

The invention relates to a process for the preparation of enantiomeric aliphatic α -hydroxycarboxylic acid esters by catalytic hydrogenation of prochiral aliphatic α -ketocarboxylic acid esters in the presence of rhodium complexes with a chiral diphosphine ligand which forms a 5-membered ring together with the rhodium atom.

The enantioselective homogeneous hydrogenation of prochiral α -ketocarboxylic acid esters in the presence of rhodium complexes containing chiral diphosphine ligands is known and described for example by B. Heil et al. in *Homogeneous Catalysis with Metal Phosphine Complexes*, Plenum Press, New York, pp. 324-332 (1983) or by B. Heil in *Wissenschaftliche Zeitschrift THLM* 27, pp. 746-750 (1985). In these publications attention is expressly drawn to the fact that chiral bidentate bis(diphenylphosphine) ligands which form a 5-membered ring with the rhodium atom are not suitable for the reduction of ketones.

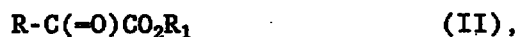
It has now been found that it is possible to attain high chemical conversions and high enantioselectivities with such rhodium catalysts which contain a 5-membered ring by using aliphatic α -ketocarboxylic acid esters as ketones and the rhodium catalyst containing a bicyclic 1,2-diphosphine.

The invention relates to a process for the preparation of optically active aliphatic α -hydroxycarboxylic acid esters of formula I



wherein R is linear or branched C_1 - C_{12} alkyl which is unsubstituted or substituted by halogen, -OH, $-CO_2R_1$, $-CO_2N(R_2)_2$, $(R_2)_2N-$, C_1 - C_6 alkoxy or C_1 - C_6 alkylthio, C_4 - C_8 cycloalkyl, C_4 - C_8 cycloalkoxy, C_4 - C_8 cycloalkylthio, phenyl, naphthyl, phenoxy, naphthoxy, phenylthio or naphthylthio, and the substituents cycloalkyl [sic], cycloalkoxy, cycloalkylthio, phenyl, naphthyl, phenoxy, naphthoxy, phenylthio and naphthylthio are themselves unsubstituted or substituted by halogen, -OH, $-CO_2R_1$, $-CO_2N(R_2)_2$, $(R_2)_2N-$, C_1 - C_6 alkoxy or C_1 - C_6 alkylthio; R_1 is C_1 - C_6 alkyl, phenyl or benzyl; both substituents R_2 are each independently of the other C_1 - C_6 alkyl, phenyl, benzyl or, when taken together, are tetramethylene, pentamethylene,

3-oxa-1,5-pentylene or N-(C₁-C₆alkyl)-3-aza-1,5-pentylene, and * denotes the predominantly R- or S-configuration, by hydrogenation of α-ketocarboxylic acid esters of formula II



wherein R and R₁ are as defined above, in the absence or presence of an inert solvent at a pressure of 0.1 to 15 MPa and at temperatures of from -20°C to 100°C, and also in the presence of catalytic amounts of a rhodium complex with chiral diphosphine ligands, which rhodium complex has the formula III



wherein X is two C₂-C₁₂olefins or a C₅-C₁₂diene, Z is Cl, Br or I, and Y is a chiral diphosphine of formula IV



wherein R₃ is phenyl, C₁-C₆alkylphenyl or C₁-C₆alkoxyphenyl, and Q is bicyclo[2.2.1]heptane-1,2-diyl or bicyclo[2.2.1]hept-4-ene-1,2-diyl.

R as alkyl preferably contains 1 to 6 and, particularly preferably, 1 to 4 carbon atoms. Alkyl is for example methyl, ethyl, and the isomers of propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl and dodecyl.

The radical R and the substituents cyloalkyl [sic], cycloalkoxy, cycloalkylthio, phenyl, naphthyl, phenoxy, naphthoxy, phenylthio and naphthylthio may be substituted by one or more, preferably by one to three, of the same or different substituents. Suitable substituents of R and the cited substituents are, in addition to -OH, as halogen, -F, -Cl and -Br; as alkoxy, preferably C₁-C₄alkoxy, for example methoxy, ethoxy, n- or isopropoxy, n-, iso- or tert-butoxy, pentoxy and hexoxy, as alkylthio, preferably C₁-C₄alkylthio, for example methylthio and ethylthio,

as cycloalkyl, preferably cyclopentyl and cyclohexyl,
as cycloalkoxy, preferably cyclopentoxy and cyclohexoxy,
as cycloalkylthio, preferably cyclopentylthio and cyclohexylthio,
as $-\text{CO}_2\text{R}_1$, preferably $-\text{CO}_2\text{CH}_3$ and $-\text{CO}_2\text{C}_2\text{H}_5$,
as $-\text{CO}_2\text{N}(\text{R}_2)_2$, preferably $-\text{CO}_2\text{N}(\text{CH}_3)_2$ and $-\text{CO}_2\text{N}(\text{C}_2\text{H}_5)_2$,
and, as $(\text{R}_2)_2\text{N}-$, preferably methylamino, ethylamino, dimethylamino and diethylamino.

R_1 and R_2 as alkyl may preferably be methyl, ethyl, n- or isopropyl, n-, iso- or tert-butyl, pentyl or hexyl.

In a preferred embodiment R is linear or branched C_1 - C_4 alkyl and, more particularly, C_1 or C_2 alkyl, which is unsubstituted or substituted by -F, -Cl, -Br, -OH, -CN, $-\text{CO}_2\text{R}_1$, $-\text{CO}_2\text{N}(\text{R}_2)_2$, $(\text{R}_2)_2\text{N}-$, C_1 - C_4 alkoxy, C_4 - C_8 cycloalkyl, phenyl, phenoxy or phenylthio, and the substituents cycloalkyl, phenyl, phenoxy and phenylthio are themselves unsubstituted or substituted by -F, -Cl, -Br, -OH, -CN, $-\text{CO}_2\text{R}_1$, $-\text{CO}_2\text{N}(\text{R}_2)_2$, $(\text{R}_2)_2\text{N}-$ or C_1 - C_4 alkoxy; R_1 is C_1 - C_4 alkyl, phenyl or benzyl; both substituents R_2 are each independently of the other H, C_1 - C_4 alkyl, phenyl or benzyl, or, when taken together, are tetramethylene, pentamethylene, 3-oxa-1,5-pentylene or N-(C_1 - C_4 alkyl)-3-aza-1,5-pentylene. Most preferably R is C_1 - C_4 alkyl, benzyl or β -phenylethyl.

In a further preferred embodiment R_1 is preferably C_1 - C_4 alkyl, phenyl or benzyl and both substituents R_2 are each independently of the other preferably methyl, ethyl, n-propyl or n-butyl or, when taken together, are tetramethylene or pentamethylene.

X as an olefin preferably contains 2 to 6 and, most preferably, 2 to 4, carbon atoms. Ethylene is especially preferred; further examples are propene and 1-butene. X as diene preferably contains 5 to 8 carbon atoms and may be an open-chain or mono- or bicyclic diene. Both olefin groups of the diene are preferably linked via one or two CH_2 groups. Examples are 1,3-pentadiene, cyclopentadiene, 1,4-hexadiene, 1,4-cyclohexadiene [sic], 1,4- or 1,5-heptadiene, 1,4- or 1,5-cycloheptadiene, 1,4- or 1,5-octadiene, 1,4- or 1,5-cyclooctadiene, norbornadiene. Preferably X is two ethylene, 1,4-hexadiene, 1,5-cyclooctadiene or norbornadiene.

Z in formula III is preferably Cl or Br.

In formula IV R_3 is preferably phenyl, methylphenyl, dimethylphenyl, methoxyphenyl or dimethoxyphenyl. Particularly preferably R_3 is phenyl.

The diphosphine of formula IV is particularly preferably 1,2-bisdiphenylphosphinobicyclo[2.2.1]hept-4-ene, which is either in the R- or S-form. This diphosphine is also termed (+)-NORPHOS or (-)-NORPHOS.

The compounds of the formula II are known and some are commercially available, or they can be prepared by analogous processes. The compounds of formula III are known; for example see EP-A-0 302 021. These rhodium catalysts are usually prepared *in situ* before the reaction and used directly. It is preferred to use the rhodium catalysts in amounts of 0.01 to 5 mol %, particularly preferably 0.05 to 2 mol %, based on the compounds of formula II. The molar ratio of compounds of formula II to compounds of formula III can be from 10,000 to 20, preferably from 2000 to 50.

The process of this invention is preferably carried out at temperatures of from 0°C to 80°C and preferably at a hydrogen pressure of 2 to 10 MPa.

The reaction can be carried out without or in the presence of an inert solvent. Examples of suitable solvents, which may be used alone or as mixtures, are alcohols such as methanol, ethanol, propanol, butanol, pentanol and hexanol. Suitable solvents for mixtures are, for example, aliphatic and aromatic hydrocarbons, such as pentane, hexane, cyclohexane, methylcyclohexane, benzene, toluene and xylene; ethers, such as diethyl ether, diethylene glycol dimethyl ether, ethylene glycol dimethyl ether, tetrahydrofuran and dioxane; esters and lactones, such as ethyl acetate, butyrolactone or valerolactone; carboxamides and lactams, such as dimethylformamide, dimethylacetamide and N-methylpyrrolidone. Preferred mixtures are those of alcohols and aromatic hydrocarbons, for example methanol/benzene or methanol/toluene. The preferred solvent is methanol alone or a mixture of methanol with

benzene or toluene.

A particularly preferred embodiment comprises using ethyl α -ketopropionate or ethyl pyruvate, an alkanol as solvent, and carrying out the hydrogenation under a pressure of from 2 to 10 MPa and at a temperature of from 0 to 80°C.

The compounds of formula I are valuable intermediates for the preparation of biologically active compounds, especially for the agrochemical and pharmaceutical fields. When R in formula I is β -phenylethyl, it is possible to prepare therefrom ACE inhibitors, for example (see EP-A-0 206 993). The compounds of formula I are generally intermediates for the preparation of optically active α -amino acids which are used for example in peptide synthesis (see R.M. Williams, Synthesis of Optically Active α -Amino Acids, Pergamon Press, New York, page 196 (1990)).

The following examples illustrate the invention in more detail.

Example 1: 1.35 g (11.64 mmol) of methyl pyruvate (substrate) are charged to a 50 ml steel autoclave which is thereafter flushed five times with argon. A catalyst solution consisting of 53.3 mg (0.116 mmol) of $[\text{Rh}(\text{norbornadiene})\text{Cl}]_2$, 117.8 mg (0.255 mmol) of (+)-NORPHOS and 10 ml each of methanol and toluene is then added using a steel capillary. The molar ratio of substrate/catalyst is 100. Then 1 MPa of hydrogen is injected in three flushing cycles and the hydrogen pressure is adjusted to 2 MPa. The reaction mixture is stirred for 13 hours at 25°C and subsequently transferred to a flask and the solvent is removed on a rotary evaporator. The chemical conversion is 100 %, affording α -hydroxypropionic acid in an enantiomer excess (ee) of 89 %.

Determination of the conversion: gas chromatography with Varian® 3700, OV 101 column, 2 m, T: 50°C isothermally.

Determination of the optical yield: gas chromatography after derivatization of the crude product with isopropyl isocyanate; Chirasil L-Val column, 50 m, T: 150°C, isothermally.

Example 2: The general procedure of Example 1 is repeated and the reaction conditions are modified as follows:

4.0 g of ethyl pyruvate, molar ratio of substrate/catalyst 800, pressure 10 MPa, temperature 35°C, reaction time 17 hours. The conversion is 100 %, ee: 80 %.

Example 3: The general procedure of Example 1 is repeated and the reaction conditions are modified as follows:

2.4 g of ethyl 1-phenyl- α -ketobutyrate, molar ratio of substrate/catalyst 50, solvent methanol, pressure 2 MPa, temperature 22°C, reaction time 2 hours. The conversion is 80 %, ee: 95.6 %.

Example 4: The general procedure of Example 3 is repeated and the reaction conditions are modified as follows:

1.0 g of ethyl 1-phenyl- α -ketobutyrate, molar ratio of substrate/catalyst 200, pressure 10 MPa, temperature 30°C, reaction time 20 hours. The conversion is 100 %, ee: 91.4 %.

Examples 5-9: The general procedure of Example 1 is repeated and the reaction conditions are modified as follows:

2.17 g (10.5 mmol) of ethyl pyruvate, 22 mg (0.048 mmol) of [Rh(norbornadiene)Cl]₂, 50 mg (0.11 mmol) of (+)-NORPHOS, 25°C, 10 MPa, 30 ml of solvent.

Further particulars are given in the following table.

Example	Solvent	Hydrogenation time (hours)	Conver- sion (%)	ee* %
5	isopropanol	17	98.5	85
6	n-butanol	17	79	84
7	tetrahydrofuran/ methanol (1:1)	19.5	85	90.5
8	ethanol/ethyl acetate (1:1)	20	88	80.5
9	methanol/ethyl acetate (1:1)	22.5	99	89

*)S configuration.

Example 10: The general procedure of Example 1 is repeated and the reaction conditions are modified as follows:

4 g of ethyl 4-phenyl- α -ketobutyrate, ratio of substrate:catalyst 200, solvent ethanol, pressure 10 MPa, temperature 30°C, hydrogenation time 18 hours. The conversion is 98 %, ee: 87 % (S).



Patent claims:

1. A process for the preparation of an optically active aliphatic α -hydroxycarboxylic acid ester of formula I



wherein R is linear or branched C_1 - C_{12} alkyl which is unsubstituted or substituted by halogen, -OH, $-\text{CO}_2\text{R}_1$, $-\text{CO}_2\text{N}(\text{R}_2)_2$, $(\text{R}_2)_2\text{N}-$, C_1 - C_6 alkoxy or C_1 - C_6 alkylthio, C_4 - C_8 cycloalkyl, C_4 - C_8 cycloalkoxy, C_4 - C_8 cycloalkylthio, phenyl, naphthyl, phenoxy, naphthoxy, phenylthio or naphthylthio, and the substituents cycloalkyl [sic], cycloalkoxy, cycloalkylthio, phenyl, naphthyl, phenoxy, naphthoxy, phenylthio and naphthylthio are themselves unsubstituted or substituted by halogen, -OH, $-\text{CO}_2\text{R}_1$, $-\text{CO}_2\text{N}(\text{R}_2)_2$, $(\text{R}_2)_2\text{N}-$, C_1 - C_6 alkoxy or C_1 - C_6 alkylthio; R_1 is C_1 - C_6 alkyl, phenyl or benzyl; both substituents R_2 are each independently of the other C_1 - C_6 alkyl, phenyl, benzyl or, when taken together, are tetramethylene, pentamethylene, 3-oxa-1,5-pentylene or N-(C_1 - C_6 alkyl)-3-aza-1,5-pentylene, and * denotes the predominantly R- or S-configuration, by hydrogenation of an α -ketocarboxylic acid ester of formula II



wherein R and R_1 are as defined above, in the absence or presence of an inert solvent at a pressure of 0.1 to 15 MPa and at temperatures of from -20°C to 100°C , and also in the presence of catalytic amounts of a rhodium complex with chiral diphosphine ligands, which rhodium complex has the formula III



wherein X is two C_2 - C_{12} olefins or a C_5 - C_{12} diene, Z is Cl, Br or I, and Y is a chiral diphosphine of formula IV



wherein R_3 is phenyl, C_1 - C_6 alkylphenyl or C_1 - C_6 alkoxyphenyl, and Q is



bicyclo[2.2.1]heptane-1,2-diyl or bicyclo[2.2.1]hept-4-ene-1,2-diyl.

2. A process according to claim 1, wherein the reaction temperature is from 0°C to 80°C.

3. A process according to claim 1, which is carried out at a pressure of from 2 to 10 MPa.

4. A process according to claim 1, wherein R in formula I is C₁-C₆alkyl which is unsubstituted or substituted as defined in claim 1.

5. A process according to claim 1, wherein R₁ is C₁-C₄alkyl, phenyl or benzyl.

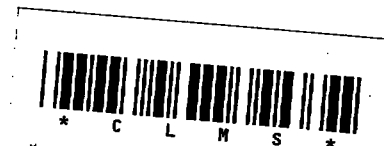
6. A process according to claim 1, wherein both substituents R₂ are each independently of the other methyl, ethyl, n-propyl or n-butyl or, when taken together, are tetramethylene or pentamethylene.

7. A process according to claim 1, wherein R is linear or branched C₁-C₄alkyl which is unsubstituted or substituted by -F, -Cl, -Br, -OH, -CO₂R₁, -CO₂N(R₂)₂, (R₂)₂N-, C₁-C₄alkoxy, C₄-C₈cycloalkyl, phenyl, phenoxy or phenylthio, and the substituents cycloalkyl, phenyl, phenoxy and phenylthio are themselves unsubstituted or substituted by -F, -Cl, -Br, -OH, -CN, -CO₂R₁, -CO₂N(R₂)₂, (R₂)₂N- or C₁-C₄alkoxy; R₁ is C₁-C₄alkyl, phenyl or benzyl; both substituents R₂ are each independently of the other C₁-C₄alkyl, phenyl or benzyl, or, when taken together, are tetramethylene, pentamethylene, 3-oxa-1,5-pentylene or N-(C₁-C₄alkyl)-3-aza-1,5-pentylene.

8. A process according to claim 1, wherein X in formula III is a C₂-C₆olefin or an open-chain or mono- or bicyclic C₅-C₈diene.

9. A process according to claim 8, wherein X is two ethylenes, 1,4-hexadiene, 1,5-cyclooctadiene or norbornadiene.

10. A process according to claim 1, wherein Z in formula III is Cl or Br.



11. A process according to claim 1, wherein R_3 in formula IV is phenyl, methylphenyl, dimethylphenyl, methoxyphenyl or dimethoxyphenyl.
12. A process according to claim 1, wherein the diphosphine of formula IV is 1,2-bis(diphenylphosphino)bicyclo[2.2.1]hept-4-ene, which is either in the R- or S-form.
13. A process according to claim 1, wherein the rhodium catalyst is used in an amount of from 0.01 to 5 mol %, based on the compounds of formula II.
14. A process according to claim 1, wherein the solvent used is methanol by itself or a mixture of methanol with benzene or toluene.
15. A process according to claim 1, which comprises using ethyl α -ketopropionate or ethyl pyruvate, an alkanol as solvent, and carrying out the hydrogenation under a pressure of from 2 to 10 MPa and at a temperature of from 0 to 80°C.