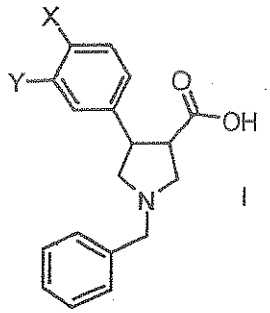
PROCESS FOR THE PREPARATION OF PYROLLIDINE-3-CARBOXYLIC ACIDS

The invention relates to a novel process for the preparation of (3*S*,4*S*)- or (3*R*,4*R*)-1-benzyl-4-(halogen-aryl)-pyrrolidine-3-carboxylic acid derivatives of formula I



I

or salts thereof,

wherein

X and Y independently of each other are hydrogen or a halogen atom, with the proviso that at least one of X or Y is a halogen atom.

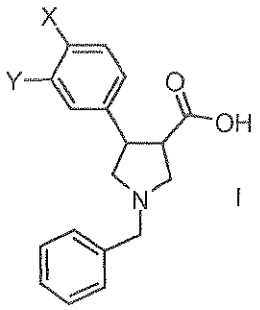
The compounds of formula I may be used as starting materials or intermediates for the preparation of pharmaceutically active compounds, especially for compounds, which may be used for the treatment of central nervous system disorders (Bioorg. Med. Chem. Lett. 1999, 9, 195; Bioorg. Med. Chem. Lett. 2004, 14, 941).

A process fort the preparation of enantiomerically enriched cyclic ß-heteroaryl carboxylic acids via enantioselective hydrogenation has been described in the PCT Publication WO 2007/113155. The process was found to be unsatisfactory with regard to the reaction conditions needed, the achievable yield and the enatiomeric purity of the reaction product.

Object of the embodiments disclosed herein therefore was to find a more economical enantioselective hydrogenation method for the preparation of the compounds of formula I, i.e. a method which can be carried out under moderate conditions and which results in high yields and high enantiomeric purity of the product.

It was found that this object could be reached with the process of the present disclosure as outlined below.

The process for the preparation of (3*S*,4*S*)-1-benzyl-4-halogen-aryl-pyrrolidine-3-carboxylic acid derivatives of formula I



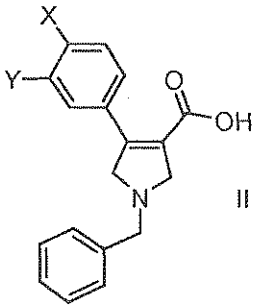
I

or salts thereof,

wherein

X and Y independently of each other are hydrogen or a halogen atom, with the proviso that at least one of X or Y is a halogen atom,

comprises a catalytic homogeneous enantioselective hydrogenation of a compound of formula



II

or salts thereof,

wherein X and Y are as above, in the presence of a Ru-catalyst of the formula

Ru (T)2 D III

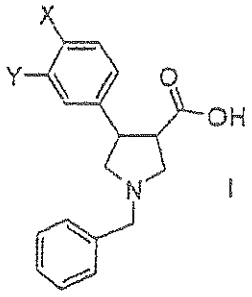
wherein,

T represents the group A-COO^-,

A represents C_{1-7}-alkyl which is optionally substituted with halogen and

D represents a chiral diphosphine ligand.

In a first aspect, there is provided a process for the preparation of (3*S*,4*S*)- or (3*R*,4*R*)-1-benzyl-4-aryl-pyrrolidine-3-carboxylic acid derivatives of formula



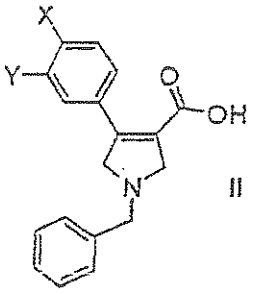
I

or salts thereof,

wherein

X and Y independently of each other are hydrogen or a halogen atom, with the proviso that at least one of X or Y is a halogen atom,

comprising catalytic homogeneous enantioselective hydrogenation of a compound of formula



II

or salts thereof,

wherein X and Y are as above, in the presence of the Ru-catalysts

[$Ru(OAc)_2$((*R*)-2-Furyl-MeOBIPHEP)] or [$Ru(OAc)_2$((*S*)-2-Furyl-MeOBIPHEP)].

Unless otherwise indicated, the following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the invention herein.

The term halogen used for X or Y preferably stands for chlorine or fluorine. In a further preferred embodiment X is chlorine or fluorine and Y is hydrogen, chlorine or fluorine. In an even more preferred embodiment X is chlorine and Y is hydrogen.

Accordingly preferred starting compounds of formula II are selected from:

1-benzyl-4-(4-chloro-phenyl)-2,5-dihydro-1H-pyrrole-3-carboxylic acid monohydrate;
1-benzyl-4-(3,4-dichloro-phenyl)-2,5-dihydro-1H-pyrrole-3-carboxylic acid;
1-benzyl-4-(3,4-difluoro-phenyl)-2,5-dihydro-1H-pyrrole-3-carboxylic acid;
1-benzyl-4-(4-chloro-3-fluoro-phenyl)-2,5-dihydro-1H-pyrrole-3-carboxylic acid.

The term "halogen" used for R^3 and / or R^4 refers to fluorine, chlorine, bromine and iodine, with fluorine, bromine and chlorine being preferred.

The term "C_{1-7}-alkyl", alone or in combination with other groups, refers to a branched or straight-chain monovalent alkyl radical of one to seven carbon atoms, preferably one to four carbon atoms. This term is further exemplified by radicals such as methyl, ethyl, n-propyl, isopropyl, n-butyl, s-butyl, isobutyl, t-butyl, n-pentyl, 3-methylbutyl, n-hexyl, 2-ethylbutyl and the like. Methyl and ethyl, particularly methyl is especially preferred.

The term "C_{1-7}-alkyl"optionally substituted with halogen" refers to a C_{1-7}-alkyl group as defined above wherein at least one of the hydrogens of the alkyl group is replaced by a halogen atom, preferably fluoro or chloro. Among the preferred halogenated lower alkyl groups are trifluoromethyl, difluoromethyl, fluoromethyl and chloromethyl.

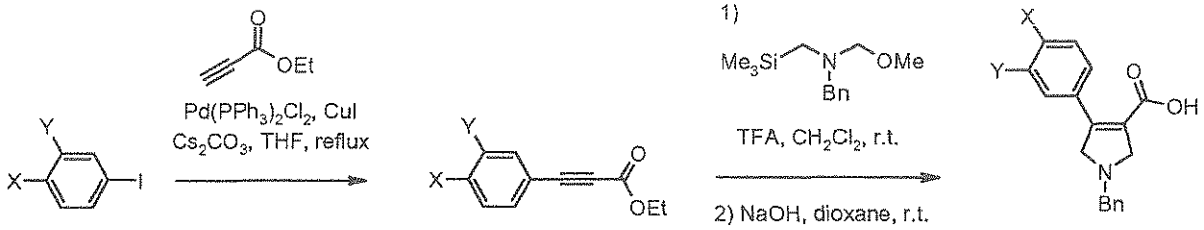
The term "C_{1-7}-alkoxy" refers to a group C_{1-7}–alkyl-O-, with the meaning of C_{1-7}-alkyl as above. Examples of C_{1-7}-alkoxy groups are e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy and hexyloxy, with methoxy being especially preferred.

The term "di-C_{1-7}-alkylamino" refers to a group $(C_{1-7}$–alkyl$)_2$-NH, with the meaning of C_{1-7}-alkyl as above. Examples of di-C_{1-7}-alkylamino groups are e.g. dimethylamino or diethylamino with dimethylaminio being preferred.

The term "tri-C_{1-7}-alkylsilyl" refers to a group $(C_{1-7}$–alkyl$)_3$-Si, with the meaning of C_{1-7}-alkyl as above. Examples of tri-C_{1-7}-alkylsilyl are e.g. trimethylsilyl or triethylsilyl, with trimethylsilyl being preferred.

The starting compounds of formula II are accessible by the method provided in the scheme below:

Scheme 1:



VIa, X = Cl, Y = H
VIb, X = Y = Cl
VIc, X = Y = F
VId, X = Cl, Y = F

Va, X = Cl, Y = H
Vb, X = Y = Cl
Vc, X = Y = F
Vd, X = Cl, Y = F

IIa, X = Cl, Y = H
IIb, X = Y = Cl
IIc, X = Y = F
IId, X = Cl, Y = F

or can be prepared in analogy as described in J. Med Chem 1992, 233-241; THL 2004, 3265 or Org. Biomol.Chem.2004,2763.

The starting compound of formula II i.e. the hydrogenation substrate preferably is in the form of the free acid or the monohydrate thereof.

Alternatively the carboxylate, which can be formed from the free acid or even from a salt of the compound of formula II by conversion with a suitable base, can be used. Suitable bases usually are tertiary amines like tri-alkyl amines. Preferred base is triethylamine.

As outlined above the Ru-catalyst used for the catalytic homogeneous enantioselective hydrogenation has the formula

$$Ru(T)_2 D \qquad III$$

wherein,

T represents the group A-COO^- wherein

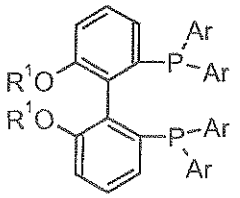
A represents C_{1-7}-alkyl which is optionally substituted with halogen and

D represents a chiral diphosphine ligand.

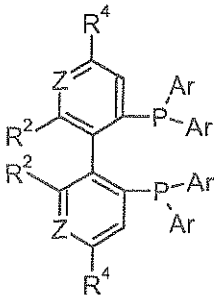
T preferably is selected from CH_3COO^- or CF_3COO^- and more preferably stands for CH_3COO^-.

A preferably stands for methyl.

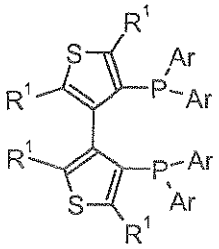
The chiral diphosphine ligand D is selected from the group consisting of



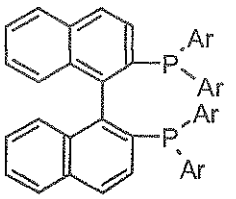
IVa



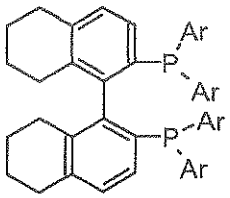
IVb



IVc



IVd



IVe

wherein

Ar		is 2-thienyl, 3-thienyl, 2-furyl, 3-furyl, phenyl or phenyl substituted by one or more C_{1-7}-alkyl, C_{1-7}-alkoxy, phenyl, di-C_{1-7}-alkylamino, *N*-morpholino or tri-C_{1-7}-alkylsilyl;
Z		is N or C-R^3;
R^1		is C_{1-7}-alkyl;
R^2		is C_{1-7}-alkyl, C_{1-7}-alkoxy, hydroxy or –OC(O)-C_{1-7}-alkyl or –OC(O)-cyclohexyl;
R^3 and R^4		independently from each other are hydrogen, C_{1-7}-alkyl, C_{1-7}-alkoxy, halogen or di-C_{1-7}-alkylamino; or

R^2 and R^3 or R^3 and R^4 which are attached to the same phenyl group or both R^2 attached to different phenyl groups, taken together,

are –X-$(CH_2)_n$-Y–; or –X-(CF_2)-X– wherein X is O or C(O)O, Y is O or N(C_{1-7}-alkyl) and n is an integer from 1 to 6.

Suitable ligands can be selected from

(*S*)- or (*R*)-MeOBIPHEP	(*S*)- or (*R*)-(6,6'-Dimethoxybiphenyl-2,2'-diyl)bis(diphenylphosphine)
(*S*)- or (*R*)-6-MeO-2-Naphthyl-MeOBIPHEP	(*S*)- or (*R*)-(6,6'-Dimethoxybiphenyl-2,2'-diyl)bis(di-2-(6-methoxy)-naphthylphosphine)
(*S*)- or (*R*)-3,5-tBu-MeOBIPHEP	(*S*)- or (*R*)-(6,6'-Dimethoxy[1,1'-biphenyl]-2,2'-diyl)bis[bis(3,5-di-*tert*-butyl-phenyl)phosphine)
(*S*)- or (*R*)-3,5-iPr-MeOBIPHEP	(*S*)- or (*R*)-(6,6'-Dimethoxy[1,1'-biphenyl]-2,2'-diyl)bis[bis(3,5-di-*iso*-propyl-phenyl)phosphine)
(*S*)- or (*R*)-2-Furyl-MeOBIPHEP	(*S*)- or (*R*)-(6,6'-Dimethoxybiphenyl-2,2'-diyl)bis(di-2-furylphosphine)
(*S*)- or (*R*)-2-Thienyl-MeOBIPHEP	(*S*)- or (*R*)-(6,6'-Dimethoxy[1,1'-biphenyl]-2,2'-diyl)bis(bis(2-thienyl)phosphine)
(*S*)- or (*R*)-3-Thienyl-MeOBIPHEP	(*S*)- or (*R*)-(6,6'-Dimethoxy[1,1'-biphenyl]-2,2'-diyl)bis(bis(3-thienyl)phosphine)
(*S*)- or (*R*)-3,5-Xyl-MeOBIPHEP	(*S*)- or (*R*)-[6,6'-Dimethoxy[1,1'-biphenyl]-2,2'-diyl]bis[bis(3,5-dimethylphenyl)phosphine
(*S*)- or (*R*)-TMBTP	(*S*)- or (*R*)-2,2',5,5'-Tetramethyl-4,4'-bis(diphenylphosphino)-3,3'-bithiophene

More preferred are the ligands of formula IVa, while the ligand (*S*)- or (*R*)-2-Furyl-MeOBIPHEP is the most preferred.

The most preferred Ru-catalysts of formula III are $[Ru(OAc)_2((R)$-2-Furyl-MeOBIPHEP)] or $[Ru(OAc)_2((S)$-2-Furyl-MeOBIPHEP)], wherein Ac stands for acetyl.

The diphosphine ligands as shown above are known in the art and are commercially available or may be prepared for example as described in the European Patent Application EP-A 0'398'132

(MeOBIPHEP, 3,5-iPr-MeOBIPHEP), the PCT Publication WO96/01831 or by T. Benincori et al., J. Org. Chem. 2000, 65, 2063 (TMBTP).

The metal complexes [$Ru(OAc)_2$(diphosphine)] are known in the art and are prepared for example as described in US Patent US-B 6'552'204 or synthesized in analogy to a general procedure reported in N. Feiken at al. Organometallics 1997, 16, 537.

The hydrogenation suitably takes place at a hydrogen pressure of 1 bar to 100 bar, preferably at 20 bar to 60 bar, more preferably at 35 to 45 bar.

The reaction temperature is selected between 20°C and 100°C, preferably between 20°C and 60°C, more preferably between 20°C and 40°C.

As a rule the hydrogenation is carried out with a catalyst to substrate ratio (mol/mol) of 250 to 100'000, preferably of 1'000 to 20'000 more preferably of 5'000 to 15'000.

The reaction is usually carried out in a lower aliphatic alcohol as solvent. Most preferred solvent is methanol.

The enantiomeric purity of the resulting (3*S*,4*S*)-1-benzyl-4-halogen-aryl-pyrrolidine-3-carboxylic acid derivative of formula I is as a rule that high that no further purification is necessary. Separation from the catalyst can happen by setting the reaction mixture to alkaline followed by extraction with an organic solvent and precipitating the product from the aqueous layer at the isoelectric point.

The following examples shall illustrate the invention without limiting it.

Examples

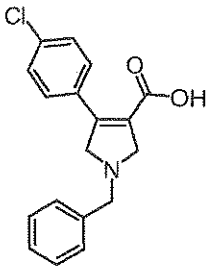
Abbreviations:

r.t. = room temperature, THF = tetrahydrofuran, TBME = tert. butyl methyl ether, LDA = lithium diisopropylamide

Preparation of the starting compounds of formula II:

Example A

1-Benzyl-4-(4-chloro-phenyl)-2,5-dihydro-1H-pyrrole-3-carboxylic acid (IIa)



IIa

a) (4-Chloro-phenyl)-propynoic acid ethyl ester (Va)

Under argon atmosphere, a four neck flask was charged with 1-chloro-4-iodo-benzene (130.0 g, 0.55 mol), bis(triphenylphosphine) palladium(II) chloride (7.57 g, 10.8 mmol, 2 mol%), copper(I) iodide (4.19 g, 22.0 mmol, 4 mol%) and dry THF (1.4 l). At r.t., cesium carbonate (355.3 g, 1.09 mol, 2 eq.) was added over 5 min. Afterwards propynoic acid ethyl ester (111.3 ml, 1.09 mol, 2 eq.) was added and the reaction mixture was stirred over night at 35°C. An additional portion of propynoic acid ethyl ester (11.1 ml, 0.11mol, 0.2 eq.) was added and the reaction stirred for an other 3 h at 35°C. The reaction mixture was evaporated to dryness and the residue was taken up in toluene (0.5 l) and heptane (1 l). The resulting suspension was stirred at 40°C for 1 h and filtered over celite. The filtrate was concentrated and the product purified by silica gel filtration (toluene / heptane 1:2) to yield 72.6 g (61%) of Va as a light yellow solid.

b) 1-Benzyl-4-(4-chloro-phenyl)-2,5-dihydro-1H-pyrrole-3-carboxylic acid (IIa)

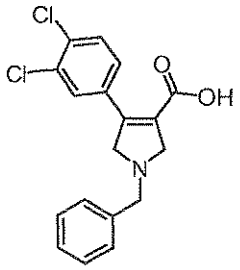
At r.t., a solution of N-(methoxymethyl)-N-(phenylmethyl)-N-(trimethylsilyl)methyl amine (116.8 g, 0.49 mol) in CH_2Cl_2 (260 ml) was added dropwise over 90 min to a stirred solution of

(4-chloro-phenyl)-propynoic acid ethyl ester (72.0 g, 0.34 mol) and trifluoroacetic acid (2.5 ml, 0.03 mol) in CH_2Cl_2 (350 ml). The reaction mixture was stirred at 25 °C over night and afterwards evaporated to dryness. The residue was dissolved in dioxane (0.8 l), an aqueous solution of NaOH (91.0 ml, 1.02 mol, 3 eq.) was added and the resulting emulsion was stirred at r.t. for 48 h. The low boiling organic solvent was removed under vacuum, water (0. 9 l) was added and the aqueous layer separated and washed with TBME (1 l). The aqueous layer was then acidified to a pH value of 2.5 by addition of 25% HCl. The resulting suspension was stirred over night, the white precipitate was filtered off, washed with water and ethanol and dried under high vacuum to yield 62.0 g (60%) of IIa as a white solid.

ES-MS m/e: 312.4 ($M-H^+$).

Example B

1-Benzyl-4-(3,4-dichloro-phenyl)-2,5-dihydro-1H-pyrrole-3-carboxylic acid (IIb)



IIb

a) (3,4-Dichloro-phenyl)-propynoic acid ethyl ester (Vb)

Under argon atmosphere, a four neck flask was charged with 1,2-dichloro-4-iodo-benzene (222.8 g, 0.80 mol), bis(triphenylphosphine) palladium(II) chloride (11.2 g, 16.0 mmol, 2 mol%), copper(I) iodide (6.09 g, 32.0 mmol, 4 mol%) and dry THF (2.4 l). At r.t., cesium carbonate (526.6 g, 1.60mol, 2 eq.) was added over 5 minutes. Afterwards, propynoic acid ethyl ester (168.6 ml, 1.60mol, 2 eq.) was added and the reaction mixture was stirred over night at 35°C. An additional portion of propynoic acid ethyl ester (17.0 ml, 0.16mol, 0.2 eq.) was added and the reaction stirred for another 4 h at 35°C. The reaction mixture was evaporated to dryness and the residue was taken up in toluene (0.8 l) and heptane (1.6 l). The resulting suspension was stirred at 40°C for 1 h and filtered over celite. The filtrate was concentrated and the product was purified by silica gel filtration (toluene / heptane 1:2) to yield 175.0 g (89%) of Vb as a white solid.

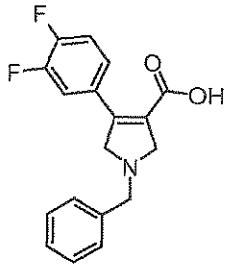
b) 1-Benzyl-4-(3,4-dichloro-phenyl)-2,5-dihydro-1H-pyrrole-3-carboxylic acid (IIb)

At r.t., a solution of N-(methoxymethyl)-N-(phenylmethyl)-N-(trimethylsilyl)methyl amine (262.5 g, 1.06 mol) in CH_2Cl_2 (0.6 l) was added dropwise over 60 min to a solution of (3,4-dichloro-phenyl)-propynoic acid ethyl ester (172.0 g, 0.71 mol) and trifluoroacetic acid (5.4 ml, 0.07 mol) in CH_2Cl_2 (0.7 l). The reaction mixture was stirred at 25 °C for 2 h. It was then evaporated to dryness and the residue was dissolved in dioxane (1.6 l). An aqueous solution of NaOH (1.0 l, 1.9mol, 2.8 eq.) was added. The resulting emulsion as stirred at r.t. for 20 h and the low boiling organic solvent was removed under vacuum. Water (2.0 l) was added, the aqueous layer separated and washed with TBME (2 times 1.2 l). The aqueous layer was then acidified to a pH value of 2.5 by addition of 25% HCl. The resulting suspension was then stirred over night and the white precipitate was filtered off, washed with water and ethanol and dried under high vacuum to yield 205.0 g (83%) of IIb as a white solid.

ES-MS m/e: 346.0 ($M-H^+$).

Example C

1-Benzyl-4-(3,4-difluoro-phenyl)-2,5-dihydro-1H-pyrrole-3-carboxylic acid (IIc)



IIc

a) (3,4-Difluoro-phenyl)-propynoic acid ethyl ester (Vc)

Under argon atmosphere, a four neck flask was charged with THF (135 ml) and 2 M LDA in THF (60.9 ml, 0.12 mol,1.18 eq.) and cooled to -78 °C. Propynoic acid ethyl ester (12.2 g, 0.12mol, 1.18 eq.) dissolved in THF (36 ml) was added dropwise within 30 min and afterwards $ZnBr_2$ (28.5 g, 0.12mol, 1.2 eq.) dissolved in THF (45 ml) was added dropwise within 30 min. After the addition of 1,2-Difluoro-4-iodo-benzene (25.0 g, 0.10 mol) and tetrakis(triphenylphosphine) palladium(0) (6.02 g, 5.15 mmol, 5 mol%), the reaction mixture was allowed to warm to r.t. and stirred for another 3 h at the same temperature. The reaction mixture was diluted with diethylether, washed with saturated aqueous NH_4I, saturated aqueous $NaHCO_3$ and brine. The organic phase was dried with Na_2SO_4, concentrated under reduced

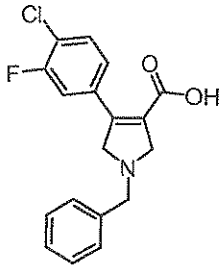
pressure and dried under vacuum. The residue was purified by silica gel filtration (heptane / ethyl acetate 98:2) to yield 16.6 g (76%) of Vc as light yellow oil.
ES-MS m/e: 210 (M^+).

b) 1-Benzyl-4-(3,4-difluoro-phenyl)-2,5-dihydro-1H-pyrrole-3-carboxylic acid (IIc)

At r.t., trifluoroacetic acid (0.11 ml, 1.34 mmol, 0.1 eq.) followed by N-(methoxymethyl)-N-(phenylmethyl)-N-(trimethylsilyl)methylamine (4.89 g, 20.2 mmol, 1.5 eq.) were added dropwise to a stirred solution of (3,4-difluoro-phenyl)-propynoic acid ethyl ester (2.83 g, 13.5 mmol) in CH_2Cl_2 (80 ml). The yellow solution was stirred at r.t. for 18 h. Trifluoroacetic acid (0.034 ml, 0.44 mmol, 0.033 eq.) and N-(methoxymethyl)-N-(phenylmethyl)-N-(trimethylsilyl) methylamine (1.66 g, 6.73 mmol, 0.5 eq.) were added and the solution was stirred for 1 h. It was evaporated to dryness and the residue dissolved in dioxane (40 ml). An aqueous solution of NaOH (18.7 ml, 37.4 mmol, 2.8 eq.) was added. The resulting emulsion was stirred at r.t. for 18 h and the low boiling organic solvent was removed under reduced pressure. Water (40 ml) was added, the aqueous layer separated and washed twice with TBME (50 ml). The organic layers were washed with the same portion of water (15 ml). The combined aqueous layers were acidified by addition of aqueous 3M HCl (12.4 ml). The resulting suspension was stirred for 48 h at r.t. The white precipitate was filtered off, washed with water and ethanol and dried under high vacuum to yield 4.25 g (58%) of IIc as a white solid.
ES-MS m/e: 316.3 ($M+H^+$).

Example D

1-Benzyl-4-(4-chloro-3-fluoro-phenyl)-2,5-dihydro-1H-pyrrole-3-carboxylic acid (IId)



IId

a) (4-Chloro-3-fluoro-phenyl)-propynoic acid ethyl ester (Vd)

Under argon atmosphere, a four neck flask was charged with 1-chloro-2-fluoro-4-iodo-benzene (50.5 g, 0.20 mol), bis(triphenylphosphine) palladium(II) chloride (2.76 g, 3.94 mmol, 2 mol%), copper(I) iodide (1.50 g, 7.80 mol, 4 mol%) and dry THF (600 ml). At r.t., cesium carbonate

(128.3 g, 0.39mol, 2 eq.) was added over 5 min. Finally, propynoic acid ethyl ester (38.6 g, 0.39 mol, 2 eq.) was added and the reaction was stirred for 48 h at 35°C. The reaction mixture was evaporated to dryness and the residue was taken up in toluene (50 ml) and heptane (100 ml). The resulting suspension was stirred at 40°C for 1 h and filtered afterwards over celite. The filtrate was concentrated and the product was purified by silica gel filtration (toluene / heptane 1:2) to yield 38.8 g (87%) of the Vd as a light yellow solid.
ES-MS m/e: 227.2 ($M-H^+$).

b) 1-Benzyl-4-(4-chloro-3-fluoro-phenyl)-2,5-dihydro-1H-pyrrole-3-carboxylic acid (IId)

At r.t., a solution of N-(methoxymethyl)-N-(phenylmethyl)-N-(trimethylsilyl)methyl amine (61.3 g, 0.26 mol) in CH_2Cl_2 (120 ml) was added drop wise over 90 minutes to a stirred solution of (4-chloro-3-fluoro-phenyl)-propynoic acid ethyl ester (39.0 g, 0.17 mol) and trifluoroacetic acid (1.30 ml, 0.02 mol) in CH_2Cl_2 (170 ml). The reaction mixture was stirred at 25 °C for 72 h and afterwards evaporated to dryness. The residue was dissolved in dioxane (390 ml). An aqueous solution of NaOH (45.0 ml, 0.48mol, 2.8 eq.) was added and the resulting emulsion was stirred at r.t. for 18 h. The low boiling organic solvent was removed under vacuum. Water (100 ml) was added, the aqueous layer separated and washed with TBME (2 times 100 ml). The aqueous layer was then acidified to a pH value of 2.5 by addition of 25% HCl. The resulting suspension was stirred over night and the white precipitate was filtered off, washed with water and ethanol and dried under high vacuum to yield 42.0 g (75%) of IId as a white solid.
ES-MS m/e: 330.1 ($M-H^+$).

Synthesis of catalyst [$Ru(OAc)_2$((*R*)-2-Furyl-MeOBIPHEP)] and of catalyst [$Ru(OAc)_2$((*S*)-2-Furyl-MeOBIPHEP)]:

Example E

[$Ru(OAc)_2$((*R*)-2-Furyl-MeOBIPHEP)]

A 500-ml round bottomed flask was charged under argon with (*R*)-2-Furyl-MeOBIPHEP (30.0 g, 51.5 mmol), [$Ru(OAc)_2$(*p*-cymene)] (18.75 g, 53.04 mmol) and toluene (525 ml). The resulting brown suspension was stirred at 80°C for 24 h. The resulting yellow-brown suspension was concentrated on vacuum to a total volume of 250 ml and stirred for 1 h at 0-5°C. The suspension was filtered and the filter cake was washed with toluene (100 ml) and pentane (150 ml) and dried

at r.t. for 16 h under vacuum to yield 36.5 g (93%) of [$Ru(OAc)_2$((*R*)-2-Furyl-MeOBIPHEP)] as a yellow solid.

^{31}P-NMR ($CDCl_3$): 31.8 ppm (singlett). FT-MS m/e: 762 (M^+).

[$Ru(OAc)_2$((*S*)-2-Furyl-MeOBIPHEP)]

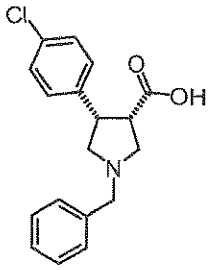
A 50-ml round bottomed flask was charged under argon with (*S*)-2-Furyl-MeOBIPHEP (500 mg, 0.92 mmol), [$Ru(OAc)_2$(*p*-cymene)] (330 mg, 0.93 mmol) and toluene (10 ml). The resulting brown suspension was stirred at 80°C for 5 h. The reaction mixture was concentrated on vacuum to a total volume of 2 ml, pentane (20 ml) was added and the mixture was stirred for 30 min at 0-5°C. The suspension was filtered and the filter cake was washed with pentane (20 ml) and dried at r.t. for 16 h under vacuum to yield 569 mg (81%) of [$Ru(OAc)_2$((*S*-2-Furyl-MeOBIPHEP)] as a yellow solid.

^{31}P-NMR ($CDCl_3$): 31.7 ppm (singlett). FT-MS m/e: 762 (M^+).

Hydrogenation examples:

Example 1

(3*S*,4*S*)-1-Benzyl-4-(4-chloro-phenyl)-pyrrolidine-3-carboxylic acid, (*S,S*)-Ia



(S,S)-Ia

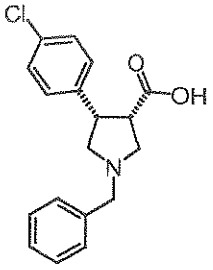
A 185-ml stainless steel autoclave was charged under argon in a glove box (O_2 content ≤ 2 ppm) with 1-benzyl-4-(4-chloro-phenyl)-2,5-dihydro-1H-pyrrole-3-carboxylic acid monohydrate (5.00 g, 15.1 mmol), [$Ru(OAc)_2$((*R*)-2-Furyl-MeOBIPHEP)] (3.83 mg, 5.02 x 10^{-6} mol, S/C 3'000) and methanol (150 ml). The asymmetric hydrogenation was run for 20 h at 30°C under 40 bar of hydrogen (99.6% conversion, 99.3% (*S,S*)-Ia with >99.9% ee). After the pressure was released, the white suspension was stirred at 0-5°C (ice-bath) for 2 h, filtered and the filter cake was washed with 20 ml ice-cold methanol and dried under vacuum at 40°C to yield 4.75 g (99%) of (*S,S*)-Ia with 99.0 % purity and >99.9% ee.

ES-MS m/e: 316.1 ($M+H^+$).

HPLC method for purity and ee determination: Chirobiotic V column (No. 461, 25 cm * 4.6 mm), 55% ammonium acetate pH 6 buffer / 45% acetonitrile, flow 1 ml/min, 25°C, 220 nm, sample preparation: 1 mg in 1 ml acetonitrile. Retention times: IIa (3.7 min), (*R,S*)- / (*S,R*)-Ia (4.3 min), (*S,S*)-Ia (4.9 min), (*R,R*)-Ia (5.4 min).

Example 2

(3*S*,4*S*)-1-Benzyl-4-(4-chloro-phenyl)-pyrrolidine-3-carboxylic acid, (*S,S*)-Ia

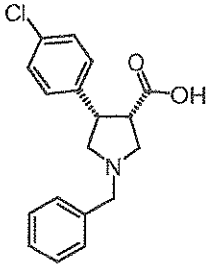


(S,S)-Ia

A 12-l stainless steel autoclave was charged on air with 1-benzyl-4-(4-chloro-phenyl)-2,5-dihydro-1H-pyrrole-3-carboxylic acid monohydrate (180.0 g, 0.54 mol), [$Ru(OAc)_2$((*R*)-2-Furyl-MeOBIPHEP)] (413.2 mg, 0.54 mmol, S/C 1'000) and methanol (7.1 l). The asymmetric hydrogenation was run for 20 h at 30°C under 40 bar of hydrogen (99.3% conversion). After the pressure was released, a sample of the white suspension was evaporated to dryness affording crude (*S,S*)-Ia with 99.0% purity and >99.9% ee. The reaction suspension was concentrated to a volume of 1.8 l and stirred for 1 h at 0-5°C. After filtration, the filter cake was washed with cold methanol and dried on vacuum to yield 176.0 g (>99%) of (*S,S*)-Ia as a white solid with 99.0% purity and >99.9% ee.

Examples 3a-c

(3*S*,4*S*)-1-Benzyl-4-(4-chloro-phenyl)-pyrrolidine-3-carboxylic acid, (S,S)-Ia



(S,S)-Ia

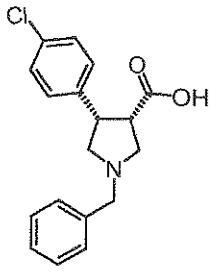
A 185-ml stainless steel autoclave was charged under argon in a glove box (O_2 content $\leq$ 2 ppm) with 1-benzyl-4-(4-chloro-phenyl)-2,5-dihydro-1H-pyrrole-3-carboxylic acid monohydrate (1.00 g, 3.01 mmol), [$Ru(OAc)_2$((*R*)-2-Furyl-MeOBIPHEP] (0.21 mg, 0.30 x 10^{-6} mol, S/C 10'000) and methanol (30 ml). The asymmetric hydrogenation was run for 20 h at 30°C under 40 bar of hydrogen (87.0% conversion). After the pressure was released, the white suspension was evaporated to dryness to yield 0.96 g (86%) of crude (*S,S*)-Ia with 88.5% purity and 98.5% ee. The reactions in Table 1 were performed according to the procedure described above using triethylamine as additive.

Table 1:

Example	Additive (Amount)	Conversion (%)	(*S,S*)-Ib Purity (%)	(*S,S*)-Ib % ee
3b	NEt_3 (1 eq. rel. to substrate)	73.8	72.8	98.6
3c	NEt_3 (0.5 eq. rel. to substrate)	90.9	90.8	98.9

Examples 4 a-c

(3*S*,4*S*)-1-Benzyl-4-(4-chloro-phenyl)-pyrrolidine-3-carboxylic acid, (*S,S*)-Ia



(S,S)-Ia

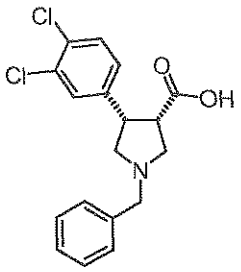
A 185-ml stainless steel autoclave was charged under argon in a glove box (O_2 content $\leq$ 2 ppm) with 1-benzyl-4-(4-chloro-phenyl)-2,5-dihydro-1H-pyrrole-3-carboxylic acid monohydrate (1.00 g3.01 mmol), [$Ru(OAc)_2$((*R*)-2-Furyl-MeOBIPHEP)] (0.77 mg, 1.00 x 10^{-6} mol, S/C 3000) and 30 ml methanol. The asymmetric hydrogenation was run for 20 h at 30°C under 40 bar of hydrogen (99.8 % conversion). After the pressure was released, the white suspension was evaporated to dryness to yield 0.96g (99%) of crude (*S,S*)-Ia with 99.1 % purity and > 99.9 %ee. The reactions in Table 2 were performed according to the procedure described above using alternative solvents to methanol.

Table 2:

Example	Solvent	Conversion (%)	(*S,S*)-Ia Purity (%)	(*S,S*)-Ia %ee
4b	ethanol	20.3	19.8	98.7
4c	2-propanol	17.3	15.2	92.1

Example 5

(3*S*,4*S*)-1-Benzyl-4-(3,4-dichloro-phenyl)-pyrrolidine-3-carboxylic acid, (*S,S*)-Ib



(S,S)-Ib

A 35-ml autoclave was charged under argon in a glove box (O_2 content ≤ 2 ppm) with the hydrochloride salt of 1-benzyl-4-(3,4-dichloro-phenyl)-2,5-dihydro-1H-pyrrole-3-carboxylic acid (0.50 g, 1.30 mmol), [Ru(OAc)$_2$((*R*)-2-Furyl-MeOBIPHEP)] (3.96 mg, 5.30 x 10^{-6} mol, S/C 250), triethylamine (0.19 ml, 1.32 mmol) and methanol (15 ml). The asymmetric hydrogenation was run for 20 h at 30°C under 40 bar of hydrogen (99.9 % conversion). After the pressure was released, the formed white suspension was evaporated to dryness to yield 0.51g (99%) of crude (*S,S*)-Ib with 99.6% purity and 99.4% ee.

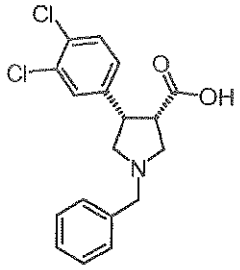
The crude product was dissolved in 0.1 M NaOH (23 ml). TBME (20 ml) was added, the aqueous layer was separated and diluted with water (23 ml). Under stirring 0.2 M HCl was added until pH 6.5. The formed precipitate was filtered off and washed with water. The filter cake was dissolved in methanol and the colourless solution evaporated to dryness to yield 0.31 g (68%) of (*S,S*)-Ia with 99.7% purity and 99.8% ee .

ES-MS m/e: 350.3 (M^+).

HPLC method for purity and ee determination: Chirobiotic V column (No. 461, 25 cm * 4.6 mm), 55% ammonium acetate pH 6 buffer / 45% acetonitrile, flow 1 ml/min, 25°C, 220 nm, sample preparation: 1 mg in 1 ml acetonitrile. Retention times: IIb (3.7 min), (*R,S*)- / (*S,R*)-Ib (4.4 min), (*S,S*)-Ib (5.1 min), (*R,R*)-Ib (6.4 min), (*S*)-Vb (14.9 min).

Example 6

(3*S*,4*S*)-1-Benzyl-4-(3,4-dichloro-phenyl)-pyrrolidine-3-carboxylic acid, (*S,S*)-Ib

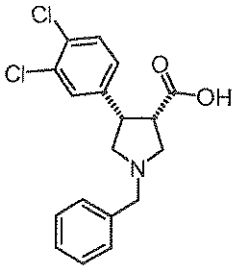


(S,S)-Ib

A 2-l Hastelloy C4 autoclave was charged under argon with 1-benzyl-4-(3,4-dichloro-phenyl)-2,5-dihydro-1H-pyrrole-3-carboxylic acid (30.0 g, 86.15 mmol), [$Ru(OAc)_2$((*R*)-2-Furyl-MeOBIPHEP)] (262.5 mg, 0.34 mmol, S/C 250) and methanol (0.9 l). The asymmetric hydrogenation was run for 18 h at 30°C and additional 2 h at 60°C under 40 bar of hydrogen (99.8% conversion). After the pressure was released, the formed white suspension was evaporated to dryness to yield 32.6 g (>99%) of crude (*S,S*)-Ib with 97.0% purity and >99.9% ee. The crude product was dissolved in 1M NaOH (140 ml). TBME (200 ml) was added, the aqueous layer was separated and diluted with water (360 ml). Under stirring 2 M HCl (81 ml) were added under stirring (pH 6.5). The formed precipitate was filtered off and washed with water. The filter cake was dissolved in methanol and the colourless solution evaporated to dryness to yield 27.2 g (90%) of (*S,S*)-Ib with 99.5% purity and >99.9% ee.

Examples 7a-g

(3*S*,4*S*)-1-Benzyl-4-(3,4-dichloro-phenyl)-pyrrolidine-3-carboxylic acid, (*S,S*)-Ib



(S,S)-Ib

A 185-ml stainless steel autoclave was charged under argon in a glove box (O_2 content $\leq$ 2 ppm) with 1-benzyl-4-(3,4-dichloro-phenyl)-2,5-dihydro-1H-pyrrole-3-carboxylic acid (1.00 g, 2.87 mmol), [$Ru(OAc)_2$((*R*)-TMBTP)] (1.16 mg, 1.44 x 10^{-6}mol, S/C 2'000) and methanol (30 ml). The asymmetric hydrogenation was run for 20 h at 30°C under 40 bar of hydrogen (18.5%

conversion). After the pressure was released, the off-white suspension was evaporated to dryness to yield 0.98 g (12%) of crude (*S,S*)-Ib with 12.1% purity and 94.5% ee.

The reactions in Table 3 were performed according to the procedure described above employing alternative catalysts.

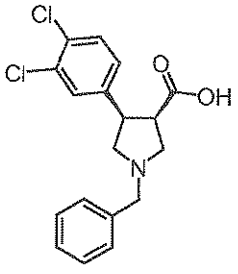
Table 3:

Example	Catalyst	Conversion (%)	(*S,S*)-Ib Purity (%)	(*S,S*)-Ib % ee
7b	[$Ru(OAc)_2$((*S*)-(6-MeO-2-Naphtyl)-MeOBIPHEP]	76.2	67.9[1]	97.4[1]
7c	[$Ru(OAc)_2$((*R*)-3,5-iPr-MeOBIPHEP)]	26.9	19.0	90.0
7d	[$Ru(OAc)_2$((*R*)-MeOBIPHEP)]	38.3	30.4	97.4
7e	[$Ru(OAc)_2$((*R*)-3,5-tBu-MeOBIPHEP)]	4.1	1.6	67.6
7f	[$Ru(OAc)_2$((*S*)-(3-Thienyl)-MeOBIPHEP)]	62.5	60.0[1]	98.0[1]
7g	[$Ru(OAc)_2$((*S*)-(2-Thienyl)-MeOBIPHEP)]	25.1	25.0[1]	99.9[1]

[1] (*R,R*)-Ib was formed in excess

Examples 7h

(3*R*,4*R*)-1-Benzyl-4-(3,4-dichloro-phenyl)-pyrrolidine-3-carboxylic acid, (*R,R*)-Ib



(R,R)-Ib

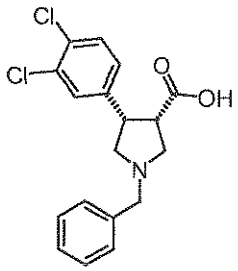
A 2-l Hastelloy C4 autoclave was charged under argon with the hydrochloride salt of 1-benzyl-4-(3,4-dichloro-phenyl)-2,5-dihydro-1H-pyrrole-3-carboxylic acid (67.0 g, 174.17 mmol), [$Ru(OAc)_2$((*S*)-2-Furyl-MeOBIPHEP)] (2.65 g, 3.48 mmol, S/C 50), triethylamine (17.62 g, 174.17 mmol) and methanol (1.3 l). The asymmetric hydrogenation was run for 20 h at 30°C under 40 bar of hydrogen (98.9% conversion). After the pressure was released, the formed gray

suspension was evaporated to dryness to yield 88.8 g of crude (*R,R*)-Ib with 95.7% purity and 99.3% ee.

The crude product was dissolved in 1M NaOH (350 ml). TBME (600 ml) was added, the aqueous layer was separated and diluted with water (900 ml). Under stirring 2 M HCl (180 ml) were added under stirring (pH 6.0). The formed precipitate was filtered off and washed with water. The filter cake was suspended in methanol / water (1:2) and the mixture was heated to reflux. After cooling to room temperature, the suspension was filtered. The filter cake was washed with methanol and dried to yield 46.15 g (74%) of (*R,R*)-Ib with 97.3% purity and 99.8% ee.

Example 8

(3*S*,4*S*)-1-Benzyl-4-(3,4-dichloro-phenyl)-pyrrolidine-3-carboxylic acid, (*S,S*)-Ib

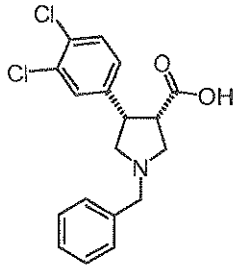


(S,S)-Ib

A 185-ml stainless steel autoclave was charged under argon in a glove box (O_2 content ≤ 2 ppm) with 1-benzyl-4-(3,4-dichloro-phenyl)-2,5-dihydro-1H-pyrrole-3-carboxylic acid (1.00 g, 2.87 mmol), [$Ru(OAc)_2$((*R*)-2-Furyl-MeOBIPHEP)] (0.44 mg, 0.57 x 10^{-6} mol, S/C 5`000) and methanol (30 ml). The asymmetric hydrogenation was run for 20 h at 80°C under 40 bar of hydrogen (99.7% conversion). After the pressure was released, the formed white suspension was evaporated to dryness to yield 1.02 g (99%) of crude (*S,S*)-Ib with 97.6% purity and 99.2% ee.

Example 9

(3*S*,4*S*)-1-Benzyl-4-(3,4-dichloro-phenyl)-pyrrolidine-3-carboxylic acid, (*S,S*)-Ib

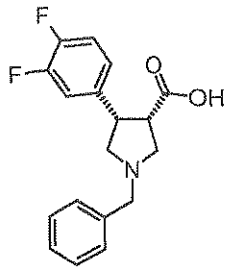


(S,S)-Ib

A 185-ml stainless steel autoclave was charged under argon in a glove box (O_2 content ≤ 2 ppm) with 1-benzyl-4-(3,4-dichloro-phenyl)-2,5-dihydro-1H-pyrrole-3-carboxylic acid (1.00 g, 2.87 mmol), [Ru(OAc)$_2$((*R*)-2-Furyl-MeOBIPHEP)] (0.22 mg, 0.29 x 10^{-6} mol, S/C 10`000) and methanol (30 ml). The asymmetric hydrogenation was run for 20 h at 80°C under 40 bar of hydrogen (99.8% conversion). After the pressure was released, the formed white suspension was evaporated to dryness to yield 1.03 g (>99%) of crude (*S,S*)-Ib with 98.0% purity and 97.6% ee.

Example 10

(3*S*,4*S*)-1-Benzyl-4-(3,4-difluoro-phenyl)-pyrrolidine-3-carboxylic acid, (*S,S*)-Ic



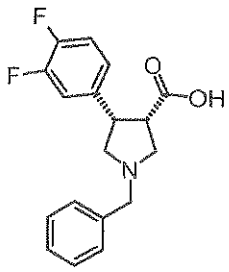
(S,S)-Ic

A 35-ml stainless steel autoclave was charged under argon in a glove box (O_2 content ≤ 2 ppm) with 1-benzyl-4-(3,4-difluoro-phenyl)-2,5-dihydro-1H-pyrrole-3-carboxylic acid (50.0 mg, 0.16 mmol), [Ru(OAc)$_2$((*R*)-2-Furyl-MeOBIPHEP)] (1.21 mg, 1.59 x 10^{-6} mol, S/C 100) and methanol (1.5 ml). The asymmetric hydrogenation was run for 20 h at 30°C under 40 bar of hydrogen (98.6 % conversion). After the pressure was released, the white suspension was evaporated to dryness to yield 51.9 mg (98%) of crude (*S,S*)-Ic with 95.6% purity and >99.9% ee. MS m/e: 318.1 ($M+H^+$).

HPLC method for purity and ee determination: Chirobiotic V column (No. 461, 25 cm * 4.6 mm), 55% ammonium acetate pH 6 buffer / 45% acetonitrile, flow 1 ml/min, 25°C, 220 nm, sample preparation: 1 mg in 1 ml acetonitrile. Retention times: IIc (3.6 min), (*R,S*)- / (*S,R*)-Ic (4.1 min), (*S,S*)-Ic (4.5 min), (*R,R*)-Ic (4.9 min).

Example 11

(3*S*,4*S*)-1-Benzyl-4-(3,4-difluoro-phenyl)-pyrrolidine-3-carboxylic acid, (*S,S*)-Ic

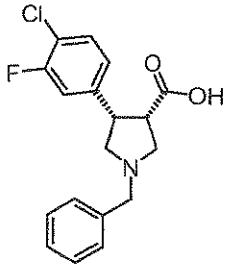


(S,S)-Ic

A 185-ml stainless steel autoclave was charged under argon in a glove box (O_2 content ≤ 2 ppm) with 1-benzyl-4-(3,4-difluoro-phenyl)-2,5-dihydro-1H-pyrrole-3-carboxylic acid (2.00 g, 6.34 mmol), [Ru(OAc)$_2$((*R*)-2-Furyl-MeOBIPHEP)] (9.66 mg, 12.7 x 10^{-6} mol, S/C 500), triethylamine (342.0 mg, 6.34 mmol) and methanol (60 ml). The asymmetric hydrogenation was run for 20 h at 30°C under 40 bar of hydrogen (>99% conversion). After the pressure was released, the formed white suspension was evaporated to dryness to yield 2.00 g of crude (*S,S*)-Ic as its ammonium salt with >99.9% purity and >99.9% ee. The salt was dissolved in 1M NaOH (10 ml). TBME (16 ml) was added to the reaction mixture, the aqueous layer was separated and diluted with water (40 ml). Under stirring 2 M HCl (7.1 ml) were added (pH 6.5). The formed precipitate was filtered off and washed with water. The filter cake was dissolved in methanol and the colourless solution evaporated to dryness to yield 1.70 g (88%) of (*S,S*)-Ic with 98.3% purity and >99.9% ee.

Example 12

(3*S*,4*S*)-1-Benzyl-4-(4-chloro-3-fluoro-phenyl)-pyrrolidine-3-carboxylic acid, (*S,S*)-Id



(S,S)-Id

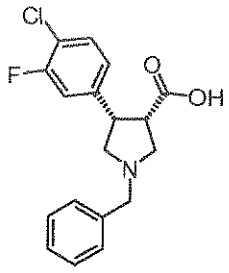
A 185-ml stainless steel autoclave was charged under argon in a glove box (O_2 content ≤ 2 ppm) with 1-benzyl-4-(4-chloro-3-fuoro-phenyl)-2,5-dihydro-1H-pyrrole-3-carboxylic acid (1.00 g, 3.01 mmol), [Ru(OAc)$_2$((*R*)-2-Furyl-MeOBIPHEP)] (4.59 mg, 6.03 x 10^{-6} mol, S/C 500) and methanol (30 ml). The asymmetric hydrogenation was run for 20 h at 30°C under 40 bar of hydrogen (99.5% conversion). After the pressure was released, the white suspension was evaporated to dryness to yield 1.03 g (>99%) of crude (*S,S*)-Id with 98.3% purity and 99.1% ee.

ES-MS m/e: 332.1 ($M-H^+$).

HPLC method for purity and ee determination: Chirobiotic V column (No. 461, 25 cm * 4.6 mm), 55% ammonium acetate pH 6 buffer / 45% acetonitrile, flow 1 ml/min, 25°C, 220 nm, sample preparation: 1 mg in 1 ml acetonitrile. Retention times: IId (3.5 min), (*R,S*)- / (*S,R*)-Id (4.3 min), (*S,S*)-Ic (4.7 min), (*R,R*)-Id (5.4 min).

Example 13

(3*S*,4*S*)-1-Benzyl-4-(4-chloro-3-fluoro-phenyl)-pyrrolidine-3-carboxylic acid, (*S,S*)-Id



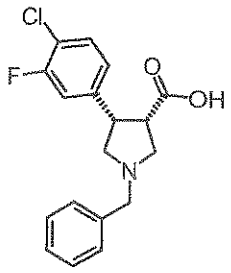
(S,S)-Id

A 185-ml stainless steel autoclave was charged under argon in a glove box (O_2 content ≤ 2 ppm) with 1-benzyl-4-(4-chloro-3-fluoro-phenyl)-2,5-dihydro-1H-pyrrole-3-carboxylic acid (1.00 g, 3.01 mmol), [$Ru(OAc)_2$((*R*)-2-Furyl-MeOBIPHEP)] (4.59 mg, 6.03 x 10^{-6} mol, S/C 500), triethylamine (305.0 mg, 3.01 mmol) and methanol (30 ml). The asymmetric hydrogenation was run for 20 h at 30°C under 40 bar of hydrogen (99.2% conversion). After the pressure was released, the formed white suspension was evaporated to dryness to yield 1.08 g of crude (S,S)-Id as its ammonium salt with 97.3% purity and >99.9% ee.

The salt was dissolved in 1M NaOH (10 ml). TBME (16 ml) was added to the reaction mixture, the aqueous layer was separated and diluted with water (40 ml). Under stirring 2 M HCl (8.2 ml) was added under stirring (pH 6.5) and the formed precipitate was filtered off and washed with water. The filter cake was dissolved in methanol and the colourless solution evaporated to dryness to yield 1.00 g (97%) of (*S,S*)-Id with 97.5% purity and >99.9% ee.

Example 14

(3*S*,4*S*)-1-Benzyl-4-(4-chloro-3-fluoro-phenyl)-pyrrolidine-3-carboxylic acid, (*S,S*)-Id

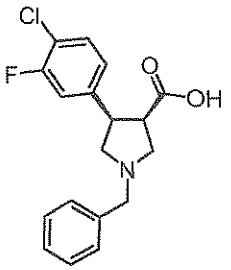


(S,S)-Id

A 2-l Hastelloy C4 autoclave was charged under argon with 1-benzyl-4-(4-chloro-3-fluoro-phenyl)-2,5-dihydro-1H-pyrrole-3-carboxylic acid (30.0 g, 90.4 mmol), [$Ru(OAc)_2$((*R*)-2-Furyl-MeOBIPHEP)] (275.5 mg, 0.36 mmol, S/C 250) and methanol (1.2 l). The asymmetric hydrogenation was run for 20 h at 30°C under 40 bar of hydrogen (99.2% conversion). After the pressure was released, a sample of the white suspension was evaporated to dryness. Crude (*S*,*S*)-Id was obtained with 97.9% purity and >99.9% ee.

Examples 15

(3*R*,4*R*)-1-Benzyl-4-(4-chloro-3-fluoro-phenyl)-pyrrolidine-3-carboxylic acid, (*R*,*R*)-Id



(R,R)-Id

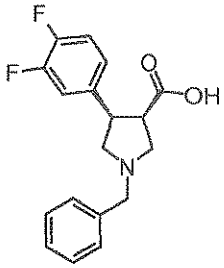
A 2-l Hastelloy C4 autoclave was charged under argon with the hydrochloride salt of 1-benzyl-4-(4-chloro-3-fluoro-phenyl)-2,5-dihydro-1H-pyrrole-3-carboxylic acid (61.3 g, 166.47 mmol), [$Ru(OAc)_2$((*S*)-2-Furyl-MeOBIPHEP)] (2.54 g, 3.33 mmol, S/C 50), triethylamine (16.84 g, 166.46 mmol) and methanol (1.3 l). The asymmetric hydrogenation was run for 20 h at 30°C under 40 bar of hydrogen (99.6% conversion). After the pressure was released, the formed gray suspension was evaporated to dryness to yield 98.0 g of crude (R,R)-Id with 97.6% purity and 99.6% ee.

The crude product was dissolved in 1M NaOH (330 ml). TBME (600 ml) was added, the aqueous layer was separated and diluted with water (800 ml). Under stirring 2 M HCl (165 ml) were added under stirring (pH 6.3). The formed precipitate was filtered off and washed with water. The filter cake was suspended in methanol / water (1:2) and the mixture was heated to

reflux. After cooling to room temperature, the suspension was filtered. The filter cake was washed with methanol and dried to yield 49.0 g (83%) of (*R*,*R*)-Id with 99.6% purity and 99.6% ee.

Examples 16

(3*R*,4*R*)-1-Benzyl-4-(3,4-difluoro-phenyl)-pyrrolidine-3-carboxylic acid, (*R*,*R*)-Ic



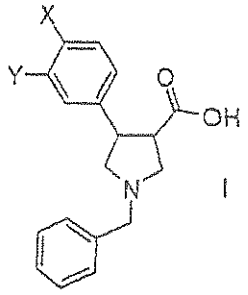
(R,R)-Ic

A 2-l Hastelloy C4 autoclave was charged under argon with the hydrochloride salt of 1-benzyl-4-(3,4-difluoro-phenyl)-2,5-dihydro-1H-pyrrole-3-carboxylic acid (45.0 g, 127.92 mmol), [$Ru(OAc)_2$((*S*)-2-Furyl-MeOBIPHEP)] (1.95 g, 2.56 mmol, S/C 50), triethylamine (12.94 g, 127.92 mmol) and methanol (1.3 l). The asymmetric hydrogenation was run for 20 h at 30°C under 40 bar of hydrogen (>99.9% conversion). After the pressure was released, the formed gray suspension was evaporated to dryness to yield 58.9 g of crude (*R*,*R*)-Ic with 99.0% purity and >99.9% ee.

The crude product was dissolved in 1M NaOH (200 ml). TBME (400 ml) was added, the aqueous layer was separated and diluted with water (800 ml). Under stirring 2 M HCl (105 ml) were added under stirring (pH 5.5). The formed precipitate was filtered off and washed with water. The filter cake was suspended in methanol / water (1:2) and the mixture was heated to reflux. After cooling to room temperature, the suspension was filtered. The filter cake was washed with methanol and dried to yield 29.10 g (71%) of (*R*,*R*)-Ic with 99.5% purity and >99.9% ee.

Claims

1. A process for the preparation of (3*S*,4*S*)- or (3*R*,4*R*)-1-benzyl-4-aryl-pyrrolidine-3-carboxylic acid derivatives of formula



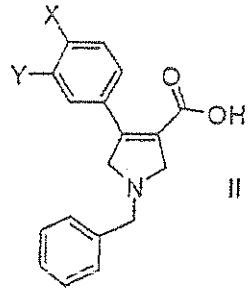
I

or salts thereof,

wherein

X and Y independently of each other are hydrogen or a halogen atom, with the proviso that at least one of X or Y is a halogen atom,

comprising catalytic homogeneous enantioselective hydrogenation of a compound of formula



II

or salts thereof,

wherein X and Y are as above, in the presence of the Ru-catalysts

[$Ru(OAc)_2$((*R*)-2-Furyl-MeOBIPHEP)] or [$Ru(OAc)_2$((*S*)-2-Furyl-MeOBIPHEP)].

2. The process of claim 1, characterized in that X or Y with the meaning of halogen stands for chlorine or fluorine.

3. The process of claims 1 and 2 characterized in that the hydrogenation is carried out at a pressure of 1 bar to 100 bar.

4. The process of claim 3 characterized in that the hydrogenation is carried out at a pressure of 20 bar to 60 bar.

5. The process of claims 1 to 4, characterized in that the hydrogenation is carried out at a temperature of 20°C to 100°C.

6. The process of claim 5, characterized in that the hydrogenation is carried out at a temperature of 20°C to 60°C.

7. The process of claims 1 to 6, characterized in that the hydrogenation is carried out with a catalyst to substrate ratio (mol/mol) of 250 to 100'000.

8. The process of claim 7, characterized in that the hydrogenation is carried out with a catalyst to substrate ratio (mol/mol) of 1'000 to 20'000.

9. The process of claims 1 to 8, characterized in that the hydrogenation is carried out in a lower aliphatic alcohol as solvent.

10. The process of claim 9, characterized in that the hydrogenation is carried out in methanol.

11. The process of claims 1 to 10, characterized in that the compound of formula II is selected from

1-benzyl-4-(4-chloro-phenyl)-2,5-dihydro-1H-pyrrole-3-carboxylic acid monohydrate;

1-benzyl-4-(3,4-dichloro-phenyl)-2,5-dihydro-1H-pyrrole-3-carboxylic acid;

1-benzyl-4-(3,4-difluoro-phenyl)-2,5-dihydro-1H-pyrrole-3-carboxylic acid;

1-benzyl-4-(4-chloro-3-fluoro-phenyl)-2,5-dihydro-1H-pyrrole-3-carboxylic acid.