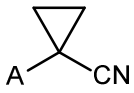
Claims

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

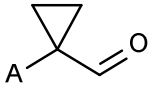
(a) reducing the nitrile moiety of a compound of formula (I) to an aldehyde



(I)

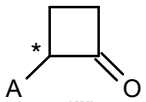
wherein A is selected from aryl, heteroaryl, , C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl and C_3-C_7-cycloalkyl, which aryl, heteroaryl, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl and C_3-C_7-cycloalkyl are unsubstituted or substituted with one or more substituents independently selected from halogen, cyano, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkylsulfanyl, C_1-C_6-haloalkylsulfanyl, C_1-C_6-alkylsulfinyl, C_1-C_6-haloalkylsulfinyl, C_1-C_6-alkylsulfonyl, C_1-C_6-haloalkylsulfonyl, C_2-C_6-haloalkenyl and C_2-C_6-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 H_2 and a metal catalyst, followed by subsequent hydrolysis to the compound of formula (II)



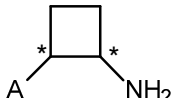
(II) , then

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



(III) wherein * indicates a stereocentre, then

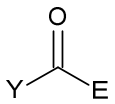
(c) reacting a compound of formula (III) with an ammonium salt and H_2 in presence of a chiral transition metal catalyst to obtain an enantiomerically and diastereomerically enriched amine of formula (IV)



(IV)

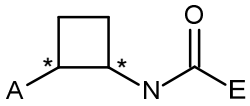
wherein * indicates a stereocentre, and then

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



(X)

wherein Y is a suitable leaving group such as OH, OR or halogen, preferably chloro, R is C_1-C_6-alkyl, and E is selected from aryl, heteroaryl, hydrogen, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl and C_3-C_7-cycloalkyl which aryl, heteroaryl, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl and C_3-C_7-cycloalkyl are unsubstituted or substituted with one or more substituents independently selected from halogen, cyano, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkylsulfanyl, C_1-C_6-haloalkylsulfanyl, C_1-C_6-alkylsulfinyl, C_1-C_6-haloalkylsulfinyl, C_1-C_6-alkylsulfonyl, C_1-C_6-haloalkylsulfonyl, C_2-C_6-haloalkenyl and C_2-C_6-haloalkynyl;
so as to form the enantiomerically and diastereomerically enriched amide of formula (VII)



(VII) .

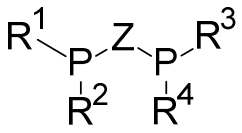
2. The process according to claim 1, wherein
A and E are selected from aryl and heteroaryl, which aryl and heteroaryl are unsubstituted or substituted with one or more substituents independently selected from halogen, cyano, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_1-C_6-alkoxy and C_1-C_6-haloalkoxy.

3. The process according to claim 1, wherein
A is phenyl and E is heteroaryl, which phenyl and heteroaryl are unsustituted or substituted with one or more substituents independently selected from halogen, cyano, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_1-C_6-alkoxy and C_1-C_6-haloalkoxy.

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 $AlCl_3$ and $GaCl_3$, preferably $AlCl_3$.

5. The process according to claim 4, wherein
1.0-1.5 mole equivalents of $AlCl_3$ or $GaCl_3$ relative to the compound of formula (II) are added in step (b).

6. The process according to any one of claims 1 to 5, 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)

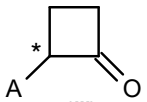
wherein Z is a linking group and R^1, R^2, R^3 and R^4 are independently selected from aryl, hetereoaryl, C_1-C_6-alkyl and C_1-C_6-cycloalkyl, each of which is unsubstituted or substituted with one or more substituents independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl and halogen.

7. The process according to claim 6, 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.

8. The process according to claim 6 or 7, 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,
(*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,
(*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,
(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-(diphenylphosphino)phenyl]ferrocene.

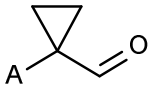
9. The process according to claim 6, wherein
the chiral transition metal catalyst is selected from [RuCl(p-cymene)((S)-DM-SEGPHOS)]Cl, [RuCl(p-cymene)((R)-DM-SEGPHOS)]Cl, $[NH_2Me_2][(RuCl((R)\text{-xylbinap}))_2(u\text{-}Cl)_3]$, $[NH_2Me_2][(RuCl((S)\text{-xylbinap}))_2(u\text{-}Cl)_3]$, $Ru(OAc)_2[(R)\text{-binap}]$, $Ru(OAc)_2[(S)\text{-binap}]$, $Ru(OAc)_2[(R)\text{-xylbinap}]$, $Ru(OAc)_2[(S)\text{-xylbinap}]$, $RuCl_2[(R)\text{-xylbinap}][(R)\text{-daipen}]$, $RuCl_2[(S)\text{-xylbinap}][(S)\text{-daipen}]$, $RuCl_2[(R)\text{-xylbinap}][(R,R)\text{-dpen}]$ and $RuCl_2[(S)\text{-xylbinap}][(S,S)\text{-dpen}]$.

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



(III)

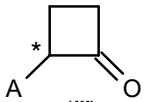
wherein A is as defined in any one of claims 1 to 3 and * indicates a stereocentre,
comprising reacting a compound of formula (II)



(II)

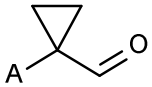
with a suitable Lewis acid.

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



(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)

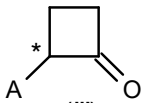


(II)

with a Lewis acid selected from $AlCl_3$ and $GaCl_3$, preferably $AlCl_3$.

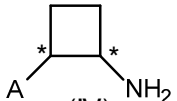
12. The process according to claim 11, wherein 1.0-1.5 mole equivalents of $AlCl_3$ or $GaCl_3$ relative to the compound of formula (II) is added.

13. The process according to any one of claims 10 to 12, wherein
the compound of formula (III)



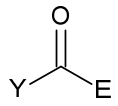
(III) ,

wherein A is as defined in any one of claims 1 to 3 and * indicates a stereocentre,
is further reacted with an ammonium salt and H_2 in presence of a chiral transition metal catalyst to obtain an enantiomerically and diastereomerically enriched amine of formula (IV)



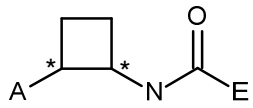
(IV)

wherein * indicates a stereocentre, and then
further reacting the amine of formula (IV) with a compound of formula (X)



(X)

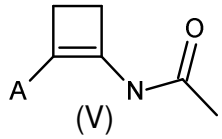
wherein Y is a suitable leaving group such as OH, OR or halogen, preferably chloro, R is C_1-C_6-alkyl, and E is selected from aryl, heteroaryl, hydrogen, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl and C_3-C_7-cycloalkyl which aryl, heteroaryl, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl and C_3-C_7-cycloalkyl are unsubstituted or substituted with one or more substituents independently selected from halogen, cyano, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_1-C_6-alkoxy, C_1-C_6-haloalkoxy, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkylsulfanyl, C_1-C_6-haloalkylsulfanyl, C_1-C_6-alkylsulfinyl, C_1-C_6-haloalkylsulfinyl, C_1-C_6-alkylsulfonyl, C_1-C_6-haloalkylsulfonyl, C_2-C_6-haloalkenyl and C_2-C_6-haloalkynyl;
so as to form the enantiomerically and diastereomerically enriched amide of formula (VII)



(VII) .

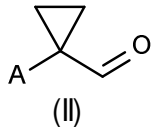
14. The process according to claim 13, wherein the chiral transition metal catalyst is as defined in any one of claims 6 to 9.

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



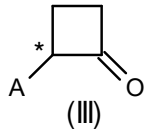
(V)

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



(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)



(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.