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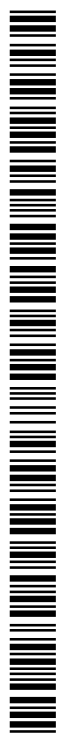
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(54) **Title:** CATALYTIC CARBOXYLATION OF ACTIVATED ALKANES AND/OR OLEFINS

(57) **Abstract:** The present invention relates to a method of reacting starting materials with an activating group, namely alkanes carrying a leaving group and/or olefins, with carbon dioxide under transition metal catalysis to give carboxyl group-containing products. It is a special feature of the method of the present invention that the carboxylation predominantly takes place at a preferred position of the molecule irrespective of the position of the activating group. The carboxylation position is either an aliphatic terminus of the molecule or it is a carbon atom adjacent to a carbon carrying an electron withdrawing group. The course of the reaction can be controlled by appropriately choosing the reaction conditions to yield the desired regioisomer.



WO 2018/010932 A1

CATALYTIC CARBOXYLATION OF ACTIVATED ALKANES AND/OR OLEFINS**Field of the invention**

5 The present invention relates to a method of reacting activated alkanes and/or olefins with carbon dioxide under transition metal catalysis to give carboxyl group-containing products and to the use of suitable reaction systems in such reactions.

Background of the invention

10

Carbon dioxide is abundantly available in the atmosphere and exists as by-product in processes such as the burning of fossil fuels. It is therefore inexpensive, available in large amounts and since it is also non-flammable and hence easy to handle, it has been recognized to an increasing extent as an attractive chemical reagent, for instance as a synthon for carboxylic acid groups.

15

In addition to traditional methods of introducing a carboxylic acid group using carbon dioxide as a reagent (such as the reaction of Grignard compounds, alkyl- or aryl-lithium compounds with carbon dioxide), metal-catalyzed carboxylation protocols have been developed which are advantageous because the reaction conditions are usually relatively mild such that other functional groups are stable and do not have a negative effect on the reaction.

20

Kirillov et al. in Dalton Trans., 2015, 44, pages 16212-162223 review the preparation of carboxylic acid derivatives by catalytic carboxylation of unsaturated hydrocarbons using either a different Ni(II) based system or a different substrate range.

25

Beller et al. in Nature Communications, January 20, 2015, 6, pages 1-15 (article no. 5933) review the use of carbon dioxide as a building block in organic synthesis.

30 Among the metal-catalyzed carboxylation protocols, Nickel-catalysts have gained particular attention.

Martin et al. in J. Am. Chem. Soc. 2013, 135, pages 1221-1224 report on the nickel-catalyzed carboxylation of benzyl halides with carbon dioxide.

35

Martin et al. in J. Am. Chem. Soc. 2014, 136, pages 11212-11215 report on the nickel-catalyzed carboxylation of primary alkyl bromides and sulfonates with carbon dioxide in which the corresponding primary carboxylic acid reaction products were formed.

- 5 Martin et al. in J. Am. Chem. Soc. 2014, 136, pages 1062-1069 report on the nickel-catalyzed carboxylation of carbon-oxygen bonds with carbon dioxide, wherein the carbon atom of the carbon-oxygen bond is an aryl ring atom or a benzyl carbon atom and the oxygen atom is the oxygen atom of a carboxylic ester moiety.
- 10 Martin et. al. in J. Am. Chem. Soc. 2014, 136, pages 17702-17705 report on the nickel-catalyzed carboxylation of allyl esters with carbon dioxide. The catalyst is formed from nickel(II) halide compounds in the presence of manganese or zinc as a reducing agent and a bipyridine, terpyridine or phenanthroline as a ligand. The reaction proceeds in a regiodivergent manner, i.e. it depends on the ligand employed in the catalyst on which carbon atom of the allyl moiety the
- 15 carboxyl group is introduced.

It would be desirable to provide a protocol for the metal-catalyzed carboxylation of further starting materials of different structure. It would also be desirable to provide such a protocol for the metal-catalyzed carboxylation that is improved in that the efficiency of the reaction is

20 increased and/or that the reaction proceeds in a regioconvergent manner. It is an object of the present invention to solve these technical problems.

The process of the present invention allows using different starting materials selected from two general classes of substances including alkenes and secondary or tertiary bromoalkanes and

25 related substances. It is even possible to make use of such starting materials that are not activated by other functional groups. In one aspect, the present invention therefore solves the further problem of providing a method for direct carboxylation, which can be carried out using a considerable variety of starting materials. In fact, the present invention describes the first method to obtain aliphatic saturated carboxylic acids via direct carboxylation of unactivated

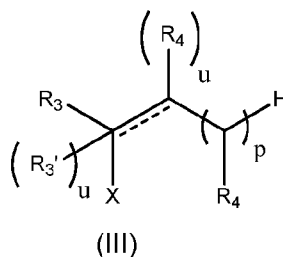
30 olefins, in which CO₂ directly participates in the carboxylation step.

Yet another benefit of the process of the present invention is its regioconvergent nature, i.e. the possibility of obtaining a single end product having a carboxyl group attached to a well-defined position even if starting materials with different structures or a mixture of such starting materials

35 is used. There is therefore less need to purify the starting material. The present invention thus allows obtaining the desired target molecule with reduced efforts. Hence, according to this aspect, the present invention solves the problem of providing a method for direct carboxylation that involves reduced purification efforts.

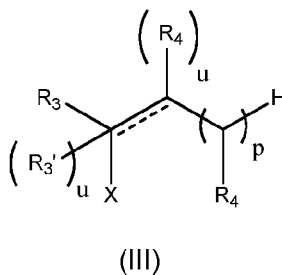
Summary of the Invention

The present invention thus provides a method of direct carboxylation of a compound represented by formula (III)



wherein the details of the method of the present invention and preferred embodiments thereof are specified in the following numbered embodiments and the subsequent detailed description.

1. Method of direct carboxylation of a compound represented by formula (III)



wherein

p is an integer from 0 to 15;

u is 0 or 1;

each R₄ represents a radical independently selected from the group consisting of

hydrogen,

a linear or branched C₁₋₂₀ alkyl group optionally carrying one or more substituents selected from fluoro and chloro,

a linear or branched C₁₋₂₀ alkyloxy group;

X represents hydrogen, a bromine atom, an iodine atom, a phenylsulfonate wherein the phenyl ring is optionally substituted with a methyl group, a methylsulfonate and a trifluoromethylsulfonate;

with the proviso that when X represents hydrogen, then the bond represented by the combination of a solid line and a dotted line is a double bond, and u is 0; and that when X is not hydrogen, then the bond represented by the combination of a solid line and a dotted line is a single bond, and u is 1;

R_3 and R_3' are each independently selected from hydrogen and a radical of formula $-Y(-Z)_n$, wherein

Y is selected from a linear C_{1-20} alkyl, a branched C_{3-20} alkyl and a C_{3-8} cycloalkyl;

n is an integer from 0 to the number of carbon atoms in Y;

5 each Z is independently selected from the group consisting of:

fluoro,

chloro,

a radical of formula $-OR_5$, a radical of formula $-C(O)R_5$, a radical of formula $-OC(O)R_5$, a radical of formula $-C(O)OR_5$, a radical of formula $-NHC(O)R_5$, a radical of formula $-C(O)NHR_5$, a radical of formula $-NHC(O)OR_5$, a radical of formula $-OC(O)NHR_5$, R_5 being independently selected from the group consisting of a linear or branched C_{1-20} alkyl groups, and a cyclic group comprising 1 ring or 2 to 5 condensed rings,

15 wherein each ring has 5 or 6 members selected from the group consisting of C, CH, CH_2 , CO, O, S, N and NR_6 ,

wherein R_6 is selected from hydrogen and C_{1-6} alkyl,

each ring being independently unsaturated, saturated or aromatic;

and each ring being further optionally substituted with one or more radicals selected from the group consisting of: fluoro, chloro, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkyloxy, C_{1-6} alkylcarbonyl, phenylcarbonyl, C_{1-6} alkylcarbonyloxy, C_{1-6} alkylcarbonylamino, and C_{1-6} alkylaminocarbonyl,

an aldehyde group,

nitro,

cyano,

25 a group of formula $-SO_2R_{11}$

wherein R_{11} is selected from C_{1-6} alkyl, C_{1-6} haloalkyl, phenyl and phenyl substituted with one or more C_{1-6} alkyl groups; and

a cyclic group comprising 1 ring or 2 to 5 condensed rings,

30 wherein each ring has 3, 4, 5 or 6 members selected from the group consisting of C, CH, CH_2 , CO, O, S, N and NR_6 ,

wherein R_6 is selected from hydrogen and C_{1-6} alkyl,

each ring being independently unsaturated, saturated or aromatic;

and each ring being further optionally substituted with one or more radicals selected from the group consisting of: fluoro, chloro, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkyloxy, C_{1-6} alkylcarbonyl, C_{1-6} alkylcarbonyloxy, C_{1-6} alkylcarbonylamino, C_{1-6} alkylaminocarbonyl, a radical of formula $-OR_5$, a radical of formula $-C(O)R_5$, a radical of formula $-OC(O)R_5$, a radical of formula $-C(O)OR_5$, a radical of formula $-NHC(O)R_5$, a radical of formula $-$

C(O)NHR₅, a radical of formula -NHC(O)OR₅, a radical of formula -OC(O)NHR₅, a radical of formula -NR₅C(O)R₅, a radical of formula -C(O)N(R₅)₂, a radical of formula -NR₅C(O)OR₅, a radical of formula -OC(O)N(R₅)₂, -R_a-R_b,

each R₅ being independently selected from the group consisting of a linear or branched C₁₋₂₀ alkyl groups, and a cyclic group comprising 1 ring or 2 to 5 condensed rings,

wherein each ring has 5 or 6 members selected from the group consisting of C, CH, CH₂, O, S, N and NR₆,

wherein R₆ is selected from hydrogen and C₁₋₆alkyl,

each ring being independently unsaturated, saturated or aromatic; and each ring being further optionally substituted with one or more radicals selected from the group consisting of: fluoro, chloro, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkyloxy, C₁₋₆alkylcarbonyl, C₁₋₆alkylcarbonyloxy, C₁₋₆alkylcarbonylamino, and C₁₋₆alkylaminocarbonyl,

and

wherein R_a is a single bond or a diradical selected from -O-, -S-, -C(=O)-, -C(=O)-O-, -O-C(=O)-, -C(=O)-NH-, -NH-C(=O)-, -O-C(=O)-NH-, -NH-C(=O)-O-, -O-C(=O)-O-, -S(O)₂-, -S(O)₂-NH-, -NH-S(O)₂-, -N=N-, -NH-C(=O)-NH-,

and

wherein R_b is selected from a C₆₋₁₀ aryl group, a C₃₋₈ cycloalkyl group optionally containing one or two double bonds, or a saturated or unsaturated heterocyclic group containing 5 to 7 ring members wherein each ring member is selected from C, CH, CH₂, O, S, B, CHR₆, C(R₆)₂, N and NR₆, wherein R₆ is selected from hydrogen and C₁₋₆alkyl;

or; alternatively, R₃ and R₃' together with the carbon atom to which they are attached form a cyclic group comprising 1 ring or 2 to 5 condensed rings, wherein each ring has 5 or 6 members selected from the group consisting of C, CH, CH₂, O, S, N and NR₆, wherein R₆ is selected from hydrogen and C₁₋₆alkyl, each ring being independently unsaturated, or saturated; and each ring being further optionally substituted with one or more radicals selected from the group consisting of: C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkyloxy, C₁₋₆alkylcarbonyl, C₁₋₆alkylcarbonyloxy, C₁₋₆alkylcarbonylamino, C₁₋₆alkylaminocarbonyl, -R_a-R_b,

wherein R_a is a single bond or a diradical selected from -O-, -S-, -C(=O)-, -C(=O)-O-, -O-C(=O)-, -C(=O)-NH-, -NH-C(=O)-, -O-

C(=O)-NH-, -NH-C(=O)-O-, -O-C(=O)-O-, -S(O)₂-, -S(O)₂-NH-, -NH-S(O)₂-, -N=N-, -NH-C(=O)-NH-,

and wherein R_b is selected from a C₆₋₁₀ aryl group, a C₃₋₈ cycloalkyl group optionally containing one or two double bonds, or a saturated or unsaturated heterocyclic group containing 5 to 7 ring members wherein each ring member is selected from C, CH, CH₂, O, S, N and NR₆, wherein R₆ is selected from hydrogen and C₁₋₆alkyl;

with the proviso that R₃ is not hydrogen if X is not hydrogen

or, in an alternative aspect of the above first embodiment, Z may be independently further selected from

hydroxyl

a radical of formula -NR₅C(O)R₅, a radical of formula -C(O)N(R₅)₂, a radical of formula -NR₅C(O)OR₅, a radical of formula -OC(O)N(R₅)₂, each

R₅ being independently selected from the group consisting of a linear or branched C₁₋₂₀ alkyl groups, and a cyclic group comprising 1 ring or 2 to 5 condensed rings,

wherein each ring has 5 or 6 members selected from the group consisting of C, CH, CH₂, CO, O, S, N and NR₆,

wherein R₆ is selected from hydrogen and C₁₋₆alkyl,

each ring being independently unsaturated, saturated or aromatic;

and each ring being further optionally substituted with one or more

radicals selected from the group consisting of: fluoro, chloro, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkyloxy, C₁₋₆alkylcarbonyl, phenylcarbonyl, C₁₋₆alkylcarbonyloxy, C₁₋₆alkylcarbonylamino, and C₁₋₆alkylaminocarbonyl,

a cyclic group comprising 1 ring or 2 to 5 condensed rings,

wherein each ring has 3, 4, 5 or 6 members selected from the group consisting of C, CH, CH₂, CO, O, S, N and NR₆,

wherein R₆ is selected from hydrogen and C₁₋₆alkyl,

each ring being independently unsaturated, saturated or aromatic;

and each ring being further optionally substituted with one or more radicals selected from the group consisting of: fluoro, chloro, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkyloxy, C₁₋₆alkylcarbonyl, C₁₋₆alkylcarbonyloxy, C₁₋₆alkylcarbonylamino, C₁₋₆alkylaminocarbonyl, a radical of formula -OR₅, a radical of formula -C(O)R₅, a radical of formula -OC(O)R₅, a radical of formula -C(O)OR₅, a radical of formula -NHC(O)R₅, a radical of formula -C(O)NHR₅, a radical of formula -NHC(O)OR₅, a radical of formula -OC(O)NHR₅, a radical of formula -NR₅C(O)R₅, a radical of

formula $-C(O)N(R_5)_2$, a radical of formula $-NR_5C(O)OR_5$, a radical of formula $-OC(O)N(R_5)_2$, $-R_a-R_b$,

each R_5 being independently selected from the group consisting of a linear or branched C_{1-20} alkyl groups, and a cyclic group comprising 1 ring or 2 to 5 condensed rings,

wherein each ring has 5 or 6 members selected from the group consisting of C, CH, CH_2 , O, S, N and NR_6 ,

wherein R_6 is selected from hydrogen and C_{1-6} alkyl,

each ring being independently unsaturated, saturated or aromatic;

and each ring being further optionally substituted with one or more radicals selected from the group consisting of: fluoro, chloro, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkyloxy, C_{1-6} alkylcarbonyl, C_{1-6} alkylcarbonyloxy, C_{1-6} alkylcarbonylamino, and C_{1-6} alkylaminocarbonyl,

and

wherein R_a is a single bond or a diradical selected from $-O-$, $-S-$, $-C(=O)-$, $-C(=O)-O-$, $-O-C(=O)-$, $-C(=O)-NH-$, $-NH-C(=O)-$, $-O-C(=O)-NH-$, $-NH-C(=O)-O-$, $-O-C(=O)-O-$, $-S(O)_2-$, $-S(O)_2-NH-$, $-NH-S(O)_2-$, $-N=N-$, $-NH-C(=O)-NH-$,

and

wherein R_b is selected from a C_{6-10} aryl group, a C_{3-8} cycloalkyl group optionally containing one or two double bonds, or a saturated or unsaturated heterocyclic group containing 5 to 7 ring members wherein each ring member is selected from C, CH, CH_2 , O, S, B, CHR_6 , $C(R_6)_2$, N and NR_6 , wherein R_6 is selected from hydrogen and C_{1-6} alkyl;

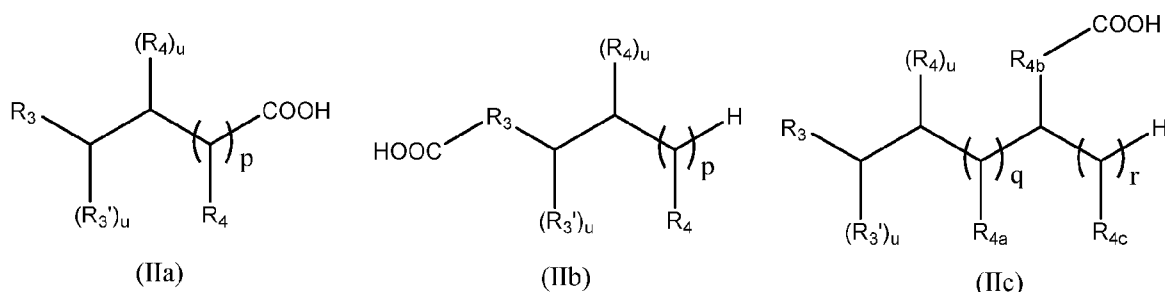
or; alternatively, one of the pairs selected from the pair R_3 and R_3' , the pair R_3 and R_4 , and the pair R_3' and R_4 , together with the carbon atom to which they are attached form a cyclic group comprising 1 ring or 2 to 5 condensed rings, wherein each ring has 5 or 6 members selected from the group consisting of C, CH, CH_2 , O, S, N and NR_6 , wherein R_6 is selected from hydrogen and C_{1-6} alkyl, each ring being independently unsaturated, or saturated; and each ring being further optionally substituted with one or more radicals selected from the group consisting of: C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkyloxy, C_{1-6} alkylcarbonyl, C_{1-6} alkylcarbonyloxy, C_{1-6} alkylcarbonylamino, C_{1-6} alkylaminocarbonyl, $-R_a-R_b$,

wherein R_a is a single bond or a diradical selected from $-O-$, $-S-$, $-C(=O)-$, $-C(=O)-O-$, $-O-C(=O)-$, $-C(=O)-NH-$, $-NH-C(=O)-$, $-O-C(=O)-NH-$, $-NH-C(=O)-O-$, $-O-C(=O)-O-$, $-S(O)_2-$, $-S(O)_2-NH-$, $-NH-S(O)_2-$, $-N=N-$, $-NH-C(=O)-NH-$,

and wherein R_b is selected from a C_{6-10} aryl group, a C_{3-8} cycloalkyl group optionally containing one or two double bonds, or a saturated or unsaturated heterocyclic group containing 5 to 7 ring members wherein each ring member is selected from C, CH, CH_2 , O, S, N and NR_6 , wherein R_6 is selected from hydrogen and C_{1-6} alkyl;

wherein also in the alternative aspect of the first embodiment the proviso applies that R_3 is not hydrogen if X is not hydrogen;

wherein the method of the first embodiment may produce a compound selected from the compounds of formula (IIa), (IIb), and (IIc)



wherein R_3 , R_3' , R_4 , n , p and u have the same meanings as specified for the respective starting materials of formula (III) above with the exception of R_3 representing a single bond in those products of formula (IIb), which are obtained from compounds of formula (III), in which R_3 represents a hydrogen atom,

and,

in the compound of formula (IIb), the carboxyl group is attached to a carbon atom of R_3 which is connected with the carbon atom derived from the activating group via a chain of secondary and tertiary carbon atoms that is not interrupted by any quaternary carbon atoms; and wherein

in the compound of formula (IIc),

q is an integer from 0 to 7;

r is an integer from 0 to 14; and $q+r+1$ is from 1 to 15;

and wherein each of R_{4a} , R_{4b} and R_{4c} independently has the same meaning as specified for R_4 , but with the proviso that R_{4b} has a terminal aliphatic carbon atom, which is connected with

the carbon atom derived from the activating group via a chain of secondary and tertiary carbon atoms that is not interrupted by any quaternary carbon atoms;

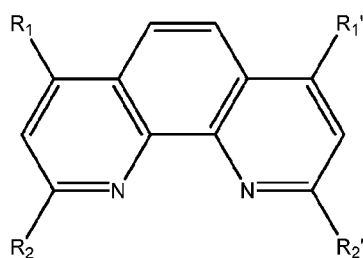
the method comprising the step of reacting the compound of formula (III) with carbon dioxide in the presence of a catalytically effective amount of a nickel catalyst and in the presence of a polar aprotic solvent,

wherein the nickel catalyst is obtainable by contacting in a polar aprotic solvent:

(a) a nickel(II) salt selected from the group consisting of nickel (II) halide, nickel (II) acetylacetonate, nickel (II) sulphate, nickel (II) perchlorate, nickel (II) trifluoromethanesulfonate, nickel (II) hexafluoroacetylacetonate, nickel (II) sulfamate, nickel (II) carbonate, nickel (II) oxalate, a compound of formula $\text{Ni}(\text{OOCR})_2$ wherein R is a linear or branched C_{1-20} alkyl or a C_{3-8} cycloalkyl optionally substituted with one or more linear or branched C_{1-6} alkyl chains, nickel hexafluorosilicate and solvates thereof;

(b) a reducing agent selected from Mn and Zn or an electrochemical reducing means, and

(c) a ligand of formula (I)



(I)

wherein

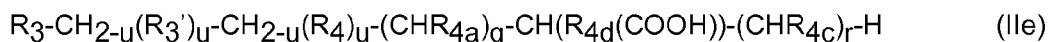
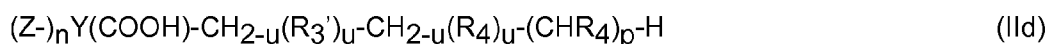
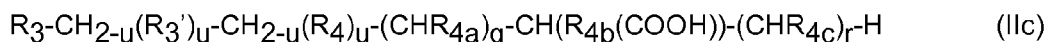
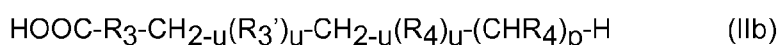
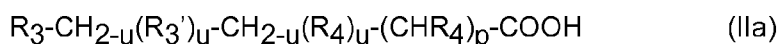
R_2 and R_2' are each independently selected from the group consisting of: hydrogen, a linear or branched C_{1-12} alkyl group, a linear or branched C_{1-12} haloalkyl group, a C_{6-20} aryl group and a C_{6-20} aryl group having at least one substituent selected from linear or branched C_{1-6} alkyl groups, linear or branched C_{1-6} alkoxy groups, linear or branched C_{1-6} haloalkyl groups, fluorine, chlorine and bromine; provided that when R_2 or, respectively, R_2' , is hydrogen, then R_2' , or, respectively, R_2 , is not hydrogen;

R_1 and R_1' are each independently selected from the groups consisting of hydrogen, halogen, a linear or branched C_{1-12} alkyl group, a linear or branched C_{1-12} haloalkyl group, a C_{6-20} aryl group and a C_{6-20} aryl group having at least one substituent selected from linear or branched C_{1-6} alkyl groups, linear or branched C_{1-6} alkoxy groups, linear or branched C_{1-6} haloalkyl groups and halogen atoms; and

(d) optionally a hydrogen source selected from water, a compound of formula $R_7R_8CH-CH_2Br$, and a compound of formula $R_7R_8CBr-CHR_9R_{10}$, wherein R_{10} , R_7 , R_8 , and R_9 are each independently selected from the group consisting of hydrogen, a linear or branched C_{1-20} alkyl optionally substituted with a radical selected from hydroxyl and C_{1-20} alkyloxy, a C_{3-8} cycloalkyl optionally substituted with a radical selected from hydroxyl and C_{1-20} alkyloxy, and a C_{6-20} aryl; or, alternatively,

one or more of the pairs of R_8 and R_7 , R_{10} and R_9 , R_7 and R_9 and R_8 and R_{10} , together with the carbon atoms to which they are attached form a ring system comprising from 1 to 3 rings, each ring being isolated, fused or bridged, and comprising from 5 to 6 members selected from the group consisting of C, CH, and CH_2 , each ring being independently unsaturated, saturated or aromatic; and each ring being further optionally substituted with one or more radicals selected from the group consisting of: hydroxyl, C_{1-6} alkyl, and C_{1-6} alkyloxy.

2. Method according to embodiment 1, wherein the direct carboxylation yields a reaction product selected from the following formulae (IIa), (IIb), (IIc), (IIId) and (IIe):



wherein u , p , q , r , R_3 , R_3' and R_4 have the meanings as specified in embodiment 1;

and wherein in formula (IIb), the carboxyl group is attached to a carbon atom of R_3 that is derived from a primary aliphatic carbon atom in the starting material, which is connected with the activating group (i.e. leaving group X or double bond) via a chain of secondary and tertiary carbon atoms that is not interrupted by any quaternary carbon atoms;

and wherein in formula (IIc), each of R_{4a} , R_{4b} and R_{4c} independently has the same meaning as specified in embodiment 1 for R_4 , but with the proviso that the carboxyl group is attached to a carbon atom of R_{4b} that is derived from a primary terminal aliphatic carbon atom in the starting material of formula (III), which is connected with the carbon atom derived from the activating group via a chain of secondary and tertiary carbon atoms that is not interrupted by any quaternary carbon atoms,

wherein in formula (IId) R_3 is represented by $(Z)_nY$, wherein Y, Z and n are as defined in embodiment 1 and wherein the carboxyl group is attached to the carbon atom of group Y that is adjacent to the carbon atom carrying a substituent group Z that is an electron withdrawing group as described below,

wherein in formula (IIe) R_{4a} and R_{4c} are as defined in embodiment 1 and wherein R_{4d} is a group as defined for R_4 in embodiment 1, but with the proviso that the group contains three atoms selected from F and Cl bonded to the same carbon atom and that the $-COOH$ group is bonded to an adjacent carbon atom that is connected with the carbon atom derived from the carbon atom of the starting material of formula (III) carrying the leaving group X or participating in the double bond via a chain of secondary and/or tertiary groups that is not interrupted by any quaternary carbon atoms.

3. Method according to embodiment 1 or 2, wherein the starting material is a compound of formula (III) as specified in embodiment 1,

wherein the dotted line, X, R_3 , R_3' , R_4 , u and p of formula (III) have the same meanings as specified in embodiment 1 with the proviso that, if the compound of formula (III) contains more than one terminal aliphatic carbon atom that is connected to the activating group by a carbon chain wherein each member of the carbon chain carries at least one hydrogen atom, the terminal carbon atom of the chain formed by $-(CHR_4)_p-$ is the terminal carbon atom closest to the activating group,

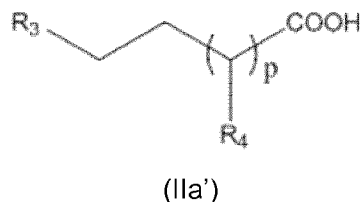
and wherein the compound of formula (III) does not contain any electron withdrawing groups that are connected with the activating group only via secondary or tertiary aliphatic carbon atoms and/or the reaction is carried out under kinetic control reaction conditions;

and wherein the direct carboxylation predominantly yields a product of formula (IIa) as specified in embodiment 2,

wherein R_3 , R_3' , R_4 , u and p have the same meanings as specified above in embodiment 1 and this embodiment,

wherein, in the compound of formula (III), u is preferably 0, so that a product of the following formula (IIa') is obtained

12



wherein R_3 , R_4 , and p have the same meanings as specified above in embodiment 1 and this
embodiment.

4. Method according to embodiment 1 or 2, wherein the starting material is a compound of formula (III) as specified in embodiment 1,

wherein the dotted line, X , R_3 , R_3' , R_4 , u and p have the same meanings as specified in embodiment 1 with the proviso that, if the compound of formula (III) contains more than one terminal aliphatic carbon atom that is connected to the activating group by a carbon chain wherein each member of the carbon chain carries at least one hydrogen atom, a terminal carbon atom of R_3 is the terminal carbon atom closest to the activating group,

wherein the carbon atom chain connecting the terminal aliphatic carbon atom of R_3 with the activating group includes only secondary and/or tertiary carbon atoms but no quaternary carbon atoms;

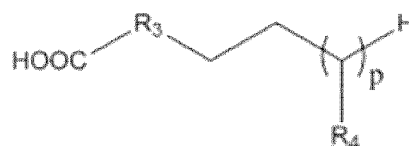
and wherein either

the compound of formula (III) does not contain any electron withdrawing groups connected with the activating group only via secondary or tertiary aliphatic carbon atoms and/or the reaction is carried out under kinetic control reaction conditions;

and wherein the direct carboxylation predominantly yields a product of formula (IIb) as specified in embodiment 2

wherein R_3 , R_3' , R_4 , u and p have the same meanings as specified above in embodiment 1 and this embodiment and wherein the COOH group binds to R_3 at the terminal carbon atom closest to the activating group,

wherein, in the compound of formula (III), u is preferably 0 so that a product of the following formula (IIb') is obtained



(IIb')

wherein R_3 , R_4 and p have the same meanings as specified above in embodiment 1 and this embodiment and wherein the COOH group binds to R_3 at a terminal carbon atom.

5. Method according to embodiment 1 or 2, wherein the starting material is a compound of formula (III) as specified in embodiment 1,

wherein the dotted line, X, R_3 , R_3' , R_4 , u and p have the same meanings as specified in embodiment 1,

wherein the direct carboxylation predominantly yields a product of formula (IIc) as specified in embodiment 2,

wherein R_3 , R_3' , R_4 , R_{4a} , R_{4b} , R_{4c} , u , q and r are as specified in embodiment 2 above and wherein the COOH group binds to R_{4b} at a terminal carbon atom,

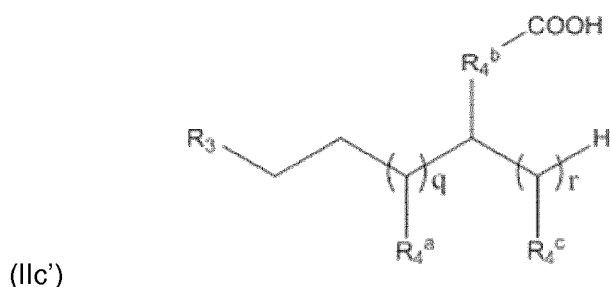
with the proviso that in the compound of formula (III) the shortest chain between terminal aliphatic carbon atom and activating group, wherein each member carries at least one hydrogen atom, is formed by the R_4 radical that gives rise to R_{4b} in the product of formula (IIc),

wherein in formula (IIc), the carboxyl group is attached to the above-mentioned terminal aliphatic carbon atom of the R_{4b} group that is a primary aliphatic carbon atom in the starting material, and that is connected with the activating group (i.e. leaving group X or double bond) via a chain of only secondary and/or tertiary carbons but no quaternary carbon atoms and

wherein either

the compound of formula (III'c) does not contain any electron withdrawing groups connected with the activating group only via secondary or tertiary aliphatic carbon atoms and/or the reaction is carried out under kinetic control reaction conditions,

wherein, in the compound of formula (III), preferably u is 0 so that a compound of the following formula (IIc') is obtained



10 R_3 , R_{4a} , R_{4b} , R_{4c} , u, q and r are as specified above in embodiment 1 and this embodiment and wherein the COOH group binds to R_{4b} at a terminal carbon atom.

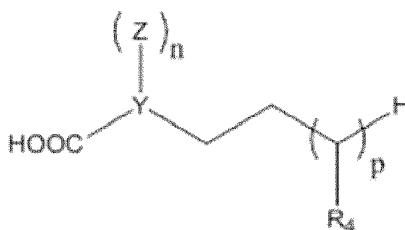
15 6. Method according to embodiment 1 or 2, wherein the starting material is a compound of formula (III) as specified in embodiment 1,

wherein the dotted line, X, R_3' , R_4 , u and p have the same meanings as specified in embodiment 1, wherein R_3 represents a group $-Y(Z)_n$ with Y, Z and n having the same meanings as specified in embodiment 1 but with the proviso that the group $-Y(Z)_n$ contains at least one substituent group Z that is an electron withdrawing group connected with the activating group, namely the leaving group X or double bond, only via secondary or tertiary aliphatic carbon atoms but without quaternary carbon atoms and the reaction is carried out under thermodynamic control reaction conditions,

25 and wherein the direct carboxylation predominantly yields a product of formula (IIId) as specified in embodiment 2 above

wherein Y, Z, R_3' , R_4 , n, u and p are as specified above in embodiment 1 and this embodiment and wherein the COOH group binds to Y at a carbon atom, which is connected with the activating group only via secondary or tertiary aliphatic carbon atoms but without quaternary carbon atoms and which is adjacent to the carbon atom carrying the substituent group Z that is an electron withdrawing group;

35 wherein, in the compound of formula (III), preferably u is 0 so that a compound of the following formula (IIId') is obtained



(IIId')

wherein Y, Z, R₄, n and p are as specified above in embodiment 1 and this embodiment and wherein the COOH group binds to Y at a carbon atom, which is connected with the activating group only via secondary or tertiary aliphatic carbon atoms but without quaternary carbon atoms and which is adjacent to the carbon atom carrying the electron withdrawing group Z.

7. Method according to embodiment 1 or 2, wherein the starting material is a compound of formula (III) as specified in embodiment 1, wherein the dotted line, X, R₃, R₃', R₄, u and p have the same meanings as specified in embodiment 1,

wherein the direct carboxylation predominantly yields a product of formula (IIe) as specified in embodiment 2,

wherein R₃, R₃', R₄, R_{4a}, R_{4c}, u, q and r have the same meanings as specified in embodiment 1, wherein R_{4d} has the same meaning as specified for R₄ in embodiment 2 but with the proviso that the group R_{4d} contains three F and/or Cl groups bonded to the same carbon atom and at least one of the adjacent carbon atoms carries at least one hydrogen atom and is connected with the activating group via an aliphatic chain having secondary and/or tertiary carbon atoms and not being interrupted by any quaternary carbon atoms

and the reaction is carried out under thermodynamic control reaction conditions,

and wherein the COOH group binds to R_{4d} at the carbon atom, which is derived from the above-mentioned carbon atom adjacent to the carbon atom carrying three F and/or Cl groups.

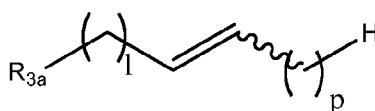
8. Method as defined in embodiment 1 or embodiment 2, wherein the compound of formula (III) is represented by formula (IIIa),



(IIIa)

wherein the double bond is in cis or trans configuration and wherein R_3 and p are as specified in embodiment 1 and if the starting material contains more than one terminal aliphatic carbon atom connected with the double bond via a carbon atom chain wherein each member of the carbon chain carries at least one hydrogen atom, direct carboxylation takes place predominantly at the terminal carbon atom that is closest to the activating group.

9. Method as defined in embodiment 8, wherein the compound of formula (III) is a compound of formula (IIIb)



(IIIb)

wherein the double bond is in cis or trans configuration and wherein

p represents an integer of 0 to 3;

l represents an integer of 0 to 3;

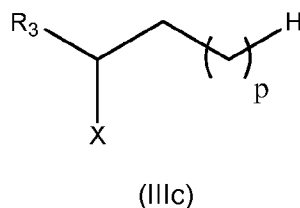
$p + l$ is less than or equal to 3;

R_{3a} represents a radical selected from a linear or branched $C_{1-(20-l)}$ alkyl group optionally substituted with a C_{6-20} aryl group, a C_{3-6} cycloalkyl group, a fluorine atom or a chlorine atom,

wherein if the starting material contains more than one terminal aliphatic carbon atom connected with the double bond via a carbon atom chain wherein each member of the carbon chain carries at least one hydrogen atom, direct carboxylation takes place predominantly at the terminal carbon atom that is closest to the activating group.

10. Method as defined in any of the preceding embodiments, wherein the compound of formula (III) is a mixture of two or more compounds of formula (III), wherein in each of these compounds X represents hydrogen and the bond represented by the combination of a solid line and a dotted line is a double bond and wherein these compounds have the same total number of carbon atoms and where groups R_3 and R_4 are such that the two or more compounds of formula (III) differ from each other only with respect to the position of the double bond and such that the same reaction product is obtained for each of these compounds.

11. Method as defined in embodiment 1 or embodiment 2, wherein the compound of formula (III) is represented by formula (IIIc),

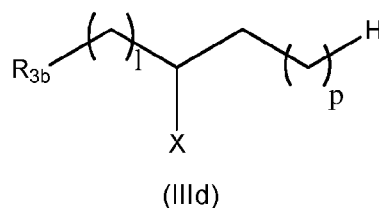


10 wherein p, X and R₃ are as defined in embodiment 1 and

wherein if the starting material contains more than one terminal aliphatic carbon atom connected with the activating group X via a carbon atom chain wherein each member of the carbon chain carries at least one hydrogen atom, direct carboxylation takes place predominantly at the terminal carbon atom that is closest to the activating group.

15

12. Method as defined in embodiment 11, wherein the compound of formula (III) is a compound of formula (IIIId)



25 wherein

p represents an integer of 0 to 3;

l represents an integer of 0 to 3;

p + l is less than or equal to 3;

X is as defined in embodiment 1;

30 R_{3b} represents a radical selected from a linear or branched C_{1-(20-l)} alkyl group optionally substituted with a C₆₋₂₀ aryl group optionally substituted with a C₁₋₆alkylcarbonyloxy, a C₃₋₆ cycloalkyl group, a radical of formula –OC(O)R₅, a radical of formula –C(O)OR₅, R₅ being selected from the group consisting of methyl, and phenyl optionally substituted with one or more radicals selected from the group consisting of:
35 fluoro, and C₁₋₆alkyloxy, a fluorine atom or a chlorine atom

wherein if the starting material contains more than one terminal aliphatic carbon atom connected with the activating group X via a carbon atom chain wherein each member of the carbon chain carries at least one hydrogen atom, direct carboxylation takes place predominantly at the terminal carbon atom that is closest to the activating group.

5
13. Method as defined in embodiments 1, 2, 3, 4, 5, 6, 7, 11 or 12, wherein the compound of formula (III) is a mixture of two or more compounds, which two or more compounds have a group X other than hydrogen as well as the same total number of carbon atoms and where groups R₃ and R₄ are such that the two or more compounds differ from each other only with respect to the position of the leaving group X and such that the same reaction product is obtained for each of these compounds.

10
14. Method as defined in any one of the preceding embodiments, wherein the reaction conditions are selected such that one or more of the following features is fulfilled:

15
(i) the catalyst is formed using Ni(II) iodide;

(ii) Mn is used as the reducing agent;

20 (iii) a ligand of formula (I) is used, wherein R₂ and R₂' are each independently selected from the group consisting of: hydrogen, a linear or branched C₁₋₁₂ alkyl group, a linear or branched C₁₋₁₂ haloalkyl group and a C₆₋₂₀ aryl group;

25 (iv) a ligand of formula (I) is used, wherein R₂ and R₂' are each independently selected from the group consisting of linear or branched C₁₋₆ alkyl groups; and

30 (v) a ligand of formula (I) is used, wherein R₁ and R₁' are each independently selected from the group consisting of a C₆₋₂₀ aryl group and a C₆₋₂₀ aryl group having at least one substituent selected from linear or branched C₁₋₆ alkyl groups, linear or branched C₁₋₆ alkoxy groups, linear or branched C₁₋₆ haloalkyl groups, fluoro, chloro and bromo

(vi) the catalyst is prepared in situ by admixing the components of the catalyst as specified in embodiment 1 with the starting material and reaction solvent wherein the addition of the individual catalyst components may be performed in any relative order;

35 (vii) the starting material is an alkene and the hydrogen source is used in an amount of 0.9 to 11 molar equivalents relative to the starting material being 1 molar equivalent.

15. Method as defined in any one of the preceding embodiments, wherein a ligand is used, which contains variable groups selected from the following alternative options:

5 (a) R_2 and R_2' are each independently selected from the group consisting of linear or branched C_{1-6} alkyl groups, while R_1 and R_1' are each independently selected from the group consisting of hydrogen, phenyl, phenyl having at least one substituent selected from linear or branched C_{1-6} haloalkyl groups and naphthyl;

10 (b) R_2 and R_2' are selected from the group consisting of CH_3 , C_2H_5 , $n-C_4H_9$, $n-C_6H_{13}$, $i-C_3H_7$ and $i-C_4H_9$ while R_1 and R_1' both represent an aryl group and more preferably a phenyl group;

15 (c) R_2 and R_2' represent both a methyl group and R_1 and R_1' are both a naphthyl group and more preferably R_1 and R_1' are both selected from the group consisting of 1-naphthyl and 2-naphthyl;

(d) R_2 and R_2' are the same and are selected from the group consisting of C_2H_5 , $n-C_4H_9$, $n-C_6H_{13}$ and $i-C_3H_7$ while R_1 and R_1' both represent a phenyl group;

20 (e) R_2 and R_2' represent both a methyl group and R_1 and R_1' are both selected from hydrogen, phenyl, C_{1-6} alkoxy-substituted phenyl, C_{1-6} haloalkyl-substituted phenyl and naphthyl group and more preferably R_1 and R_1' are both selected from the group consisting of phenyl and methoxy-substituted phenyl, in particular phenyl, para-methoxy-substituted phenyl and ortho,para-dimethoxy-substituted phenyl; or

25 (f) at least one of R_2 and R_2' represents an n-butyl group while the other one of R_2 and R_2' may represent an n-butyl group or a methyl group, and wherein R_1 and R_1' both represent a phenyl group;

30 wherein preferably R_1 and R_1' are the same and/or R_2 and R_2' are the same.

16. Method as defined in any one of the preceding embodiments 1 to 15, wherein a hydrogen source is used, which is selected from water and the group of compounds characterized by the general formula $R_7R_8CH-CH_2-Br$, wherein R_7 and R_8 are independently selected from hydrogen, a linear or branched C_{1-20} alkyl group optionally substituted with a radical selected from hydroxyl and C_{1-20} alkyloxy, a C_{3-8} cycloalkyl optionally substituted with a radical selected from hydroxyl and C_{1-20} alkyloxy, and a C_{6-20} aryl.

35

17. Method as defined in any one of the preceding embodiments, wherein the Ni(II) salt is used in an amount of 0.9 mol% to 11 mol% with respect to the starting material being 100 mol% and/or the compound of formula (I) is used in an amount of 0.9 mol% to 55 mol% with respect to the starting material being 100 mol% and/or wherein the reducing agent is advantageously used in an amount of 100 mol% to 550 mol% with respect to the starting material being 100 mol%.
18. Method as defined in any one of the preceding embodiments, wherein the reaction is carried out at a temperature in the range of from 0 to 90°C and preferably in the range of from 5 to 85°C if the starting material is a compound with a leaving group X other than hydrogen or in the range of from 45 to 90°C if the starting material is a compound wherein X represents hydrogen.
19. Method as defined in any one of the preceding embodiments, wherein the reaction is carried out in a solvent consisting of or containing a solvent selected from DMF (N,N-Dimethylformamide), N,N-diethylformamide, DMSO (dimethylsulfoxide), DMA (N,N-dimethylacetamide), NMP (N-methylpyrrolidine), N,N-dibutylformamide and 1-formylpyrrolidine.

Preferred embodiments become apparent from the following description.

Detailed Description of the invention

Definitions and general Remarks

Unless specified otherwise, all amount indications are provided on a molar basis, with absolute indications being provided in the unit of moles and relative indications being provided as mol% with the total of the respective composition being 100 mol%.

Unless specified otherwise, all indications of point values are intended to allow variation of $\pm 10\%$, preferably of $\pm 5\%$ and most preferably $\pm 0\%$ of the specified value around the point value.

Unless specified otherwise, the present application uses the term "radical" to characterize an atomic group that is monovalent and that is bonded to the remainder of the molecule via a covalent single bond. Correspondingly, the present application uses the term "diradical" to characterize an atomic group that is divalent and thus binds to two other moieties via two covalent bonds. The term "substituent" is also used herein to have the same meaning as the term radical.

Unless specified otherwise, the term “comprising” is intended to permit the additional presence of unspecified further components or measures. It is however a preferred embodiment that no further components or measures are present, i.e. the term “comprising” encompasses also the meaning “consisting of” as a preferred embodiment.

The term “aryl” is defined in the context of the present disclosure as a carbocyclic aromatic ring or a system of 2 to 5 condensed carbocyclic rings wherein at least one of these condensed rings is aromatic. It is further conceived that the aryl group may carry one or more additional aromatic carbocyclic rings being attached to the primary aromatic ring (or condensed ring system) via covalent single bonds, provided that the total number of carbocyclic rings does not exceed five. Examples include, in a non-limitative way, phenyl, naphthyl, indenyl, phenanthrenyl, anthracenyl, biphenyl, perylenyl, and phenylnaphthalenyl. The aryl group may be unsubstituted or be further substituted (in addition to any aryl substituents bonded to the primary aryl ring (or condensed ring system) mentioned above).

Unless specified otherwise, the term “polar aprotic solvent” is intended to refer to a solvent that has a dielectric constant above 25.0 and/or a dipole moment above 2.5 D and which does not release any protons under the conditions of the method of the present invention. Typical examples are N-methylpyrrolidone, THF, ethyl acetate, acetone, DMF, acetonitrile, dimethyl sulfoxide, HMPT, and propylene carbonate.

Unless specified otherwise, the term “catalytically effective amount” is intended to characterize an amount of the respective catalytically active substance, which gives rise to at least one of an increase in yield or reaction rate of at least 10% in comparison with a corresponding reaction being carried out in the absence of the catalytically active substance.

The expression “secondary” in relation to a carbon atom means that the carbon atom is attached to two bonding partners other than hydrogen. A “secondary carbon” as an internal member of a carbon chain is a carbon atom that is bonded to two carbon atom chain members as well as two hydrogen atoms. The expression “secondary position” is used to characterize the position of a group of interest (e.g. a leaving group) to characterize that the particular group of interest is attached to a carbon atom that is connected to two adjacent carbon atoms and one hydrogen atom and thus a carbon atom which is neither a terminal carbon atom nor a carbon atom that has three further bonding partners (other than hydrogen). Similarly, a “quaternary” carbon atom refers to a carbon atom which is substituted with 4 groups different from hydrogen. Similarly, a “tertiary” carbon atom refers to a carbon atom which is substituted with 3 groups different from hydrogen and is further substituted with 1 hydrogen atom.

Unless specified otherwise, all specified atoms and groups of atoms are intended to have saturated valences. Hence, if an atom has more valences than bonding partners shown or apparent from the context, all remaining valences are meant to be saturated with hydrogen atoms. Similarly, if different atoms or groups of atoms are listed as alternatives for the formation of different moieties, it is intended that a selection is to be made only from those atoms and atom groups, which offer a sufficient number of free valences for incorporation into the target moiety. For instance, if there is a reference to CH and CH₂ as members of saturated or aromatic rings, it should be understood that the CH₂ ring member is available only for the saturated ring option but not the aromatic ring option.

Unless it is apparent from the context that a different meaning is intended, all terms and expressions used herein are to be understood as having their generally accepted meaning, as represented by standard chemistry textbooks and encyclopedias such as Clayden, Jonathan; Greeves, Nick; Warren, Stuart; Wothers, Peter (2001); Organic Chemistry (1st ed.), Oxford University Press, ISBN 978-0-19-850346-0.

Unless specified otherwise, references to the method of the present invention are to be understood as references to the direct carboxylation reaction described below. This method optionally includes the preparation of a nickel catalyst, which can either be done in situ or separately. However, unless specified otherwise, references to the conditions of the method or reaction of the invention (e.g. regarding solvent or temperature) are to be understood as references to the conditions of the direct carboxylation reaction forming the core of the invention - and not as references to the nickel catalyst formation reaction, if carried out separately.

Unless specified otherwise, the direct carboxylation reaction of the present invention may yield the product not only in the free acid form, but also in the form of a salt. Consequently, all references to reaction compounds carrying a group -COOH are to be understood as encompassing also a reference to the group -COOM, wherein M represents a counter-ion. This can be any organic or inorganic counter-ion including in particular ammonium ions such as NR₄⁺ with each R being independently hydrogen or an alkyl group of 1-4 carbon atoms, alkali ions such as Na⁺ and K⁺ as well as alkaline earth ions such as Mg²⁺ and Ca²⁺ or other transition metals such as Mn²⁺ or Zn²⁺. Of course, if an alkaline earth ion or other ion with a multiple positive charge is used, the stoichiometry must be adjusted to ensure that the resulting product is not electrically charged. That is, if the counter-ion carries n positive charges, 1/n moles of counter-ion are present per mole of carboxyl group.

Unless expressly specified otherwise, all references to carbon-carbon double bonds are intended to characterize both cis (Z) and trans (E) geometries. This applies even to cases where a structural formula is shown that may suggest a particular cis (Z) or trans (E) geometry when applying standard conventions for drawing chemical formulae.

5

In the context of the present invention, the term “activating group” is used to characterize a carbon-carbon double bond or a leaving group X, wherein X is as defined below but with X being other than hydrogen.

10 In the context of the present invention, the term “electron withdrawing group” characterizes a group that withdraws electron density from the atom to which the group is attached. Electron withdrawing groups in the sense of the present invention are groups which have a Hammett constant σ (para) value higher than 0.25 if used as a substituent of an aromatic system. Suitable electron withdrawing groups in the context of the invention are selected in particular from the
15 group consisting of a C₁₋₆ alkylcarbonyl, a C₁₋₆alkyloxycarbonyl, a C₁₋₆alkylaminocarbonyl, an aldehyde group, nitro, cyano, sulfones, sulfoxides and sulfonates. Electron withdrawing groups as defined herein may be attached to any structural element including saturated hydrocarbon groups, which may be linear, cyclic or branched.

20 In the context of the present invention, when the carboxylation may occur at one or more atoms in the compound of formula(III), the term “kinetic control reaction conditions” characterizes conditions of reaction where the fastest carboxylation process is predominant. In other words, these are conditions yielding predominantly the same product as the product obtained at lowest possible temperature at which the reaction of the present invention can be carried out.

25

In the context of the present invention, when the carboxylation may occur at one or more atoms in the compound of formula (III), the term “thermodynamic control reaction conditions” characterizes conditions where the most stable carboxylation product is predominantly obtained. In other words, these are conditions yielding predominantly the same product as the
30 product obtained at highest possible temperature at which the reaction of the present invention can be carried out.

In the context of the present invention, the term “predominantly” is used in its normal sense, e.g. having the meaning of “mainly”. By consequence, references to a product being “predominantly”
35 obtained may be understood as indicating that the respective product is mainly obtained, i.e. as the main product. In one preferred embodiment, a predominantly obtained product is obtained in an amount that is at least twice the amount of the by-product derived from the same starting material, which is obtained in the second-greatest amount (hereinafter: “main by-product”).

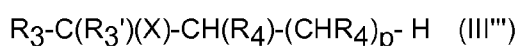
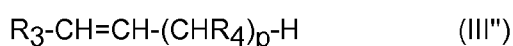
More preferably, the amount of the predominant product is at least five times, more preferably at least 10 times, the amount of of the main by-product.

Overview

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The present invention provides a method for direct carboxylation of specific starting materials. Said starting materials are compounds with an aliphatic chain that is activated by a leaving group or by a carbon-carbon double bond as represented by general formula (III) above.

10 More specifically, the starting materials can be characterized by the following general formulae:



15

The meanings of variable groups R_3 , R_3' , R_4 , of p and of leaving group X are defined herein above and in more detail below.

20 The course of the reaction and the resulting product of the direct carboxylation reaction are determined by the specific structure of the starting material and, to some extent, by the reaction conditions.

(i) Impact of structure of starting material

25 The direct carboxylation of the present invention normally yields primary carboxylic acids, i.e. carboxylic acids wherein the carboxyl group is attached to a carbon atom that is bonded via a single bond to the remainder of the molecule. Said primary carboxylic acids are formed by attaching the carboxyl group to a terminal aliphatic carbon atom of the starting material. The method of the present invention thus extends the carbon chain of the starting material by
30 creation of a new carbon-carbon bond.

The activating group (i.e. the leaving group X or the double bond) not being located at a terminal position of the starting material, the course of the reaction can be explained by a "chain walking mechanism". To allow such a chain walking mechanism, it is a prerequisite that each
35 member of the carbon chain between the activating group and the terminal carbon atom carries at least one hydrogen atom. Consequently, it is a prerequisite that the compound of formula (III) does not comprise any quaternary carbon atom between the carbon atom bearing the X group

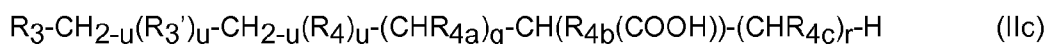
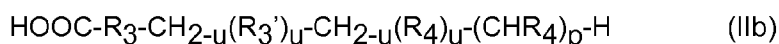
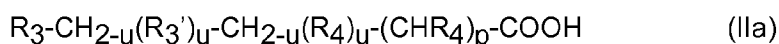
or double bond and the carbon atom to which the carboxyl group is attached in the product of the reaction.

If the starting material contains more than one terminal aliphatic carbon atom fulfilling the above requirement for chain walking, direct carboxylation normally could in theory take place in different positions. However, in practice, direct carboxylation normally takes place predominantly at the terminal carbon atom that is closest to the activating group.

For instance, in one embodiment of a starting material with $u=0$ and the dotted line representing a double bond as the activating group, wherein the R_3 group of the starting material represents a linear alkyl group and all R_4 groups represent hydrogen atoms, the terminal aliphatic carbon atom at the side of $-(CHR_4)_p-H$ is closest and will therefore be carboxylated if p is smaller than the number of carbon atoms in R_3 . Conversely, if the number of carbon atoms in R_3 is smaller than p , carboxylation will predominantly take place at the terminal carbon atom of the R_3 group.

If X represents a leaving group as the activating group and $u=1$, the situation is similar to the situation above except for the fact that the carbon atom characterized in formula (III) as $-CH(R_4)_u-$ does not form part of the activating group (unlike its participation in the double bond in the above example), so that the position of predominant carboxylation depends on the question whether the number of carbon atoms in R_3 is greater or smaller than $p+1$.

Hence, if the starting material contains susceptible terminal aliphatic carbon atoms as part of R_3 and/or R_4 , the following alternative reaction products can be envisaged, depending on the question which of the termini has the shortest chain to the activating group:



wherein u is 0 or 1 and preferably 0, R_3 and R_4 have the meanings specified herein above and below, and wherein each of R_{4a} , R_{4b} and R_{4c} independently has the same meaning as specified for R_4 , but with the proviso that R_{4b} has a terminal aliphatic carbon atom, which is connected with the activating group (i.e. leaving group X or double bond) via a chain of secondary and tertiary carbon atoms that is not interrupted by any quaternary carbon atoms;

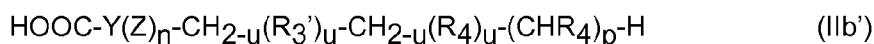
wherein the product of formula (IIa) can only be formed if the terminal carbon atom of the chain $-(\text{CHR}_4)_p-$ is indeed a terminal carbon atom, which means that the group R_4 attached to the carbon atom of the chain $-(\text{CHR}_4)_p-$, which is furthest away from the activating group, must not be an alkyl group. Products of formula (IIa) are preferably formed using starting materials, wherein the last carbon atom of the chain $-(\text{CHR}_4)_p-$ carries a hydrogen atom as group R_4 , such that the chain $-(\text{CHR}_4)_p-$ becomes a $-(\text{CHR}_4)_{p-1}-\text{CH}_2-$ chain. Otherwise, the terminus of this aliphatic chain would be found in group R_4 , so that the resulting product would be of the type of formula (IIc) (with $r=0$);

wherein $q = 0 - 7$, $r = 0 - 14$ and $q + r + 1 = 1 - 15$;

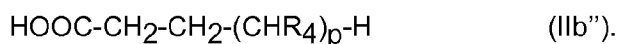
and wherein in formula (IIb), the carboxyl group is attached to a carbon atom of R_3 that is a primary aliphatic carbon atom in the starting material, which is connected with the activating group (i.e. leaving group X or double bond) via a chain of secondary and tertiary carbon atoms that is not interrupted by any quaternary carbon atoms;

and wherein in formula (IIc), the carboxyl group is attached to the above-mentioned terminal aliphatic carbon atom of the R_{4b} group that is a primary aliphatic carbon atom in the starting material, and that is connected with the activating group (i.e. leaving group X or double bond) via a chain of secondary and tertiary carbon atoms that is not interrupted by any quaternary carbon atoms.

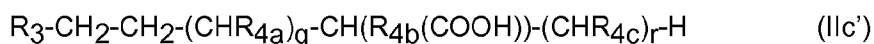
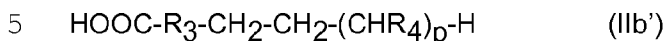
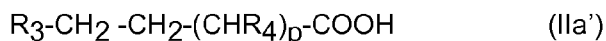
As noted above, the group R_3 represents a hydrogen atom or a group $-\text{Y}(\text{Z})_n$. Incorporating the latter meaning into formula (IIb) yields the following formula (IIb'):



If R_3 represents a hydrogen atom, formula (IIb) can be simplified in a different manner: Of course, the hydrogen atom cannot form a further bond to the newly filed carboxylic acid. In such a case of a terminal olefinic double bond, there is no room for a chain walking mechanism and the carboxyl group is added directly to the terminal carbon of said olefinic double bond. The resulting compound can be characterized by the following formula:



In preferred embodiments, in the compound of formula (III), $u=0$. Therefore, the compounds of formulae (IIa), (IIb) and (IIc) are simplified to the compounds of formulae (IIa'), (IIb') and (IIc') respectively:



Apart from the length of the carbon chain, the course of the reaction may further be influenced by electronic effects of further substituents that may be present. This is illustrated in sub-section (ii) below.

(ii) Impact of reaction conditions – kinetic versus thermodynamic control

Different reaction products may be obtained if the starting material contains a substituent group that has an electron withdrawing effect and is especially one of the following groups:

a radical of formula $-C(O)R_5$,

a radical of formula $-C(O)OR_5$,

a radical of formula $-C(O)NHR_5$, R_5 being as defined above

an aldehyde group,

cyano,

nitro, and

a group of formula $-SO_2R_{11}$

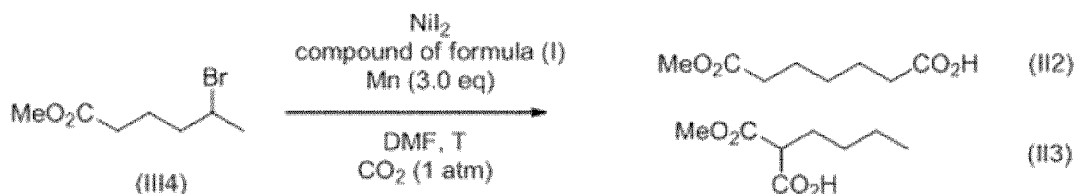
wherein R_{11} is selected from C_{1-6} alkyl, C_{1-6} haloalkyl, phenyl and phenyl substituted with one or more C_{1-6} alkyl groups.

For such starting materials, the course of the reaction depends not only on the chain lengths mentioned above, but also on the reaction conditions. It is also a prerequisite that the compound of formula (III) does not comprise any quaternary carbon atom between the carbon atom bearing the X group and the carbon atom to which the carboxyl group is attached in the product of the reaction. In particular, different reaction products are obtained depending whether conditions are chosen such that the reaction is thermodynamically controlled (e.g. high reaction temperature, fast reaction) or kinetically controlled (e.g. low temperature, slow reaction).

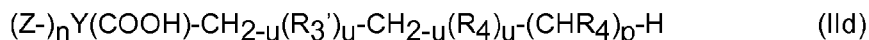
Specifically, kinetic control leads to direct carboxylation of a terminal aliphatic carbon atom as described under item (i) above.

Conversely, thermodynamic control leads to direct carboxylation of the carbon atom adjacent to the above electron withdrawing group, which provides the most stable (i.e. energetically favoured) product.

- 5 The situation can be illustrated by the following example reaction, which is based on Example 5 below:

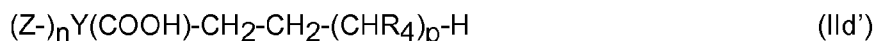


- 10 At high temperatures (i.e. under thermodynamic reaction control conditions), the carbon atom adjacent to the electron withdrawing group (methyl ester group) is carboxylated (product (II3)), whereas the primary aliphatic carbon atom at the opposite terminus is carboxylated at low temperatures (i.e. under kinetic reaction control conditions, product (II2)).
- 15 Hence, in addition to the reaction products (IIa), (IIb) and (IIc) above, it is also conceivable for some starting materials to control reaction conditions such that the following thermodynamic reaction control product (IIId) is obtained:



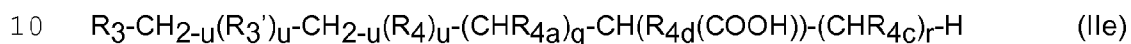
- 20 wherein R_3 in this structural formula is represented by $(Z-)_n Y$, and wherein the carboxyl group is attached to the carbon atom of group Y that is adjacent to the carbon atom carrying a substituent group Z that is an electron withdrawing group as described above, and wherein R_4 , n , u and p are as defined above.

- 25 In a preferred embodiment, $u = 0$, so that formula (IIId) is simplified to



- 30 Again, if different carbon atoms are available for direct carboxylation via thermodynamic control because they have adjacent carbons carrying an electron withdrawing group Z , the reaction proceeds in practice such that predominantly the carbon atom is carboxylated, which provides the most stable (i.e. energetically favoured) product.

A thermodynamic reaction control product similar to the product (II_d) above can also be obtained if at least one R₄ group of the starting material contains three F and/or Cl groups bonded to the same carbon atom and at least one of the adjacent carbon atoms carries at least one hydrogen atom and is connected with the activating group via a chain of secondary and/or tertiary groups that is not interrupted by any quaternary carbon atoms. The combined electron-withdrawing effect of these halogen atoms may also direct the direct carboxylation reaction to the adjacent carbon atom if suitable thermodynamic control conditions are chosen for the reaction. The resulting product can be characterized by the following formula (II_e):



wherein R₃, R₄, R_{4a}, R_{4c}, u, q and r are as defined above and wherein R_{4d} is a group as defined for R₄ above, but with the proviso that the group contains three atoms selected from F and Cl bonded to the same carbon atom and that the –COOH group is bonded to an adjacent carbon atom that is connected with the activating group via a chain of secondary and/or tertiary groups that is not interrupted by any quaternary carbon atoms.

Depending on the synthetic target, all of the above-mentioned products may be valuable. All of the above alternative courses of the direct carboxylation reaction are therefore to be regarded as different variants of the method of the present invention. As indicated above, a variety of different reaction products (II_a) to (II_e) are conceivable for the method of the present invention. The method of the present invention is nevertheless a valuable synthetic tool because – depending on starting material and reaction conditions – only one of these reaction products is predominantly obtained. The above general rules determining the predominant reaction product can be summarized as follows:

A product of formula (II_a) is predominantly obtained if all of the following conditions for the compound of formula (III) are fulfilled:

- The number of carbon atoms between the activating group and the terminal carbon atom of the chain formed by –(CHR₄)_p– is smaller than the number of carbon atoms in any other aliphatic carbon atom chain involving R₃, R_{3'} or R₄, and connecting a terminal aliphatic carbon atom with the activating group, namely the leaving group X or double bond, only via secondary and/or tertiary carbons but without quaternary carbon atoms;
- (i) either the compound of formula (III) does not contain any electron withdrawing groups that are connected with the activating group only via secondary or tertiary aliphatic

carbon atoms and the reaction is carried out under kinetic or thermodynamic control conditions;

(ii) or the compound of formula (III) does contain one or more electron withdrawing groups that are connected with the activating group only via secondary or tertiary aliphatic carbon atoms and the reaction is carried out under kinetic control reaction conditions.

A product of formula (IIb) is predominantly obtained if all of the following conditions for the compound of formula (III) are fulfilled:

- the number of carbon atoms between the activating group and the terminal aliphatic carbon atom of R_3 is smaller than the number of carbon atoms between the activating group and the terminal aliphatic carbon atom in any other aliphatic carbon atom chain involving R_3' and/or $-(CHR_4)_p-$ and/or parts of $-(CHR_4)_p-$ together with individual R_4 groups connecting a terminal aliphatic carbon atom with the activating group only via secondary and/or tertiary carbons but without quaternary carbon atoms;
- the carbon atom chain connecting the terminal aliphatic carbon atom of R_3 with the activating group, namely the leaving group X or double bond, includes only secondary and/or tertiary carbon atoms but no quaternary carbon atoms;
- (i) either the compound of formula (III) does not contain any electron withdrawing groups connected with the activating group only via secondary or tertiary aliphatic carbon atoms and the reaction is carried out under kinetic or thermodynamic control conditions;
(ii) or the compound of formula (III) does contain one or more electron withdrawing groups connected with the activating group only via secondary or tertiary aliphatic carbon atoms and the reaction is carried out under kinetic control reaction conditions;

A product of formula (IIc) is predominantly obtained if all of the following conditions for the compound of formula (III) are fulfilled:

- The number of carbon atoms between the activating group and the terminal carbon atom of R_{4b} is smaller than the number of carbon atoms in any other aliphatic carbon atom chain involving R_3 or $-(CHR_4)_p-$, connecting a terminal aliphatic carbon atom with the activating group, namely the leaving group X or double bond, only via secondary and/or tertiary carbons but without quaternary carbon atoms;

- the carbon atom chain connecting the terminal aliphatic carbon atom of R_{4b} with the activating group includes only secondary and/or tertiary carbons but no quaternary carbon atoms;
- (i) either the compound of formula (III'c) does not contain any electron withdrawing groups connected with the activating group only via secondary or tertiary aliphatic carbon atoms and the reaction is carried out under kinetic or thermodynamic reaction conditions
- (ii) or the compound of formula (III'c) does contain one or more electron withdrawing groups connected with the activating group only via secondary or tertiary aliphatic carbon atoms and the reaction is carried out under kinetic control reaction conditions,

A product of formula (IIId) is predominantly obtained if all of the following conditions for the compound of formula (III) are fulfilled:

- R_3 represents the group $-Y(Z)_n$ and the group $-Y(Z)_n$ contains at least one electron withdrawing group connected with the activating group, namely the leaving group X or double bond, only via secondary or tertiary aliphatic carbon atoms but without quaternary carbon atoms and
- the reaction is carried out under thermodynamic control reaction conditions.

A product of formula (IIe) is predominantly obtained if all of the following conditions for the compound of formula (III) are fulfilled:

- at least one R_4 group of the starting material contains three F and/or Cl groups bonded to the same carbon atom and at least one of the adjacent carbon atoms carries at least one hydrogen atom and is connected with the activating group via an aliphatic chain having secondary and/or tertiary carbon atoms and not being interrupted by any quaternary carbon atoms and
- the reaction is carried out under thermodynamic control reaction conditions.

(A) The starting material

The method of the present invention can be carried out using two different general types of starting materials, namely aliphatic compounds carrying a leaving group in a secondary or tertiary position, and aliphatic compounds having a carbon-carbon double bond. The leaving group is preferably a bromine atom. However, other leaving groups such as an iodine atom, a tosylate group, mesylate group, triflate group or related groups may also be used. The starting material may be linear, branched, cyclic or any combination thereof. The starting material may

preferably have from 2 to 100 carbon atoms, more preferably from 2 to 50 carbon atoms and most preferably from 2 to 20 carbon atoms. The starting material may carry one or more further substituents as long as these substituents do not interfere with the reaction underlying the method of the present invention. A list of suitable substituents is provided for instance in
 5 appended claim 1. It should however be clear that further substituents may exist that are also compatible with the method of the present invention.

The position of the leaving group X is not particularly restricted as long as it is attached to a secondary carbon atom or a tertiary carbon atom that is adjacent to a carbon atom carrying a
 10 hydrogen atom. For instance, if the starting material is a linear bromoalkane having a backbone of n carbon atoms, the bromo substituent can be attached to any one of carbon atoms 2, 3, ..., n-1. The same applies, of course, to other leaving groups.

Similarly, if an alkene is used as the starting material, the position of the carbon-carbon double
 15 bond is also not particularly restricted. For instance, in the case of a linear alkene with a backbone of n carbon atoms, said double bond can be in anyone of positions 1 and 2, 2 and 3, 3 and 4, ..., (n-1) and n.

Suitable starting materials are especially those of the general formula (III), as described herein
 20 above and below.

Preferred starting materials are those where u is 0, i.e. starting materials wherein general formula (III) falls within the scope of preferred formula (III') as specified herein above.

25 Preferred starting materials are characterized by the following formula (IIIa):



(IIIa)

30 wherein the double bond is in cis or trans configuration and wherein R_3 and p are as specified herein above.

A preferred starting material is that wherein R_3 is a radical selected from the group consisting of:
 35 hydrogen and a radical of formula $-\text{Y}(-\text{Z})_n$, wherein
 Y is selected from a linear C_{1-20} alkyl group,
 a branched C_{3-20} alkyl group, and

and a C₃₋₈ cycloalkyl group,

wherein each Z is independently selected from the group consisting of:

fluoro, chloro, a radical of formula $-OR_5$, a radical of formula $-OC(O)R_5$, a radical of formula $-C(O)OR_5$, R₅ being selected from the group consisting of a linear or branched C₁₋₂₀ alkyl groups, and a cyclic group comprising 1 ring or 2 to 5 condensed rings,

wherein each ring has 5 or 6 members selected from the group consisting of C, CH, and CH₂,

each ring being independently unsaturated, saturated or aromatic;

and each ring being further optionally substituted with one or more radicals selected from the group consisting of: fluoro, chloro, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkyloxy, C₁₋₆alkylcarbonyl, C₁₋₆alkylcarbonyloxy, C₁₋₆alkylcarbonylamino, and C₁₋₆alkylaminocarbonyl,

a cyclic group comprising 1 ring or 2 to 5 condensed rings,

wherein each ring has 6 members selected from the group consisting of C, CH, and CH₂,

each ring being independently unsaturated, saturated or aromatic;

and each ring being further optionally substituted with one or more radicals selected from the group consisting of: C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkyloxy, C₁₋₆alkylcarbonyl, C₁₋₆alkylcarbonyloxy, C₁₋₆alkylcarbonylamino, C₁₋₆alkylaminocarbonyl, and -R_b, wherein R_b is a C₆₋₁₀ aryl group.

Another preferred starting material is that wherein R₃ is a radical selected from the group consisting of:

hydrogen and a radical of formula $-Y(-Z)_n$, wherein

Y is selected from a linear C₁₋₂₀ alkyl group,

and a branched C₃₋₂₀ alkyl group, and

a C₃₋₈ cycloalkyl group,

wherein each Z is independently a radical of formula $-OC(O)R_5$, a radical of formula $-C(O)OR_5$, R₅ being selected from the group consisting of a linear or branched C₁₋₂₀ alkyl groups, and a cyclic group comprising 1 ring or 2 condensed aromatic rings,

wherein each ring has 5 or 6 members selected from the group consisting of C, and CH;

and each ring being further optionally substituted with one or more radicals selected from the group consisting of: fluoro, C₁₋₆alkyl, C₁₋₆haloalkyl, and C₁₋₆alkyloxy, or a cyclic group comprising 1 ring or 2 to 5 condensed rings, wherein each ring has 6 members

selected from the group consisting of C, CH, and CH₂, each ring being independently unsaturated, saturated or aromatic; and each ring being further optionally substituted with one or more radicals selected from the group consisting of: C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkyloxy, C₁₋₆alkylcarbonyl, C₁₋₆alkylcarbonyloxy, C₁₋₆alkylcarbonylamino, C₁₋₆alkylaminocarbonyl, and -R_b, wherein R_b is a C₆₋₁₀ aryl group.

Another preferred starting material is that wherein R₃ is a radical selected from the group consisting of:

hydrogen and a radical of formula -Y(-Z)_n, wherein

Y is selected from

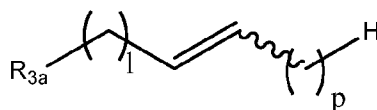
a linear C₁₋₂₀ alkyl group,

and a branched C₃₋₂₀ alkyl group,

wherein each Z is independently a radical of formula -OC(O)R₅, a radical of formula -C(O)OR₅, R₅ being selected from the group consisting of methyl, and phenyl optionally substituted with one or more radicals selected from the group consisting of: fluoro, and C₁₋₆alkyloxy, or a phenyl ring optionally substituted with one or more radicals selected from the group consisting of: C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkyloxy, C₁₋₆alkylcarbonyl, C₁₋₆alkylcarbonyloxy, C₁₋₆alkylcarbonylamino, C₁₋₆alkylaminocarbonyl, and -R_b, wherein R_b is a C₆₋₁₀ aryl group.

Another preferred starting material is that wherein R₃ is a C₁₋₁₀ alkyl group optionally substituted with a phenyl ring, the phenyl ring being optionally substituted with a *tert*-butylcarbonyloxy, or a radical of formula -OC(O)R₅, a radical of formula -C(O)OR₅, R₅ being selected from the group consisting of methyl, and phenyl optionally substituted with one or more radicals selected from the group consisting of: fluoro, and methyloxy.

Another preferred starting material is characterized by the following formula (IIIb):



(IIIb)

wherein

p represents an integer of 0 to 3;

l represents an integer of 0 to 3;

p + l is less than or equal to 3;

R_{3a} represents a radical selected from a linear or branched C₁-(20-l) alkyl group optionally substituted with

a C₆₋₂₀ aryl group, which is optionally substituted with a C₁₋₆alkylcarbonyloxy or C₁₋₆alkoxycarbonyl or optionally condensed with a five- or six-membered heterocycle with ring atoms selected from C, N, O, S and P,

a C₃₋₆ cycloalkyl group,

a radical of formula -OC(O)R₅,

a radical of formula -C(O)OR₅,

a radical of formula -OR₅,

a radical of formula -C(O)R₅,

a radical of formula -C(O)N(R₅)₂,

a radical of formula -CHO,

a mono- or bicyclic saturated,

unsaturated or aromatic heterocycle with each ring having 3 to 8 ring atoms selected from C, N, O, S and P, optionally substituted with a C₁₋₆alkylcarbonyloxy or C₁₋₆alkoxycarbonyl;

each R₅ being independently selected from the group consisting of methyl, ethyl, propyl, butyl and phenyl optionally substituted with one or more radicals selected from the group consisting of: C₁₋₆alkyloxy, C₁₋₆alkyloxycarbonyl, C₁₋₆alkylcarbonyloxy, a fluorine atom, a chlorine atom, phenylcarbonyl, phenoxycarbonyl, phenylcarbonyloxy, and phenoxy,

a fluorine atom or

a chlorine atom.

Yet another preferred starting material is characterized by the following formula (IIIb) as defined above wherein:

p represents an integer of 0 to 3;

l represents an integer of 0 to 3;

p + l is less than or equal to 3;

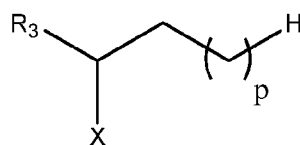
R_{3a} represents a radical selected from a linear or branched C₁-(20-l) alkyl group optionally substituted with

a C₆₋₂₀ aryl group, a C₃₋₆ cycloalkyl group, a fluorine atom or

a chlorine atom.

Yet another preferred starting material is characterized by the following formula (IIIc):

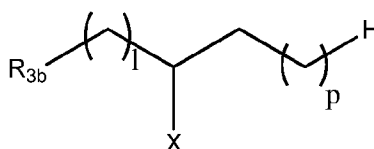
36



(IIIc)

wherein p, X and R₃ are as defined above.

Further preferred starting material is characterized by the following formula (IIIId):



(IIIId)

wherein

p represents an integer of 0 to 3;

l represents an integer of 0 to 3;

p + l is less than or equal to 3;

X is as defined in claim 1;

R_{3b} represents a radical selected from a linear or branched C₁-(20-l) alkyl group optionally substituted with a C₆₋₂₀ aryl group optionally substituted with a C₁₋₆alkylcarbonyloxy, a C₃₋₆ cycloalkyl group, a radical of formula -OC(O)R₅, a radical of formula -C(O)OR₅, R₅ being selected from the group consisting of methyl, and phenyl optionally substituted with one or more radicals selected from the group consisting of: fluoro, and C₁₋₆alkyloxy, a fluorine atom or a chlorine atom.

Another preferred starting material is that wherein p is an integer from 0 to 8.

Another preferred starting material is that wherein p is an integer from 0 to 4 and each R₄ represents a hydrogen atom.

Another preferred starting material is that wherein X is bromine and the combination of solid and dotted lines represents a single bond. More preferred starting materials are characterized by this structural element in combination with any one of the other structural elements described

herein as being preferred for the starting material (with the exception of the structural element directly underneath).

Another preferred starting material is that wherein X is hydrogen and the combination of solid and dotted lines represents a double bond. More preferred starting materials are characterized by this structural element in combination with any one of the other structural elements described herein as being preferred for the starting material (with the exception of the structural element directly above).

Another preferred starting material is that wherein p is an integer from 0 to 4 and each R₄ represents a hydrogen atom; and wherein R₃ is a C₁₋₁₀ alkyl group optionally substituted with a phenyl ring optionally substituted with a C₁₋₆alkylcarbonyloxy, a radical of formula –OC(O)R₅, or a radical of formula –C(O)OR₅, R₅ being selected from the group consisting of C₁₋₂₀alkyl, and phenyl optionally substituted with one or more radicals selected from the group consisting of: fluoro, and C₁₋₆alkyloxy.

Another preferred starting material is that wherein p is an integer from 0 to 4 and each R₄ represents a hydrogen atom; R₃ is a C₁₋₁₀ alkyl group optionally substituted with a phenyl ring optionally substituted with a C₁₋₆alkylcarbonyloxy, a radical of formula –OC(O)R₅, or a radical of formula –C(O)OR₅, R₅ being selected from the group consisting of C₁₋₂₀alkyl, and phenyl optionally substituted with one or more radicals selected from the group consisting of: fluoro, and C₁₋₆alkyloxy; and X is bromine and the combination of solid and dotted lines represents a single bond; or, alternatively, X is hydrogen and the the combination of solid and dotted lines represents a double bond.

It is a characteristic of the method of the present invention that the direct carboxylation predominantly takes place at a terminal carbon atom of the starting material (as long as the starting material does not contain any electron withdrawing groups that are connected with the activating group only via secondary and/or tertiary carbon atoms but without quaternary carbons and/or as long as the reaction is carried out under kinetic control reaction conditions). This is independent of the position of the activating group (i.e. leaving group X or double bond) in the starting compound. For instance, in case of bromo-substituted heptanes as starting material, the method of the invention always yields octanoic acid with the carboxyl group in position 1 as the major product, irrespective whether the starting material is 2-bromoheptane, 3-bromoheptane or 4-bromoheptane.

The method of the present invention is regioconvergent such that a variety of different types of compounds are suitable as starting materials. Thus, it is possible to use a single compound as a

starting material or a mixture of two or more compounds suitable as the starting material, while the same product is obtained.

Any mixture of starting materials can be used, provided that the individual members of the mixture are all suitable starting materials for the method of the present invention, as defined above. However, to accomplish the benefit of a regioconvergent reaction, mixtures of starting materials should be used, wherein the starting materials differ from each other only with respect to the activating group and/or position of activating group and only to such an extent that each starting material still yields the same reaction product. For instance, no benefits of a regioconvergent reaction can be accomplished if a mixture of starting materials is used, wherein starting materials differ from each other in size and/or substitution pattern.

Provided a suitable mixture of starting materials is used and due to the above-mentioned regioconvergent character of the method of the present invention, a possibly tedious and cumbersome purification of a mixture of compounds can hence be avoided which renders the method suitable for the preparation of carboxylic acids from mixtures of starting materials resulting from industrial processes, for instance.

A mixture of compounds of formula (III) where X is bromine and having the same aliphatic carbon skeleton can be obtained by radical bromination of an aliphatic compound.

(B) The catalyst

The catalyst is a Nickel compound suitable for promoting the method of the present invention. It is preferably prepared in situ by combining in a suitable solvent

- (a) a nickel(II) salt,
- (b) a reducing agent, and
- (c) a ligand, and, optionally
- (d) a hydrogen source

under the conditions specified below.

To form the catalyst, the Ni(II) species is converted to a Ni(0) species by means of reducing agent (b). The reducing agent further serves to regenerate the catalytically active Ni(0) species in the course of the reaction and it should therefore be provided in at least approximately stoichiometric amounts with respect to the starting material to ensure that a catalytically active amount of the catalyst. Hydrogen source (d) is also used in at least approximately stoichiometric amounts when the starting material is an alkene, i.e. when the bond with the dotted line in formula (III) represents a double bond. If the starting material contains a leaving group X as

activating group, the use of a hydrogen source is optional, so that it may be used also in lower amounts, or not at all.

The following materials can advantageously be used.

(a) Nickel(II) salt

The nickel(II) salt is selected from the group consisting of nickel (II) halide, nickel (II) acetylacetonate, nickel (II) sulphate, nickel (II) perchlorate, nickel (II) trifluoromethanesulfonate, nickel (II) hexafluoroacetylacetonate, nickel (II) sulfamate, nickel (II) carbonate, nickel (II) oxalate, a compound of formula $\text{Ni}(\text{OOCR})_2$ wherein R is a linear or branched C_{1-20} alkyl or a C_{3-8} cycloalkyl optionally substituted with one or more linear or branched C_{1-6} alkyl chains, nickel hexafluorosilicate and solvates thereof. A preferred member of the group formed by the compounds of formula $\text{Ni}(\text{OOCR})_2$ is nickel (II) acetate. It is also possible to use a mixture of two or more of these nickel(II) salts.

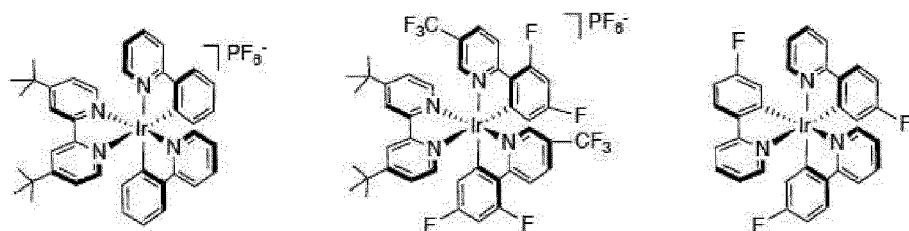
If the starting material is a bromoalkane or related compound with a leaving group X other than hydrogen, the nickel(II) salt is selected from nickel(II) bromide, nickel(II) chloride, nickel(II) iodide, nickel(II) acetylacetonate, nickel(II) perchlorate hexahydrate, nickel(II) triflate and solvates of such salts. Preferred solvates are nickel(II) chloride glyme solvate, nickel(II) bromide glyme solvate, nickel(II) bromide diglyme solvate. The use of nickel(II) iodide is particularly preferred. "Glyme" refers to 1,2-dimethoxyethane and "diglyme" refers to bis(2-methoxyethyl) ether.

If the starting material is an alkene, the same nickel(II) salts as listed above can be used. The use of nickel(II) iodide, nickel(II) bromide glyme solvate and nickel(II) bromide trihydrate is preferred.

(b) Reducing agent

The reducing agent is used to convert Ni(II) to a Ni(0) species. Hence, it does not become part of the catalyst but it is nevertheless essential for forming or regenerating the catalyst. The reducing agent is selected from Mn, Zn, and mixtures thereof. The use of Mn is preferred. Alternatively, electrochemical reduction means may also be used, as described for instance in Beilstein J. Org. Chem. 2014, 10, 2484, Appl. Organometal. Chem. 2001, 15, 135 and Synlett 1990, 2, 361.

Alternatively, photochemical reduction means may also be used. Suitable photochemical reduction means may consist of the combination of a photosensitizer with an electron donor compound. Suitable photosensitizers are known in the art and may be selected from the group consisting of organic dyes, such as those described in Chem. Rev., 2016, 116, 10075, and light-harvesting coordination complexes such as those described in Chem. Rev., 2013, 113, 5322. Preferably, the suitable photosensitizer comprised in the photocatalytic reduction means is selected from the light-harvesting coordination complexes of copper (I), iron (II), ruthenium (II) or iridium (III) with at least one monodentate or bidentate nitrogenated ligand, such as a ligand containing a 2,2'-bipyridine moiety or containing a 1,10-phenanthroline moiety or containing a 2-phenylpyridine moiety. Alternative photocatalytic reduction means may consist of Au(I) and Cu(I) coordination complexes with phosphine ligands. More preferably, the suitable photosensitizer comprised in the photocatalytic reduction means is selected from the group consisting of the complexes of formulae $[\text{Ru}(\text{bpy})_3]^{2+}$, $[\text{Ir}(\text{ppy})_3]$ and $[\text{Ir}(\text{ppy})_2(\text{bpy})]^+$, wherein bpy represents 2,2'-bipyridine wherein each pyridine ring is optionally substituted with one or more radicals selected from the group consisting of halo (wherein "halo" as used herein stands for an atom selected from fluorine, chlorine, bromine or iodine), a linear or branched C_{1-6} alkyl group, a linear or branched C_{1-6} alkyloxy group, a C_{6-20} aryl group and linear or branched C_{1-6} haloalkyl group; and wherein ppy represents 2-phenylpyridine wherein each of the pyridine and phenyl rings are optionally substituted with one or more radicals selected from the group consisting of halo, a linear or branched C_{1-6} alkyl group, a linear or branched C_{1-6} alkyloxy group, a C_{6-20} aryl group and linear or branched C_{1-6} haloalkyl group. In a particular embodiment, the suitable photosensitizer comprised in the photocatalytic reduction means is selected from the complexes of formulae $[\text{Ir}(\text{ppy})_3]$ and $[\text{Ir}(\text{ppy})_2(\text{bpy})]^+$, wherein ppy represents 2-phenylpyridine wherein each of the pyridine and phenyl rings are optionally substituted with one or more radicals selected from the group consisting of fluoro, *tert*-butyl and trifluoromethyl. In a more particular embodiment, the suitable photosensitizer comprised in the photocatalytic reduction means is selected from the complexes of formulae



Suitable electron donors in photochemical reduction means are known in the art and may be selected from tertiary amines, which may be aromatic or aliphatic. Preferably, the suitable electron donor comprised in the photochemical reduction means is a

compound of formula $N(RR'R'')$ wherein each of R, R' and R'' is a linear or branched C_{1-6} alkyl group, R, R' and R'' being the same or different and wherein the alkyl group may further be substituted with one or more hydroxyl groups. More preferably, the suitable electron donor comprised in the photochemical reduction means is selected from the group consisting of trimethylamine, triethylamine, triethanolamine and diisopropylethylamine. When the reducing agent is a photochemical reduction means, the method of the invention is further carried out under light irradiation, preferably using visible light or ultra-violet irradiation.

Furthermore, when the reducing agent is a photochemical reduction means, the method of the invention may optionally further be carried out in the presence of a base additive. Such a base additive is particularly optionally used when the electron donor is a tertiary amine such a compound of formula $N(RR'R'')$ as defined above. Such a base may preferably be selected from the group consisting of alkali or alkali-earth carbonate salts and alkali and alkali-earth C_{1-6} alkyloxide salts. In a particular embodiment, when the reducing agent is a photochemical reduction means, the method of the invention is carried out in the presence of a base selected from the group consisting of cesium carbonate, lithium *tert*-butoxide, potassium *tert*-butoxide and sodium *tert*-butoxide.

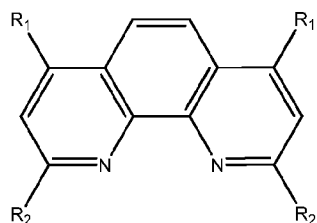
When the reducing agent is a photochemical reduction means, the amount of photosensitizer compound comprised in the photochemical reduction means ranges from 0.001 to 0.1 mole per each mole of compound of formula (III). Typically, the amount of photosensitizer compound comprised in the photochemical reduction means is from 0.005 to 0.015 mole and especially about 0.01 mole per each mole of compound of formula (III).

When the reducing agent is a photochemical reduction means, the amount of electron donor compound comprised in the photochemical reduction means ranges from 1 to 10 moles per each mole of compound of formula (III). Typically, the amount of electron donor compound comprised in the photochemical reduction means is from 2 to 4 moles and especially about 3 moles per each mole of compound of formula (III).

When the reducing agent is a photochemical reduction means, the amount of the base additive compound comprised in the photochemical reduction means ranges from 1 to 5 moles per each mole of compound of formula (III). Typically, the amount of base additive compound comprised in the photochemical reduction means ranges from 1 to 3 moles per each mole of compound of formula (III).

(c) Ligand

The ligand is selected from the compounds of formula (I)



(I)

wherein

R₂ and R₂' are each independently selected from the group consisting of: hydrogen, a linear or branched C₁₋₁₂ alkyl group, a linear or branched C₁₋₁₂ haloalkyl group, a C₆₋₂₀ aryl group and a C₆₋₂₀ aryl group having at least one substituent selected from linear or branched C₁₋₆ alkyl groups, linear or branched C₁₋₆ alkoxy groups, linear or branched C₁₋₆ haloalkyl groups, fluoro, chloro and bromo; provided that R₂ and R₂' are not simultaneously hydrogen. Preferably, R₂ and R₂' are each independently selected from the group consisting of: a linear or branched C₁₋₁₂ alkyl group, a linear or branched C₁₋₁₂ haloalkyl group and a C₆₋₂₀ aryl group.

More preferably, R₂ and R₂' are each independently selected from the group consisting of linear or branched C₁₋₆ alkyl groups.

R₁ and R₁' are each independently selected from the group consisting of hydrogen, halogen, a linear or branched C₁₋₁₂ alkyl group, a linear or branched C₁₋₁₂ haloalkyl group, a C₆₋₂₀ aryl group and a C₆₋₂₀ aryl group having at least one substituent selected from linear or branched C₁₋₆ alkyl groups, linear or branched C₁₋₆ alkoxy groups, linear or branched C₁₋₆ haloalkyl groups, fluoro, chloro and bromo. Preferably, R₁ and R₁' are each independently selected from the group consisting of a C₆₋₂₀ aryl group and a C₆₋₂₀ aryl group having at least one substituent selected from linear or branched C₁₋₆ alkyl groups, linear or branched C₁₋₆ alkoxy groups, linear or branched C₁₋₆ haloalkyl groups, fluoro, chloro and bromo.

If the starting material is a bromoalkane or related compound with a leaving group X other than hydrogen, the following substitution patterns are advantageously used:

According to a first preferred embodiment, R_2 and R_2' are each independently selected from the group consisting of linear or branched C_{1-6} alkyl groups, while R_1 and R_1' are each independently selected from the group consisting of hydrogen, phenyl, phenyl having at least one substituent selected from linear or branched C_{1-6} haloalkyl groups and naphthyl.

According to a second preferred embodiment, R_2 and R_2' are selected from the group consisting of CH_3 , C_2H_5 , $n-C_4H_9$, $n-C_6H_{13}$, $i-C_3H_7$ and $i-C_4H_9$ while R_1 and R_1' both represent an aryl group and more preferably a phenyl group.

According to a third preferred embodiment, R_2 and R_2' represent both a methyl group and R_1 and R_1' are both a naphthyl group and more preferably R_1 and R_1' are both selected from the group consisting of 1-naphthyl and 2-naphthyl.

Among the above preferred meanings and embodiments, it is even more preferred if R_1 and R_1' are the same and/or if R_2 and R_2' are the same.

Particularly preferred are the ligands wherein R_2 and R_2' are the same and are selected from the group consisting of C_2H_5 , $n-C_4H_9$, $n-C_6H_{13}$ and $i-C_3H_7$ while R_1 and R_1' both represent a phenyl group.

If the starting material is an alkene, the same substitution patterns as specified above can be used. In addition, the following substitution patterns are preferred:

According to a fourth preferred embodiment, R_2 and R_2' represent both a methyl group, ethyl group or propyl group and R_1 and R_1' are both selected from hydrogen, naphthyl and phenyl, the phenyl being optionally substituted with a radical selected from linear or branched C_{1-6} alkyl groups, linear or branched C_{1-6} alkoxy groups, linear or branched C_{1-6} haloalkyl groups and halogen atoms, more preferably R_2 and R_2' represent both a methyl group and R_1 and R_1' are both selected from hydrogen, phenyl, C_{1-6} alkoxy-substituted phenyl, C_{1-6} haloalkyl-substituted phenyl and naphthyl group and even more preferably R_1 and R_1' are both selected from the group consisting of phenyl and methoxy-substituted phenyl, in particular phenyl, para-methoxy-substituted phenyl and ortho,para-dimethoxy-substituted phenyl.

According to a fifth preferred embodiment, at least one of R_2 and R_2' represents an n-butyl group while the other one of R_2 and R_2' may represent an n-butyl group or a methyl group, and wherein R_1 and R_1' both represent a phenyl group.

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(d) Hydrogen Source

A hydrogen source is also present when X is hydrogen and the combination of solid and dotted lines represents a double bond. When X is a leaving group, i.e. a group other than hydrogen, the hydrogen source is optionally present. The hydrogen source, if present, is selected from water and a compound of formula $R_7R_8CBr-CHR_9R_{10}$, wherein R_{10} , R_7 , R_8 , and R_9 are each independently selected from the group consisting of hydrogen, a linear or branched C_{1-20} alkyl group optionally substituted with a radical selected from hydroxyl and C_{1-20} alkyloxy, a C_{3-8} cycloalkyl optionally substituted with a radical selected from hydroxyl and C_{1-20} alkyloxy, and a C_{6-20} aryl; or, alternatively, one or more of the pairs of R_8 and R_7 , R_{10} and R_9 , R_7 and R_9 and R_8 and R_{10} , together with the carbon atoms to which they are attached form a ring system comprising from 1 to 3 rings, each ring may be isolated, or two or three rings may be fused or form a bridged structure, and comprising from 5 to 6 members selected from the group consisting of C, CH, and CH_2 , each ring being independently unsaturated, saturated or aromatic; and each ring being further optionally substituted with one or more radicals selected from the group consisting of: hydroxyl, C_{1-6} alkyl, and C_{1-6} alkyloxy.

Preferably, the hydrogen source is a compound selected from the compounds of formula $R_7R_8CH-CH_2Br$, wherein R_7 and R_8 are as defined above.

Generally, if the starting material is a compound with X being a leaving group and not hydrogen, the hydrogen source can be used in an amount of 0-12 molar equivalents and preferably 0-8 molar equivalents in relation to the amount of starting material being 1 molar equivalent.

If a bromoalkane or related compound with a leaving group X other than hydrogen is used as a starting material, water is tolerated in amounts of up to 8 molar equivalents in relation to the starting material being 1 molar equivalent.

35

If the starting material is an alkene, the hydrogen source is preferably selected from the group consisting of ethyl bromide, cyclohexyl bromide, dicyclohexylbromomethane, 2-

bromocyclopentanol, 2-bromocyclohexanol and water. Among these hydrogen sources, the use of cyclohexyl bromide, water and 2-bromocyclopentanol is particularly preferred.

If the starting material is an alkene, the hydrogen source should be used at least in approximately stoichiometric amounts with respect to the starting material. For alkene starting materials, it is preferred to use the hydrogen source in an amount of 0.9 to 11 molar equivalents relative to the starting material being 1 molar equivalent. Particularly preferable is the use of the hydrogen source in a molar amount of 1.8 to 5.5 equivalents relative to the starting material (alkene) being 1 molar equivalent.

It is also possible to use a combination of two or more of the above hydrogen sources.

(e) Amounts and ratio of Ni(II) salt and compound of formula (I)

The Ni(II) salt is typically used in an amount of more than 0 mol% and 20 mol% or less with respect to the starting material being 100 mol%. It is advantageously used in an amount of 0.9 mol% to 11 mol% with respect to the starting material being 100 mol%.

The compound of formula (I) is used in an amount of between more than 0 mol% and 80 mol% or less with respect to the starting material being 100 mol%. It is advantageously used in an amount of from 0.9 mol% to 55 mol% with respect to the starting material being 100 mol%. It is more advantageously used in an amount of from 2 mol% to 30 mol% with respect to the starting material being 100 mol%.

The Ni(II) salt and the compound of formula (I) are advantageously used such that the molar ratio of compound of formula (I) : Ni(II) salt is in the range of from 1 to 5 and preferably in the range of from 1 to 3, more preferably in the range of from 1.5 to 2.

(f) Amount of reducing agent

The reducing agent is advantageously used in an amount of 100 mol% to 550 mol% with respect to the starting material being 100 mol%.

If the starting material is an alkene, it is preferred that the reducing agent is used in an amount of 180 mol% to 550 mol% with respect to the starting material being 100 mol%.

(g) Solvent

The nickel catalyst is preferably prepared in situ using the same solvent as specified below for the method of the invention. If the nickel catalyst is prepared in advance, it is also conceivable to rely on a different solvent. In such a case, it is nevertheless preferred to select the solvent among the different solvents described below for the method of the invention.

The in situ preparation of catalytically active Nickel species is described by Martin et al. in J. Am. Chem. Soc. 2015, 137, pages 6476-6479, for instance. The in situ preparation of the catalyst may for instance take place simultaneously with the preparation of the reaction mixture for carrying out the method of the present invention. That is, the components of the catalyst can be added to the reaction vessel at the same time, before or after the addition of the starting material. In one embodiment it is for instance possible to add the Ni(II) salt and the ligand first, followed by the starting material, while adding reducing agent and/or the hydrogen source in two or more portions before and during the reaction.

(C) Reaction Temperature

The reaction temperature is not particularly restricted. It is advantageous to carry out the reaction at a temperature in the range of from -10 to 90°C.

If a bromoalkane or related compound with a leaving group X other than hydrogen is used as the starting material, it is preferred to employ a reaction temperature of from 0 to 90°C. If an alkene is used as the starting material, it is preferred to employ a reaction temperature of from 45 to 90°C.

The reaction temperature is preferably chosen in accordance with the starting material and the desired product, in the following manner:

Starting material	Desired product	Preferred Temperature [°C]
Formula (III') or (III''), compound has no electron withdrawing group	Formula (IIa), (IIb) or (IIc)	0 – 90
Formula (III') or (III''), compound has electron withdrawing group	Formula (IIa), (IIb) or (IIc)	0 – 20
Formula (III') or (III''), compound has electron withdrawing group	Formula (IId) or (Ile)	35 – 90

Formula (III'') , compound has no electron withdrawing group	Formula (IIa), (IIb) or (IIc)	25 - 90
Formula (III'') , compound has electron withdrawing group	Formula (IIa), (IIb) or (IIc)	5 - 25
Formula (III'') , compound has electron withdrawing group	Formula (II'd) or (IIe)	40 - 90

(D) Carbon Dioxide

Carbon dioxide is provided as a reagent. It is advantageous to provide carbon dioxide in gaseous form. The carbon dioxide pressure is not particularly limited. Supplying carbon dioxide at atmospheric pressure (1 atm) is advantageous as this pressure is easy to handle.

(E) Solvent

The method of the present invention is carried out in the presence of a polar aprotic solvent. Said polar aprotic solvent can also be a mixture of two or more polar aprotic solvents.

One or more additional solvents selected from non-polar solvents and polar protic solvents may optionally be used together with the polar aprotic solvent mentioned above, provided the amount of such additional solvents is so small that it does not interfere with the method of the present invention. Water is a polar protic solvent. Nevertheless, to avoid confusion when determining relative amounts of components, water is to be regarded solely as a hydrogen source and not as a solvent in the context of the present invention.

The use of a solvent selected from DMF (N,N-Dimethylformamide), N,N-diethylformamide, DMSO (dimethylsulfoxide), DMA (N,N-dimethylacetamide), and NMP (N-methylpyrrolidine) is preferred but N,N-dibutylformamide and 1-Formylpyrrolidine can also be used.

It is also possible and preferred to use DMF in combination with another solvent selected from toluene, hexane and 1,4-dioxane. If such a mixture of DMF with another solvent is used, DMF and the other solvent should be present in relative volume ratio of from 1:0 to 1:1.2.

Yet further solvents may also be added in minor amounts (e.g. relative amounts of less than 10 wt.% based on the entire solvent amount) as long as they do not interfere with the reaction of the method of the present invention.

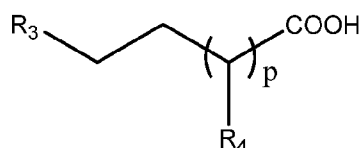
The use of DMF alone or of DMSO alone is particularly preferred. This applies especially to those embodiments, wherein the starting material is a bromoalkane or related compound with a leaving group X other than hydrogen.

5 (F) Products

The method of the invention predominantly favors the formation of terminal carboxylic acids, in particular when the compound of formula (III) does not comprise an electron withdrawing group.

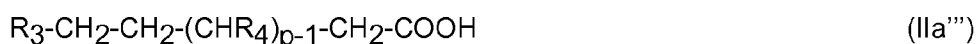
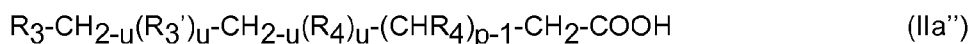
10 Consequently, when the conditions relative to the compound of formula (III) for the predominant formation of a compound of formula (IIa) described above are fulfilled, the method of the invention provides a compound of formula (IIa) as the predominant product.

Preferably, $u=0$, so that the above formula (IIa) can be simplified to formula (IIa'):



(IIa')

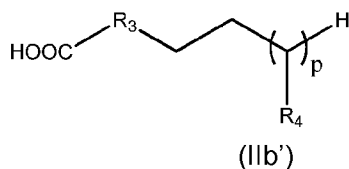
20 Preferably, a starting material is used wherein the R_4 radical of the terminal carbon atom represents hydrogen, so that the reaction provides a compound of formula (IIa''). In a preferred variant, $u = 0$, so that the product is of formula (IIa'''):



30 wherein R_3 , R_3' , p , u and R_4 are as described in any of the embodiments of the invention described above for the compound of formula (III).

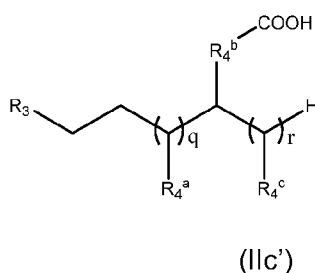
35 In a similar manner, when the conditions relative to the compound of formula (III) for the predominant formation of a compound of formula (IIb) described above are fulfilled, and in particular, when Y is not a C_{3-8} cycloalkyl, the method of the invention is preferably carried out with a starting material such that it provides a compound of formula (IIb) as described above where the COOH group is attached to the remainder of the molecule through a methylene diradical.

A preferred reaction product of formula (IIb) is a product wherein $u=0$, so that the formula (IIb) can be simplified to (IIb'):



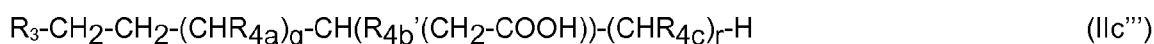
wherein R_3 , p and R_4 are as described above for the compound of formula (IIb).

A preferred reaction product of formula (IIc) is a product wherein $u=0$, so that the formula (IIc) can be simplified to (IIc'):



wherein R_3 , q , r , R_4^a , R_4^b and R_4^c are as described above for the compound of formula (IIc).

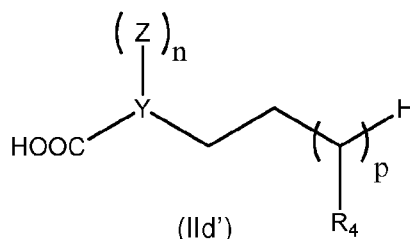
In a similar manner, when the conditions relative to the compound of formula (III) for the predominant formation of a compound of formula (IIc) described above are fulfilled, the method of the invention is preferably carried out with a starting material such that it provides a compound of formula (IIc') and more preferably a compound of formula (IIc''), for which $u = 0$.



wherein R_3 , R_3' , R_4^a , R_4^c , q and r are as described in any of the embodiments of the invention described above for the compound of formula (IIc) and R_4^b' is either a single bond or a linear or branched C_{1-19} alkyl.

A preferred reaction product of formula (IIId) is a product wherein $u=0$, so that the formula (IIId) can be simplified to (IIId'):

50



wherein Y, Z, R₄, n and p are as described above for the compound of formula (IIId).

Particularly preferred Embodiments

It is particularly preferred to carry out the method of the present invention in such a manner that two or more of the features of the invention are selected among the preferred embodiments.

For instance, it is particularly preferred to use the starting materials that are specified above as being preferred (or more preferred or the like) together with a nickel catalyst that is prepared in situ using a preferred Ni(II) salt and/or a preferred ligand of formula (I) and/or the preferred reducing agent Mn and/or a preferred hydrogen source and/or the use of these components in the preferred relative amounts.

Similarly, it is particularly preferred to carry out the preferred embodiments of the method of the invention (in terms of starting material and/or in situ prepared nickel catalyst) in a reaction solvent that is specified above as being preferred and/or at a reaction temperature that is specified as being preferred.

Of course, the degree of preference increases with an increasing number of features selected from the features described above as being preferred.

Thus, for instance, it is particularly preferred to carry out the method of the present invention using a secondary bromoalkane or alkene of formula (III) as a starting material, more preferably a secondary bromoalkane or alkene of formula (III) which does not contain an electron withdrawing group, and to form the nickel catalyst in situ and carry out the direct carboxylation reaction;

using a nickel(II) salt selected from nickel(II) bromide, nickel(II) chloride, nickel(II) iodide, nickel(II) acetylacetonate, nickel(II) perchlorate hexahydrate, nickel(II) triflate, nickel(II) chloride glyme solvate, nickel(II) bromide glyme solvate, and nickel(II) bromide diglyme solvate, in an amount of 0.9 mol% to 11 mol% with respect to the starting material being 100 mol%; and

using Mn as the reducing agent in an amount of 90 mol% to 550 mol% with respect to the starting material being 100 mol%; and

using a ligand of formula (I), wherein the ligand fulfills one or more of the following conditions (i) to (ix):

(i) R_2 and R_2' are each independently selected from the group consisting of: hydrogen, a linear or branched C_{1-12} alkyl group, a linear or branched C_{1-12} haloalkyl group and a C_{6-20} aryl group;

(ii) R_2 and R_2' are each independently selected from the group consisting of linear or branched C_{1-6} alkyl groups;

(iii) R_1 and R_1' are each independently selected from the group consisting of a C_{6-20} aryl group and a C_{6-20} aryl group having at least one substituent selected from linear or branched C_{1-6} alkyl groups, linear or branched C_{1-6} alkoxy groups, linear or branched C_{1-6} haloalkyl groups, fluoro, chloro and bromo;

(iv) R_2 and R_2' are each independently selected from the group consisting of linear or branched C_{1-6} alkyl groups, while R_1 and R_1' are each independently selected from the group consisting of hydrogen, phenyl, phenyl having at least one substituent selected from linear or branched C_{1-6} haloalkyl groups and naphthyl;

(v) R_2 and R_2' are selected from the group consisting of CH_3 , C_2H_5 , $n-C_4H_9$, $n-C_6H_{13}$, $i-C_3H_7$ and $i-C_4H_9$ while R_1 and R_1' both represent an aryl group and more preferably a phenyl group;

(vi) R_2 and R_2' represent both a methyl group and R_1 and R_1' are both a naphthyl group and more preferably R_1 and R_1' are both selected from the group consisting of 1-naphthyl and 2-naphthyl;

(vii) R_2 and R_2' are the same and are selected from the group consisting of C_2H_5 , $n-C_4H_9$, $n-C_6H_{13}$ and $i-C_3H_7$ while R_1 and R_1' both represent a phenyl group; or

(viii) R_2 and R_2' represent both a methyl group and R_1 and R_1' are both selected from hydrogen, phenyl, C_{1-6} alkoxy-substituted phenyl, C_{1-6} haloalkyl-substituted phenyl and naphthyl group and more preferably R_1 and R_1' are both selected from the

group consisting of phenyl and methoxy-substituted phenyl, in particular phenyl, para-methoxy-substituted phenyl and ortho,para-dimethoxy-substituted phenyl; or

- (ix) at least one of R_2 and R_2' represents an n-butyl group while the other one of R_2 and R_2' may represent an n-butyl group or a methyl group, and wherein R_1 and R_1' both represent a phenyl group;

in an amount of 0.9 mol% to 55 mol% with respect to the starting material being 100 mol%; wherein preferably R_1 and R_1' are the same and/or R_2 and R_2' are the same; and

optionally using a hydrogen source, which is selected from water and the group of compounds characterized by the general formula $R_7R_8CH-CH_2-Br$, wherein R_7 and R_8 are independently selected from hydrogen, a linear or branched C_{1-20} alkyl group optionally substituted with a radical selected from hydroxyl and C_{1-20} alkyloxy, a C_{3-8} cycloalkyl optionally substituted with a radical selected from hydroxyl and C_{1-20} alkyloxy, and a C_{6-20} aryl; and

carrying out the reaction at a temperature in the range of from 0 to 90°C; and

carrying out the reaction in a solvent consisting of or containing a solvent selected from DMF (N,N-Dimethylformamide), N,N-diethylformamide, DMSO (dimethylsulfoxide), DMA (N,N-dimethylacetamide), NMP (N-methylpyrrolidine), N,N-dibutylformamide and 1-formylpyrrolidine.

Another particularly preferred embodiment is characterized by a feature combination relating to the use of a bromoalkane of formula (III), more preferably a secondary bromoalkane of formula (III) which does not contain an electron withdrawing group, such as especially a bromoalkane of formula (IIIc) or (IIId) which does not contain an electron withdrawing group as specified above or below, as a starting material and to form the nickel catalyst in situ and carry out the direct carboxylation reaction

using a nickel(II) salt selected from nickel(II) bromide, nickel(II) chloride, nickel(II) iodide, nickel(II) acetylacetonate, nickel(II) perchlorate hexahydrate, nickel(II) triflate, nickel(II) chloride glyme solvate, nickel(II) bromide glyme solvate, and nickel(II) bromide diglyme solvate, in an amount of 0.9 mol% to 11 mol% with respect to the starting material being 100 mol%; and

using Mn as the reducing agent in an amount of 100 mol% to 550 mol% with respect to the starting material being 100 mol%; and

using a ligand of formula (I), wherein the ligand fulfills one or more of the following conditions:

- (a) R_2 and R_2' are each independently selected from the group consisting of linear or branched C_{1-6} alkyl groups, while R_1 and R_1' are each independently selected from the group consisting of hydrogen, phenyl, phenyl having at least one substituent selected from linear or branched C_{1-6} haloalkyl groups and naphthyl,
- (b) R_2 and R_2' are selected from the group consisting of CH_3 , C_2H_5 , $n-C_4H_9$, $n-C_6H_{13}$, $i-C_3H_7$ and $i-C_4H_9$ while R_1 and R_1' both represent an aryl group and more preferably a phenyl group,
- (c) R_2 and R_2' represent both a methyl group and R_1 and R_1' are both a naphthyl group and more preferably R_1 and R_1' are both selected from the group consisting of 1-naphthyl and 2-naphthyl,
- (d) R_2 and R_2' are the same and are selected from the group consisting of C_2H_5 , $n-C_4H_9$, $n-C_6H_{13}$ and $i-C_3H_7$ while R_1 and R_1' both represent a phenyl group,

in an amount of 0.9 mol% to 55 mol% with respect to the starting material being 100 mol%; wherein preferably R_1 and R_1' are the same and/or R_2 and R_2' are the same;

carrying out the reaction at a temperature in the range of from 14 to 66°C; and

carrying out the reaction in a solvent consisting of or containing a solvent selected from DMF (N,N-Dimethylformamide), N,N-diethylformamide, DMSO (dimethylsulfoxide), DMA (N,N-dimethylacetamide), NMP (N-methylpyrrolidine), N,N-dibutylformamide and 1-formylpyrrolidine.

Yet another particularly preferred embodiment is characterized by a feature combination relating to the use of an alkene of formula (III), wherein X represents hydrogen and the bond with the dashed line represents a carbon-carbon double bond, such as especially an alkene of formula (IIIa) or (IIIb) as specified above or below, which preferably does not contain an electron withdrawing group, as a starting material and to form the nickel catalyst in situ and carry out the direct carboxylation reaction

using a nickel(II) salt selected from nickel(II) bromide, nickel(II) chloride, nickel(II) iodide, nickel(II) acetylacetonate, nickel(II) perchlorate hexahydrate, nickel(II) triflate, nickel(II) chloride glyme solvate, nickel(II) bromide glyme solvate, and nickel(II) bromide diglyme solvate, in an amount of 0.9 mol% to 11 mol% with respect to the starting material being 100 mol%; and

using Mn as the reducing agent in an amount of 180 mol% to 550 mol% with respect to the starting material being 100 mol%; and

using a ligand of formula (I), wherein the ligand fulfills one or more of the following conditions:

(1) R_2 and R_2' represent both a methyl group and R_1 and R_1' are both selected from hydrogen, phenyl, C_{1-6} alkoxy-substituted phenyl, C_{1-6} haloalkyl-substituted phenyl and naphthyl group and more preferably R_1 and R_1' are both selected from the group consisting of phenyl and methoxy-substituted phenyl, in particular phenyl, para-methoxy-substituted phenyl and ortho,para-dimethoxy-substituted phenyl,

(2) at least one of R_2 and R_2' represents an n-butyl group while the other one of R_2 and R_2' may represent an n-butyl group or a methyl group, and wherein R_1 and R_1' both represent a phenyl group,

in an amount of 0.9 mol% to 55 mol% with respect to the starting material being 100 mol%; wherein preferably R_1 and R_1' are the same and/or R_2 and R_2' are the same;

carrying out the reaction at a temperature in the range of from 45 to 90°C;

optionally in the presence of a hydrogen source that is preferably selected from the group consisting of ethyl bromide, cyclohexyl bromide, dicyclohexylbromomethane, 2-bromocyclopentanol, 2-bromocyclohexanol and water; and

carrying out the reaction in a solvent consisting of or containing a solvent selected from DMF (N,N-Dimethylformamide), N,N-diethylformamide, DMSO (dimethylsulfoxide), DMA (N,N-dimethylacetamide), NMP (N-methylpyrrolidine).

Another particularly preferred embodiment of the present invention involves using as the starting material a starting material of formula (III') or (III''), wherein the group R_3 contains at least one electron withdrawing group Z, and forming the nickel catalyst in situ and carrying out the direct carboxylation reaction

using a nickel(II) salt selected from nickel(II) bromide, nickel(II) chloride, nickel(II) iodide, nickel(II) acetylacetonate, nickel(II) perchlorate hexahydrate, nickel(II) triflate, nickel(II) chloride glyme solvate, nickel(II) bromide glyme solvate, and nickel(II) bromide diglyme solvate, in an amount of 0.9 mol% to 11 mol% with respect to the starting material being 100 mol%; and

using Mn as the reducing agent in an amount of 100 mol% to 550 mol% with respect to the starting material being 100 mol%; and

using a ligand of formula (I), wherein the ligand fulfills one or more of the following conditions:

(a) R_2 and R_2' are each independently selected from the group consisting of linear or branched C_{1-6} alkyl groups, while R_1 and R_1' are each independently selected from the group consisting of hydrogen, phenyl, phenyl having at least one substituent selected from linear or branched C_{1-6} haloalkyl groups and naphthyl,

(b) R_2 and R_2' are selected from the group consisting of CH_3 , C_2H_5 , $n-C_4H_9$, $n-C_6H_{13}$, $i-C_3H_7$ and $i-C_4H_9$ while R_1 and R_1' both represent an aryl group and more preferably a phenyl group,

(c) R_2 and R_2' represent both a methyl group and R_1 and R_1' are both a naphthyl group and more preferably R_1 and R_1' are both selected from the group consisting of 1-naphthyl and 2-naphthyl,

(d) R_2 and R_2' are the same and are selected from the group consisting of C_2H_5 , $n-C_4H_9$, $n-C_6H_{13}$ and $i-C_3H_7$ while R_1 and R_1' both represent a phenyl group,

in an amount of 0.9 mol% to 55 mol% with respect to the starting material being 100 mol%; wherein preferably R_1 and R_1' are the same and/or R_2 and R_2' are the same;

carrying out the reaction at a temperature in the range of from -10 to $25^\circ C$ if a product of formula (IIa), (IIb) or (IIc) is desired, or, alternatively, carrying out the reaction at a temperature in the range of from 35 to $90^\circ C$ if a product of formula (II d) or (II e) is desired; and

carrying out the reaction in a solvent consisting of or containing a solvent selected from DMF (N,N-Dimethylformamide), N,N-diethylformamide, DMSO (dimethylsulfoxide), DMA (N,N-dimethylacetamide), NMP (N-methylpyrrolidine), N,N-dibutylformamide and 1-formylpyrrolidine.

According to a further particularly preferred embodiment, the method involves using as a starting material a compound of formula (III''), wherein the group R_3 contains at least one electron withdrawing group Z, and to form the nickel catalyst in situ and carry out the direct carboxylation reaction

using a nickel(II) salt selected from nickel(II) bromide, nickel(II) chloride, nickel(II) iodide, nickel(II) acetylacetonate, nickel(II) perchlorate hexahydrate, nickel(II) triflate, nickel(II) chloride glyme solvate, nickel(II) bromide glyme solvate, and nickel(II) bromide diglyme solvate, in an amount of 0.9 mol% to 11 mol% with respect to the starting material being 100 mol%; and

using Mn as the reducing agent in an amount of 180 mol% to 550 mol% with respect to the starting material being 100 mol%; and

using a ligand of formula (I), wherein the ligand fulfills one or more of the following conditions:

(1) R_2 and R_2' represent both a methyl group and R_1 and R_1' are both selected from hydrogen, phenyl, C_{1-6} alkoxy-substituted phenyl, C_{1-6} haloalkyl-substituted phenyl and naphthyl group and more preferably R_1 and R_1' are both selected from the group consisting of phenyl and methoxy-substituted phenyl, in particular phenyl, para-methoxy-substituted phenyl and ortho,para-dimethoxy-substituted phenyl,

(2) at least one of R_2 and R_2' represents an n-butyl group while the other one of R_2 and R_2' may represent an n-butyl group or a methyl group, and wherein R_1 and R_1' both represent a phenyl group,

in an amount of 0.9 mol% to 55 mol% with respect to the starting material being 100 mol%; wherein preferably R_1 and R_1' are the same and/or R_2 and R_2' are the same;

carrying out the reaction at a temperature in the range of from -5 to 25°C if a product of formula (IIa), (IIb) or (IIc) is desired, or, alternatively, carrying out the reaction at a temperature in the range of from 40 to 90°C if a product of formula (II d) or (IIe) is desired;

optionally in the presence of a hydrogen source that is preferably selected from the group consisting of ethyl bromide, cyclohexyl bromide, dicyclohexylbromomethane, 2-bromocyclopentanol, 2-bromocyclohexanol and water; and

carrying out the reaction in a solvent consisting of or containing a solvent selected from DMF (N,N-Dimethylformamide), N,N-diethylformamide, DMSO (dimethylsulfoxide), DMA (N,N-dimethylacetamide), NMP (N-methylpyrrolidine).

Use of Reaction system

The present invention also pertains to a use of the reaction system described herein, comprising carbon dioxide, a polar aprotic solvent as well as components (a), (b), (c) and

optionally (d). More specifically, the reaction system may be used in accordance with the present invention for direct carboxylation of alkenes and/or alkanes carrying a leaving group. This use may involve the starting materials of formula (III) as described herein. In this case, the use of the invention essentially reflects the methods of the invention as described hereinabove and below.

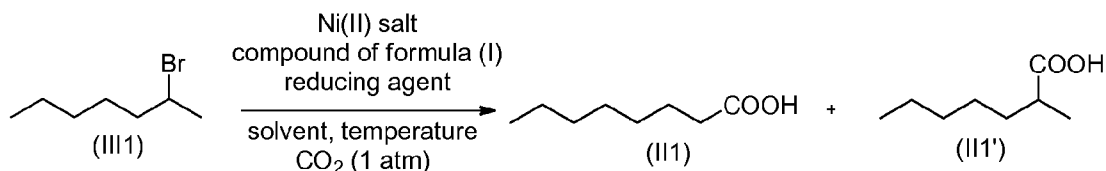
Alternatively, the use of the invention may involve another starting material selected from alkenes and leaving group-containing alkanes, which are suitable for the chain walking mechanism described herein to generate a compound derived from the starting material that no longer contains the carbon-carbon double bond or leaving group but instead carries the carboxyl group in a terminal position,

The suitability of starting materials can be determined by checking in a first step whether the compound of interest has a terminal carbon atom carrying at least one hydrogen atom, which terminal carbon atom is connected with the carbon-carbon double bond or leaving group by a chain of carbon atoms that consists only of secondary and tertiary carbon atoms but no quaternary carbon atoms. In a second step, the potential starting material may be subjected to reaction conditions described for the methods of the present invention. The resulting product may then be analysed to determine whether direct carboxylation at a terminal carbon atom has occurred.

Further potentially useful starting materials may for instance be identified by applying a systematic step-wise approach, wherein starting materials described herein by means of formula (III) are modified by "conservative" structural changes. Such "conservative" structural changes may for instance be a replacement of a substituent by a related substituent that is known or expected to show a similar reactivity and/or addition of a further substituent at a position that does not interfere with the chain walking mechanism described herein and/or combining two or more substituents that are not involved in the chain walking mechanism to generate a cyclic structure. If the compounds obtained by such conservative modifications of the described starting materials, when subjected to suitable experimental conditions, prove to be suitable for direct carboxylation in accordance with the present invention, they may themselves be used as a starting point for further conservative modifications, and so forth.

Examples

Example 1: Carboxylation of 2-bromoheptane



5

General procedure

An oven-dried schlenk tube containing a stirring bar was charged with the nickel (II) salt indicated in Tables 1-7 in the amount indicated in Tables 1-7, the compound of formula (I) as indicated in Tables 1-7 in the amount indicated in Tables 1-7 and the reducing agent indicated in Tables 1-7 in the amount indicated in Tables 1-7. The schlenk tube was then evacuated and back-filled under a carbon dioxide flow (this sequence was repeated three times) and finally an atmospheric pressure of CO₂ was established. A 1 M solution of the bromoheptane compound (III1) in the solvent indicated in Tables 1-7 was subsequently added by syringe and the solution was stirred for 17 h at the temperature indicated in Tables 1-7. The mixture was then carefully quenched with 2 M aqueous hydrochloric solution to hydrolyze the resulting carboxylate and extracted with ethyl acetate. A sample of such obtained solution was next analyzed by gas chromatography using anisole as an internal standard. The resulting carboxylic acid can further be purified by silica gel column chromatography using Hexanes/Ethyl Acetate (3/1) as elution system.

Table 1: Scope of nickel (II) salt precursor

In Entries 1-10:

- (i) the compound of formula (I) is that wherein R₁ and R₁' are both phenyl, and R₂ and R₂' are both methyl, and its amount is one fourth the amount of 2-bromoheptane engaged in the reaction;
- (ii) the amount of nickel (II) salt is one tenth the amount of 2-bromoheptane engaged in the reaction;
- (iii) the reducing agent is manganese and its amount is 3.6 times the amount of 2-bromoheptane engaged in the reaction;
- (iv) the solvent is N,N-dimethylformamide; and
- (v) the temperature is 50 °C.

Entry	Nickel (II) salt	Yield of (II1) (%)	Ratio (II1):(II1')
1	NiCl ₂ · glyme	38	19:1
2	NiBr ₂ · glyme	45	12:1
3	NiBr ₂ · diglyme	46	13:1

4	NiI ₂	49	25:1
5	NiBr ₂	45	15:1
6	NiCl ₂	15	>15:1
7	NiF ₂	7	>7:1
8	Ni(acac) ₂ (acac=acetylacetonate)	29	15:1
9	Ni(ClO ₄) ₂ · 6 H ₂ O	16	15:1
10	Ni(OTf) ₂	34	16:1

OTf refers to triflate, i.e. -O-S(O)₂-CF₃

Table 2: Scope of solvent

In Entries 11-17:

- 5 (i) the compound of formula (I) is that wherein R₁ and R₁' are both phenyl, and R₂ and R₂' are both methyl, and its amount is one fourth the amount of 2-bromoheptane engaged in the reaction;
- (ii) the nickel (II) salt is nickel (II) iodide and the amount of nickel (II) iodide is one tenth the amount of 2-bromoheptane engaged in the reaction;
- 10 (iii) the reducing agent is manganese and its amount is 3.6 times the amount of 2-bromoheptane engaged in the reaction;
- (v) the temperature is 50 °C.

Entry	Solvent	Yield of (II1) (%)	Ratio (II1):(II1')
11	DMF	49	25:1
12	DMF:Toluene (1:1)	20	19:1
13	DMF:Hexane (1:1)	32	11:1
14	DMF:1,4-Dioxane (1:1)	16	>16:1
15	DMSO	41	40:1
16	DMA	39	38:1
17	NMP	34	16:1

- 15 DMF is N,N-dimethylformamide, DMSO is dimethylsulfoxide, DMA is N,N-dimethylacetamide and NMP is N-methylpyrrolidine.

Table 3: Scope of temperature

In Entries 19-22:

- 20 (i) the compound of formula (I) is that wherein R₁ and R₁' are both phenyl, and R₂ and R₂' are both methyl, and its amount is one fourth the amount of 2-bromoheptane engaged in the reaction;

- (ii) the nickel (II) salt is nickel (II) iodide and the amount of nickel (II) iodide is one tenth the amount of 2-bromoheptane engaged in the reaction;
- (iii) the reducing agent is manganese and its amount is 3.6 times the amount of 2-bromoheptane engaged in the reaction;
- 5 (v) the solvent is DMF.

Entry	Temperature (°C)	Yield of (II1) (%)	Ratio (II1):(II1')
18	30	9	>9:1
19	40	47	46:1
20	50	49	25:1
21	60	40	20:1
22	70	29	28:1

Table 4: Water/moisture tolerance

In Entries 23-26:

- 10 (i) the compound of formula (I) is that wherein R₁ and R₁' are both phenyl, and R₂ and R₂' are both methyl, and its amount is one fourth the amount of 2-bromoheptane engaged in the reaction;
- (ii) the nickel (II) salt is nickel (II) iodide and the amount of nickel (II) iodide is one tenth the amount of 2-bromoheptane engaged in the reaction;
- 15 (iii) the reducing agent is manganese and its amount is 3.6 times the amount of 2-bromoheptane engaged in the reaction;
- (v) the solvent is DMF;
- (vi) the temperature is 50 °C; and
- (vii) the amount of water indicated in Table 4 has been added to the reaction mixture.

20

Entry	Added water (with respect to 2-bromoheptane)	Yield of (II1) (%)	Ratio (II1):(II1')
23	2 equivalents	19	>19:1
24	4 equivalents	14	>14:1
25	6 equivalents	20	>20:1
26	8 equivalents	17	>17:1

Table 5: Scope of compound of formula (I)

In Entries 27-39:

- (i) the compound of formula (I) is that wherein R₁, R₁', R₂ and R₂' are as indicated in Table 5,
- 25 and its amount is one fourth the amount of 2-bromoheptane engaged in the reaction;

- (ii) the nickel (II) salt is nickel (II) iodide and the amount of nickel (II) iodide is one tenth the amount of 2-bromoheptane engaged in the reaction;
- (iii) the reducing agent is manganese and its amount is 3.6 times the amount of 2-bromoheptane engaged in the reaction;
- 5 (v) the solvent is DMF;
- (vi) the temperature is 30 °C.

Entry	Compound of formula (I)				Yield of (II1) (%)	Ratio (II1):(II1')
	R ₁	R ₁ '	R ₂	R ₂ '		
27	H	H	H	H	0	-
28	H	H	CH ₃	CH ₃	4	>10:1
29	C ₆ H ₅	C ₆ H ₅	CH ₃	CH ₃	7	>10:1
30	<i>p</i> -CF ₃ -C ₆ H ₄	<i>p</i> -CF ₃ -C ₆ H ₄	CH ₃	CH ₃	8	>10:1
31	1-naphthyl	1-naphthyl	CH ₃	CH ₃	26	21:1
32	2-naphthyl	2-naphthyl	CH ₃	CH ₃	29	24:1
33	C ₆ H ₅	C ₆ H ₅	C ₂ H ₅	C ₂ H ₅	69	30:1
34	C ₆ H ₅	C ₆ H ₅	<i>n</i> -C ₄ H ₉	<i>n</i> -C ₄ H ₉	65	29:1
35	C ₆ H ₅	C ₆ H ₅	<i>n</i> -C ₄ H ₉	H	8	>10:1
36	C ₆ H ₅	C ₆ H ₅	<i>n</i> -C ₆ H ₁₃	<i>n</i> -C ₆ H ₁₃	72	28:1
37	C ₆ H ₅	C ₆ H ₅	<i>i</i> -C ₃ H ₇	<i>i</i> -C ₃ H ₇	62	21:1
38	C ₆ H ₅	C ₆ H ₅	<i>i</i> -C ₄ H ₉	<i>i</i> -C ₄ H ₉	29	29:1
39	Cl	Cl	CH ₃	CH ₃	8	>8:1

Table 6: Screening of the ratio of nickel (II) salt to compound of formula (I)

10 In Entries 40-49:

- (i) the compound of formula (I) is that wherein R₁ and R₁' are phenyl and R₂ and R₂' are *n*-hexyl (entry 36), and its amount is as indicated in Table 6;
- (ii) the nickel (II) salt is nickel (II) iodide and its amount is as indicated in Table 6;
- (iii) the reducing agent is manganese and its amount is 3.6 times the amount of 2-bromoheptane engaged in the reaction;
- 15 (v) the solvent is DMF;
- (vi) the temperature is as indicated in Table 6.

Entry	Temp. (°C)	Amount of NiI ₂ (mol %)	Amt. cpd. formula (I) (mol %)	Ratio Ni:(I)	Yield of (II1) (%)	Ratio (II1):(II1')
40	50	10	15	0.67	48	24:1

41	27	5	5	1.00	10	>10:1
42	27	5	6.25	0.80	55	26:1
43	27	5	7.5	0.67	35	34:1
44	27	5	8.75	0.57	56	55:1
45	25	10	17.5	0.57	78	39:1
46	25	10	15	0.67	92	50:1
47	25	5	8.75	0.57	85	43:1
48	25	2.5	4.40	0.57	96	40:1
49	25	1	1.8	0.56	40	39:1

Table 7: Screening of loading of reducing agent

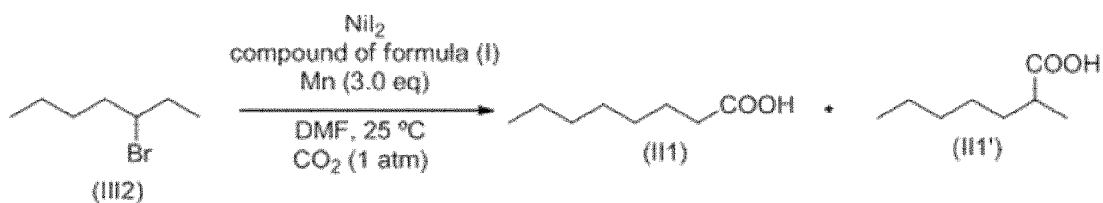
In Entries 50-55:

- (i) the compound of formula (I) is that wherein R₁ and R₁' are phenyl and R₂ and R₂' are n-hexyl (entry 36), and its amount is 4.40 mol%;
- 5 (ii) the nickel (II) salt is nickel (II) iodide and its amount is 2.5 mol%;
- (iii) the reducing agent is as indicated in Table 7 and its amount is as indicated in Table 7;
- (v) the solvent is DMF;
- (vi) the temperature is 25 °C.

Entry	Reducing agent	Amount of reducing agents (in equivalents)	Yield of (II1) (%)	Ratio (II1):(II1')
50	Mn	1	55	30:1
51	Mn	1.5	75	35:1
52	Mn	2	88	45:1
53	Mn	3	94	40:1
54	Mn	3.5	96	40:1
55 ^a	Zn	3.5	9	>9:1

10 ^aIn entry 55, 10 mol% of NiI₂ and 15 mol% of compound of formula (I) were used.

Example 2: Carboxylation of 3-bromoheptane

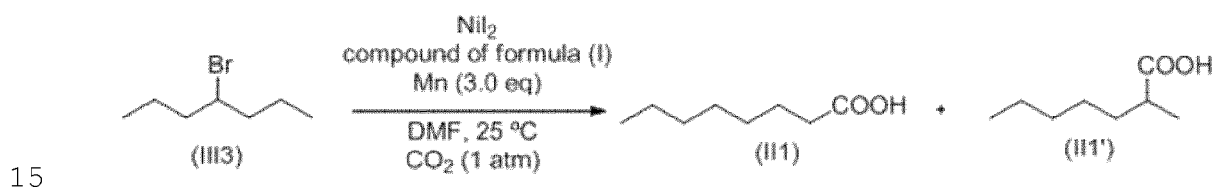


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3-bromoheptane (IIIb) was carboxylated to 1-octanoic acid following the general procedure of Example 1, using:

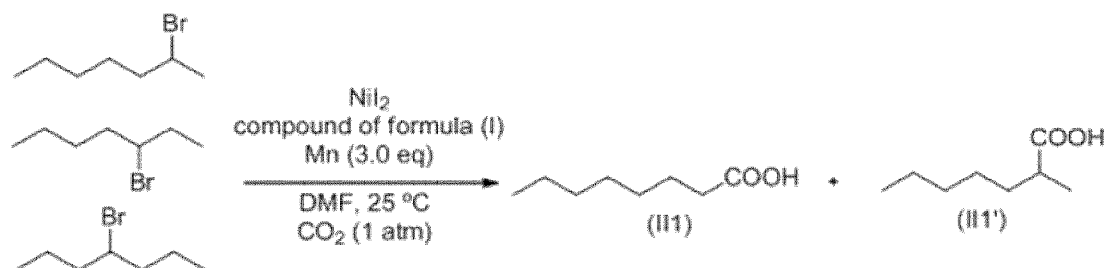
- 5 (i) a compound of formula (I) wherein R_1 and R_1' are phenyl and R_2 and R_2' are n-hexyl, in an amount of 8.80 mol%;
 - (ii) 5.0 mol% of NiI_2 as nickel (II) salt;
 - (iii) 3.0 equivalents of manganese as reducing agent
 - (iv) DMF as a solvent and at a temperature of 25 °C.
- 10 In these conditions the process of the invention provides octanoic acid in 81% isolated yield, with a ratio of (II1):(II1') of 25 to 1.

Example 3: Carboxylation of 4-bromoheptane



4-bromoheptane (IIIc) was carboxylated to 1-octanoic acid following the general procedure of Example 1, using:

- 20 (i) a compound of formula (I) wherein R_1 and R_1' are phenyl and R_2 and R_2' are n-hexyl, in an amount of 8.80 mol%;
 - (ii) 5.0 mol% of NiI_2 as nickel (II) salt;
 - (iii) 3.0 equivalents of manganese as reducing agent
 - (iv) DMF as a solvent and at a temperature of 25 °C.
- 25 In these conditions the process of the invention provides octanoic acid in 72% isolated yield, with a ratio of (II1):(II1') of 24 to 1.



Example 4: Carboxylation of a mixture of bromoheptane isomers

An equimolar mixture (1:1:1) of 2-bromoheptane, 3-bromoheptane and 4-bromoheptane was carboxylated to 1-octanoic acid following the general procedure of Example 1, using:

(i) a compound of formula (I) wherein R_1 and R_1' are phenyl and R_2 and R_2' are n-hexyl, in an amount of 8.80 mol%;

5 (ii) 5.0 mol% of NiI_2 as nickel (II) salt;

(iii) 3.0 equivalents of manganese as reducing agent

(iv) DMF as a solvent and at a temperature of 25 °C.

In these conditions the process of the invention provides octanoic acid in 85% isolated yield, with a ratio of (II1):(II1') of 25 to 1.

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Example 5: Carboxylation of methyl 5-bromohexanoate

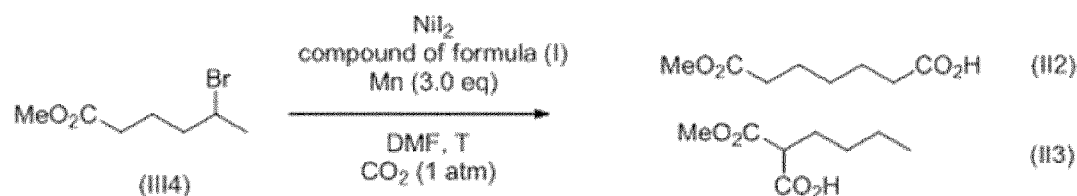


Table 8: Scope of temperature

In Entries 56-61:

15 (i) the compound of formula (I) is that wherein R_1 and R_1' are phenyl and R_2 and R_2' are n-hexyl (entry 36), and its amount is 4.40 mol%;

(ii) the nickel (II) salt is nickel (II) iodide and its amount is 2.5 mol%;

(iii) the reducing agent is manganese and its amount is 3.0 times the amount of methyl 5-bromohexanoate engaged in the reaction;

20 (iv) the solvent is DMF;

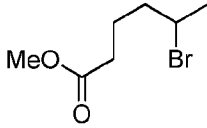
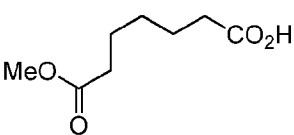
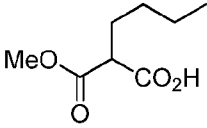
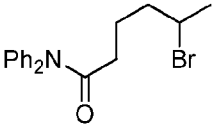
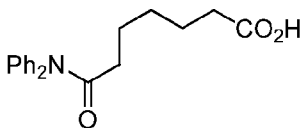
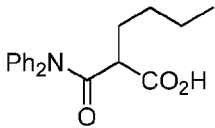
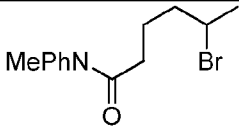
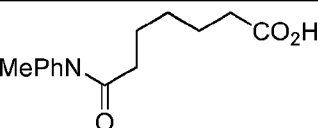
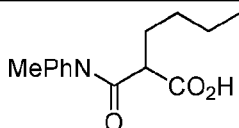
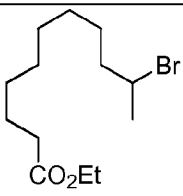
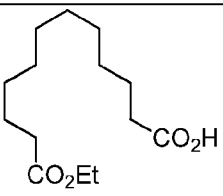
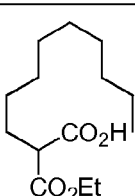
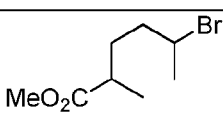
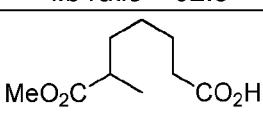
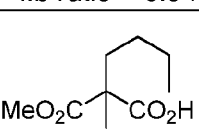
(vi) the temperature is as indicated in Table 8.

Entry	Temperature (°C)	Yield of (II2)+(II3) (%)	Ratio (II2):(II3)
56	10	86	85:15
57	15	90	75:25
58	25	96	59:41
59	31	94	50:50
60	38	85	14:86
61	42	81	4:96

Similarly, and following the same procedure as described above but using the starting material indicated in Table 8' at the indicated temperature, the following compounds were obtained

25

Table 8': Scope of Temperature

Compound of formula (III)	Product formed at 10 °C	Product formed at 42 °C
	 86 % yield l:b ratio = 85:15	 81 % yield l:b ratio = 8:92
	 84 % yield l:b ratio = 99:1	 78 % yield l:b ratio = 1:99
	 74 % yield l:b ratio = 99:1	 77 % yield l:b ratio = 1:99
	 80 % yield l:b ratio = 92:8	 78 % yield l:b ratio = 6:94
	 63 % yield l:b ratio = 85:15	 51 % yield l:b ratio = 1:99

Example 6: Carboxylation of various alkyl bromides

5 Table 9: Substrate scope

In Entries 62-63, the carboxylation method was carried out using the compound of formula (III) described in Table 9 and following the general procedure of Example 5, entry 56.

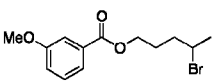
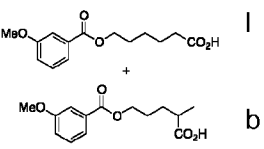
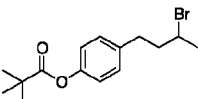
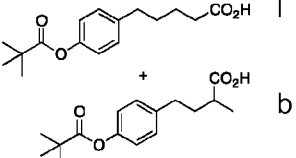
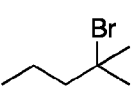
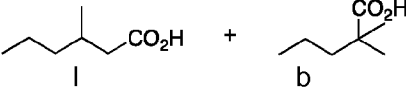
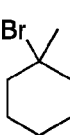
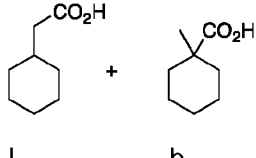
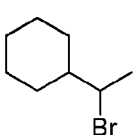
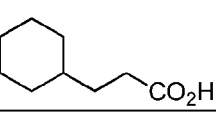
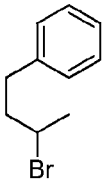
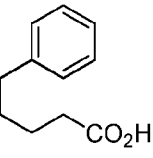
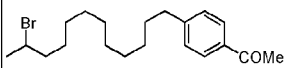
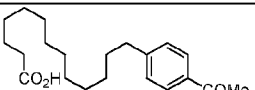
In Entries 64-65, the carboxylation method was carried out using the compound of formula (III) described in Table 9 and following the general procedure of Example 2, but at a temperature of 10 °C.

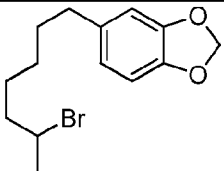
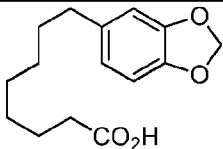
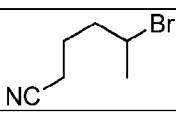
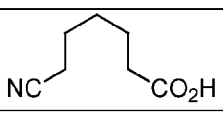
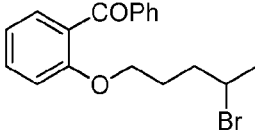
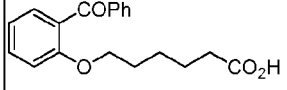
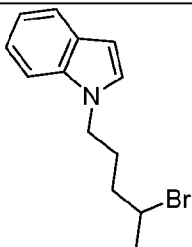
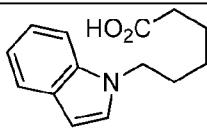
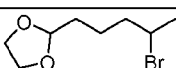
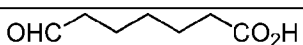
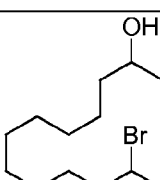
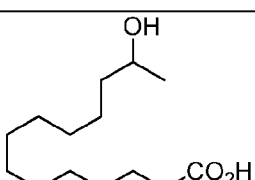
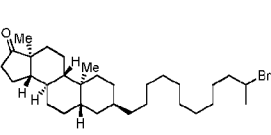
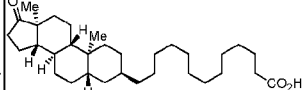
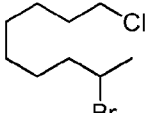
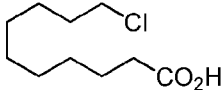
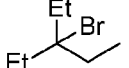
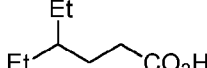
In Entries 66-78, the carboxylation method was carried out using the compound of formula (III) described in Table 9 and wherein:

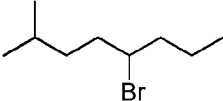
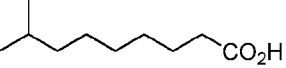
(i) the nickel (II) salt is nickel (II) iodide and its amount is 2.5 mol%,

(ii) the reducing agent is manganese and its amount is 1.5 times the amount of the compound of formula (III),

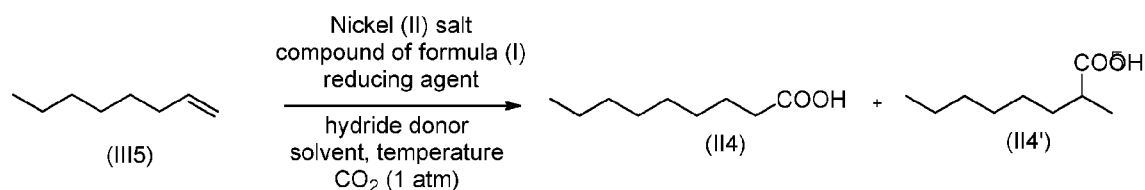
(iii) the compound of formula (I) is that wherein R1 and R1' are phenyl and R2 and R2' are n-hexyl, and its amount is 4.5 mol%.

Entry	Compound (III)	Products (II)	Yield	Ratio I/b
62			74	>19:1
63			61	>19:1
64			30	>19:1
65			50	>19:1
66			58	-
67			77	-
68			51	-

69			61	-
70			82	-
71			44	-
72			59	-
73			57	-
74			51	-
75			50	-
76			54	-
77			38	-

78			42	-
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Example 7: Carboxylation of 1-octene



General procedure

An oven-dried schlenk tube containing a stirring bar was charged with the nickel (II) salt indicated in Tables 10-15 in the amount indicated in Tables 10-15, the compound of formula (I) as indicated in Tables 10-15 in the amount indicated in Tables 10-15 and the reducing agent indicated in Tables 8-14 in the amount indicated in Tables 10-15. The schlenk tube was then evacuated and back-filled under a carbon dioxide flow (this sequence was repeated three times) and finally an atmospheric pressure of CO₂ was established. A 1 M solution of the alkene compound in the solvent indicated in Tables 10-15 and further comprising the hydrogen source indicated in Tables 10-15 in the amount indicated in Tables 9-14 was subsequently added by syringe and the solution was stirred for 40 h at the temperature indicated in Tables 10-15. The mixture was then carefully quenched with 2 M aqueous hydrochloric solution to hydrolyze the resulting carboxylate and extracted with ethyl acetate. A sample of such obtained solution was next analyzed by gas chromatography using anisole as an internal standard. The resulting carboxylic acid can further be purified by silica gel column chromatography using Hexanes/Ethyl Acetate (3/1) as elution system.

Table 10: Scope of the hydrogen source

In Entries 1-13:

- (i) the compound of formula (I) is that wherein R₁ and R₁' are both phenyl, and R₂ and R₂' are both methyl, and its amount is one fourth the amount of 1-octene engaged in the reaction;
- (ii) the nickel (II) salt is nickel (II) iodide and its amount is one tenth the amount of 1-octene engaged in the reaction;
- (iii) the reducing agent is manganese and its amount is 3.6 times the amount of 1-octene engaged in the reaction;
- (iv) the solvent is N,N-dimethylformamide; and
- (v) the temperature is 50 °C.

Entry	Hydrogen source / amount of hydrogen source (equivalents)	Yield of (II4) (%)	Ratio (II4):(II4')
1	Ethyl bromide / 1	23	>23:1
2	Cyclohexyl bromide / 2	59	>59:1
3	Cyclohexyl bromide / 5	84	42:1
4	Dicyclohexylbromomethane / 2	22	>22:1
5	2-bromocyclopentanol / 2	41	40:1
6	2-bromocyclohexanol / 2	39	38:1
7	Water / 0.5	5	>5:1
8	Water / 1	4	>4:1
9	Water / 2	14	>14:1
10	Water / 4	17	>17:1
11	Water / 6	31	30:1
12	Water / 8	23	22:1
13	Water / 10	19	>19:1

Table 11: Scope of nickel (II) salts

In Entries 14-17:

- 5 (i) the compound of formula (I) is that wherein R_1 and R_1' are both phenyl, and R_2 and R_2' are both methyl, and its amount is one fourth the amount of 1-octene engaged in the reaction;
- (ii) the amount of nickel (II) salt is one tenth the amount of 1-octene engaged in the reaction;
- (iii) the reducing agent is manganese and its amount is 3.6 times the amount of 1-octene engaged in the reaction;
- 10 (iv) the solvent is N,N-dimethylformamide;
- (v) the temperature is 50 °C;
- (vi) the hydrogen source is water, in an amount of 6 equivalents.

Entry	Nickel (II) salt	Yield of (II4) (%)	Ratio (II4):(II4')
14	NiI_2	31	30:1
15	NiBr_2	5	>5:1
16	$\text{NiBr}_2 \cdot \text{glyme}$	13	>13:1
17	$\text{NiBr}_2 \cdot 3 \text{H}_2\text{O}$	16	>16:1

15 Table 12: Scope of temperature

In Entries 18-21:

- (i) the compound of formula (I) is that wherein R_1 and R_1' are both phenyl, and R_2 and R_2' are both methyl, and its amount is one fourth the amount of 1-octene engaged in the reaction;
- (ii) the nickel (II) salt is nickel (II) iodide and its amount is one tenth the amount of 1-octene engaged in the reaction;
- 5 (iii) the reducing agent is manganese and its amount is 3.6 times the amount of 1-octene engaged in the reaction;
- (iv) the solvent is N,N-dimethylformamide;
- (v) the hydrogen source is water, in an amount of 6 equivalents.

Entry	Temperature (°C)	Yield of (II4) (%)	Ratio (II4):(II4')
18	50	31	30:1
19	60	25	24:1
20	70	32	31:1
21	80	25	24:1

10 Table 13: Screening of solvents

In Entries 22-27:

- (i) the compound of formula (I) is that wherein R_1 and R_1' are both phenyl, and R_2 and R_2' are both methyl, and its amount is one fourth the amount of 1-octene engaged in the reaction;
- (ii) the nickel (II) salt is nickel (II) iodide and its amount is one tenth the amount of 1-octene engaged in the reaction;
- 15 (iii) the reducing agent is manganese and its amount is 3.6 times the amount of 1-octene engaged in the reaction;
- (iv) the temperature is 50 °C;
- (v) the hydrogen source is water, in an amount of 6 equivalents.

20

Entry	Solvent	Yield of (II4) (%)	Ratio (II4):(II4')
22	DMF	31	30:1
23	N,N-diethylformamide	18	>18:1
24	N,N-dibutylformamide	5	>5:1
25	1-Formylpyrrolidine	5	>5:1
26	N,N-dimethylacetamide	20	>20:1
27	N-methylpyrrolidine	19	>19:1

Table 14: Scope of loading of reducing agent

In Entries 28-32:

- (i) the compound of formula (I) is that wherein R_1 and R_1' are both phenyl, and R_2 and R_2' are both methyl, and its amount is one fourth the amount of 1-octene engaged in the reaction;
- (ii) the nickel (II) salt is nickel (II) iodide and its amount is one tenth the amount of 1-octene engaged in the reaction;
- 5 (iii) the reducing agent is manganese;
- (iv) the solvent is N,N-dimethylformamide;
- (v) the temperature is 50 °C;
- (vi) the hydrogen source is water, in an amount of 6 equivalents.

Entry	Loading of reducing agent (equivalents)	Yield of (II4) (%)	Ratio (II4):(II4')
28	1	9	>9:1
29	2	34	33:1
30	3	26	25:1
31	3.6	31	30:1
32	5	35	34:1

10

Table 15: Scope of loading of compound of formula (I)

In Entries 33-37:

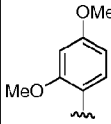
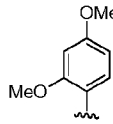
- (i) the compound of formula (I) is that wherein R_1 and R_1' are both phenyl, and R_2 and R_2' are both methyl;
- 15 (ii) the nickel (II) salt is nickel (II) iodide and its amount is one tenth the amount of 1-octene engaged in the reaction (10 mol%);
- (iii) the reducing agent is manganese and its amount is 3.6 equivalents;
- (iv) the solvent is N,N-dimethylformamide;
- (v) the temperature is 50 °C;
- 20 (vi) the hydrogen source is water, in an amount of 6 equivalents.

Entry	Loading of compound of formula (I) (mol%)	Yield of (II4) (%)	Ratio (II4):(II4')
33	15	16	>16:1
34	20	25	24:1
35	25	31	30:1
36	35	51	50:1
37	50	27	26:1

Table 16: Scope of compound of formula (I)

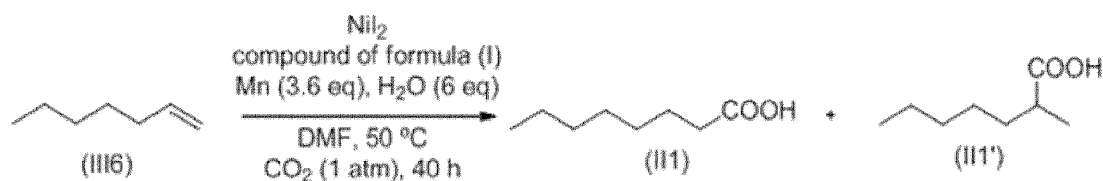
In Entries 38-47:

- (i) the amount of the compound of formula (I) is 35 mol%;
- (ii) the nickel (II) salt is nickel (II) iodide and its amount is one tenth the amount of 1-octene engaged in the reaction (10 mol%);
- 5 (iii) the reducing agent is manganese and its amount is 3.6 equivalents;
- (iv) the solvent is N,N-dimethylformamide;
- (v) the temperature is 50 °C;
- (vi) the hydrogen source is water, in an amount of 6 equivalents.

Entry	Compound of formula (I)				Yield of (II4) (%)	Ratio (II4):(II4')
	R ₁	R ₁ '	R ₂	R ₂ '		
38	H	H	CH ₃	CH ₃	18	>50:1
39	C ₆ H ₅	C ₆ H ₅	CH ₃	CH ₃	51	50:1
40	<i>p</i> -CF ₃ -C ₆ H ₄	<i>p</i> -CF ₃ -C ₆ H ₄	CH ₃	CH ₃	22	>50:1
41	1-naphthyl	1-naphthyl	CH ₃	CH ₃	17	>50:1
42	2-naphthyl	2-naphthyl	CH ₃	CH ₃	26	>50:1
43	C ₆ H ₅	C ₆ H ₅	<i>n</i> -C ₄ H ₉	<i>n</i> -C ₄ H ₉	28	>50:1
44	C ₆ H ₅	C ₆ H ₅	<i>n</i> -C ₄ H ₉	CH ₃	31	30:1
45 ^a	C ₆ H ₅	C ₆ H ₅	CH ₃	CH ₃	27	26:1
46 ^a	<i>p</i> -OCH ₃ -C ₆ H ₄	<i>p</i> -OCH ₃ -C ₆ H ₄	CH ₃	CH ₃	49	48:1
47 ^a			CH ₃	CH ₃	56	29:1

10 ^a15 h reaction time instead of 40 h.

Example 8: Carboxylation of 1-heptene



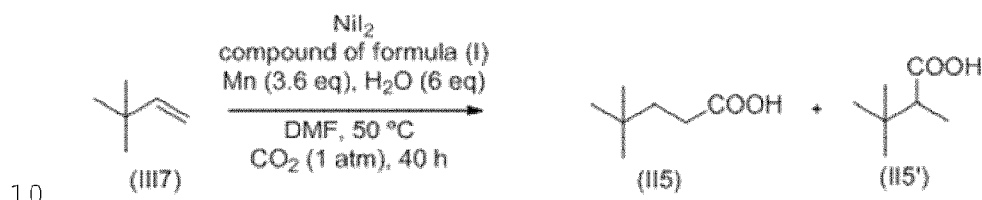
15 1-heptene (IIIe) was carboxylated to 1-octanoic acid following the general procedure of Example 5, using:

- (i) a compound of formula (I) wherein R₁ and R₁' are phenyl and R₂ and R₂' are methyl, in an amount of 35 mol%;
- (ii) 10 mol% of NiI₂ as nickel (II) salt;

- (iii) 3.6 equivalents of manganese as reducing agent;
- (iv) 6 equivalents of water as hydrogen source; and
- (iv) DMF as a solvent and at a temperature of 50 °C.

- 5 In these conditions the process of the invention provides octanoic acid in 49% isolated yield, with a ratio of (II1):(II1') of 49 to 1.

Example 9: Carboxylation of 3,3-dimethylbut-1-ene

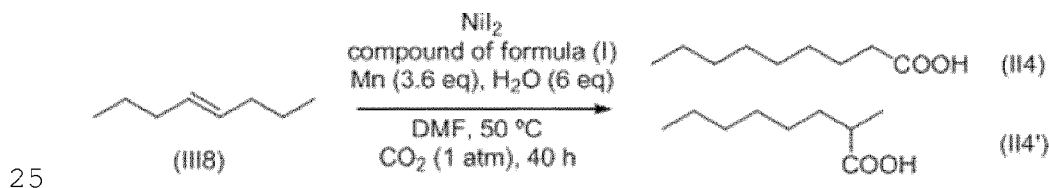


3,3-dimethylbut-1-ene (III7) was carboxylated to the corresponding carboxylic acid following the general procedure of Example 5, using:

- (i) a compound of formula (I) wherein R_1 and R_1' are phenyl and R_2 and R_2' are methyl, in an amount of 35 mol%;
- 15 (ii) 10 mol% of NiI_2 as nickel (II) salt;
- (iii) 3.6 equivalents of manganese as reducing agent;
- (iv) 6 equivalents of water as hydrogen source; and
- (iv) DMF as a solvent and at a temperature of 50 °C.

- 20 In these conditions the process of the invention provides compound (II5) in 30% isolated yield, with a ratio of (II5):(II5') of >30:1.

Example 10: Carboxylation of 4-octene



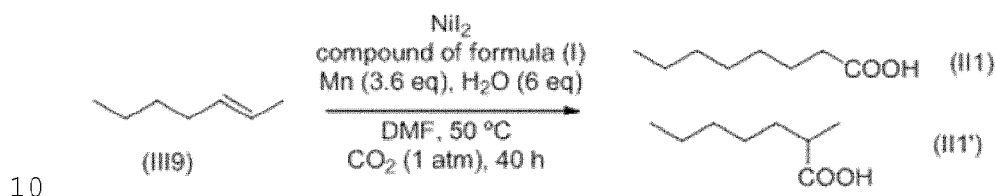
4-octene (III8) was carboxylated to the corresponding carboxylic acid following the general procedure of Example 5, using:

- (i) a compound of formula (I) wherein R_1 and R_1' are phenyl and R_2 and R_2' are methyl, in an amount of 35 mol%;
- 30 (ii) 10 mol% of NiI_2 as nickel (II) salt;

- (iii) 3.6 equivalents of manganese as reducing agent;
- (iv) 6 equivalents of water as hydrogen source; and
- (iv) DMF as a solvent and at a temperature of 50 °C.

- 5 In these conditions the process of the invention provides compound (II4) in 10% isolated yield, with a ratio of (II4):(II4') of >10:1.

Example 11: Carboxylation of 2-heptene

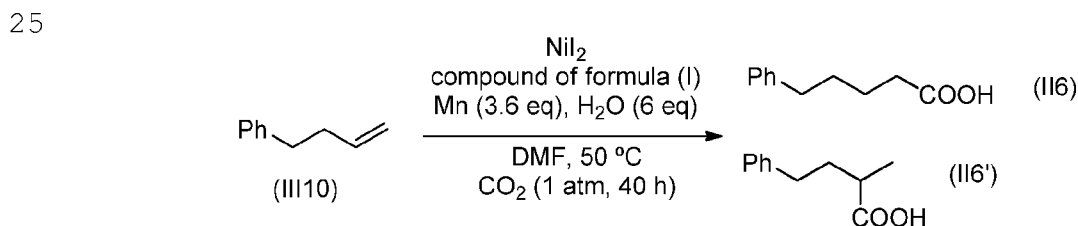


2-heptene (IIIh) was carboxylated to the corresponding carboxylic acid following the general procedure of Example 5, using:

- (i) a compound of formula (I) wherein R_1 and R_1' are phenyl and R_2 and R_2' are methyl, in an amount of 35 mol%;
- (ii) 10 mol% of NiI_2 as nickel (II) salt;
- (iii) 3.6 equivalents of manganese as reducing agent;
- (iv) 6 equivalents of water as hydrogen source; and
- (iv) DMF as a solvent and at a temperature of 50 °C.

In these conditions the process of the invention provides compound (II1) in 15% isolated yield, with a ratio of (II1):(II1') of >15:1.

Example 12: Carboxylation of but-3-en-1-ylbenzene



But-3-en-1-ylbenzene (IIIi) was carboxylated to the corresponding carboxylic acid following the general procedure of Example 5, using:

- (i) a compound of formula (I) wherein R_1 and R_1' are phenyl and R_2 and R_2' are methyl, in an amount of 35 mol%;
- (ii) 10 mol% of NiI_2 as nickel (II) salt;

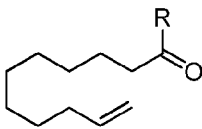
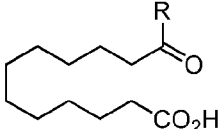
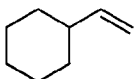
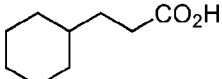
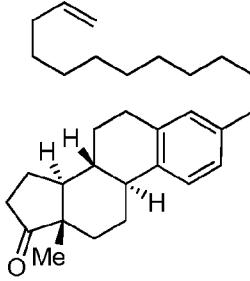
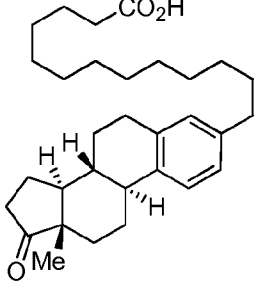
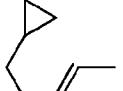
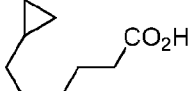
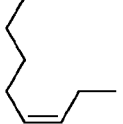
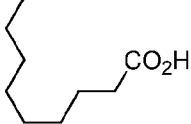
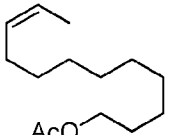
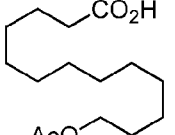
- (iii) 3.6 equivalents of manganese as reducing agent;
- (iv) 6 equivalents of water as hydrogen source; and
- (iv) DMF as a solvent and at a temperature of 50 °C.

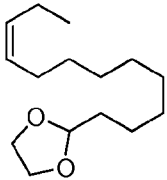
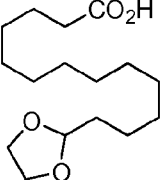
- 5 In these conditions the process of the invention provides compound (II6) in 40% isolated yield, with a ratio of (II6):(II6') of 39 to 1.

Example 13: Carboxylation of various olefins

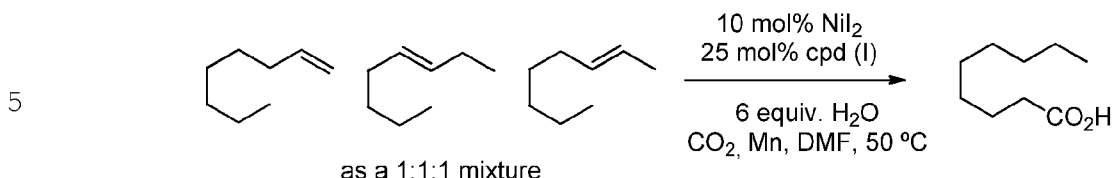
- 10 Following the general procedure described in Example 12 but using the starting material described in Table 17, the products indicated in Table 17 were obtained in the yields indicated in Table 17.

Table 17: Scope of starting material

Compound of formula (III)	Product	Yield (%)
Cyclopentene	cyclopentanecarboxylic acid	40
4,4-dimethylpent-1-ene	5,5-dimethylhexanoic acid	57
4,4-diphenylbut-1-ene	5,5-diphenylpentanoic acid	51
		R=OEt (51) R=Me (59)
		56
		42
		58
		54
		52

Compound of formula (III)	Product	Yield (%)
		50

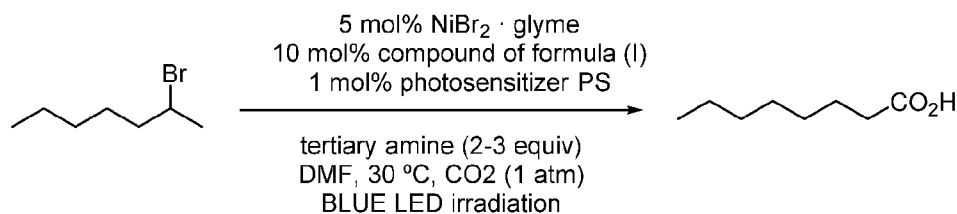
Example 14: Carboxylation of a mixture of octene isomers



10 Following the general procedure described in Example 12 but using an equimolar mixture of 1-octene, 2-octene and 3-octene, 1-nonaic acid was obtained in 51% yield.

15 The project leading to this application has received funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme under grant agreement No 713677.

Example 15: Use of a photocatalytic reduction means in the carboxylation of 2-bromoheptane



20

General procedure: An oven-dried schlenk tube containing a stirring bar was charged with NiBr₂·glyme (3.9 mg, 5 mol%), the corresponding compound of formula (I) (10 mol%), the photosensitizer compound PS as indicated in Table 18 (1 mol%) and a base additive as indicated in Table 18 (2-3 equiv.). The schlenk tube was then evacuated and back-filled under a carbon dioxide flow (this sequence was repeated three times) and finally an atmospheric pressure of CO₂ was established. DMF (2.0 mL, 0.125 M), the corresponding tertiary amine (3 equiv.) and 2-bromoheptane (0.25 mmol) were subsequently added by syringe and the solution was stirred at 30 °C under blue LED irradiation for 24 h. The mixture was then carefully quenched with 2 M HCl to hydrolyze the resulting carboxylate and extracted with EtOAc. A

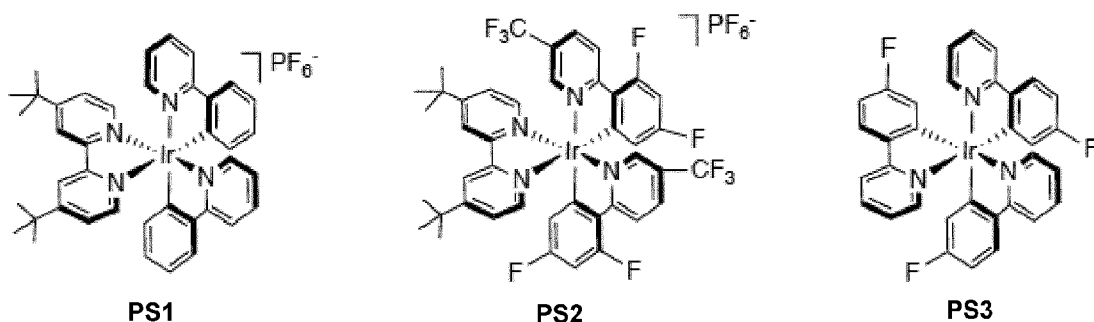
25

sample of such obtained solution was next analyzed by GC using anisole as internal standard and eventually, when required, the resulting carboxylic acid was purified by conventional flash chromatography (hexanes/EtOAc 3/1).

5 Table 18: Photocatalytic carboxylation of 2-bromoheptane

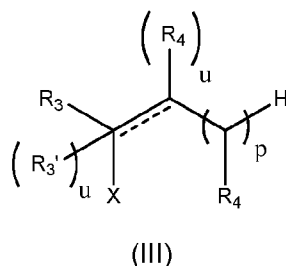
Entry	Compound of formula (I)		PS compound	Base additive (equiv.)	Tertiary amine	Yield (%)	Selectivity (l:b)
	R ₁ , R ₁ '	R ₂ , R ₂ '					
1	Ph	<i>n</i> -butyl	PS2	Li ^t BuO (2 eq.)	DIPEA	25	> 25:1
2	Ph	<i>n</i> -hexyl	PS2	Li ^t BuO (2 eq.)	DIPEA	17	> 17:1
3	Ph	<i>n</i> -hexyl	PS2	Li ^t BuO (3 eq.)	DIPEA	24	> 24:1
4	Ph	<i>n</i> -hexyl	PS3	Li ^t BuO (2 eq.)	DIPEA	9	> 9:1
5	Ph	<i>n</i> -hexyl	PS1	Li ^t BuO (2 eq.)	DIPEA	16	> 16:1
6	Ph	<i>n</i> -hexyl	PS1	-	DIPEA	7	> 7:1
7	Ph	<i>n</i> -hexyl	PS1	Li ^t BuO (2 eq.)	triethanolamine	17	> 17:1
8	Ph	<i>n</i> -hexyl	PS1	Na ^t BuO (2 eq.)	triethanolamine	19	19:2
9	Ph	<i>n</i> -hexyl	PS1	Cs ₂ CO ₃ (2 eq.)	triethanolamine	5	> 5:1
10	Ph	<i>n</i> -hexyl	PS1	Li ^t BuO (2 eq.)	triethylamine	8	> 8:1

DIPEA: N,N-diisopropylethylamine



CLAIMS

1. Method of direct carboxylation of a compound represented by formula (III)



10 wherein:

p is an integer from 0 to 15;

u is 0 or 1;

each R_4 represents a radical independently selected from the group consisting of

hydrogen,

15 a linear or branched C_{1-20} alkyl group optionally carrying one or more substituents selected from fluoro and chloro,

a linear or branched C_{1-20} alkyloxy group;

20 X represents hydrogen or a group which acts as a leaving group in the direct carboxylation and which is selected from a bromine atom, an iodine atom, a phenylsulfonate wherein the phenyl ring is optionally substituted with a methyl group, a methylsulfonate and a trifluoromethylsulfonate;

25 with the proviso that when X represents hydrogen, then the bond represented by the combination of a solid line and a dotted line is a double bond, and u is 0; and that when X is not hydrogen, then the bond represented by the combination of a solid line and a dotted line is a single bond, and u is 1;

R_3 and R_3' are each independently selected from hydrogen and a radical of formula $-Y(-Z)_n$, wherein

Y is selected from a linear C_{1-20} alkyl, a branched C_{3-20} alkyl and a C_{3-8} cycloalkyl;

n is an integer from 0 to the number of carbon atoms in Y;

30 each Z is independently selected from the group consisting of:

fluoro,

chloro,

hydroxyl,

35 a radical of formula $-OR_5$, a radical of formula $-C(O)R_5$, a radical of formula $-OC(O)R_5$, a radical of formula $-C(O)OR_5$, a radical of formula $-NHC(O)R_5$, a radical of formula $-C(O)NHR_5$, a radical of formula $-NHC(O)OR_5$, a radical of formula $-OC(O)NHR_5$, a radical of formula $-NR_5C(O)R_5$, a radical of formula $-C(O)N(R_5)_2$, a radical of formula $-NR_5C(O)OR_5$, a radical of

formula $-\text{OC}(\text{O})\text{N}(\text{R}_5)_2$, each R_5 being independently selected from the group consisting of a linear or branched C_{1-20} alkyl groups, and a cyclic group comprising 1 ring or 2 to 5 condensed rings,

wherein each ring has 5 or 6 members selected from the group consisting of C, CH, CH_2 , CO, O, S, N and NR_6 ,

wherein R_6 is selected from hydrogen and C_{1-6} alkyl,

each ring being independently unsaturated, saturated or aromatic;

and each ring being further optionally substituted with one or more radicals selected from the group consisting of: fluoro, chloro, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkyloxy, C_{1-6} alkylcarbonyl, phenylcarbonyl, C_{1-6} alkylcarbonyloxy, C_{1-6} alkylcarbonylamino, and C_{1-6} alkylaminocarbonyl,

an aldehyde group,

nitro,

cyano,

a group of formula $-\text{SO}_2\text{R}_{11}$

wherein R_{11} is selected from C_{1-6} alkyl, C_{1-6} haloalkyl, phenyl and phenyl substituted with one or more C_{1-6} alkyl groups; and

a cyclic group comprising 1 ring or 2 to 5 condensed rings,

wherein each ring has 3, 4, 5 or 6 members selected from the group consisting of C, CH, CH_2 , CO, O, S, N and NR_6 ,

wherein R_6 is selected from hydrogen and C_{1-6} alkyl,

each ring being independently unsaturated, saturated or aromatic;

and each ring being further optionally substituted with one or more radicals selected from the group consisting of: fluoro, chloro, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkyloxy, C_{1-6} alkylcarbonyl, C_{1-6} alkylcarbonyloxy, C_{1-6} alkylcarbonylamino, C_{1-6} alkylaminocarbonyl, a radical of formula $-\text{OR}_5$, a radical of formula $-\text{C}(\text{O})\text{R}_5$, a radical of formula $-\text{OC}(\text{O})\text{R}_5$, a radical of formula $-\text{C}(\text{O})\text{OR}_5$, a radical of formula $-\text{NHC}(\text{O})\text{R}_5$, a radical of formula $-\text{C}(\text{O})\text{NHR}_5$, a radical of formula $-\text{NHC}(\text{O})\text{OR}_5$, a radical of formula $-\text{OC}(\text{O})\text{NHR}_5$, a radical of formula $-\text{NR}_5\text{C}(\text{O})\text{R}_5$, a radical of formula $-\text{C}(\text{O})\text{N}(\text{R}_5)_2$, a radical of formula $-\text{NR}_5\text{C}(\text{O})\text{OR}_5$, a radical of formula $-\text{OC}(\text{O})\text{N}(\text{R}_5)_2$, $-\text{R}_a-\text{R}_b$,

each R_5 being independently selected from the group consisting of a linear or branched C_{1-20} alkyl groups, and a cyclic group comprising 1 ring or 2 to 5 condensed rings,

wherein each ring has 5 or 6 members selected from the group consisting of C, CH, CH_2 , O, S, N and NR_6 ,

wherein R_6 is selected from hydrogen and C_{1-6} alkyl,

each ring being independently unsaturated, saturated or aromatic;
and each ring being further optionally substituted with one or more
radicals selected from the group consisting of: fluoro, chloro, C₁₋₆
alkyl, C₁₋₆haloalkyl, C₁₋₆alkyloxy, C₁₋₆alkylcarbonyl, C₁₋₆
alkylcarbonyloxy, C₁₋₆alkylcarbonylamino, and C₁₋₆
alkylaminocarbonyl,

and

wherein R_a is a single bond or a diradical selected from -O-, -S-, -
C(=O)-, -C(=O)-O-, -O-C(=O)-, -C(=O)-NH-, -NH-C(=O)-, -O-
C(=O)-NH-, -NH-C(=O)-O-, -O-C(=O)-O-, -S(O)₂-, -S(O)₂-NH-, -
NH-S(O)₂-, -N=N-, -NH-C(=O)-NH-,

and

wherein R_b is selected from a C₆₋₁₀ aryl group, a C₃₋₈ cycloalkyl
group optionally containing one or two double bonds, or a
saturated or unsaturated heterocyclic group containing 5 to 7 ring
members wherein each ring member is selected from C, CH, CH₂,
O, S, B, CHR₆, C(R₆)₂, N and NR₆, wherein R₆ is selected from
hydrogen and C₁₋₆alkyl;

or; alternatively, one of the pairs selected from the pair R₃ and R₃', the pair R₃ and R₄, and the
pair R₃' and R₄, together with the carbon atom to which they are attached form a cyclic group
comprising 1 ring or 2 to 5 condensed rings, wherein each ring has 5 or 6 members selected
from the group consisting of C, CH, CH₂, O, S, N and NR₆, wherein R₆ is selected from
hydrogen and C₁₋₆alkyl, each ring being independently unsaturated, or saturated; and each ring
being further optionally substituted with one or more radicals selected from the group consisting
of: C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkyloxy, C₁₋₆alkylcarbonyl, C₁₋₆alkylcarbonyloxy, C₁₋₆
alkylcarbonylamino, C₁₋₆alkylaminocarbonyl, -R_a-R_b,

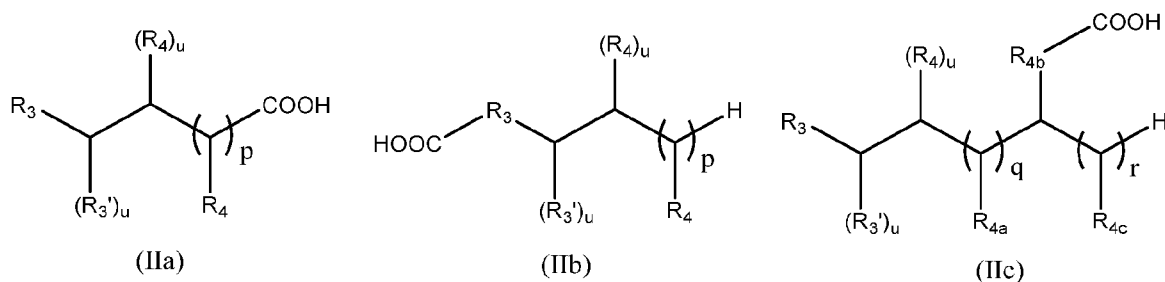
wherein R_a is a single bond or a diradical selected from -O-, -S-, -
C(=O)-, -C(=O)-O-, -O-C(=O)-, -C(=O)-NH-, -NH-C(=O)-, -O-
C(=O)-NH-, -NH-C(=O)-O-, -O-C(=O)-O-, -S(O)₂-, -S(O)₂-NH-, -
NH-S(O)₂-, -N=N-, -NH-C(=O)-NH-,

and wherein R_b is selected from a C₆₋₁₀ aryl group, a C₃₋₈ cycloalkyl group
optionally containing one or two double bonds, or a saturated or
unsaturated heterocyclic group containing 5 to 7 ring members wherein
each ring member is selected from C, CH, CH₂, O, S, N and NR₆, wherein
R₆ is selected from hydrogen and C₁₋₆alkyl;

with the proviso that R₃ is not hydrogen if X is not hydrogen

to produce a compound selected from the compounds of formula (IIa), (IIb), and (IIc) or a salt thereof,

5 wherein



wherein R₃, R₃', R₄, n, p and u have the same meanings as specified for the respective starting materials of formula (III) above with the exception of R₃ representing a single bond in those products of formula (IIb), which are obtained from compounds of formula (III), in which R₃ represents a hydrogen atom,

and,

in the compound of formula (IIb), the carboxyl group is attached to a carbon atom of R₃ which is connected with the carbon atom derived from the carbon atom bearing the activating group in the starting material via a chain of secondary and tertiary carbon atoms that is not interrupted by any quaternary carbon atoms; and wherein

in the compound of formula (IIc),

q is an integer from 0 to 7;

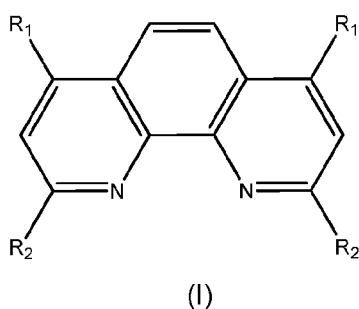
r is an integer from 0 to 14; and q+r+1 is from 1 to 15;

and wherein each of R_{4a}, R_{4b} and R_{4c} independently has the same meaning as specified for R₄, but with the proviso that R_{4b} has a terminal aliphatic carbon atom, which is connected with the carbon atom derived from the carbon atom bearing the activating group in the starting material via a chain of secondary and tertiary carbon atoms that is not interrupted by any quaternary carbon atoms;

the method comprising the step of contacting the compound of formula (III) with carbon dioxide in the presence of a polar aprotic solvent, which has a dielectric constant above 25.0 and/or a

dipole moment above 2.5 D and which does not release any protons under the conditions of the method of the present invention, and

- (a) a catalytically effective amount of a nickel(II) salt selected from the group consisting of nickel (II) halide, nickel (II) acetylacetonate, nickel (II) sulphate, nickel (II) perchlorate, nickel (II) trifluoromethanesulfonate, nickel (II) hexafluoroacetylacetonate, nickel (II) sulfamate, nickel (II) carbonate, nickel (II) oxalate, a compound of formula $\text{Ni}(\text{OOCR})_2$ wherein R is a linear or branched C_{1-20} alkyl or a C_{3-8} cycloalkyl optionally substituted with one or more linear or branched C_{1-6} alkyl chains, nickel hexafluorosilicate and solvates thereof;
- (b) a reducing agent selected from Mn and Zn or an electrochemical or photochemical reducing means, and
- (c) a catalytically effective amount of a ligand of formula (I)



wherein

R_2 and R_2' are each independently selected from the group consisting of: hydrogen, a linear or branched C_{1-12} alkyl group, a linear or branched C_{1-12} haloalkyl group, a C_{6-20} aryl group and a C_{6-20} aryl group having at least one substituent selected from linear or branched C_{1-6} alkyl groups, linear or branched C_{1-6} alkoxy groups, linear or branched C_{1-6} haloalkyl groups, fluorine, chlorine and bromine; provided that when R_2 or, respectively, R_2' , is hydrogen, then R_2' , or, respectively, R_2 , is not hydrogen;

R_1 and R_1' are each independently selected from the groups consisting of hydrogen, halogen, a linear or branched C_{1-12} alkyl group, a linear or branched C_{1-12} haloalkyl group, a C_{6-20} aryl group and a C_{6-20} aryl group having at least one substituent selected from linear or branched C_{1-6} alkyl groups, linear or branched C_{1-6} alkoxy groups, linear or branched C_{1-6} haloalkyl groups and halogen atoms; and

- (d) a hydrogen source selected from water, a compound of formula $\text{R}_7\text{R}_8\text{CH}-\text{CH}_2\text{Br}$, and a compound of formula $\text{R}_7\text{R}_8\text{CBr}-\text{CHR}_9\text{R}_{10}$, wherein R_{10} , R_7 , R_8 , and R_9 are each

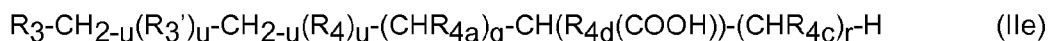
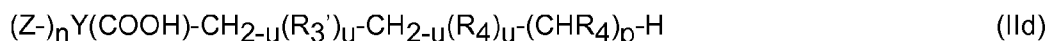
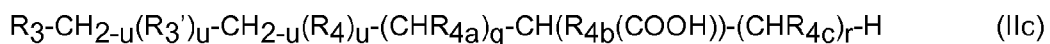
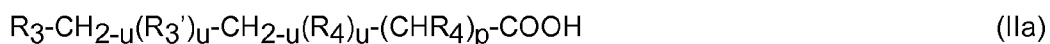
independently selected from the group consisting of hydrogen, a linear or branched C₁₋₂₀ alkyl optionally substituted with a radical selected from hydroxyl and C₁₋₂₀ alkyloxy, a C₃₋₈ cycloalkyl optionally substituted with a radical selected from hydroxyl and C₁₋₂₀ alkyloxy, and a C₆₋₂₀ aryl; or, alternatively,

one or more of the pairs of R₈ and R₇, R₁₀ and R₉, R₇ and R₉ and R₈ and R₁₀, together with the carbon atoms to which they are attached form a ring system comprising from 1 to 3 rings, each ring being isolated, fused or bridged, and comprising from 5 to 6 members selected from the group consisting of C, CH, and CH₂, each ring being independently unsaturated, saturated or aromatic; and each ring being further optionally substituted with one or more radicals selected from the group consisting of: hydroxyl, C₁₋₆alkyl, and C₁₋₆alkyloxy, wherein said hydrogen source is optional if X represents a leaving group

wherein the term aryl characterizes a carbocyclic aromatic ring or a system of 2 to 5 condensed carbocyclic rings wherein at least one of these condensed rings is aromatic.

2. Method according to claim 1, wherein the reducing agent is selected from Mn and Zn or an electrochemical reducing means.

3. Method according to claim 1 or 2, wherein the direct carboxylation yields a reaction product selected from the following formulae (IIa), (IIb), (IIc), (IIId) and (IIe) or a salt thereof:



wherein u, p, q, r, R₃, R_{3'} and R₄ have the meanings as specified in claim 1;

and wherein in formula (IIb), the carboxyl group is attached to a carbon atom of R₃ that is derived from a primary aliphatic carbon atom in the starting material, which is connected with the activating group (i.e. leaving group X or double bond) via a chain of secondary and tertiary carbon atoms that is not interrupted by any quaternary carbon atoms;

and wherein in formula (IIc), each of R_{4a} , R_{4b} and R_{4c} independently has the same meaning as specified in claim 1 for R_4 , but with the proviso that the carboxyl group is attached to a carbon atom of R_{4b} that is derived from a primary terminal aliphatic carbon atom in the starting material of formula (III), which is connected with the carbon atom derived from the activating group via a chain of secondary and tertiary carbon atoms that is not interrupted by any quaternary carbon atoms,

wherein in formula (IId) R_3 is represented by $(Z-)_nY$, wherein Y, Z and n are as defined in claim 1 and wherein the carboxyl group is attached to the carbon atom of group Y that is adjacent to the carbon atom carrying a substituent group Z that is an electron withdrawing group as described above,

wherein in formula (Ile) R_{4a} and R_{4c} are as defined in claim 1 and wherein R_{4d} is a group as defined for R_4 in claim 1, but with the proviso that the group contains three atoms selected from F and Cl bonded to the same carbon atom and that the $-COOH$ group is bonded to an adjacent carbon atom that is connected with the carbon atom derived from the carbon atom of the starting material of formula (III) carrying the leaving group X or participating in the double bond via a chain of secondary and/or tertiary groups that is not interrupted by any quaternary carbon atoms.

4. Method according to any of the claims 1 to 3, wherein the starting material is a compound of formula (III) as specified in claim 1,

wherein the dotted line, X, R_3 , R_3' , R_4 , u and p of formula (III) have the same meanings as specified in claim 1 with the proviso that the number of carbon atoms between the activating group, namely the leaving group X or double bond, and the terminal carbon atom of the chain formed by $-(CHR_4)_p-$ is smaller than the number of carbon atoms in any other aliphatic carbon atom chain involving R_3 , R_3' or R_4 , and connecting a terminal aliphatic carbon atom with the activating group, namely the leaving group X or double bond, only via secondary and/or tertiary carbons but without quaternary carbon atoms,

and wherein

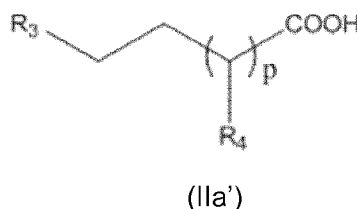
- (i) either the compound of formula (III) does not contain any electron withdrawing groups that are connected with the activating group only via secondary or tertiary aliphatic carbon atoms and the reaction is carried out under kinetic or thermodynamic control conditions

- (ii) or the compound of formula (III) does contain one or more electron withdrawing groups that are connected with the activating group only via secondary or tertiary aliphatic carbon atoms and the reaction is carried out under kinetic control reaction conditions;

and wherein the direct carboxylation predominantly yields a product of formula (IIa) or a salt thereof as specified in claim 3,

wherein R_3 , R_3' , R_4 , u and p have the same meanings as specified for formula (III) in this claim,

wherein, in the compound of formula (III), u is preferably 0, so that a product of the following formula (IIa') or a salt thereof is obtained



wherein R_3 , R_4 , and p have the same meanings as specified for formula (III) in this claim.

5. Method according to any of the claims 1 to 3, wherein the starting material is a compound of formula (III) as specified in claim 1,

wherein the dotted line, X , R_3 , R_3' , R_4 , u and p have the same meanings as specified in claim 1 with the proviso that the carbon atom chain connecting the terminal aliphatic carbon atom of R_3 with the activating group, namely the leaving group X or double bond, includes only secondary and/or tertiary carbon atoms but no quaternary carbon atoms, wherein the number of carbon atoms between the activating group and the terminal aliphatic carbon atom of R_3 is smaller than the number of carbon atoms between the activating group and the terminal aliphatic carbon atom in any other aliphatic carbon atom chain involving R_3' and/or $-(CHR_4)_p$ - and/or parts of $-(CHR_4)_p$ - together with individual R_4 groups connecting a terminal aliphatic carbon atom with the activating group only via secondary and/or tertiary carbons but without quaternary carbon atoms,

wherein the carbon atom chain connecting the terminal aliphatic carbon atom of R_3 with the activating group includes only secondary and/or tertiary carbon atoms but no quaternary carbon atoms;

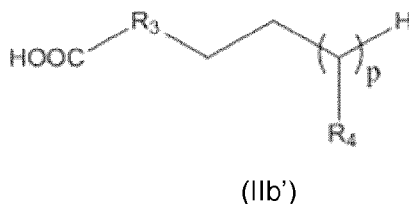
and wherein either

- (i) the compound of formula (III) does not contain any electron withdrawing groups connected with the activating group only via secondary or tertiary aliphatic carbon atoms and the reaction is carried out under kinetic or thermodynamic control conditions or
- (ii) the compound of formula (III) does contain one or more electron withdrawing groups connected with the activating group only via secondary or tertiary aliphatic carbon atoms and the reaction is carried out under kinetic control reaction conditions;

and wherein the direct carboxylation predominantly yields a product of formula (IIb) or a salt thereof as specified in claim 3

wherein R_3 , R_3' , R_4 , u and p have the same meanings as specified for formula (III) in this claim and wherein the COOH group binds to R_3 at the terminal carbon atom closest to the activating group,

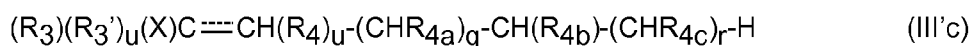
wherein, in the compound of formula (III), u is preferably 0 so that a product of the following formula (IIb') or a salt thereof is obtained



wherein R_3 , R_4 and p have the same meanings as specified for formula (III) in this claim and wherein the COOH group binds to R_3 at a terminal carbon atom.

6. Method according to any of the claims 1 to 3 wherein the starting material is a compound of formula (III) as specified in claim 1,

wherein the dotted line, X , R_3 , R_3' , R_4 , u and p have the same meanings as specified in claim 1 with the proviso that the compound of formula (III) is a compound of formula (III'c)



wherein the dotted line, X, R₃, R_{3'}, R₄ and u have the same meanings as specified in claim 1, R_{4a}, R_{4b} and R_{4c} are individually selected among the same meanings as specified above for R₄ and q and r are as specified in claim 1 above, and wherein the number of carbon atoms between the terminal aliphatic carbon atom of R_{4b} and the activating group is smaller than the number of carbon atoms between the activating group and the terminal carbon atom of any other aliphatic chain of R₄, R_{3'}, R₃, R_{4a} and R_{4c} that is connected to the activating group only via secondary and/or tertiary carbons but no quaternary carbon atoms,

wherein the carbon atom chain connecting the terminal aliphatic carbon atom of R_{4b} with the activating group includes only secondary and/or tertiary carbons but no quaternary carbon atoms and

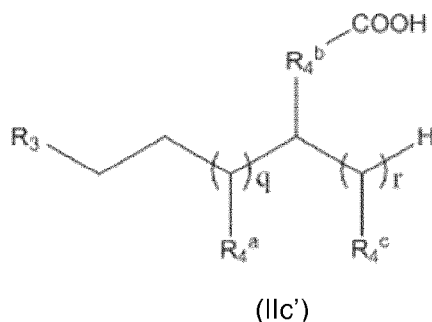
wherein either

- (i) the compound of formula (III'c) does not contain any electron withdrawing groups connected with the activating group only via secondary or tertiary aliphatic carbon atoms and the reaction is carried out under kinetic or thermodynamic reaction conditions or
- (ii) the compound of formula (III'c) does contain one or more electron withdrawing groups connected with the activating group only via secondary or tertiary aliphatic carbon atoms and the reaction is carried out under kinetic control reaction conditions,

and wherein the direct carboxylation predominantly yields a product of formula (IIc) or a salt thereof as specified in claim 3

wherein R₃, R_{3'}, R₄, R_{4a}, R_{4b}, R_{4c}, u, q and r are as specified for formulae (III) and (III'c) in this claim and wherein the COOH group binds to R_{4b} at a terminal carbon atom,

wherein, in the compound of formula (III), u is preferably 0 so that a compound of the following formula (IIc') or a salt thereof is obtained



R_3 , R_{4a} , R_{4b} , R_{4c} , q and r are as specified for formulae (III) and (III'c) in this claim and wherein the COOH group binds to R_{4b} at a terminal carbon atom.

7. Method according to any of the claims 1 to 3, wherein the starting material is a compound of formula (III) as specified in claim 1,

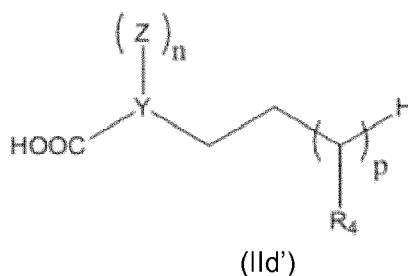
wherein the dotted line, X , R_3' , R_4 , u and p have the same meanings as specified in claim 1, wherein R_3 represents a group $-Y(Z)_n$ with Y , Z and n having the same meanings as specified in claim 1 but with the proviso that the group $-Y(Z)_n$ contains at least one electron withdrawing group connected with the activating group, namely the leaving group X or double bond, only via secondary or tertiary aliphatic carbon atoms but without quaternary carbon atoms

and the reaction is carried out under thermodynamic control reaction conditions,

and wherein the direct carboxylation predominantly yields a product of formula (IIId) or a salt thereof as specified in claim 3 above

wherein Y , Z , R_3' , R_4 , n , u and p are as specified for formula (III) in this claim and wherein the COOH group binds to Y at a carbon atom, which is connected with the activating group only via secondary or tertiary aliphatic carbon atoms but without quaternary carbon atoms and which is adjacent to the carbon atom carrying the electron withdrawing group;

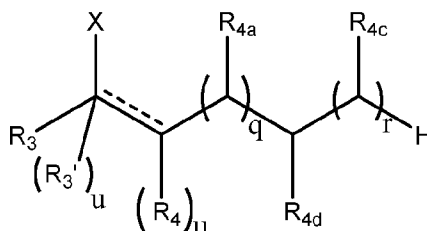
and wherein, in the compound of formula (III), u is preferably 0 so that a compound of the following formula (IIId') or a salt thereof is obtained



wherein Y , Z , R_4 , n and p are as specified for formula (III) in this claim and wherein the COOH group binds to Y at a carbon atom, which is connected with the activating group only via secondary or tertiary aliphatic carbon atoms but without quaternary carbon atoms and which is adjacent to the carbon atom carrying the electron withdrawing group.

8. Method according to any of the claims 1 to 3, wherein the starting material is a compound of formula (III) as specified in claim 1,

wherein the compound of formula (III) is a compound of formula (III'e)

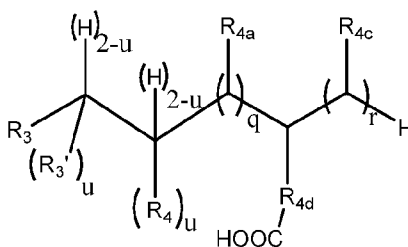


(III'e)

wherein the dotted line, X, R₃, R_{3'}, R₄, R_{4a}, R_{4c}, u, q and r have the same meanings as specified in claim 1, wherein R_{4d} has the same meaning as specified for R₄ in claim 1 but with the proviso that the group R_{4d} contains three F and/or Cl groups bonded to the same carbon atom and at least one of the adjacent carbon atoms carries at least one hydrogen atom and is connected with the activating group via an aliphatic chain having secondary and/or tertiary carbon atoms and not being interrupted by any quaternary carbon atoms

and the reaction is carried out under thermodynamic control reaction conditions,

and wherein the direct carboxylation predominantly yields a product of formula (IIe) or a salt thereof



(IIe)

wherein the R₃, R_{3'}, R₄, R_{4a}, R_{4c}, R_{4d}, u, q and r are as specified for formulae (III) and (III'e) in this claim and wherein the COOH group binds to R_{4d} at the carbon atom, which is derived from the above-mentioned carbon atom adjacent to the carbon atom carrying three F and/or Cl groups.

9. Method according to any of the claims 1 to 3, wherein the compound of formula (III) is represented by formula (IIIa),

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(IIIa)

wherein the double bond is in cis or trans configuration and wherein R_3 and p are as specified in claim 1,

wherein at least one of the following conditions is fulfilled:

- (i) R_3 does not carry any electron withdrawing groups;
- (ii) the method is carried out under kinetic control reaction conditions;

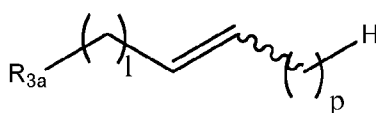
and the method is in accordance with one of the following aspects (a), (b) and (c):

(a) in formula (IIIa) p is smaller than the number of carbon atoms in any hydrocarbon chain of R_3 having a terminal carbon atom separated from the activating group, namely the double bond, only via secondary or tertiary aliphatic carbon atoms but without quaternary carbon atoms and the direct carboxylation reaction yields predominantly a reaction product characterized by the formula $R_3-(CH_2)_{p+2}-COOH$ or a salt thereof; and

(b) in formula (IIIa) p is higher than the number of carbon atoms in the shortest hydrocarbon chain forming part of R_3 having a terminal aliphatic carbon atom separated from the activating group, namely the double bond, only via secondary or tertiary aliphatic carbon atoms but without quaternary carbon atoms, and the direct carboxylation reaction yields predominantly a reaction product characterized by formula $HOOC-R_3-(CH_2)_{p+1}-CH_3$ or a salt thereof, wherein the $-COOH$ group is bonded to a terminal carbon atom of R_3 ; and

(c) R_3 in formula (IIIa) represents a hydrogen atom and the direct carboxylation reaction yields predominantly a reaction product characterized by formula $HOOC-(CH_2)_{p+1}-CH_3$ or a salt thereof.

10. Method as defined in claim 9, wherein the compound of formula (III) is a compound of formula (IIIb)



(IIIb)

wherein the double bond is in cis or trans configuration and wherein

p represents an integer of 0 to 3;

l represents an integer of 0 to 3;

p + l is less than or equal to 3;

5 R_{3a} represents a radical selected from a linear or branched $C_{1-(20-l)}$ alkyl group optionally substituted with a C_{6-20} aryl group, a C_{3-6} cycloalkyl group, a fluorine atom or a chlorine atom,

wherein at least one of the following conditions is fulfilled:

- 10 (i) R_3 does not carry any electron withdrawing groups;
(ii) the method is carried out under kinetic control reaction conditions;

and the method is in accordance with one of the following aspects (a') and, (b'):

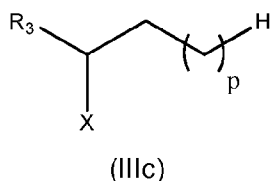
15 (a') in formula (IIIb) p is smaller than the number of carbon atoms in any hydrocarbon chain of $-(CH_2)_l-R_{3a}$ having a terminal carbon atom separated from the activating group, namely the double bond, only via secondary or tertiary aliphatic carbon atoms but without quaternary carbon atoms and the direct carboxylation reaction yields predominantly a reaction product characterized by the formula $R_{3a}-(CH_2)_{p+l+2}-COOH$
20 or a salt thereof; and

(b') in formula (IIIb) p is higher than the number of carbon atoms in the shortest hydrocarbon chain of $-(CH_2)_l-R_{3a}$ having a terminal carbon atom separated from the activating group, namely the double bond, only via secondary or tertiary aliphatic carbon
25 atoms but without quaternary carbon atoms, and the direct carboxylation reaction yields predominantly a reaction product characterized by formula $HOOC-R_{3a}-(CH_2)_{p+l+1}-CH_3$ or a salt thereof wherein the $-COOH$ group is bonded to said terminal carbon atom of R_{3a} .

30 11. Method as defined in any of the preceding claims, wherein the compound of formula (III) is a mixture of two or more compounds of formula (III), wherein in each of these compounds X represents hydrogen and the bond represented by the combination of a solid line and a dotted line is a double bond and wherein these compounds have the same total number of carbon atoms and where groups R_3 and R_4 are such that the two
35 or more compounds of formula (III) differ from each other only with respect to the

position of the double bond and such that the same reaction product is obtained for each of these compounds.

12. Method according to any of the claims 1 to 3, wherein the compound of formula (III) is represented by formula (IIIc),



wherein p, X and R₃ are as defined in claim 1

wherein at least one of the following conditions is fulfilled:

- (i) R₃ does not carry any electron withdrawing groups;
- (ii) the method is carried out under kinetic control reaction conditions;

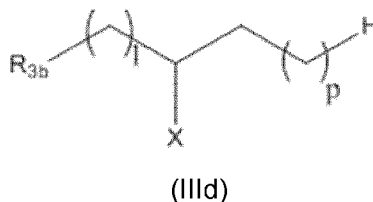
and the method is in accordance with one of the following aspects (aa) and, (bb):

(aa) in formula (IIIc) p+1 is smaller than the number of carbon atoms in any hydrocarbon chain of R₃ having a terminal carbon atom separated from the activating group, namely the group X, only via secondary or tertiary aliphatic carbon atoms but without quaternary carbon atoms and the direct carboxylation reaction yields predominantly a reaction product characterized by the formula R₃-(CH₂)_{p+2}-COOH or a salt thereof; and

(bb) in formula (IIIc) p+1 is higher than the number of carbon atoms between the activating group X and the terminal carbon atom of the shortest hydrocarbon chain forming part of R₃ having a terminal carbon atom separated from the activating group, namely the group X, only via secondary or tertiary aliphatic carbon atoms but without quaternary carbon atoms, and the direct carboxylation reaction yields predominantly a reaction product characterized by formula HOOC-R₃-(CH₂)_{p+1}-CH₃ or a salt thereof, wherein the -COOH group is bonded to said terminal carbon atom of R₃.

13. Method as defined in claim 12, wherein the compound of formula (III) is a compound of formula (IIId)

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wherein

p represents an integer of 0 to 3;

l represents an integer of 0 to 3;

p + l is less than or equal to 3;

X is as defined in claim 1;

R_{3b} represents a radical selected from a linear or branched C₁-(20-l) alkyl group optionally substituted with

a C₆-20 aryl group optionally substituted with a C₁₋₆alkylcarbonyloxy or C₁₋₆alkoxycarbonyl or optionally condensed with a five- or six-membered heterocycle with ring atoms selected from C, N, O, S and P,

a C₃-6 cycloalkyl group,

a radical of formula -OC(O)R₅,

a radical of formula -C(O)OR₅,

a radical of formula -OR₅,

a radical of formula -C(O)R₅,

a radical of formula -C(O)N(R₅)₂,

a radical of formula -CHO,

a mono- or bicyclic saturated,

unsaturated or aromatic heterocycle with each ring having 3 to 8 ring atoms selected from C, N, O, S and P, optionally substituted with a C₁₋₆alkylcarbonyloxy or C₁₋₆alkoxycarbonyl;

each R₅ being independently selected from the group consisting of methyl, ethyl, propyl, butyl and phenyl optionally substituted with one or more radicals selected from the group consisting of: C₁₋₆alkyloxy, C₁₋₆alkyloxycarbonyl, C₁₋₆alkylcarbonyloxy, a fluorine atom, a chlorine atom, phenylcarbonyl, phenoxy, phenylcarbonyloxy, and phenoxy,

wherein at least one of the following conditions is fulfilled:

(i) R₃ does not carry any electron withdrawing groups;

(ii) the method is carried out under kinetic control reaction conditions;

and the method is in accordance with one of the following aspects (aa') and, (bb'):

(aa') in formula (IIId) $p+1$ is smaller than the number of carbon atoms in any hydrocarbon chain of $-(CH_2)_l-R_{3b}$ having a terminal carbon atom separated from the activating group X only via secondary or tertiary aliphatic carbon atoms but without quaternary carbon atoms and the direct carboxylation reaction yields predominantly a reaction product characterized by the formula $R_{3b}-(CH_2)_{l+p+2}-COOH$ or a salt thereof; and

(bb'), in formula (IIId) $p+1$ is higher than the number of carbon atoms between the activating group X and the terminal carbon atom of the shortest hydrocarbon chain forming part of $-(CH_2)_l-R_{3b}$ having a terminal carbon atom separated from the activating group, namely the group X, only via secondary or tertiary aliphatic carbon atoms but without quaternary carbon atoms, and the direct carboxylation reaction yields predominantly a reaction product characterized by formula $HOOC-R_{3b}-(CH_2)_{l+p+1}-CH_3$ or a salt thereof wherein the $-COOH$ group is bonded to said terminal carbon atom of R_{3b} .

14. Method as defined in claims 1, 2, 3, 4, 5, 6, 7, 8, 12 or 13, wherein the compound of formula (III) is a mixture of two or more compounds, which two or more compounds have a group X other than hydrogen as well as the same total number of carbon atoms and where groups R_3 and R_4 are such that the two or more compounds differ from each other only with respect to the position of the leaving group X and such that the same reaction product is obtained for each of these compounds.
15. Method as defined in any one of the preceding claims, wherein the reaction conditions are selected such that one or more of the following features is fulfilled:
- (i) the catalyst is formed using Ni(II) iodide;
 - (ii) a photochemical reducing means is used;
 - (iii) a ligand of formula (I) is used, wherein R_2 and R_2' are each independently selected from the group consisting of: hydrogen, a linear or branched C_{1-12} alkyl group, a linear or branched C_{1-12} haloalkyl group and a C_{6-20} aryl group;
 - (iv) a ligand of formula (I) is used, wherein R_2 and R_2' are each independently selected from the group consisting of linear or branched C_{1-6} alkyl groups; and

- (v) a ligand of formula (I) is used, wherein R_1 and R_1' are each independently selected from the group consisting of a C_{6-20} aryl group and a C_{6-20} aryl group having at least one substituent selected from linear or branched C_{1-6} alkyl groups, linear or branched C_{1-6} alkoxy groups, linear or branched C_{1-6} haloalkyl groups, fluoro, chloro and bromo

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- (vi) the catalyst is prepared in situ by admixing the components of the catalyst as specified in claim 1 with the starting material and reaction solvent wherein the addition of the individual catalyst components may be performed in any relative order;

- 10 (vii) the starting material is an alkene and the hydrogen source is used in an amount of 0.9 to 11 molar equivalents relative to the starting material being 1 molar equivalent.

16. Method as defined in claim 15 wherein a photochemical reducing means is used and the photochemical reducing means is consisting of the combination of a photosensitizer with an electron donor compound.

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17. Method as defined in claim 16 wherein the photosensitizer is selected from the group consisting of the complexes of formulae $[Ru(bpy)_3]^{2+}$, $[Ir(ppy)_3]$ and $[Ir(ppy)_2(bpy)]^+$, wherein bpy represents 2,2'-bipyridine wherein each pyridine ring is optionally substituted with one or more radicals selected from the group consisting of halo, a linear or branched C_{1-6} alkyl group, a linear or branched C_{1-6} alkoxy group, a C_{6-20} aryl group and linear or branched C_{1-6} haloalkyl group ; and wherein ppy represents 2-phenylpyridine wherein each of the pyridine and phenyl rings are optionally substituted with one or more radicals selected from the group consisting of halo, a linear or branched C_{1-6} alkyl group and linear or branched C_{1-6} haloalkyl groups.

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18. Method as defined in claim 16 or 17 wherein the electron donor compound is a compound of formula $N(RR'R'')$ wherein each of R, R' and R'' is a linear or branched C_{1-6} alkyl group, R, R' and R'' being the same or different and wherein the alkyl group may further be substituted with one or more hydroxyl groups.

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19. Method as defined in any one of claims 1 to 14, wherein the reaction conditions are selected such that one or more of the following features is fulfilled:

- 35 (i) the catalyst is formed using Ni(II) iodide;

- (ii) Mn is used as the reducing agent;

(iii) a ligand of formula (I) is used, wherein R_2 and R_2' are each independently selected from the group consisting of: hydrogen, a linear or branched C_{1-12} alkyl group, a linear or branched C_{1-12} haloalkyl group and a C_{6-20} aryl group;

(iv) a ligand of formula (I) is used, wherein R_2 and R_2' are each independently selected from the group consisting of linear or branched C_{1-6} alkyl groups; and

(v) a ligand of formula (I) is used, wherein R_1 and R_1' are each independently selected from the group consisting of a C_{6-20} aryl group and a C_{6-20} aryl group having at least one substituent selected from linear or branched C_{1-6} alkyl groups, linear or branched C_{1-6} alkoxy groups, linear or branched C_{1-6} haloalkyl groups, fluoro, chloro and bromo

(vi) the catalyst is prepared in situ by admixing the components of the catalyst as specified in claim 1 with the starting material and reaction solvent wherein the addition of the individual catalyst components may be performed in any relative order;

(vii) the starting material is an alkene and the hydrogen source is used in an amount of 0.9 to 11 molar equivalents relative to the starting material being 1 molar equivalent.

20. Method as defined in any one of the preceding claims, wherein a ligand is used, which contains variable groups selected from the following alternative options:

(a) R_2 and R_2' are each independently selected from the group consisting of linear or branched C_{1-6} alkyl groups, while R_1 and R_1' are each independently selected from the group consisting of hydrogen, phenyl, phenyl having at least one substituent selected from linear or branched C_{1-6} haloalkyl groups and naphthyl;

(b) R_2 and R_2' are selected from the group consisting of CH_3 , C_2H_5 , $n-C_4H_9$, $n-C_6H_{13}$, $i-C_3H_7$ and $i-C_4H_9$ while R_1 and R_1' both represent an aryl group and more preferably a phenyl group;

(c) R_2 and R_2' represent both a methyl group and R_1 and R_1' are both a naphthyl group and more preferably R_1 and R_1' are both selected from the group consisting of 1-naphthyl and 2-naphthyl;

(d) R_2 and R_2' are the same and are selected from the group consisting of C_2H_5 , $n-C_4H_9$, $n-C_6H_{13}$ and $i-C_3H_7$ while R_1 and R_1' both represent a phenyl group;

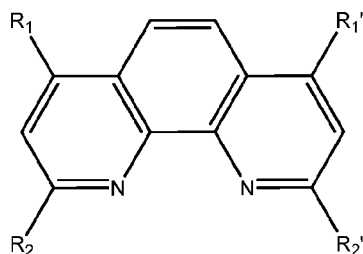
- (e) R_2 and R_2' represent both a methyl group and R_1 and R_1' are both selected from hydrogen, phenyl, C_{1-6} alkoxy-substituted phenyl, C_{1-6} haloalkyl-substituted phenyl and naphthyl group and more preferably R_1 and R_1' are both selected from the group consisting of phenyl and methoxy-substituted phenyl, in particular phenyl, para-methoxy-substituted phenyl and ortho,para-dimethoxy-substituted phenyl; or
- (f) at least one of R_2 and R_2' represents an n-butyl group while the other one of R_2 and R_2' may represent an n-butyl group or a methyl group, and wherein R_1 and R_1' both represent a phenyl group;

wherein preferably R_1 and R_1' are the same and/or R_2 and R_2' are the same.

21. Method as defined in any one of the preceding claims 1 to 20, wherein a hydrogen source is used, which is selected from water and the group of compounds characterized by the general formula $R_7R_8CH-CH_2-Br$, wherein R_7 and R_8 are independently selected from hydrogen, a linear or branched C_{1-20} alkyl group optionally substituted with a radical selected from hydroxyl and C_{1-20} alkyloxy, a C_{3-8} cycloalkyl optionally substituted with a radical selected from hydroxyl and C_{1-20} alkyloxy, and a C_{6-20} aryl.
22. Method as defined in any one of the preceding claims, wherein the Ni(II) salt is used in an amount of 0.9 mol% to 11 mol% with respect to the starting material being 100 mol% and/or the compound of formula (I) is used in an amount of 0.9 mol% to 55 mol% with respect to the starting material being 100 mol% and/or wherein the reducing agent is advantageously used in an amount of 100 mol% to 550 mol% with respect to the starting material being 100 mol%.
23. Method as defined in any one of the preceding claims, wherein the reaction is carried out at a temperature in the range of from 0 to 90°C and preferably in the range of from 5 to 85°C if the starting material is a compound with a leaving group X other than hydrogen or in the range of from 45 to 90°C if the starting material is a compound wherein X represents hydrogen.
24. Method as defined in any one of the preceding claims, wherein the reaction is carried out in a solvent consisting of or containing a solvent selected from DMF (N,N-Dimethylformamide), N,N-diethylformamide, DMSO (dimethylsulfoxide), DMA (N,N-dimethylacetamide), NMP (N-methylpyrrolidine), N,N-dibutylformamide and 1-formylpyrrolidine.

25. Use of a reaction system for binding a carboxyl group to a starting material selected from an alkene and a leaving group-containing alkane, the starting material being preferably selected from the compounds of formula (III) as specified in claim 1 above, to generate a compound derived from the starting material that no longer contains the carbon-carbon double bond or leaving group but carries the carboxyl group in a terminal position, wherein said reaction system comprises carbon dioxide, a polar aprotic solvent as well as

- (a) a nickel(II) salt, preferably in a catalytically effective amount, which is selected from the group consisting of nickel (II) halide, nickel (II) acetylacetonate, nickel (II) sulphate, nickel (II) perchlorate, nickel (II) trifluoromethanesulfonate, nickel (II) hexafluoroacetylacetonate, nickel (II) sulfamate, nickel (II) carbonate, nickel (II) oxalate, a compound of formula $\text{Ni}(\text{OOCR})_2$ wherein R is a linear or branched C_{1-20} alkyl or a C_{3-8} cycloalkyl optionally substituted with one or more linear or branched C_{1-6} alkyl chains, nickel hexafluorosilicate and solvates thereof;
- (b) a reducing agent selected from Mn and Zn or an electrochemical or photochemical reducing means, and
- (c) a ligand of formula (I)



(I)

preferably in a catalytically effective amount, wherein

R_2 and R_2' are each independently selected from the group consisting of: hydrogen, a linear or branched C_{1-12} alkyl group, a linear or branched C_{1-12} haloalkyl group, a C_{6-20} aryl group and a C_{6-20} aryl group having at least one substituent selected from linear or branched C_{1-6} alkyl groups, linear or branched C_{1-6} alkoxy groups, linear or branched C_{1-6} haloalkyl groups, fluorine, chlorine and bromine; provided that when R_2 or, respectively, R_2' , is hydrogen, then R_2' , or, respectively, R_2 , is not hydrogen;

R_1 and R_1' are each independently selected from the groups consisting of hydrogen, halogen, a linear or branched C_{1-12} alkyl group, a linear or branched C_{1-12} haloalkyl

group, a C₆₋₂₀ aryl group and a C₆₋₂₀ aryl group having at least one substituent selected from linear or branched C₁₋₆ alkyl groups, linear or branched C₁₋₆ alkoxy groups, linear or branched C₁₋₆ haloalkyl groups and halogen atoms; and

(d) a hydrogen source selected from water, a compound of formula R₇R₈CH-CH₂Br, and a compound of formula R₇R₈CBr-CHR₉R₁₀, wherein R₁₀, R₇, R₈, and R₉ are each independently selected from the group consisting of hydrogen, a linear or branched C₁₋₂₀ alkyl optionally substituted with a radical selected from hydroxyl and C₁₋₂₀ alkyloxy, a C₃₋₈ cycloalkyl optionally substituted with a radical selected from hydroxyl and C₁₋₂₀ alkyloxy, and a C₆₋₂₀ aryl; or, alternatively,

one or more of the pairs of R₈ and R₇, R₁₀ and R₉, R₇ and R₉ and R₈ and R₁₀, together with the carbon atoms to which they are attached form a ring system comprising from 1 to 3 rings, each ring being isolated, fused or bridged, and comprising from 5 to 6 members selected from the group consisting of C, CH, and CH₂, each ring being independently unsaturated, saturated or aromatic; and each ring being further optionally substituted with one or more radicals selected from the group consisting of: hydroxyl, C₁₋₆alkyl, and C₁₋₆alkyloxy, wherein said hydrogen source is optional if the starting material is a leaving group-containing alkane as defined in this claim.

26. Use according to claim 25 wherein a photochemical reducing means is used.

27. Use according to claim 26 wherein the photochemical reducing means is consisting of the combination of (i) a photosensitizer selected from the group consisting of the complexes of formulae [Ru(bpy)₃]²⁺, [Ir(ppy)₃] and [Ir(ppy)₂(bpy)]⁺, wherein bpy represents 2,2'-bipyridine wherein each pyridine ring is optionally substituted with one or more radicals selected from the group consisting of halo, a linear or branched C₁₋₆ alkyl group, a linear or branched C₁₋₆ alkyloxy group, a C₆₋₂₀ aryl group and linear or branched C₁₋₆ haloalkyl group; and wherein ppy represents 2-phenylpyridine wherein each of the pyridine and phenyl rings are optionally substituted with one or more radicals selected from the group consisting of halo, a linear or branched C₁₋₆ alkyl group, a linear or branched C₁₋₆ alkyloxy group, a C₆₋₂₀ aryl group and linear or branched C₁₋₆ haloalkyl group and (ii) a compound of formula N(RR'R'') wherein each of R, R' and R'' is a linear or branched C₁₋₆ alkyl group, R, R' and R'' being the same or different and wherein the alkyl group may further be substituted with one or more hydroxyl groups as electron donor compound.

28. Use according to claim 25 wherein Mn is used as reducing agent.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2017/065389

A. CLASSIFICATION OF SUBJECT MATTER				
INV.	C07C51/15	C07C53/126	C07C53/128	C07C53/134
	C07C59/01	C07C59/147	C07C61/06	C07C67/29
	C07C69/24	C07C69/34	C07C231/12	C07C233/07
				C07C57/30
				C07C67/313
				C07C253/30
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 C07D C07J				
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, CHEM ABS Data, WPI Data				
C. DOCUMENTS CONSIDERED TO BE RELEVANT				
Category*	Citation of document, with indication, where appropriate, of the relevant passages			Relevant to claim No.
X	MARINO BÖRJESSON ET AL: "Ni-Catalyzed Carboxylation of Unactivated Alkyl Chlorides with CO ₂ ", JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 138, no. 24, 7 June 2016 (2016-06-07), pages 7504-7507, XP055329468, US			25,28
Y	ISSN: 0002-7863, DOI: 10.1021/jacs.6b04088 the whole document			1-3,15, 19-24
A	----- -/--			4-14, 16-18, 26,27
☒ Further documents are listed in the continuation of Box C. ☐ 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 application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "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 24 August 2017			Date of mailing of the international search report 01/09/2017	
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016			Authorized officer Mooren, Nicolai	

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2017/065389

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	YU LIU ET AL: "Ni-Catalyzed Carboxylation of Unactivated Primary Alkyl Bromides and Sulfonates with CO ₂ ", JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 136, no. 32, 28 July 2014 (2014-07-28), pages 11212-11215, XP055329429, US ISSN: 0002-7863, DOI: 10.1021/ja5064586	25,28
Y	the whole document	1-3,15, 19-24
A	Footnote 17	4-14, 16-18, 26,27
A	----- CATHERINE M. WILLIAMS ET AL: "Nickel-Catalyzed Reductive Carboxylation of Styrenes Using CO ₂ ", JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 130, no. 45, 12 November 2008 (2008-11-12), pages 14936-14937, XP055400358, US ISSN: 0002-7863, DOI: 10.1021/ja8062925 the whole document	1-28
X,P	----- FRANCISCO JULIÁ-HERNÁNDEZ ET AL: "Remote carboxylation of halogenated aliphatic hydrocarbons with carbon dioxide", NATURE, vol. 545, no. 7652, 3 May 2017 (2017-05-03), pages 84-88, XP055400032, ISSN: 0028-0836, DOI: 10.1038/nature22316	1-15, 19-25,28
A,P	the whole document	16-18, 26,27
