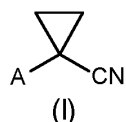


Claims

1. A process for the preparation of enantiomerically and diastereomerically enriched cyclobutane amides comprising

- 5 (a) reducing the nitrile moiety of a compound of formula (I) to an aldehyde

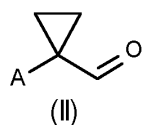


wherein A is selected from aryl, heteroaryl, , C₁-C₆-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl and C₃-C₇-cycloalkyl, which aryl, heteroaryl, C₁-C₆-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl and C₃-C₇-cycloalkyl are unsubstituted or substituted with one or more substituents independently selected from halogen, cyano,

- 10 C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₁-C₆-alkoxy, C₁-C₆-haloalkoxy, C₂-C₆-alkenyl, C₂-C₆-alkynyl, C₁-C₆-alkylsulfanyl, C₁-C₆-haloalkylsulfanyl, C₁-C₆-alkylsulfinyl, C₁-C₆-haloalkylsulfinyl, C₁-C₆-alkylsulfonyl, C₁-C₆-haloalkylsulfonyl, C₂-C₆-haloalkenyl and C₂-C₆-haloalkynyl;

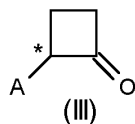
wherein the reduction of the nitrile moiety of the compound of formula (I) is carried out via partial hydrogenation to the corresponding intermediate imine applying H₂ and a metal catalyst, followed by

- 15 subsequent hydrolysis to the compound of formula (II)



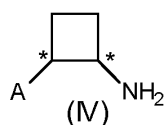
, then

(b) reacting the compound of formula (II) in the presence of a suitable Lewis acid to obtain a compound of formula (III)



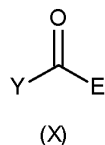
wherein * indicates a stereocentre, then

- 20 (c) reacting a compound of formula (III) with an ammonium salt and H₂ in presence of a chiral transition metal catalyst to obtain an enantiomerically and diastereomerically enriched amine of formula (IV)



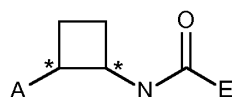
wherein * indicates a stereocentre, and then

further reacting the amine of formula (IV) with a compound of formula (X)



25

- wherein Y is a suitable leaving group such as OH, OR or halogen, preferably chloro, R is C₁-C₆-alkyl, and E is selected from aryl, heteroaryl, hydrogen, C₁-C₆-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl and C₃-C₇-cycloalkyl which aryl, heteroaryl, C₁-C₆-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl and C₃-C₇-cycloalkyl are unsubstituted or substituted with one or more substituents independently selected from halogen, cyano,
- 5 C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₁-C₆-alkoxy, C₁-C₆-haloalkoxy, C₂-C₆-alkenyl, C₂-C₆-alkynyl, C₁-C₆-alkylsulfanyl, C₁-C₆-haloalkylsulfanyl, C₁-C₆-alkylsulfinyl, C₁-C₆-haloalkylsulfinyl, C₁-C₆-alkylsulfonyl, C₁-C₆-haloalkylsulfonyl, C₂-C₆-haloalkenyl and C₂-C₆-haloalkynyl;
- so as to form the enantiomerically and diastereomerically enriched amide of formula (VII)



(VII)

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2. The process according to claim 1, wherein

A and E are selected from aryl and heteroaryl, which aryl and heteroaryl are unsubstituted or substituted with one or more substituents independently selected from halogen, cyano, C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₁-C₆-alkoxy and C₁-C₆-haloalkoxy.

15

3. The process according to claim 1, wherein

A is phenyl and E is heteroaryl, which phenyl and heteroaryl are unsubstituted or substituted with one or more substituents independently selected from halogen, cyano, C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₁-C₆-alkoxy and C₁-C₆-haloalkoxy.

20

4. The process according to any one of claims 1 to 3, wherein

the compound of formula (II) is reacted in step (b) in the presence of a Lewis acid selected from AlCl₃ and GaCl₃, preferably AlCl₃.

25

5. The process according to claim 4, wherein

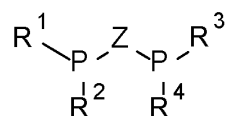
the solvent used in step (b) is a chlorinated hydrocarbon or a chlorinated aromatic solvent, particularly dichloromethane, chlorobenzene or dichlorobenzene.

6. The process according to claim 4 or 5, wherein

30 1.0-1.5 mole equivalents of AlCl₃ or GaCl₃ relative to the compound of formula (II) are added in step (b).

7. The process according to any one of claims 1 to 6, wherein

the chiral transition metal catalyst in step (c) comprises a transition metal selected from Ru, Rh, Ir and Pd, preferably Ru, and a chiral ligand with a bidentate phosphor of the general formula (VIII)



(VIII)

wherein Z is a linking group and R¹, R², R³ and R⁴ are independently selected from aryl, heteroaryl, C₁-C₆-alkyl and C₁-C₆-cycloalkyl, each of which is unsubstituted or substituted with one or more substituents independently selected from C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl and halogen.

5

8. The process according to claim 7, wherein

the linking group Z is selected from (R and S)- 1,1'-binaphtyl, (R and S)- 4,4'-bi-1, 3-benzodioxole, (R and S)- 2, 2', 6,6'-tetramethoxy-3, 3'-bipyridine, (R and S)- 6,6'-dimethoxy-1, 1'-biphenyl, (R and S)- 4,4', 6,6' tetramethoxy-1, 1'-biphenyl, 2, 2'-bis-[(R)-cx-(dimethylamino)benzyl]ferrocene, ferrocenyl methyl, ferrocene, benzene and ethyl, preferably (R and S)- 1,1'-binaphtyl.

10

9. The process according to claim 7 or 8, wherein the chiral ligand is selected from

(R)-2,2'-bis(diphenylphosphino)-1,1'-binaphtyl,

(R)-2,2'-bis(di-*p*-tolylphosphino)-1,1'-binaphtyl,

15 (R)-2,2'-bis[di(3,5-xylyl)phosphino]-1,1'-binaphtyl,

(R)-5,5'-bis(diphenylphosphino)-4,4'-bi-1,3-benzodioxole,

(R)-5,5'-bis[di(3,5-xylyl)phosphino]-4,4'-bi-1,3-benzodioxole,

(R)-5,5'-bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4'-bi-1,3-benzodioxole,

(S)-1,13-bis(diphenylphosphino)-7,8-dihydro-6H-dibenzo[f,h][1,5]dioxin,

20 (R)-2,2',6,6'-tetramethoxy-4,4'-bis(di(3,5-xylyl)phosphino)-3,3'-bipyridine,

(R)-2,2'-bis(diphenylphosphino)-6,6'-dimethoxy-1,1'-biphenyl,

(R)-2,2'-bis(diphenylphosphino)-4,4',6,6'-tetramethoxy-1,1'-biphenyl,

(R)-6,6'-bis(diphenylphosphino)-2,2',3,3'-tetrahydro-5,5'-bi-1,4-benzodioxin,

(R)-(+)-2,2'-bis(diphenylphosphino)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl,

25 (R)-(+)-2,2'-bis(di-3,5-xylylphosphino)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl,

(R)-5,5'-bis(diphenylphosphino)-2,2,2',2'-tetrafluoro-4,4'-bi-1,3-benzodioxole,

(S)-1-[(S)-1-[di(3,5-xylyl)phosphino]ethyl]-2-[2-[di(3,5-xylyl)phosphino]phenyl]ferrocene,

and

(S)-1-[(S)-1-[bis(3,5-bis(trifluoromethyl)phenyl)phosphino]ethyl]-2-[2-

30 (diphenylphosphino)phenyl]ferrocene.

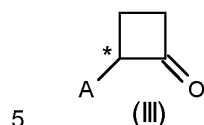
10. The process according to claim 7 or 8, wherein

the chiral transition metal catalyst is selected from [RuCl(p-cymene)((S)-DM-SEGPHOS)]Cl, [RuCl(p-cymene)((R)-DM-SEGPHOS)]Cl, [NH₂Me₂][[(RuCl((R)-xylbinap))₂(u-Cl)₃], [NH₂Me₂][[(RuCl((S)-xylbinap))₂(u-Cl)₃], Ru(OAc)₂[(R)-binap], Ru(OAc)₂[(S)-binap], Ru(OAc)₂[(R)-xylbinap], Ru(OAc)₂[(S)-

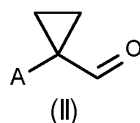
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xylbinap], $\text{RuCl}_2[(R)\text{-xylbinap}][(R)\text{-daipen}]$, $\text{RuCl}_2[(S)\text{-xylbinap}][(S)\text{-daipen}]$, $\text{RuCl}_2[(R)\text{-xylbinap}][(R,R)\text{-dpen}]$ and $\text{RuCl}_2[(S)\text{-xylbinap}][(S,S)\text{-dpen}]$.

11. A process for the preparation of a compound of formula (III)



wherein A is as defined in any one of claims 1 to 3 and * indicates a stereocentre, comprising reacting a compound of formula (II)



in the presence of a Lewis acid selected from AlCl_3 and GaCl_3 , preferably AlCl_3 .

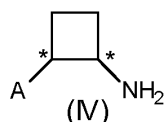
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12. The process according to claim 11, wherein 1.0-1.5 mole equivalents of AlCl_3 or GaCl_3 relative to the compound of formula (II) is added.

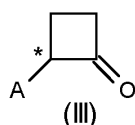
13. The process according to claim 11 and 12, wherein the reaction is carried out in a chlorinated aromatic solvent at a temperature of 50-60°C.

15

14. A process for the preparation of an enantiomerically and diastereomerically enriched cyclobutane amine of formula (IV)



20 wherein * indicates a stereocentre and wherein A is as defined in any one of claims 1 to 3, comprising reacting a compound of formula (III)



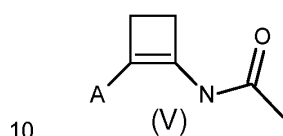
25 with an ammonium salt and H_2 in presence of a chiral transition metal catalyst, wherein the amount of chiral transition metal catalyst added to the reaction mixture is between 0.0001 and 0.1 mole equivalents relative to the compound of formula (III), preferably between 0.0005 and 0.01 mole equivalents relative to the compound of formula (III), and wherein the reaction mixture is charged (i) with 1-10 mole equivalents relative to the compound of formula (III) of a pre-formed ammonium salt selected from ammonium acetate, ammonium 2-methoxypropionate, ammonium tetrahydrofuran-2-carboxylate, ammonium o-methoxybenzoate, ammonium p-methoxybenzoate, ammonium chloroacetate, ammonium methoxyacetate, ammonium phenoxyacetate, ammonium p-chlorophenoxy

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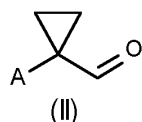
acetate, ammonium 4-*tert*-butylphenoxy acetate, ammonium furan-2-carboxylate and ammonium salicylate, or

- (ii) with 1-10 mole equivalents relative to the compound of formula (III) of ammonia and an acid selected from acetic acid, methoxyacetic acid, 2-methoxypropionic acid, tetrahydrofuran-2-carboxylic acid, o-methoxybenzoic acid, p-methoxybenzoic acid, phenoxy acetic acid, 2-furan-carboxylic acid, p-chlorophenoxy acetic acid, salicylic acid, 4-*tert*-butylphenoxyacetic acid, acetic acid and chloroacetic acid, to form the ammonium salt *in situ*.

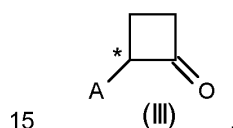
15. A process for the preparation of a compound of formula (V)



wherein A is as defined in any one of claims 1 to 3, which comprises reacting a compound of formula (II)



in the presence of a Lewis acid selected from AlCl_3 and GaCl_3 , preferably AlCl_3 , to obtain a compound of formula (III)



and further reacting the compound of formula (III) with acetonitrile and a suitable additive, wherein the additive is selected from acyl chlorides, anhydrides or esters, preferably the additive is selected from acetyl chloride, isopropenyl acetate, 4-methoxybenzoyl chloride and p-anisic anhydride.