alkyl, C₁-C₄-aryl or C₅-C₁₂-heteroaryl.

In yet another embodiment R¹⁹ is hydrogen, methyl ethyl, propyl, phenyl or naphthyl.

In another embodiment R²⁰ is hydrogen, C₁-C₂-alkyl, C₁-C₄-aryl or C₅-C₁₂-heteroaryl.

In another embodiment R²⁰ is hydrogen, methyl ethyl, propyl or butyl.

In another embodiment R²¹ is hydrogen or C₁-C₄ alkyl.

In another preferred embodiment R²¹ is hydrogen.

In another embodiment R²² is hydrogen, methyl, ethyl, propyl or butyl.

In another embodiment R²² is hydrogen, methyl or ethyl.

In another embodiment R²³ is hydrogen or C₁-C₄-alkyl.

In another preferred embodiment R²³ is hydrogen, methyl, ethyl, propyl or butyl.

In another embodiment R²⁴ is hydrogen methyl, ethyl, propyl or butyl.

In another embodiment, at least one phosphine compound is allyldiphenylphosphine; 1,3-bis(diphenylphosphino)propane; di-ethylphosphine diphenylphosphine tetrafluoroborate; (2-ammonioethyl) di-ethyl-7-butylphosphonium b/s(tetrafluoroborate); (2-ammonioethyl) disopropylphosphonium b/s(tetrafluoroborate); (3-ammonioethyl) di-ethyl-7-butylphosphonium...
(3-ammoniopropyl) diisopropylphosphonium b/s(tetrafluoroborate); b/s(3.5-b/-trifluoromethyl)phenyl)(2^86 b/s(isopropoxy)-3,6-dimethoxybiphenyl-2-yl)phosphine; benzylidiphenylphosphine; (2-biphenyl)di-1 -adamantylphosphine; 1-[2-[bis(tert-butyli)phosphino]phenyl]-3,5-diphenyl-1 H-pyrazole; b/s[2-(diadamantylphosphino)ethyl]amine; 2- [bis(3,5-di-tert-butyl-4-methoxyphenyl)phosphino]benzaldehyde; 2,6-[bi(s(di-tert-butylphosphinomethyl)pyridine; b/s(dicyclohexylphosphinophenyl)ether; b/s(diethylamino)phenylphosphine; b/s(dimethylamino)chlorophosphine; 2-|b/s(3,5-dimethylphenyl)phosphino]benzaldehyde; b/s[4-(3,3,4,4,5,5,5-heptafluoro-2,2-bis(trifluoromethyl)pentyl)phenyl]phenylphosphine; b/s(2-methoxyphenyl)phosphine; b/s[4-(1H,1H,2H,2H-perfluorodecyl)phenyl]phenylphosphine; 1,1-|b/s(phenylphosphinidene)ferrocene; (2-bromophenyl)dicyclohexylphosphine; (2-bromophenyl)di phenylphosphine; tert-butyldicyclohexylphosphine; te/f-butyldicyclohexylphosphonium tetrafluoroborate; tert-butyldiisopropylphosphine; fe/7-butyldiethylphosphine; 1-(dicyclohexylphosphino)-2,2-Diphenyl-1-methylcyclopropane; cyclohexylidiphenylphosphine; di(1-adamantyl)-2-dimethylaminophenylphosphine; di-1 -adamantyl phosphine; di(1-adamantyl)-(2-trisopropylsiloxylphenyl)phosphine; (5H-dibenzo[a,d]cyclohepten-5-yl)diphenylphosphine; di-f/e-7-butyldicyclohexylphosphine; di-|tert-butyl N,N-diisopropylphosphoramidite; 6-|tert-butylmethylphosphine; di-te/f-butyl(methyl)phosphonium tetrafluoroborate; 6|tert-butyl(methyl)phosphonium tetrafluoroborate; di-fe/7-butylneopentylphosphine; 6|tert-butynepentylphosphonium tetrafluoroborate; di-f/e-7-butylphenylphosphine; 6|tert-butyldiethylphosphate potassium salt; 2'-|di-f/e-7-butylphosphino)acetophenone ethylene ketal; 2-(di-te/f-butylphosphino)dimethylaminobenzene; 2-(di-f/e-7-butylphosphino)ethylamine; 2-(6'-|tert-butyldicyclohexylphosphinomethyl)-6-diethylaminomethyl)pyridine; 5-(di-f/e-7-butylphosphino)-1-(naphthalen-1-yl)-1 H-pyrazole; 5-(di-f/e/7butylphosphino)-1', 3', 5'-triphenyl-1'H-[1 ,4']bipyrazole; 3-(di-tert-butylphosphinophenyl)propane sulfonate; P,P'-dichloroferroacenylphosphine; dicyclohexyl-(2,6-diisopropophenyl)phosphine; dicyclohexyl(2,4,6-trimethylphenyl)phosphine; 2-(dicyclohexylphosphino)acetophenone ethylene ketal; 2-(dicyclohexylphosphino)benzophenone; 2-(dicyclohexylphosphino)-N,N-diisopropyl-1 H-indole-1-carboxamide; N-(dicyclohexyl phosphino)-2-[2'-methoxyphenyl]indole; 2-[dicyclohexylphosphino)methyl]-1 ,3-b/s(2,6-diisopropophenyl)-4,5-dimethylimidazolium iodide; 2-(dicyclohexylphosphinophenyl)-1 ,3-dioxolane; 2-(dicyclohexylphosphino)phenyl]-N-methylindole; dicyclohexyl(2,4,6-trimethylphenyl)phosphine; diethylphenylphosphine; diethylphosphine; 4-(diethylphosphino)-N,N-dimethylaniline; 9-[2-(diisopropylphosphino)phenyl]-9H-carbazole; 2-[di(2-methoxyphenyl)phosphinobenzensulfonic acid; dimethylaminophenylchlorophosphine; 4-(dimethylaminophenyl)diphenylphosphine; 2-(1 ',1 -dimethylpropyl)-6-(diphenylphosphino)pyridine; diphenyl(2-methoxyphenyl)phosphine; 4-diphenylphosphinylbenzoic acid; 2-(diphenylphosphino)benzaldehyde; 2-(diphenylphosphino)benzaldehyde oxime; 3-(diphenylphosphino)benzensulfonic acid sodium salt; 2-(diphenylphosphino)benzoic acid; 4-(diphenylphosphino)benzoic acid; N-[2-(diphenylphosphino)benzylidene] cyclohexylamine; 2-(diphenylphosphino)-N,N-dimethylbenzylamine; 2-(diphenylphosphino)ethanaminium tetrafluoroborate; 2-(diphenylphosphino)ethylamine; 2-[2-(diphenylphosphino)ethyl]pyridine; 3-
In the present invention, the at least one solvent of step (A) is alcohol, ether, amide or aromatic solvent.

The amount of at least one phosphine compound is in the range of 1.0:0.001 to 1:0.25 equivalent, in particular in the range of 1.0:0.001 to 1:0.1 equivalent per 1 equivalent of the compound of formula (II).

In an embodiment, reaction temperature of the step (A) is kept within a range of from 40°C to 150°C, preferably in the range of from 50°C to 130°C, more preferably in the range of from 55°C to 120°C. Generally, it is also preferred to have a reaction temperature of at least 70°C, in particular at least 95°C. In a further embodiment, the temperature is at least 90°C to 140°C.

In present invention, the at least one solvent of step (A) is alcohol, ether, amide or aromatic solvent.
In one embodiment, solvent of step (A) is 2-methylbutan-2-ol, benzyl alcohol, 1,4-butanediol, 1,2,4-butaneletriol, 2-butanol, 1-butanol, 2-methylpropan-1-ol, 2-methylpropan-2-ol, methanol, 2-(2-methoxyethoxy)ethanol, 2-methyl-1-butanol, 2-methyl-1-pentanol, 3-methyl-2-butanol, diethylene glycol, ethanol, ethylene glycol, 2-ethylhexanol, furfuryl alcohol, glycerol, propan-2-ol, neopentyl alcohol, 1-pentanol, 2-pentanol, 1,3-propanediol, 1-propanol, propylene glycol, di-tert-butyl ether, diethyl ether, diethylene glycol diethyl ether, diglyme, diisopropyl ether, dimethoxyethane, dimethoxymethane, 1,4-dioxane, dimethylacetamide, dimethylformamide, formamide, N-methyl-2-pyrrolidone, N-methylformamide, 2-pyrrolidone, N-vinylacetamide, N-vinylpyrrolidone, toluene, xylene or mono-chlorobenzene.

In more preferred embodiment the solvent is 1-butanol, 2-methylpropan-2-ol, 2-methylpropan-1-ol, 2-methylbutan-2-ol, 1-propanol, propan-2-ol or 1-pentanol, even more preferably 1-butanol or 2-methylpropan-1-ol.

In an embodiment, the volume ratio of the compound of formula II to solvent is in the range of 1:30 to 1:0.

Step (B) for the preparation of compounds of formula V and/or Va particularly is as follows:

(B) Converting a compound of general formula (IV) in the presence of at least one acid or at least one base or at least one buffer into a compound of general formula (V) or (Va),

\[ \text{(V) or (Va),} \]

wherein

in a compound of formula (V) \( R^3 \) is F or Cl and

in a compound of formula (Va) \( R^3 \) is

\[ \text{wherein } R^4 \text{ is F or Cl.} \]

In the present invention the at least one acid of step (B) is organic acid or inorganic acid.

In one embodiment, the at least one organic acid of step (B) is oxalic acid, formic acid, malonic acid, acetic acid, citric acid, propionic acid or butyric acid.

In another embodiment, the at least one inorganic acid of step (B) is phosphoric acid, sulphuric acid, hydrochloric acid, hydrobromic acid, hydroiodic acid or nitric acid, more preferable hydrochloric acid.

The amount of at least one acid is in the range of 1.0:0.01 to 1:50 equivalent, in particular in the range of 1:0.1 to 1:20 equivalent per 1 equivalent of the compound of formula (II).

In the present invention the at least one buffer of step (B) is sodium acetate.

In present invention at least one base of step (A) and/or step (B) is an organic base and/or inorganic base.

In one embodiment an organic base is N(R^{24})_{3}, N-methyl piperidine, N-methyl pyrrolidine, N-methyl morpholine, piperidine, dimethyl amino pyridine, pyridine, lithium hexamethyldisilazide,
sodium hexamethyldisilazide and tetra-Cl-C6-alkyl ammonium hydroxide, wherein R26 is, identical or different, hydrogen, Cl-C6-alkyl, Cs-C14-aryl, or C3-C6-cycloalkyl.

In another embodiment an inorganic base is alkali metal hydroxide, alkaline earth hydroxide, alkali metal bicarbonate, alkaline earth bicarbonate, alkali metal carbonate, alkaline earth carbonate, alkali metal phosphate, alkali metal alkoxide or alkaline earth alkoxide.

In more preferred embodiment an inorganic base is lithium hydroxide, sodium hydroxide, potassium hydroxide, rubidium hydroxide, cesium hydroxide magnesium hydroxide, calcium hydroxide, strontium hydroxide, barium hydroxide, lithium bicarbonate, sodium bicarbonate, potassium bicarbonate, rubidium bicarbonate, cesium bicarbonate, magnesium bicarbonate, calcium bicarbonate, strontium bicarbonate, barium bicarbonate, lithium carbonate, sodium carbonate, potassium carbonate, rubidium carbonate, cesium carbonate, magnesium carbonate, calcium carbonate, strontium carbonate, barium carbonate, monosodium phosphate, disodium phosphate, trisodium phosphate, monopotassium phosphate, dipotassium phosphate, tripotassium phosphate, NaOR27, KOR27, RbOR27, CsOR27, Mg(OR27)2, Ca(OR27)2 and Ba(OR27)2, whereby R27 is, identical or different, Cl-C4-alkyl.

The amount of at least one base used in step (A) and/or step (B) is preferably equal to or less than 5 equivalent, in particular less than 4 equivalent, more preferably equal to or more than 0.8 equivalent, even more preferably equal to or more than 1 equivalents per 1 equivalent of the compound of formula (II). Preferably, at least 1 equivalent, more preferably at least 1.2 equivalent, more specifically at least 1.4 equivalent base per 1 equivalent of the compound of formula (II) is used.

In an embodiment, reaction temperature of the step (B) is kept within a range of from -30°C to 110°C, preferably in the range of from 5°C to 100°C, more preferably in the range of from 20°C to 70°C. Generally, it is also preferred to have a reaction temperature of at least 20°C, in particular at least room temperature, in particular at least 25°C. In a further embodiment, the temperature is at least 30°C. It may be preferred if the temperature is at least 35°C.

Step (C) for the preparation of compound of formula Va particularly is as follows:

In the present invention the compound of general formula (V) is converted into a compound of general formula (Va) in the presence of at least one base.

![Compound Va](image)

wherein

R4 is F or Cl.

Step (D) for the preparation of compound of formula VI particularly is as follows:
In the present invention the compound of formula (Va) is converted into a compound of general formula (VI) in the presence of trimethylsulf(on)onium halide ((CH3)3S·(O)H) (VII) or in the presence of trimethylsulfonium methylsulfate of the formula (VIII) (CH3)3S·CH3SO4·;

wherein

R4 is F or α,
Hal is halogen.

In this process step using trimethylsulfonium methylsulfate of the formula VIII, preferably, 1 to 4 equivalents, in particular 1.2 to 3.5 eq, more specifically 1.5 to 3.3 eq, of water in relation to one equivalent of compound of formula II are used. It may be favorable, if more than 1.5 eq of water, in particular more than 1.5 eq of water to 4 eq of water, more specifically more than 1.5 eq to 3.5 eq of water, even more particularly more than 1.5 eq water to 2.5 eq water per mole of compound of formula II are used. In particular the ratios of 1.6 to 3.8, more specifically 1.7 to 3.3 eq, more specifically 1.8 to 2.8 eq or 1.9 to 2.5 of water per mole of compound of formula II may be favorable according to the present invention.

In general, the reagent of formula VIII can be prepared from dimethylsulfide and dimethylsulfate. According to one embodiment, reagent VIII is prepared in-situ by adding dimethylsulfide to the reaction mixture containing dimethylsulfide. The dimethylsulfide is usually used in excess.

Steps (E) and (F) for the preparation of compound of formula I particularly is as follows:

(E) In the present invention the compound of formula (VI) is reacted with 1H-1,2,4-triazole in the presence of at least one base to obtain compounds of formula (I) wherein R2 is hydrogen, and

(F) optionally reacting a compound of formula (I), wherein R2 is hydrogen, in the presence of at least one base with at least one compound of formula R2-LG; wherein LG is a leaving group and R2 is C₆₋₋₆-alkyl, C2-C6-alkenyl, C2-C6-alkynyl, Cs-Cs-cycloalkyl, C3-Cs-cycloalkyl-C₆₋₋₆-alkyl, phenyl, phenyl-C₁-C₄-alkyl, phenyl-C₂-C₄-alkenyl or phenyl-C₂-C₄-alkynyl; whereby

the aliphatic moieties of R² are unsubstiuted or further substituted by 1, 2 or 3 identical or different groups R₁² which are independently selected from the group consisting of halogen, OH, CN, nitro, C₁-C₄-alkoxy, Cs-Cs-cycloalkyl, Cs-Cs-halocycloalkyl and C₁-C₄-halogenalkoxy and the cycloalkyl and phenyl moieties or R² are unsubstiuted or further substituted by 1, 2, 3, 4 or 5 identical or different groups R₁² which are independently selected from halogen, OH, CN, nitro, C₁-C₄-alkoxy, Cs-Cs-cycloalkyl, Cs-Cs-halocycloalkyl and C₁-C₄-halogenalkoxy; to obtain a compound of general formula (I),

wherein R2 is C₆₋₋₆-alkyl, C2-C6-alkenyl, C2-C6-alkynyl, Cs-Cs-cycloalkyl, C3-Cs-cycloalkyl-C₆₋₋₆-alkyl, phenyl, phenyl-C₁-C₄-alkyl, phenyl-C₂-C₄-alkenyl or phenyl-C₂-C₄-alkynyl; whereby

the aliphatic moieties of R² are unsubstiuted or further substituted by 1, 2 or 3 identical or different groups R₁² which are independently selected from the group consisting of halogen, OH, CN, nitro, C₁-C₄-alkoxy, Cs-Cs-cycloalkyl, Cs-Cs-halocycloalkyl and C₁-C₄-halogenalkoxy and the cycloalkyl and phenyl moieties or R² are unsubstiuted or further substituted by 1, 2, 3, 4 or 5
identical or different groups $R^{12b}$ which are independently selected from halogen, OH, CN, nitro, $C_1$-$C_4$-alkoxy, $Cs$-$Cs$-cycloalkyl, $Cs$-$Cs$-halocycloalkyl and $C_1$-$C_4$-halogenalkoxy. preferably in aqueous solution in the presence of a base.

Reacting the oxirane of the formula (VI) with 1H-1,2,4-triazole and a base, resulting in compounds of formula (I), wherein $R^2$ is hydrogen,

and, for obtaining compounds wherein $R^2$ is different from hydrogen, derivatizing the compound of formula (I) under basic conditions with $R^2$-LG, wherein LG is a nucleophilically replaceable leaving group as defined above.

In the present invention at least two steps of step (A) to (F) are carried out in a single pot.

In preferred embodiment the steps (A) and (B) are carried out in a single pot.

In one embodiment at least one compound from compounds of formulae (IV), (V), (Va) and (VI) is not isolated.

In preferred embodiment at least one compound from compounds of formulae (IV), (V) and (Va) is not isolated.

A second aspect of the present invention relates to a compound of formula (IVa)

\[
\begin{array}{c}
\text{F} \\
\text{CF}_3 \\
\text{O} \\
\text{Z}
\end{array}
\]

wherein

$Z$ is $C_1$-$C_6$ alkyl.

In one embodiment $Z$ is selected from methyl, ethyl, propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 2,2-dimethylpropyl, 1-ethylpropyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, hexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-ethylbutyl, 2-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-1-methylpropyl and 1-ethyl-2-methylpropyl.

In preferred embodiment $Z$ is n-butyl or 2-methylpropyl.

EXAMPLES

The characterization can be done by coupled High Performance Liquid Chromatography / mass spectrometry (HPLC/MS), Gas chromatography (GC), by NMR or by their melting points.

HPLC method 1: Waters Xbridge C18, 150mmx4.6mm IDx5um

Gradient A= Water, B= Acetonitrile.

Flow= 1.4 ml/min., column oven temperature= 30 °C

Gradient program= 10% B - 100% B - 5min, hold for 2min, 3min - 10% B.

Run Time = 10 min
HPLC method 2: Agilent Eclipse C18, 150mmx4.6mm IDx5um
Gradient A = 0.1 % TFA in Water, B = 0.1 % TFA in Acetonitrile.
Flow= 1.4 ml/min., column oven temperature= 30 °C
Gradient program= 10% B - 100% B - 5min, hold for 2min, 3min - 10% B.

Run Time = 10 min

LCMS method: Agilent Eclipse C18, 150mmx4.6mm IDx5um
Gradient A = 0.05% ammonia in Water, B = 0.05% ammonia in Methanol
Flow= 1.2 ml/min., column oven temperature= 30 °C
Gradient program= 10 % B to 100 % B in 1.5 min., hold for 1 min 100 % B, 2 min - 10 % B

Run time: 4.5 min

GCMS method: RTX-5 MS, 30mx0.25mmx0.25um
Carrier gas= Helium; Ion source temperature= 230 °C; Interface temperature= 280 °C
Gradient program= 50 °C hold for 1 min, 35 °C/min to 300 °C, hold for 3 min at 300 °C
Run time: 11.2 min;

1H-NMR: The signals are characterized by chemical shift (ppm) vs. tetramethylsilane, by their multiplicity and by their integral (relative number of hydrogen atoms given). The following abbreviations are used to characterize the multiplicity of the signals: m = multiplet, q = quartet, t = triplet, d = doublet and s = singlet.
Abbreviations used are: h for hour(s), min for minute(s), rt for retention time and ambient temperature for 20-25°C.

General Procedure:
With due modification of the starting compounds, the compound of formula V or Va can be prepared by procedures as given in below schemes.

Step (A)

A stirred solution of substituted trifluoromethyl benzene (1 eq.) in a solvent such as n-butanol, iso-butanol, n-propanol, iso-propanol (3 to 15 volume of formula II) was degassed at temperature range of 55°C to 120°C. To the stirred solution was added a base (0.8 to 5 equivalent of formula II), vinyl ether, metal (1:0.001 to 1:0.07 equivalent of formula II) and phosphine compound (0 to 0.25 equivalent of formula II). The reaction was again degassed and subsequently heated to 70°C - 100°C. The reaction mixture was stirred for 10-18 hours at 100°C. After the completion of the reaction, the temperature of the reaction mixture was brought to 25°C and the mixture was filtered through celite bed. The celite bed was washed with solvent such as n-butanol and filtrate was concentrated to obtain the desired coupled product.
The coupled product and acid such as aqueous hydrochloric acid were stirred together at 25°C for 0.5-2 hours. After the completion of the reaction, the organic phase was separated from aqueous phase, washed with water and distilled under reduced pressure to obtain the desired product.

Example 1: Preparation of 1-[4-fluoro-2-(trifluoromethyl)phenyl]ethenone

1a: Preparation of 1-(1-butoxyvinyl)-4-fluoro-2-(trifluoromethyl)benzene

A 500ml three-necked flask equipped with a Teflon-blade stirrer, reflux condenser and thermo pocket was charged with 1-bromo-4-fluoro-2-(trifluoromethyl)benzene (40 g) and n-butanol (120 ml). The resulting mixture was degassed with nitrogen at 25°C for 30 minutes. To the stirred solution was added potassium carbonate (27.2 g), n-butyl vinyl ether (53.4 ml), palladium acetate (18.4 mg) and di-tert-butyl(phenyl)phosphine tetrafluoroborate (51 mg). The reaction mixture was again degassed with nitrogen for 15 minutes while stirring and heated to 100°C. The reaction mixture was stirred for 12-18 hours at 100°C. After the completion of the reaction, the temperature of the reaction mixture was bought to 25°C and the mixture was filtered through a glass celite bed. The celite bed was washed with n-butanol (100 ml) and filtrate was concentrated to obtain 1-(1-butoxyvinyl)-4-fluoro-2-(trifluoromethyl)benzene [m/z = 263 amu (M+H+)].

Example 2: Preparation of 1-[4-fluoro-2-(trifluoromethyl)phenyl]ethenone

A 50ml three-necked flask equipped with a Teflon-blade stirrer, reflux condenser and thermo pocket was charged with 1-bromo-4-fluoro-2-(trifluoromethyl)benzene (2 g) and n-butanol (6 ml), potassium carbonate (1.36 g) and n-butyl vinyl ether (2.67 ml) at 25°C. The resulting mixture was degassed with nitrogen at 25°C for 30 minutes followed by palladium acetate (5.5 mg) and 2-(dicyclohexylphosphino)-3,6-dimethoxy-2',4',6'-tri-isopropyl-1 1'-biphenyl (26.5 mg). The reaction mixture was again degassed with nitrogen for 15 minutes while stirring and heated to 100°C. The reaction mixture was stirred for 16-18 hours at 100°C. After the completion of the reaction, the temperature of the reaction mixture was bought to 25°C and the mixture was filtered through a glass celite bed. The celite bed was washed with n-butanol (6 ml) and filtrate was transferred to a 50ml three-necked flask equipped with magnetic bar and thermo pocket and 6 M aq. hydrochloric acid (6 ml.) was added at 25°C. The reaction mixture was stirred for 1 hour.
The reaction mixture was extracted with methyl-fe/7-butyl ether (6 mL). The two phases were separated and the organic phase was washed with water. The organic phase was separated and product was distilled under reduced pressure to obtain 1-[4-fluoro-2-(trifluoromethyl)phenyl]ethenone.

Yield (%): 88 [m/z = 207 amu (M+H+)]

Examples 3-8: The following examples in Table 2 further illustrate the process for the preparation of compound of formula V (steps A and B) of the present invention and do not restrict the invention in any manner.
<table>
<thead>
<tr>
<th>S.No</th>
<th>Compound of formula II</th>
<th>Compound of formula III</th>
<th>M and/or MLn</th>
<th>Base</th>
<th>Phosphine compound</th>
<th>Solvent</th>
<th>Acid</th>
<th>Yield % (V)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Step A</td>
<td>Step B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>R³ = F</td>
<td>R¹ = n-butyl</td>
<td>Pd(OOCOCH₃)₂</td>
<td>K₂CO₃</td>
<td>di-tert-butyl(phenyl)phosphine tetrafluoroborate</td>
<td>n-butanol</td>
<td>6 M aq. HCl</td>
<td>74</td>
</tr>
<tr>
<td>4.</td>
<td>R³ = F</td>
<td>R¹ = n-butyl</td>
<td>PdCl₂</td>
<td>K₂CO₃</td>
<td>tris-(α-tolyl)phosphine</td>
<td>n-butanol</td>
<td>6 M aq. HCl</td>
<td>90</td>
</tr>
<tr>
<td>5.</td>
<td>R³ = F</td>
<td>R¹ = n-butyl</td>
<td>Pd(OOCOCH₃)₂</td>
<td>K₂CO₃</td>
<td>di-tert-butyl(phenyl)phosphine</td>
<td>n-butanol</td>
<td>6 M aq. HCl</td>
<td>93</td>
</tr>
<tr>
<td>6.</td>
<td>R³ = F</td>
<td>R¹ = isobutyl</td>
<td>PdCl₂</td>
<td>K₂CO₃</td>
<td>tris-(α-tolyl)phosphine</td>
<td>iso-butanol</td>
<td>6 M aq. HCl</td>
<td>91</td>
</tr>
<tr>
<td>7.</td>
<td>R³ = F</td>
<td>R¹ = n-butyl</td>
<td>Pd(OOCOCH₃)₂</td>
<td>K₂CO₃</td>
<td>2-(dicyclohexylphosphino)-3,6-dimethoxy-2′,4′,6′-triisopropyl-1,1′-biphenyl</td>
<td>n-butanol</td>
<td>6 M aq. HCl</td>
<td>87</td>
</tr>
<tr>
<td>8.</td>
<td>R³ = F</td>
<td>R¹ = n-butyl</td>
<td>Pd(OOCOCH₃)₂</td>
<td>K₂CO₃</td>
<td>1,3-bis(diphenylphosphino)propane</td>
<td>n-butanol</td>
<td>6 M aq. HCl</td>
<td>82</td>
</tr>
</tbody>
</table>
Example 9: Process for the preparation of 1-[4-(4-chlorophenoxy)-2-(trifluoromethyl)phenyl]ethenone

9a: The 1-[4-fluoro-2-(trifluoromethyl)phenyl]ethenone was prepared by following any of the aforementioned examples.

9b: A 50ml-three-necked flask equipped with a Teflon-blade stirrer, reflux condenser, and a thermos-pocket was charged with dimethyl formamide (4 mL), 1-[4-fluoro-2-(trifluoromethyl)phenyl]ethenone (1.0 g, 1.0 eq.), 4-chlorophenol (0.62 g, 1.0 eq) and potassium carbonate (1.0 g, 1.0 eq). The resulting reaction mixture was stirred at 110 °C for 2 h and reaction was monitored by HPLC. The reaction was quenched with water (2 mL) and extracted with methyl-fer/butyl ether (5 mL x 3). The combined organic layer was dried with sodium sulphate and concentrated to afford the title compound.

Yield (%) = 85
Claims

1. A process for the preparation of a compound of the general formula (I) or its salts

\[
\begin{align*}
\text{R}^4 & \quad \text{O} \\
\text{CF}_3 & \quad \text{O} \\
\text{R}^2 & \quad \text{N} \quad \text{N}
\end{align*}
\]

(I)

wherein

\( R^2 \) is hydrogen, Ci-C6-alkyl, C2-C6-alkenyl, C2-C6-alkynyl, Cs-Cs-cycloalkyl, C3-Cs-cycloalkyl-
Ci-C6-alkyl, phenyl, phenyl-Ci-C4-alkyl, phenyl-C2-C4-alkenyl or phenyl-C2-C4-alkynyl; whereby
the aliphatic moieties of \( R^2 \) are unsubstituted or further substituted by 1, 2 or 3 identical or differ-
ent groups \( R^{12a} \) which are independently selected from the group consisting of halogen, O H,
C N, nitro, Ci-C4-alkoxy, Cs-Cs-cycloalkyl, Cs-Cs-halocycloalkyl, Ci-C4-halogenalkoxy and phenyl
moieties or \( R^2 \) are unsubstituted or further substituted by 1, 2, 3, 4 or 5 identical or different
groups \( R^{12b} \) which are independently selected from halogen, O H, C N, nitro, Ci-C4-alkoxy, Cs-Cs-
cycloalkyl, C3-Cs-halocycloalkyl and Ci-C4-halogenalkoxy; and

\( R^4 \) is F or Cl;

comprising at least the steps of:

(A) reacting a compound of formula (II)

\[
\begin{align*}
\text{R}^3 & \quad \text{CF}_3 \\
\text{X} & \quad \text{O} \\
\end{align*}
\]

(II)

wherein

\( R^3 \) is F and \( X \) is Br, Cl, I or Ci-C4-alkoxy; or

\( R^3 \) is Cl and \( X \) is Br, I, SO3-CF3, SO3-C4H6-CH3, S03-CH3 or Ci-C4-alkoxy; or

\( R^3 \) is:

\[
\begin{align*}
\text{R}^4 & \quad \text{O} \\
\text{X} & \quad \text{O}
\end{align*}
\]

(III)

wherein \( R^4 \) is F or Cl, and \( X \) is Br, I, SO3-CF3, SO3-C4H6-CH3, SO3-CH3 or Ci-C4-alkoxy;
with a compound of general formula (III)

\[
\begin{align*}
\text{R}^1 & \quad \text{R}^4
\end{align*}
\]

(HI)

wherein

\( R^1 \) is OR5 or NR5R7, wherein \( R^5 \) is Ci-C6-alkyl or C3-C8-cycloalkyl, and \( R^6 \) and \( R^7 \), iden-
tical or different, are hydrogen, Ci-C6-alkyl, Cs-Cs-cycloalkyl, or C(=0)-Ci-C6-alkyl

in the presence of at least one metal, at least one base and at least one phosphine compound,
to obtain a compound of general formula (IV),
wherein

R\textsuperscript{4} is F or Cl;

R\textsuperscript{i} is OR\textsuperscript{5} or NR\textsuperscript{6}R\textsuperscript{7}, wherein R\textsuperscript{5} is C\textsubscript{6}-alkyl or C\textsubscript{3}-C\textsubscript{8}-cycloalkyl, and R\textsuperscript{6} and R\textsuperscript{7}, identical or different, are hydrogen, C\textsubscript{6}-alkyl, C\textsubscript{3}-C\textsubscript{8}-cycloalkyl;

(B) converting a compound of general formula (IV) in the presence of at least one acid or at least one base or at least one buffer into a compound of general formula (V) or (Va),

\begin{equation}
\text{IV}
\end{equation}

\begin{equation}
\text{V or (Va)},
\end{equation}

wherein

in a compound of formula (V) R\textsuperscript{3} is F or Cl and

in a compound of formula (Va) R\textsuperscript{3} is F or Cl.

2. The process according to claim 1 further comprising the step of

(C) converting the compound of general formula (V) in the presence of at least one base into a compound of general formula (Va)

\begin{equation}
\text{(Va)}
\end{equation}

wherein

R\textsuperscript{4} is F or Cl.

3. The process according to claim 1 further comprising the steps of

(D) converting the compound of formula (Va) as defined in claim 1 or 2 in the presence of trimethylsulf(ox)onium halide [(CH\textsubscript{3})\textsubscript{3}S - (O)H\textsubscript{a}] (VII), wherein Hal is halogen, or in the presence of trimethylsulfonium methylsulfate of the formula (VIII) (CH\textsubscript{3})\textsubscript{3}S-CH\textsubscript{3}SO\textsubscript{4}, into a compound of general formula (VI),
wherein
R⁺ is F or Cl,

(E) reacting the compound of formula (VI) with 1H-1,2,4-triazole in the presence of at least one base to obtain compounds of formula (I), wherein R² is hydrogen, and

(F) optionally reacting a compound of formula (I), wherein R² is hydrogen, in the presence of at least one base with at least one compound of formula R²-LG; wherein LG is a leaving group and R² is c₁-C₆-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, cs-cs-cycloalkyl, C₃-C₈-cycloalkyl-Cl-C₆-alkyl, phenyl, phenyl-c₁-C₄-alkyl, phenyl-C₂-C₄-alkenyl or phenyl-C₂-C₄-alkynyl; whereby the aliphatic moieties of R² are unsubstituted or further substituted by 1, 2 or 3 identical or different groups R¹₂a which are independently selected from the group consisting of halogen, OH, CN, nitro, c₁-C₄-alkoxy, cs-cs-cycloalkyl, cs-cs-halocycloalkyl and c₁-C₄-halogenalkoxy and the cycloalkyl and phenyl moieties or R² are unsubstituted or further substituted by 1, 2, 3, 4 or 5 identical or different groups R¹₂b which are independently selected from halogen, OH, CN, nitro, c₁-C₄-alkoxy, cs-cs-cycloalkyl, C₃-C₈-halocycloalkyl and c₁-C₄-halogenalkoxy;

to obtain a compound of general formula (I),

wherein R² is c₁-C₆-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, cs-cs-cycloalkyl, cs-cs-cycloalkyl-c₁-C₆-alkyl, phenyl, phenyl-c₁-C₄-alkyl, phenyl-C₂-C₄-alkenyl or phenyl-C₂-C₄-alkynyl;

whereby the aliphatic moieties of R² are unsubstituted or further substituted by 1, 2 or 3 identical or different groups R¹₂a which are independently selected from the group consisting of halogen, OH, CN, nitro, c₁-C₄-alkoxy, cs-cs-cycloalkyl, cs-cs-halocycloalkyl and c₁-C₄-halogenalkoxy and the cycloalkyl and phenyl moieties or R² are unsubstituted or further substituted by 1, 2, 3, 4 or 5 identical or different groups R¹₂b which are independently selected from halogen, OH, CN, nitro, c₁-C₄-alkoxy, cs-cs-cycloalkyl, cs-cs-halocycloalkyl and c₁-C₄-halogenalkoxy.

4. The process according to one or more of claims 1 to 3 wherein at least two steps of step (A) to (F) are carried out in a single pot.

5. The process according to one or more of claims 1 to 3 wherein at least one compound from compounds of formulae (IV), (V), (Va) and (VI) is not isolated.

6. The process according to claim 1 wherein R² is hydrogen, c₁-C₆-alkyl, allyl, propargyl or benzyl.

7. The process according to claim 1 wherein the at least one metal is in a form of a free state of formula M or in a form of a metal complex of formula M(L)ₙ.
wherein

M is selected from the group consisting of nickel (Ni), cobalt (Co), iron (Fe), ruthenium (Ru), rhodium (Rh), palladium (Pd), iridium (Ir), platinum (Pt), silver (Ag), copper (Cu), zinc (Zn), molybdenum (Mo) and tungsten (W);

L is, identical or different, selected from the group consisting of Cl, Br, I, P(Cs-Cs-aryl)m, P(C5-C12-heteroaryl)m, P(C1-Ci4-aryl)3-m, CN, d-Ce-alkyl, Ci-C6-alkyl-0-Ci-C6-alkyl, -0-CO-Ci-C6-alkyl, OH, -0-Ci-C6-alkyl, C1-C4-haloalkoxy, Cs-Cs-cycloalkyl, Cs-Cs-halocycloalkyl, Cs-Cs-cycloalkenyl, Cs-Cu-aryl, c s-Ci4-aryl-(CH2)o-(Q)p-(CH2)o-C5-Ci4-aryl and 1,1'-b/s(diphenyl phosphino)ferrocene; whereby Q represents a bridging group selected from the group consisting of -CR8R9, -0-, -S-, -NR10R11, -SiR12R13 and -CO-, wherein R8 and R9, identical or different, are hydrogen, C1-C12 alkyl, Cs-Cu-aryl or Cs-Ci2-heteroaryl; wherein R10, R11, R12 and R13, identical or different, are hydrogen or C1-C4 alkyl or R10 together with R11 forms Cs-Ci2-membered heterocycloalkyl, Cs-Cu-membered heterocycloalkenyl or Cs-Ci2-membered heteroaryl; and L is unsubstituted or further substituted by 1, 2, 3, 4 or 5 identical or different groups selected from the group consisting of Cl; F; Br; I; CN; -NO2; -NR10R11; -P(phenyl)2; -OH, unsubstituted or substituted Ci-Ci2-alkyl, C2-C6-alkenyl, C2-C6-alkyl; unsubstituted or substituted Cs-Cu-aryl, unsubstituted or substituted Cs-Ci2-heteroaryl, Cs-Ci2-membered heterocycloalkenyl, Cs-Cu-membered heterocycloalkenyl, -0-(CH2)2-0-, -C(=0)R14-0-C(=0)-0-R15-, -C=N-R16-, -SO3H, -0-Ci-C6-alkyl and -0-Si-Ci-C4-alkyl; or

L is supported on silica gel, dendrimers, polystyrenes or mesoporous siliceous foam

wherein

R14 is hydrogen or Ci-C4-alkyl;

R15 is hydrogen or Ci-C4-alkyl;

R16 is hydrogen, Ci-Ci2-alkyl, C2-C6-alkeny1, C2-C6-alkyl, Cs-Cu-aryl, c s-Ci2-heteroaryl or c s-Ci2-cycloalkyl;

n is 0, 1, 2, 3, 4, 5 or 6;

m is 1, 2 or 3;

o is 0, 1 or 2

p is 0, 1 or 2 and

r is 1, 2, 3, 4 or 5

or their acceptable salts thereof.

8. The process according to claim 1 or 7, wherein the at least one metal (M) is selected from the group consisting of nickel (Ni), iron (Fe), palladium (Pd) and copper (Cu).

9. The process according to claim 7, wherein L is, identical or different, selected from the group consisting of Cl, Br, I, P(cs-Ci4-aryl)m, CN, unsubstituted or substituted Ci-Ci2-alkyl, Cs-Cs-cycloalkenyl, -0-CO-Ci-C6-alkyl, Cs-Cu-aryl, 1,1'-b/s(diphenyl phosphino)ferrocene and c s-Ci4-aryl-(CH2)o-(Q)p-(CH2)o-c s-Ci4-aryl, whereby m, o, Q and p are as defined in claim 5.
10. The process according to one or more of claims 1 to 9, wherein metal complex of formula
\[
\text{M(L)}_n\text{ is selected from group consisting of Pd(OCOCH}_3)_2, \text{PdCl}_2, \text{PdCl}_2(\text{CH}_3\text{CN})_2, \text{Pd(1.1-}
\[
text{b/s(diphenyl phosphino)ferrocene})\text{Cl}_2, \text{Pd(2(dibenzylideneacetone})_3, \text{Pd(dibenzyldieneacetone})_2, \text{NiCl}_2(\text{triphenylphosphine})_2 \text{ and Ni(1.5-cyclooctadiene})_2.
\]

11. The process according to claim 1, wherein the at least one phosphine compound is of
\[
\text{formula P(X)}_i\text{X(2(B))}_q, \text{ whereby X, X2and X3, identical or different, are F, Cl, Br, I, -NR}_i^3\text{-R}^{18}\text{-hydrogen, -0-d-C}_e\text{-alkyl, -0-CO-C}_e\text{-alkyl, -Cl-C}_2\text{-alkyl, -C}_2\text{-C}_e\text{-alkenyl, -C}_2\text{-C}_6\text{-alkynyl, -Cs-Cu-aryl, Cs-Ci2-heteroaryl, C3-Ci2-cycloalkyl, C3-Ci2-cycloalkenyl, C3-Ci2-heterocycloalkyl, C3-C4-heterocycloalkenyl or -Si-(Cl-Ci2)alkyl3, whereby B is}
\[
\text{C}_R^3\text{R}^{20}-\text{0-phenyl-O-phenyl, -S-, -NR}_i^3\text{-R}^{18}\text{-SiR}_3^{21}\text{R}^{22} \text{or -C}(=\text{0)-, wherein R}^{18} \text{and R}^{20}, \text{identical or different, are hydrogen, Cl-Ci2-alkyl, Cs-Cu-aryl or C5-Ci2-heteroaryl, wherein R}^{17}, \text{R}^{18}, \text{R}^{21} \text{and R}^{22}, \text{identical or different, are hydrogen or Cl-C4-alkyl or R}^{17} \text{together with}
\[
\text{R}^{18}\text{forms C5-Ci2-membered heterocycloalkyl, Cs-Cu-membered heterocycloalkenyl or}
\[
c5-Ci2-heteroaryl; \text{whereby Xi, X2and X3, identical or different, are unsubstituted or substi-
\[
tuted by 1, 2, 3, 4 or 5 identical or different groups selected from the group consisting of}
\[
\text{Cl; F; Br; I;CN; -NO}_2; -NR}_i^3\text{-R}^{18}\text{-P(phenyl)}_2; -OH, unsubstituted or substituted C1-Ci2-
\[
\text{-alkyl, C2-Ci6-alkenyl, C2-Ci6-alkynyl, unsubstituted or substituted Cs-Cu-aryl, unsubstituted}
\[
or substituted C5-Ci2-heteroaryl, -0-(CH}_2)_r-0-, -C(=0)R}_3^{23}, -C(=0)-0-R}_4^{24}, -C=N-R}_5^{25}, -SO3H,
\[
\text{-0-Ci6-alkyl and -0-Si-Ci-C4-alkyl, Cs-Ci2-membered heterocycloalkyl, c5-Ci4-
\[
\text{membered heterocycloalkenyl and c5-Ci2-heteroaryl; wherein q is 1,2,3,4,5 or 6;}
\[
r is 1,2,3,4 or 5;
\[
\text{R}^{23} \text{is hydrogen or Cl-C4-alkyl;}
\]
\text{R}^{24} \text{is hydrogen or Cl-C4-alkyl; and}
\text{R}^{25} \text{is hydrogen, C1-Ci2-alkyl, C2-Ci6-alkenyl, C2-Ci6-alkynyl, Cs-Cu-aryl, Cs-Ci2-heteroaryl}
\text{or c3-Ci2-cycloalkyl; or their acceptable salts thereof.}
\]

12. The process according to one or more of claims 1 to 10, wherein the at least one phos-
\[
\text{phine compound is selected from the group consisting of}
\text{allyldiphenylphosphine; 1,3-b/s(diphenylphosphino)propane; di-tert-
\text{butyl(phenyl)phosphino tetrafluoroborate; (2-ammonioethyl) di-Fe/7-butylphosphonium}
\text{b/s(tetrafluoroborate); (2-ammonioethyl) diisopropylphosphonium b/s(tetrafluoroborate);}
\text{(3-ammoniopropyl) di-Fe/7-butylphosphonium b/s(tetrafluoroborate); (3-ammoniopropyl)}
\text{diisopropylphosphonium b/s(tetrafluoroborate); b/s(3,5-b/s(trifluoromethyl)phenyl)(2',6'-}
\text{b/s(isopropoxy)-3,6-dimethoxybiphenyl-2-yl)phosphine; benzylidiphenylphosphine; (2-
\text{biphenyldi-1-adamantylphosphine; 1-^-b/s/site-f-butyophosphinophenylO-S^-diphenyl-l}}
\text{H-pyrazole; b/s[2-(diadamantylphosphino)ethyl]amine; 2^-b/s[3,5-di-Fe/2butyl-4-
\text{methoxypyphenyl]phosphino]benzaldehyde; 2.6-b/s(di-di tert-butylphosphinomethyl)pyridine;}
\text{b/s(dicyclohexylphosphinophenyl)ether; b/s(diethylamino)phosphino]benzaldehyde;}
\text{b/s(dimethyldimino)chlorophosphine; 2^-b/s[3,5-dimethylphenyl]phosphino]benzaldehyde;}
\text{b/s[4-(3,3,4,4,5,5-heptafluoro-2,2`-b/s(trifluoromethyl)pentyl)phenyl]phenylphosphine;}
perfluorodecyl)phenyl[phenylphosphine; 1,1,’b/s(phenylphosphinidene)ferrocene; (2-bromophenyl)dicyclohexylphosphine; (2-bromophenyl)diphenylphosphine; tert-butylidicyclohexylphosphine; fe/7-butylidicyclohexylphosphonium tetrafluoroborate; tert-butylidiisopropylphosphine; fe/7-butylidiphenylphosphine; 1-(dicyclohexylphosphino)-2,2-Diphenyl-1 -methylcyclopropane; cyclohexyldiphenylphosphine; di(1-adamantyl)-2-dimethylaminophenylphosphine; di{(1-adamantyl)-(2-trisopropylsiloxyphenyl)phosphine; (5H-dibenzo[a,d]cyclohepten-5-yl)diphenylphosphine; di-fe/7-butyldicyclohexylphosphonium [1,4]bipyrazole; 3-(di-te/f-butylphosphonium)propane sulfonate; P,P-dichloroferrocenylphosphine; dicyclohexyl-(2,6-diisopropylphenyl)phosphine; dicyclohexyl(4-(N,N-dimethylamino)phenyl)phosphine; dicyclohexyl(ethyl)phosphine; dicyclohexyl(4-isopropylphenyl)phosphine; dicyclohexyl(2-methylphenyl)phosphine; dicyclohexylphenylphosphine; 2’-(dicyclohexylphosphino)acetophenone ethylene ketal; 2’-(dicyclohexylphosphino)benzophenone; 2-(dicyclohexylphosphino)-N,N-diisopropyl-1H-indole-1-carboxamide; N-(dicyclohexyl phosphino)benzylamine; 2-(diphenylphosphino)benzaldehyde; 2-(diphenylphosphino)benzaldehyde oxime; 3-(diphenylphosphino)benzenesulfonic acid sodium salt; 2-(diphenylphosphino)benzonic acid; 4-(diphenylphosphino)benzylic acid; N-(2-diphenylphosphino)benzylidene] cyclohexylamine; 2-(diphenylphosphino)-N,N-dimethylbenzylamine; 2-(diphenylphosphino)ethanaminium tetrafluoroborate; 2-(diphenylphosphino)ethylamine; 2-(2-(diphenylphosphino)ethyl)pyridine; 3-(diphenylphosphino)propan-1 -aminium tetrafluoroborate; 3-(diphenylphosphino)-1 -propylamine; 4-(diphenylphosphino) styrene; 2-(diphenylphosphino)-N,N,N-trimethylbenzlammonium triflate; diphenyl-2-pyridylphosphine; diphenyl(o-toly)phosphine; diphenyl(p-toly)phosphine; diphenylvinylphosphine; 2-(di-p-tolyphosphino)benzaldehyde; ethyldiphenylphosphine; [4-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,1,0,10,10-heptadecafluoredecyl)phenyl] diphenylphosphine; (4-hydroxyphenyl)diphenylphosphine; isopropylidiphenylphosphine; 1-methyl-2-(2-dicyclohexylphosphinophenyl)-1 H-benzoimidazole; 1-methyl-2-(2-diisopropylphosphinophenyl)-1 H-benzoimidazole; methyl-
1. H-benzoimidazole;
1,2,3,4,5-pentaphenyl-1-(di-Fe/butylphosphino)ferrocene, phenyl b/s[4-
(3,3,4,4,5,5,6,7,7,8,8,8-tridecafluoroocetyl)phenyl]phosphine; phenyl(tri-tolyl)phosphine;
phenylphosphate; 4,4’-(phenylphosphinidene)b/s(benzenesulfonic acid) dipotassium salt hydrate; tetrapropanylphosphonium bromide; triallylphosphine; tribenzylphosphine; tri-
butylphosphine; tri-n-butylphosphine; tri-Fe/7-butylphosphine; tri-Fe/7-butylphosphine; tri-
(tert-butyl)phosphine; tributylphosphine tetrafluoroborate; tri-Fe/t-butylphosphonium tetra-
fluoroborate; tricyclohexylphosphine; tricyclohexylphosphine; tricyclohexylphosphine tetra-
fluoroborate; tricyclohexylphosphine; triethylphosphine; triethylphosphine; ((4-trifluoro-
ethylmethyl)phenyl)di-Fe/7-butylphosphine; tri(2-furyl)phosphine, ((2,4,6-tri-isopropyl)phenyl)-di-
cyclohexylphosphine; trisopropylphosphine; trisopropylphosphonium tetrafluoroborate;
trimethylphosphonium tetrafluoroborate; tri-1-naphthylphosphine; triocylphosphine; tri-
phenylphosphine; triphenylphosphine hydrobromide; 4-(triphenylphosphonio)butane-1-
sulfonate; tripropylphosphine; tris[3,5-b/s(trifluoromethyl)phenyl]phosphine; tris(4-
chlorophenyl)phosphine; tris(diethylamino)phosphine; tris(2,6-
dimethoxyphenyl)phosphine; tris(dimethylamino)phosphine; tris(3,5-
dimethylphenyl)phosphine; tris(2,4-dimethyl-5-sulfanatophenyl)phosphine trisodium salt;
tris[2-(diphenylphosphino)ethyl]phosphine; tris(4-fluoro)phosphine; tris[4-
(heptadecafluoroocetyl)phenyl]phosphine; tris(hydroxymethyl)phosphine; tris(4-methoxy-
3,5-dimethylphenyl)phosphine; tris(o-methoxyphenyl)phosphine; tris(4-
methoxyphenyl)phosphine; tris(4-methyl-1-piperazinyl)phosphine;
tris(pentafluorophenyl)phosphine; tris(1-pyrrolidinyl)phosphine; tris[4-
(tridecafluorohexyl)phenyl]phosphine; tris[4-(3,3,4,4,5,5,6,7,7,8,8,8-
tridecafluoroocetyl)phenyl]phosphine; tris(4-trifluoromethylphenyl)phosphine; tris(2,4,6-
trimethoxyphenyl)phosphine; tris(2,4,6-trimethylphenyl)phosphine;
tris(trimethylsilyl)phosphine; tri(o-tolyl)phosphine; tri(p-tolyl)phosphine; tri-o-tolylphosphine tetra-
fluoroborate; and 2-(dicyclohexylphosphino)-3,6-dimethoxy-2’,4’,6’-trisopropyl-1-V-
biphenyl or acceptable salts thereof.

13. The process according to one or more of claims 1 to 3, wherein the at least one base in
step (A) or step (B) is selected from the group consisting of organic base and inorganic
base.

14. The process according to claim 13, wherein the organic base is selected from the group
consisting of \(N(R^{26})_{3}\), N-methyl piperidine, N-methyl pyrrolidine, N-methyl morpholine,
pyrrolidine, dimethyl amino pyridine, pyridine, lithium hexamethyldisilazide, sodium hexa-
methyldisilazide and tetra-\(\text{C}_{12}\)-alkyl ammonium hydroxide, wherein \(R^{26}\) is, identical or dif-
f erent, hydrogen, \(\text{Cl-}C_{6}\)-alkyl, \(\text{CsC}_{12}-\text{aryl}\), or \(\text{C}_{3}-\text{C}_{6}\)-cycloalkyl.

15. The process according to claim 13, wherein the inorganic base is selected from the group
consisting of alkali metal hydroxide, alkaline earth hydroxide, alkali metal bicarbonate,
al-Kaline earth bicarbonate, alkali metal carbonate, alkaline earth carbonate, alkali metal
phosphate, alkali metal alkoxide and alkaline earth alkoxide.
16. The process according to claim 15, wherein the alkali metal hydroxide is selected from group consisting of lithium hydroxide, sodium hydroxide, potassium hydroxide, rubidium hydroxide and cesium hydroxide; wherein alkaline earth hydroxide is selected from the group consisting of magnesium hydroxide, calcium hydroxide, strontium hydroxide and barium hydroxide; wherein alkali metal bicarbonate is selected from the group consisting of lithium bicarbonate, sodium bicarbonate, potassium bicarbonate, rubidium bicarbonate and cesium bicarbonate; wherein alkaline earth bicarbonate is selected from the group consisting of magnesium bicarbonate, calcium bicarbonate, strontium bicarbonate and barium bicarbonate; wherein alkali metal carbonate is selected from the group consisting of lithium carbonate, sodium carbonate, potassium carbonate, rubidium carbonate and cesium carbonate; wherein alkaline earth carbonate is selected from group the consisting of magnesium carbonate, calcium carbonate, strontium carbonate and barium carbonate; wherein alkali metal phosphate is selected from the group consisting of monosodium phosphate, disodium phosphate, trisodium phosphate, monopotassium phosphate, dipotassium phosphate and tripotassium phosphate; wherein alkali metal alkoxide is selected from the group consisting of NaOR$^{27}$, KOR$^{27}$, RbOR$^{27}$ and CsOR$^{27}$ wherein alkaline earth alkoxide is selected from the group consisting of Mg(OR$^{27}$)$_2$, Ca(OR$^{27}$)$_2$ and Ba(OR$^{27}$)$_2$; whereby R$^{27}$ is, identical or different, Cl-C$_4$-alkyl.

17. The process according to claim 13, wherein the at least one inorganic base is selected from the group consisting of sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, monosodium phosphate, disodium phosphate, trisodium phosphate, monopotassium phosphate, dipotassium phosphate and tripotassium phosphate, monopotassium phosphate, dipotassium phosphate and tripotassium phosphate.

18. The process according to claim 1, further comprising in step (A) at least one solvent which is selected from the group consisting of alcohol, ether, amide and aromatic solvent.

19. The process according to claim 18, wherein the alcohol is selected from the group consisting of 2-methylbutan-2-ol, benzyl alcohol, 1,4-butanediol, 1,2,4-butanetriol, 2-butanol, 1-butanol, 2-methylpropan-1-ol, 2-methylpropan-2-ol, methanol, 2-(2-methoxyethoxy)ethanol, 2-methyl-1-butanol, 2-methyl-1-pentanol, 3-methyl-2-butanol, diethylene glycol, ethanol, ethylene glycol, 2-ethylhexanol, furfuryl alcohol, glycerol, propan-2-ol, neopentyl alcohol, 2-pentanol, 1,3-propanediol, 1-propanol and propylene glycol; wherein the ether is selected from the group consisting of di-$\text{tert}$-butyl ether, diethyl ether, diethylene glycol diethyl ether, diglyme, disopropyl ether, dimethoxyethane, dimethoxymethane and 1,4-dioxane; wherein the amide is selected from the group consisting of dimethylacetamide, dimethylformamide, formamide, N-methyl-2-pyrrolidone, N-methylformamide, 2-pyrrolidone, N-vinylacetamide and N-vinylpyrrolidone; wherein the aromatic solvent is selected from the group consisting of toluene, xylene and monochlorobenzene.
20. The process according to claim 18, wherein the at least one solvent is selected from the group consisting of 1-butanol, 2-methylpropan-2-ol, 2-methylpropan-1-ol, 2-methylbutan-2-ol, 1-propanol, propan-2-ol and 1-pentanol.

21. The process according to claim 1, wherein the at least one acid in step (B) is selected from the group consisting of organic acids and inorganic acids.

22. The process according to claim 21, wherein the organic acid is selected from the group consisting of oxalic acid, formic acid, malonic acid, acetic acid, citric acid, propionic acid and butyric acid.

23. The process according to claim 21, wherein the inorganic acid is selected from the group consisting of phosphoric acid, sulphuric acid, hydrochloric acid, hydrobromic acid, hydroiodic acid and nitric acid.

24. A compound of formula (IVa)

![IVa](image)

wherein

\[ \text{Z is C}_1\text{-C}_6 \text{ alkyl.} \]

25. The compound of formula (IVa) according to claim 24, wherein \( \text{Z} \) is selected from n-butyl or 2-methylpropyl.
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

INV. C07D249/08  C07C43/174  C07C45/42

ADD.

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)

C07D  C07C

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 practicable, search terms used)

EPO-Internal, WPI Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<td>wo 2013/007767 AI (BASF SE [DE]; DI ETZ JOCHEN [DE]; RIGGS RICHARD [DE]; BOUDET NADEGE [DE] 17 January 2013 (2013-01-17) cited in the application on the whole document; in particular claim 8; page 3, line 20 to page 5, line 13; table 26 on page 18; table A entries 4, 7 on page 22; page 23f; examples, e.g. example 5)</td>
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<td>wo 2014/099633 A2 (MERCK SHARP &amp; DOHME [US]; PASTERNAK ALEXANDER [US]; DEJESUS REYNALDA K) 26 June 2014 (2014-06-26) the whole document; in particular schemes 1, 11, 12; preparation of intermediates, e.g. intermediate 3; intermediate 15B method 1 steps B, C and method 2 step B; intermediate ates 26A/B steps D-F</td>
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**Date of the actual completion of the international search**

26 September 2018

**Date of mailing of the international search report**

05/10/2018

**Name and mailing address of the ISA**

European Patent Office, P.B. 5818 Patentlaan 2
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Fax: (+31-70) 340-3016

Hani sch, Inken

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<td>Y</td>
<td>WO 2010/129379 Al (MERCK SHARP &amp; DOHME [US]; PASTERNAK ALEXANDER [US]; SHAHRI POUR AURASH) 11 November 2010 (2010-11-11) the whole document; in particular schemes 2, 4a, 4b, 5-7 etc.; preparation of intermediate compounds, e.g. intermediate 3, intermediate 3B method 2 step E</td>
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<td>US 2017081296 AI</td>
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|                                       |                | US 2015329557 AI        | 19-11-2015      |
|                                       |                | Wo 2014099633 A2        | 26-06-2014      |

<p>| wo 2010129379 Al                       | 11-11-2010     | AR 076836 AI            | 13-07-2011      |
|                                       |                | AU 2010246269 Al        | 24-11-2011      |
|                                       |                | CA 2759399 Al           | 11-11-2010      |
|                                       |                | CN 102459216 A          | 16-05-2012      |
|                                       |                | CO 6460758 A2           | 15-06-2012      |
|                                       |                | CR 20110578 A           | 09-01-2012      |
|                                       |                | EA 201171361 AI         | 30-05-2012      |
|                                       |                | EC SP110111444 A        | 30-12-2011      |
|                                       |                | EP 2427444 AI           | 14-03-2012      |
|                                       |                | ES 2561654 T3           | 29-02-2016      |
|                                       |                | GT 201100278 A          | 20-05-2015      |
|                                       |                | HN 2011002933 A         | 08-09-2014      |
|                                       |                | JP 5092068 B2           | 05-12-2012      |
|                                       |                | JP 2012526118 A         | 25-10-2012      |
|                                       |                | JP 2013014607 A         | 24-01-2013      |
|                                       |                | KR 20120011069 A        | 06-02-2012      |
|                                       |                | MA 33342 Bl             | 01-06-2012      |
|                                       |                | MX 337570 B             | 10-03-2016      |
|                                       |                | MY 157525 A             | 15-06-2016      |
|                                       |                | NZ 596229 A             | 20-12-2013      |
|                                       |                | PE 03462012 AI          | 06-05-2012      |
|                                       |                | SG 175841 A             | 29-12-2011      |
|                                       |                | TN 2011000540 AI        | 24-05-2013      |
|                                       |                | TW 201043615 A          | 16-12-2010      |</p>
<table>
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<td>24-06-2015</td>
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