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(54) Title: PROCESS FOR THE PREPARATION OF AMINE INTERMEDIATES

(57) Abstract: The present disclosure relates a process for the preparation of amines as intermediates for the synthesis of triazines, which are suitable for use as herbicides for controlling weeds.

PROCESS FOR THE PREPARATION OF AMINE INTERMEDIATES

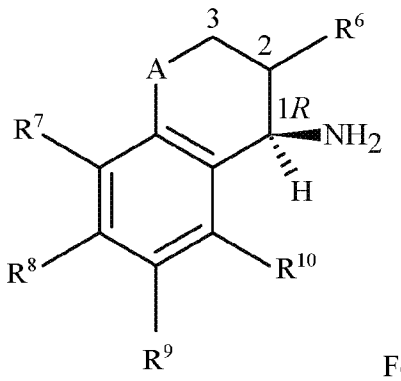
TECHNICAL FIELD

The present disclosure relates to the field of agrochemistry. More specifically, it is directed to a process for preparation of amines as intermediates for the synthesis of triazines, which are suitable as herbicides for controlling weeds.

BACKGROUND

Triazine compounds are a class of compounds suitable for being used as herbicides. Triazine compounds such as Atrazine, Ametryne, Indaziflam or Triaziflam are among the compounds that are used as herbicides.

The synthesis of Indaziflam was disclosed for the first time in document WO04/069814 A1. A compound of Formula (V) is mentioned as starting material in one of the alternative syntheses described in said prior art document.



Formula (V)

wherein:

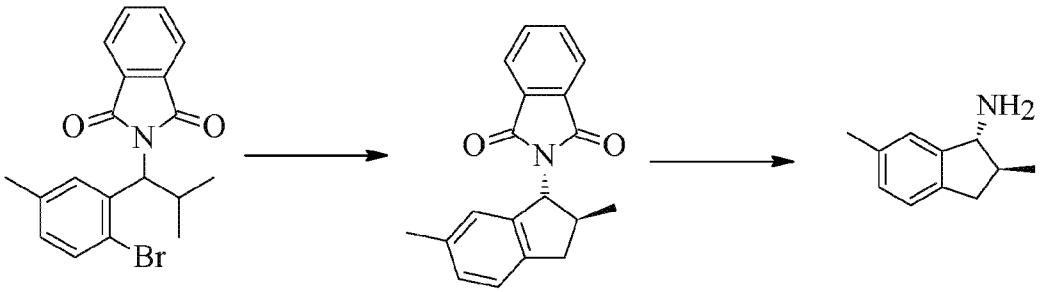
R^6 is $(C_1\text{-}C_6)$alkyl;

R^7, R^8, R^9 and R^{10} are each independently H, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_3)$haloalkyl, halogen, $(C_1\text{-}C_3)$alkoxy, $(C_1\text{-}C_3)$haloalkoxy or CN;

A is CH_2, O or a direct bond, according to document WO 04/069814 A1.

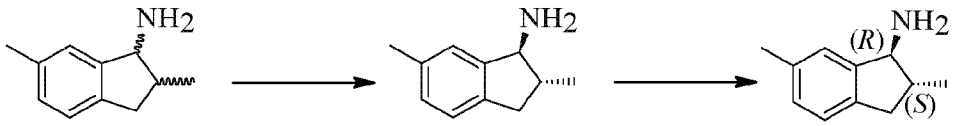
Compounds of Formula (V) were described to be prepared according to known methods, for example by reductive amination of ketones or the corresponding oximes. However, this synthesis requires the separation of mixtures of 4 isomers, i.e., cis/trans isomers and enantiomers, as disclosed in the examples of that document.

The synthesis of a compound of Formula (1*R*,2*S*)-2,6-dimethyl-2,3-dihydro-1-indan-1-amine was also described in the document WO 2015/113903 A1:



(1*R*,2*S*)-2,6-dimethyl-2,3-dihydro-1-indan-1-amine was prepared from 2-[1-(2-bromo-5-methylphenyl)-2-methylpropyl]-1H-isoindole-1,3(2H)-dione via 2-[(1*R*,2*S*)-2,6-dimethyl-2,3-dihydro-1H-inden-1-yl]-1H-isoindole-1,3(2H)-dione by using a palladium tetraphenyl-phosphine catalyst with a yield of 55% from the halogenated compound.

An additional approach described in document CN 108794339, which refers to the separation of (1*R*,2*S*)-2,6-dimethyl-1-aminoindan (I) from the mixture (III) of four isomers as raw material. Initially, an enantiomer mixture of compounds of Formula (II), enriched in the trans-isomers, is prepared through a method of hydrogenation at the presence of a palladium catalyst, or a method of salifying crystallization with achiral organic acid or the two methods; using R-mandelic acid to split an enantiomer mixture of Formula (II) to obtain enantiomer RS-(I) enriched (1*R*,2*S*)-2,6-dimethyl-1-aminoindan. Waste isomer generated in the preparation method can be converted into the compound shown as the Formula (II) and enriched with the trans-isomer through a palladium catalytic hydrogenation method for recycling.

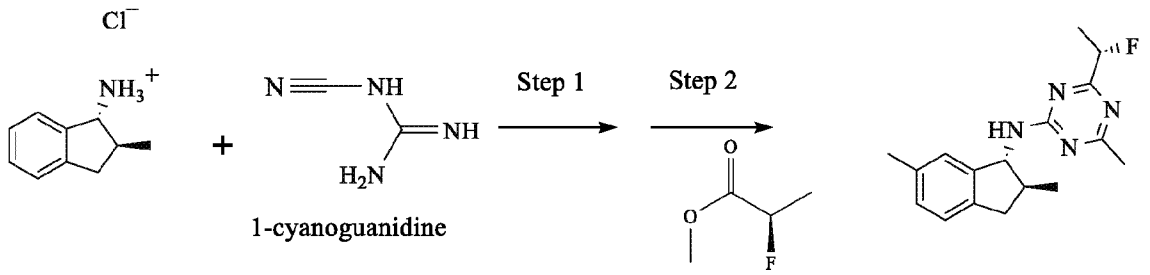


(III) (II) Racemate RS-(I)

Bayer's process for the synthesis of Indaziflam is described in document US 2004/157739. According to this process, in Step 1, a homogeneous mixture of (1*R*,2*S*)-1-amino-2-methylindane hydrochloride and 1-cyanoguanidine in 1,3-dichlorobenzene was heated at 140-150° C. The cooled mixture was diluted with toluene and the solid filtered off to give solid (1*R*,2*S*)-1-(bisguanidino)-2-methylindane monohydrochloride.

In Step 2, a 30% solution of sodium methoxide in methanol was added to a stirred suspension of (1*R*,2*S*)-1-(bisguanidino)-2-methylindane monohydrochloride in methanol.

Then methyl-(2*R*)-2-fluoropropanoate was added at room temperature, followed by an additional quantity of 30% solution of sodium methoxide. The residue was purified by column chromatography, eluting with a mixture of ethyl acetate:heptane (7:3) as eluent to give 2-amino-4-[(1*R*,2*S*)-2-methyl-1-indanylamino]-6-[(1*R*)-1-fluoroethyl]-1,3,5-triazine (Indaziflam).

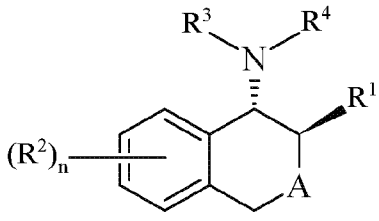


Therefore, due to the complex synthesis of Indaziflam intermediate, (1*R*,2*S*)-2,6-dimethyl-2,3-dihydro-1H-inden-1-amine, there is a need in the art for a simple to operate reaction, with high enantioselectivity and/or yield, and from a simple and available starting material.

SUMMARY

Some embodiments of the present disclosure provide an alternative to the existing methods for the preparation of Indaziflam intermediates. It is further an object of the present disclosure, to provide a process which solves at least some of the drawbacks of prior art methods such as non-enantioselective synthesis and/or low yield.

Some embodiments relate to a process for the preparation of an amine compound of Formula (I):



Formula (I)

wherein:

R^1 and R^2 may each independently be hydrogen or an optionally substituted C_1-C_4 alkyl group, and wherein R^1 and R^2 are not both hydrogen;

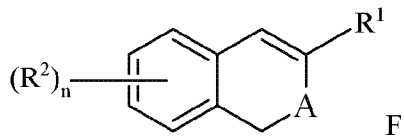
R^3 and R^4 may each independently be hydrogen, an optionally substituted C_1-C_3 alkyl group, an optionally substituted C_1-C_3 alkenyl group, an optionally substituted aryl group, a phenyl or an aralkyl group with a C_1-C_4 alkyl chain;

wherein the optional substituent may be selected from the group comprising halogen, aliphatic, halo aliphatic, alicyclic, alkoxy, thioalkyl, hydroxy, cyano, aryl and nitro group;

A may be $-CH_2-$, -O- or a direct bond; and

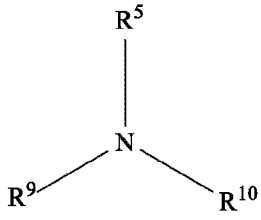
n may be 0, 1, 2 or 3;

which may comprise amination of an indene compound of Formula (II)

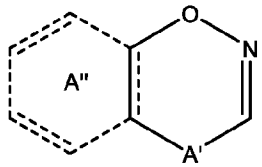


Formula (II)

with an amination agent selected from a compound of Formula (IV) or Formula (VI),



Formula (IV)



Formula (VI)

wherein:

R^5 is $COOR^6$, OR^7 or $OC{=}OR^8$;

R^6, R^7 and R^8 are each independently hydrogen, an optionally substituted C_1-C_4 alkyl chain, or an optionally substituted aryl group, wherein the optional substituent is selected from one or more substituents of the group comprising halogen, C_1-C_4 alkyl chain, halo aliphatic, alicyclic, alkoxy, thioalkyl, hydroxy, cyano, aryl and nitro group;

R^9 and R^{10} are each independently an optionally substituted C_1-C_4 alkyl chain, or an optionally substituted aryl group, wherein the optional substituent is selected from one or more substituents of the group comprising halogen, C_1-C_4 alkyl chain, halo aliphatic, alicyclic, alkoxy, thioalkyl, hydroxy, cyano, aryl and nitro group;

A' may be $-CH_2-$, or a direct bond; and

A'' may be an optional fused benzene ring optionally substituted with $(R^2)_n$, wherein n and R^2 may be as defined in Formula (I);

wherein the amination may be in the presence of a hydrosilane reducing agent and a catalyst, wherein the catalyst may be a complex of a transition metal with a monodentate, bidentate or polydentate chiral ligand.

According to some embodiments, R^1 and R^2 may each independently be a C_1-C_4 alkyl group and n may be 1. According to some embodiments, R^3 and R^4 may each independently be hydrogen.

According to some embodiments, the amination may be carried out in a solvent. According to some embodiments, the solvent may be selected from a group including tetrahydrofuran, 2-methyl tetrahydrofuran, cyclohexane, methyl cyclohexane, toluene, n-heptane, methyl tert-butyl ether, cyclopentyl methyl ether, chlorobenzene, diethyl ether, dichloromethane, 1,2-dichloroethane, 1,4-dioxane, acetonitrile, dimethylacetamide, dimethoxymethane, 2-methyl tetrahydrofuran, and xylene.

According to some embodiments, the solvent may be selected from a group including tetrahydrofuran, 2-methyl tetrahydrofuran, cyclohexane, methyl cyclohexane, toluene and n-heptane. Alternatively, according to some embodiments, the solvent may preferentially be selected from a group including tetrahydrofuran, 1,2-dichloroethane, 1,4-dioxane, acetonitrile, dimethylacetamide, dichloromethane, cyclopentyl methyl ether, and dimethoxymethane.

According to some embodiments, the hydrosilane reducing agent may be selected from the group including alkoxy hydrosilanes or hydrosiloxanes. According to some embodiments, the hydrosilane reducing agent may be selected from the group including methyldimethoxysilane, trimethoxysilane or poly(methylhydrosiloxane).

According to some embodiments, the transition metal may be a cationic transition metal. According to some embodiments, the transition metal may have an oxidation state of 0, +1, +2, +3, or +4. According to some embodiments, the transition metal may preferably have a transition state of +2. According to some embodiments, the transition metal may be selected from the group including Cu^{2+}, Ni^{2+}, Pd^{2+}, Pt^{2+}, Fe^{2+}, Ru^{2+}, Cr^{2+}, Mo^{2+}, W^{2+}, Co^{2+} or Mn^{2+}. According to some embodiments, the transition metal may preferably be Cu^{2+} or Ni^{2+}.

According to some embodiments, the Cu^{2+} may be selected from the group including copper (II) acetate, copper (II) nitrate, copper (II) carbonate, copper (II) sulfate, copper (II)

trifluoroacetate, copper (II) triflate, copper (II) bis(trifluoromethylsulfonyl)imide, copper (II) perchlorate, copper (II) tetrafluoroborate hexahydrate.

According to some embodiments, the Ni^{2+} may be selected from the group including Nickel diiodide, Nickel (II) tetrafluoroborate hexahydrate, Nickel (II) bis(acetylacetonate), Nickel dichloride, Nickel difluoride tetrahydrate and Nickel (II) trifluoroacetate.

According to some embodiments, the catalyst is a complex of a transition metal with a chiral ligand may be prepared *in situ* or *ex situ*.

According to some embodiments, the chiral ligand may be a monodentate, bidentate or polydentate chiral ligand. According to some embodiments, the chiral ligand may be a bidentate chiral ligand. According to some embodiments, the chiral ligand may be a phosphorous-containing bidentate chiral ligand. According to some embodiments, the chiral ligand may be a nitrogen-containing bidentate chiral ligand.

According to some embodiments, the phosphorous-containing bidentate chiral ligand selected from the group including (+)-1,2-bis((2*S*,5*S*)-2,5-diphenylphospholano)ethane, (+)-1,2-bis((2*S*,5*S*)-2,5-dipropylphospholano)ethane, (−)-1,2-bis[(2*R*,5*R*)-2,5-diethylphospholano]benzene, (−)-1,2-bis[(2*R*,5*R*)-2,5-dimethylphospholano]benzene, 1,2-bis(diphenylphosphino) ethane (DPPE), (+)-2,2-dimethyl-4,5-((diphenyl-phosphino)dimethyl)dioxolane, (2*S*,4*S*)-(−)-4-diphenyl-phosphino-2-(diphenylphosphino-methyl)pyrrolidine, 2,2′-bis(diphenyl-phosphino)-1,1′-binaphthyl) (BINAP), and (−)-1,2-bis[(2*R*,5*R*)-2,5-dimethylphospholano]benzene, derivatives and enantiomers thereof. According to some embodiments, the phosphorous-containing bidentate chiral ligand may be (+)-1,2-bis((2*S*,5*S*)-2,5-diphenylphospholano)ethane.

According to some embodiments, the nitrogen-containing bidentate chiral ligand may be selected from the group including: (3a*R*,3'a*R*,8a*S*,8'a*S*)-3a,3'a,8a,8'a-tetrahydro-8H,8'H-2,2'-biindeno[1,2-d]oxazole, (5*R*,5'*R*)-5,5'-diisobutyl-4,4',5,5'-tetrahydro-2,2'-bioxazole, (5*R*,5'*R*)-5,5'-diphenyl-4,4',5,5'-tetrahydro-2,2'-bioxazole, (5*R*,5'*R*)-5,5'-dibenzyl-4,4',5,5'-tetrahydro-2,2'-bioxazole, (5*R*,5'*R*)-5,5'-di-tert-butyl-4,4',5,5'-tetrahydro-2,2'-bioxazole, (5*R*,5'*R*)-5,5'-dimethyl-4,4',5,5'-tetrahydro-2,2'-bioxazole, (5*R*,5'*R*)-5,5'-diisopropyl-4,4',5,5'-tetra hydro-2,2'-bioxazole, derivatives and enantiomers thereof. According to some embodiments, the nitrogen-containing bidentate chiral ligand may preferentially be selected from the group including: (3a*R*,3'a*R*,8a*S*,8'a*S*)-3a,3'a,8a,8'a-tetrahydro-8H,8'H-2,2'-biindeno[1,2-d]oxazole, (5*R*,5'*R*)-5,5'-di-tert-butyl-4,4',5,5'-tetrahydro-2,2'-bioxazole and (5*R*,5'*R*)-5,5'-diphenyl-

4,4',5,5'-tetrahydro-2,2'-bioxazole. According to some embodiments, the nitrogen-containing bidentate chiral ligand may most preferentially be (3a*R*,3'a*R*,8a*S*,8'a*S*)-3a,3'a,8a,8'a-tetrahydro-8H,8'H-2,2'-biindeno[1,2-d]oxazole or (5*R*,5'*R*)-5,5'-di-tert-butyl-4,4',5,5'-tetrahydro-2,2'-bioxazole.

According to some embodiments, the amination agent may be a compound of Formula (IV) wherein:

R^5 is $COOR^6$, OR^7 or $OC{=}OR^8$;

R^6, R^7 and R^8 are each independently hydrogen, an optionally substituted C_1-C_4 alkyl chain, or an optionally substituted aryl group, wherein the optional substituent is selected from one or more substituents of the group comprising halogen, C_1-C_4 alkyl chain, halo aliphatic, alicyclic, alkoxy, thioalkyl, hydroxy, cyano, aryl and nitro group;

R^9 and R^{10} are each independently an optionally substituted C_1-C_4 alkyl chain, or an optionally substituted aryl group, wherein the optional substituent is selected from one or more substituents of the group comprising halogen, C_1-C_4 alkyl chain, halo aliphatic, alicyclic, alkoxy, thioalkyl, hydroxy, cyano, aryl and nitro group;

or a compound of Formula (VI) wherein

A' may be $-CH_2-$;

A" may be an optional fused benzene ring optionally substituted with $(R^2)_n$, wherein n and R^2 may be as defined in Formula (I); and

n may be 0.

According to some embodiments, the amination agent may be selected from the group including 1,2-benzisoxazole, $(Bn)_2NOBz$ (O-benzoyl-N,N-dibenzylhydroxylamine), $(Bn)_2NOAc$ (O-acetyl-N,N-dibenzylhydroxylamine) and $(Bn)_2NCO_2Et$. According to some embodiments, the amination agent may preferably be 1,2-benzisoxazole $(Bn)_2NOBz$ or $(Bn)_2NOAc$.

According to some embodiments, the amination may take place at a temperature in the range between about 0-100°C.

According to some embodiments, the amination may take place at a temperature in the range between about 0-40°C when the transition metal is Ni.

According to some embodiments, the amination may take place at a temperature in the range between about 0-40°C when the transition metal is Ni^{2+}.

According to some embodiments, the amination may take place at a temperature in the range between about 30-80°C when the transition metal is Cu.

According to some embodiments, the amination may take place at a temperature in the range between about 30-80°C when the transition metal is Cu^{2+}.

According to some embodiments, the amination may take place under atmospheric pressure.

According to some embodiments, the process may include addition of a hydrolyzing agent for hydrolyzing an initially formed imine derivative to obtain a free amine or a salt thereof. According to some embodiments, the hydrolyzing agent may be selected from: $NH_2OH{\cdot}HCl$, NH_3 (ammonia), N_2H_4 (hydrazine), and NH_2OH 50 wt% in H_2O.

According to some embodiments, the amination agent may be a compound of Formula (IV) wherein:

R^5 is $COOR^6$, OR^7 or $OC{=}OR^8$;

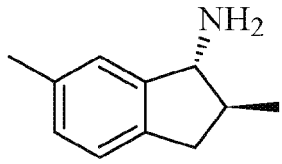
R^6, R^7 and R^8 are each independently hydrogen, an optionally substituted C_1-C_4 alkyl chain, or an optionally substituted aryl group, wherein the optional substituent is selected from one or more substituents of the group comprising halogen, C_1-C_4 alkyl chain, halo aliphatic, alicyclic, alkoxy, thioalkyl, hydroxy, cyano, aryl and nitro group;

R^9 and R^{10} are each independently an optionally substituted C_1-C_4 alkyl chain, or an optionally substituted aryl group, wherein the optional substituent is selected from one or more substituents of the group comprising halogen, C_1-C_4 alkyl chain, halo aliphatic, alicyclic, alkoxy, thioalkyl, hydroxy, cyano, aryl and nitro group.

According to some embodiments, the process may include addition of an additive selected from the group including sodium iodide (NaI), potassium iodide (KI), lithium iodide (LiI) and cesium iodide (CsI).

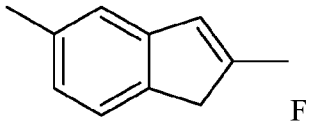
According to some embodiments, the compound of Formula (I) may be (1*R*,2*S*)-1-amino-2,6-dimethylindane (Formula VII) or (1*R*,2*S*)-1-dibenzylamino-2,6-dimethylindane.

According to some embodiments, (1*R*,2*S*)-1-amino-2,6-dimethylindane (Formula (VII))



Formula (VII)

may be produced by reacting 2,5-dimethylindene having a Formula (VIII)



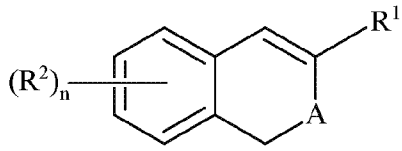
Formula (VIII)

with 1,2-benzisoxazole in the presence of copper (II) acetate ($Cu(OAc)_2$), (+)-1,2-bis(2*S*,5*S*)-2,5-diphenylphospholano)ethane ((*S*,*S*)-Ph-BPE) and poly(methylhydrosiloxane) (PMHS).

According to some embodiments, the process to produce (1*R*,2*S*)-1-amino-2,6-dimethylindane (Formula (VII)) may further include adding $NH_2OH{\cdot}HCl$.

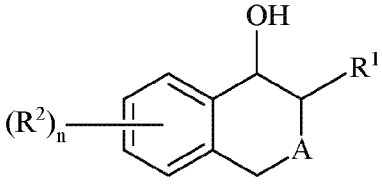
According to some embodiments, the process may take place under a nitrogen atmosphere.

Some embodiments relate to a process for the preparation of an indene compound of Formula (II):



Formula (II)

by dehydration of an indanol compound of Formula (III):



Formula (III)

wherein:

R^1 and R^2 may each independently be hydrogen and wherein R^1 and R^2 are not both hydrogen or an optionally substituted C_1-C_4 alkyl group, wherein the optional substituents may be selected from the group including halogen, aliphatic, halo aliphatic, alicyclic, alkoxy, thioalkyl, cyano or nitro groups;

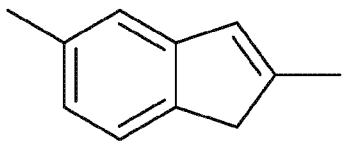
A may be $-CH_2-$, -O- or a direct bond; and

n may be 0, 1, 2 or 3.

According to some embodiments, dehydration may be carried out in a solvent. According to some embodiments, the dehydration solvent may be selected from the group including toluene, chlorobenzene, dichloroethane and xylene. According to some embodiments, the dehydration solvent may preferably be toluene.

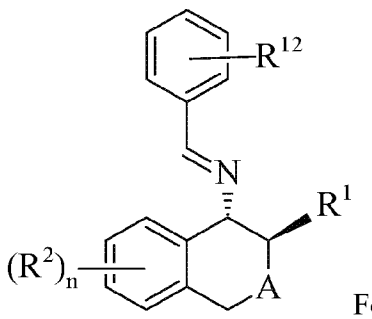
According to some embodiments, dehydration may be carried out in the presence of a catalyst. According to some embodiments, the catalyst may be selected from the group including p-toluene sulfonic acid, pyridinium p-toluene sulfonic acid, sulfosalicylic acid, ethane sulphonic acid, methanesulfonic acid, benzene sulfonic acid, camphorsulfonic acid, p-brominesulphonic acid, sulfuric acid, trifluoromethanesulfonic acid and hydrochloric acid.

Some embodiments relate to a 2,5-dimethylindene compound of Formula (VIII):



Formula (VIII).

Some embodiments relate to a compound of Formula (X):



Formula (X)

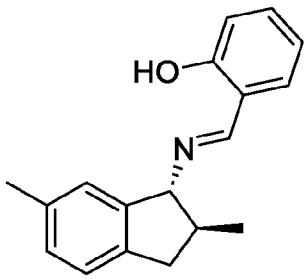
wherein:

R^1 and R^2 may each independently be hydrogen and wherein R^1 and R^2 are not both hydrogen or an optionally substituted C_1-C_4 alkyl group, and wherein R^1 and R^2 may not both be hydrogen;

R^{12} may be hydrogen, an optionally substituted C_1-C_4 alkyl chain, or an optionally substituted aryl group, wherein the optional substituent may be selected from one or more substituents of the group including halogen, C_1-C_4 alkyl chain, halo aliphatic, alicyclic, alkoxy, thioalkyl, hydroxy, cyano, aryl and nitro group; and

A may be -CH_2-, -O- or a direct bond.

Some embodiments relate to a compound of Formula (IX):



Formula (IX).

According to some embodiments, a compound of Formula (IX) or Formula (X) may be an intermediate in the preparation of a compound of Formula (I).

Some embodiments relate to a process for the preparation of Indaziflam, the process comprising preparing a compound of Formula (I) according to a process as disclosed herein.

Some embodiments relate to Indaziflam produced according to a process as disclosed herein.

The compound of Formula (I) is an important intermediate and is used in the preparation of Indaziflam, as described in WO 2009/077059 and US 2004/0157739 incorporated herein by reference in its entirety.

According to some embodiments, a further aspect of the subject matter there is provided a process for preparation of Indaziflam including:

a) preparing compound of Formula (I) as described herein;

b) providing reaction conditions for preparation of Indaziflam.

According to an embodiment the reaction conditions in step (b) include but are not limited to nucleophilic addition reaction and cyclization to obtain Indaziflam.

Some embodiments relate to a process for the preparation of Indaziflam, the process including:

a. reacting (1*R*,2*S*)-1-amino-2,6-dimethylindane prepared according to any one of the disclosed embodiments with 1-cyanoguanidine in the presence of a solvent to obtain (1*R*,2*S*)-1-(bisguanidino)-2,6-dimethylindane; and

b. reacting said (1*R*,2*S*)-1-(bisguanidino)-2,6-dimethylindane with methyl-(2*R*)-2-fluoropropanoate in the presence of a base and in the presence of a solvent.

Some embodiments relate to a process for the preparation of Indaziflam, the process including:

a. reacting (1*R*,2*S*)-1-amino-2,6-dimethylindane prepared according to any one of the disclosed embodiments with 1-cyanoguanidine and metal isopropoxide in the presence of a solvent to obtain (1*R*,2*S*)-1-(bisguanidino)-2,6-dimethylindane; and

b. reacting said (1*R*,2*S*)-1-(bisguanidino)-2,6-dimethylindane with methyl-(2*R*)-2-fluoropropanoate.

Some embodiments relate to a process for the preparation of Indaziflam, the process including:

a. reacting (1*R*,2*S*)-1-amino-2,6-dimethylindane prepared according to any one of the disclosed embodiments with cyanoguanidine and aluminum isopropoxide in the presence of a solvent to obtain (1*R*,2*S*)-1-(bisguanidino)-2,6-dimethylindane; and

b. reacting said (1*R*,2*S*)-1-(bisguanidino)-2,6-dimethylindane with methyl-(2*R*)-2-fluoropropanoate.

Additional features and advantages of the present disclosure will become apparent to those skilled in the art upon consideration of the following detailed description of the illustrative embodiments exemplifying the best mode of carrying out the utility described herein as presently perceived.

DETAILED DESCRIPTION

According to some embodiments, an alternative to the existing methods for the preparation of Indaziflam intermediates is provided. Advantageously, in some embodiments, a chiral synthesis may be used to prepare Indaziflam intermediates. Advantageously, by careful selection of a chiral ligand, the enantiomeric excess and/or yield may be controlled.

Definitions

Embodiments of the present disclosure are discussed in detail below. In describing the embodiments, specific terminology is employed for the sake of clarity. However, the disclosure is not intended to be limited to the specific terminology so selected. While specific exemplary embodiments are discussed, it should be understood that this is done for illustration purposes only. A person skilled in the relevant art will recognize that other components and configurations can be used without parting from the spirit and scope of the disclosure. While a number of embodiments and features are described herein, it is to be understood that the various features of the disclosure and aspects of embodiments, even if described separately, may be combined unless mutually exclusive or contrary to the specific description. All references cited herein are incorporated by reference as if each had been individually incorporated.

As used herein, the transitional term "comprising" or “that comprises”, which is synonymous with "including," or "containing," is inclusive or open-ended and does not exclude additional, un-recited elements or method steps. However, in each recitation of "comprising" herein, it is intended that the term also encompass, as alternative embodiments, the phrases "consisting essentially of" and "consisting of", where "consisting of" excludes any element or step not specified and "consisting essentially of" permits the inclusion of additional un-recited elements or steps that do not materially affect the essential or basic and novel characteristics of the composition or method under consideration.

Further, unless expressly stated to the contrary, "or" refers to an inclusive or and not to an exclusive or. For example, a condition A or B is satisfied by any one of the following: A is true (or present) and B is false (or not present), A is false (or not present) and B is true (or present), and both A and B are true (or present).

Prior to setting forth the present subject matter in detail, the definitions of certain terms to be used herein are provided. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this subject matter pertains.

The term "a" or "an" as used herein as used herein in accordance with some embodiments, may include the singular and the plural, unless specifically stated otherwise. Therefore, the terms "a", "an" or "at least one" can be used interchangeably in this application.

As used herein, the term "compound" may include all forms thereof including, but not limited to, salts, solid forms such as amorphous, crystalline, solvate or hydrate.

As used herein, the term "aryl group" as used herein in accordance with some embodiments, may refer to an optionally substituted aromatic carbocyclic or heterocyclic group which has between 4 and 10, between 5 and 10, between 5 and 8 carbon atoms, which comprises 1 aromatic ring or 2 fused aromatic rings, wherein the optional substituents are selected from the group including halogen, aliphatic, halo aliphatic, alkoxy, thioalkyl, cyano or nitro groups. In the case of a heterocyclic aryl group, i.e., "heteroaryl group", 1, 2 or 3 of the atoms in the ring or rings of the aryl group, is an element other than carbon, such as nitrogen, oxygen or sulfur.

The term "aralkyl group" as used herein in accordance with some embodiments, may refer to an aryl-substituted alkyl group.

The term "alkoxy group as used herein in accordance with some embodiments, may refer to an alkyl group bound to oxygen.

The term "aryloxy group" as used herein in accordance with some embodiments may refer to an aryl group bound to oxygen.

The term "aralkoxy group" as used herein in accordance with some embodiments, may refer to an aralkyl group bound to oxygen.

The term "aralkoxyamine group" as used herein in accordance with some embodiments, may refer to an aralkyl group bound to oxygen which is in turn bound to nitrogen by a single bond.

The term "alkoxyamine" as used herein in accordance with some embodiments, may refer to an alkyl group bound to oxygen which is in turn bound to nitrogen by a single bond.

The term "isoxazole" as used herein in accordance with some embodiments, may refer to aromatic heterocycle containing an N–O bond.

The term "benzisoxazole" as used herein in accordance with some embodiments, may refer to a bicyclic heterocycle including a benzene ring fused to an aromatic heterocycle containing an N–O bond.

The term "thioalkyl group" as used herein in accordance with some embodiments, may refer to an alkyl group bound to sulfur. The term "halo aliphatic group" as used herein in accordance with some embodiments, may refer to an aliphatic group substituted with at least one halogen atom.

The term "aliphatic group" as used herein in accordance with some embodiments may cover, for example and not restricted to, the linear or branched alkyl, alkenyl and alkynyl groups.

The term "alkyl group" as used herein in accordance with some embodiments, may refer to a saturated, linear or branched group, which has between 1 and 24, between 1 and 16, between 1 and 14, between 1 and 12, or 1, 2, 3, 4, 5 or 6 carbon atoms and is bound to the rest of the molecule by a single bond, including, for example and not restricted to, methyl, ethyl, isopropyl, isobutyl, tert-butyl, heptyl, octyl, decyl, dodecyl, hexadecyl, octadecyl, amyl, 2-ethylhexyl, 2-methylbutyl, 5-methylhexyl and similar.

The term "alkenyl group" as used herein in accordance with some embodiments, may refer to a linear or branched group, which has between 2 and 24, between 2 and 16, between 2 and 14, between 2 and 12, or 2, 3, 4, 5 or 6 carbon atoms, with 1, 2 or 3 carbon-carbon double bonds, conjugated or unconjugated, which is bound to the rest of the molecule by a single bond, including, for example and not restricted to, ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, pentenyl, and similar groups.

The term "alkynyl group" as used herein in accordance with some embodiments, may refer to a linear or branched group, which has between 2 and 24, between 2 and 16, between 2 and 14, between 2 and 12, or 2, 3, 4, 5 or 6 carbon atoms, with 1, 2 or 3 carbon-carbon triple bonds, conjugated or unconjugated, which is bound to the rest of the molecule by a single bond, including, for example and not restricted to, an ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, pentynyl, such as 1-pentynyl, and similar.

The term “alkylidene group” as used herein in accordance with some embodiments, may refer to a saturated, linear or branched group, which has between 1 and 24, between 1 and 16, between 1 and 14, between 1 and 12, or 1, 2, 3, 4, 5 or 6 carbon atoms and is bound to the rest of the molecule by a double bond, including, for example and not restricted to, methylidene, ethylidene, isopropylidene, isobutylidene, tert-butylidene, heptylidene, octylidene, decylidene, dodecylidene, hexadecylidene and similar.

The term "alicyclic group" as used in accordance with some embodiments, may cover, for example and not restricted to, cycloalkyl, cycloalkenyl and/or cycloalkynyl groups.

The term "cycloalkyl" as used herein in accordance with some embodiments, may refer to a saturated mono- or polycyclic aliphatic group which has between 3 and 24, between 3 and 16, between 3 and 14, between 3 and 12, or 3, 4, 5 or 6 carbon atoms and which is bound to

the rest of the molecule by a single bond, including, for example and not restricted to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, methyl cyclohexyl, dimethyl cyclohexyl, octahydroindene, decahydronaphthalene, dodecahydrophenalene and/or similar.

The term "cycloalkenyl" as used herein in accordance with some embodiments, may refer to a non-aromatic mono- or polycyclic aliphatic group which has between 5 and 24, between 5 and 16, between 5 and 14, between 5 and 12, or 5 or 6 carbon atoms, with 1, 2 or 3 carbon-carbon double bonds, conjugated or unconjugated, and which is bound to the rest of the molecule by a single bond, including, for example and not restricted to, the cyclopent-1-en-1-yl group and/or similar.

The term "cycloalkynyl" as used herein in accordance with some embodiments, may refer to a non-aromatic mono- or polycyclic aliphatic group which has between 8 and 24, between 8 and 16, between 8 and 14, between 8 and 12, or 8 or 9 carbon atoms, with 1, 2 or 3 carbon-carbon triple bonds, conjugated or unconjugated, and which is bound to the rest of the molecule by a single bond, including, for example and not restricted to, the cyclooct-2-in-1-yl group and/or similar.

The term "hydrosilane" as used herein in accordance with some embodiments, may refer to any organic tetravalent silicon compound containing one or more Si-H bonds. The term "alkoxy hydrosilane" as used herein refers to any organic tetravalent silicon compound containing one or more Si-H bonds and one or more alkoxy groups bound to silicon. For example, and not restricted to, methyldimethoxysilane, trimethoxysilane, dimethoxysilane, diethyoxysilane, triethoxysilane, poly(methylhydrosilane), oligosilanes and/or similar.

The term "hydrosiloxane" as used herein in accordance with some embodiments, may refer to any organosilicon compound containing at least one Si−O−Si group where each Si atom carries two aliphatic or aralkyl groups. The term "alkoxy hydrosiloxanes" as used herein refers to any organosilicon compound containing at least one Si−O−Si group where each Si atom carries two aliphatic or aralkyl groups, at least one of which is an alkoxy group. For example, and not restricted to, polymethylhydrosiloxane (PMHS), phenylsiloxane, oligosiloxane, methyldimethoxysiloxane, trimethoxysiloxane, dimethoxysiloxane, diethyoxysiloxane, and/or similar.

The terms "monodentate chiral ligand", "bidentate chiral ligand" and "polydentate chiral ligand" as used herein in accordance with some embodiments, may refer to a chiral ligand bound to the rest of the molecule by a single bond or a double bond, and the rest of the molecule

may be an organic or organometallic molecule, wherein the chiral ligand include a single donor atom, two donor atoms or multiple donor atoms.

Non-limiting examples of monodentate ligands are: [(1*R*)-2′-methoxy[1,1′-binaphthalen]-2-yl]diphenylphosphine, (1*R*)-[1,1′-binaphthalen]-2-yldiphenyl-phosphine, [(2*S*)-2-(1-naphthalenyl)[1,1′-biphenyl]-3-yl]diphenyl-phosphine, [(1*S*,2*S*,5*R*)-5-methyl-2-(1-methylethyl)cyclohexyl]diphenylphosphine, 3-(diphenylphosphino)-2-[(*R*)-methoxyphenylmethyl]-(3*S*)-ferrocene, derivatives or enantiomers thereof and/or similar.

The term "phosphorous-containing bidentate chiral ligand" as used herein in accordance with some embodiments, may refer to a bidentate chiral ligand containing one or more phosphorous atoms, which is bound to the rest of the molecule by a single bond or a double bond, and the rest of the molecule may be an organic or organometallic molecule. For example, and not restricted to: (+)-1,2-bis((2*S*,5*S*)-2,5-diphenylphospholano)ethane, (+)-1,2-bis((2*S*,5*S*)-2,5-dipropyl phospholano)ethane, (−)-1,2-bis[(2*R*,5*R*)-2,5-diethylphospholano] benzene, (−)-1,2-bis[(2*R*,5*R*)-2,5-dimethylphospholano]benzene, (−)-1,2-bis[(2*R*,5*R*)-2,5-dimethylphospholano]benzene, (−)-1,2-bis[(2*S*,5*S*)-2,5-dimethylphospholano]ethane, 1-(*S*)-1,2-bis(diphenylphosphino)ferrocenyl]ethylamine, 1,2-bis(diphenylphosphino) ethane (DPPE), 1,2-bis(dicyclohexylphosphino)ethane (DCPE), 1,3-bis(diphenyl phosphino)propane (DPPP), 1,4-bis(diphenylphosphino)butane (DPPB), 1,1'-bis(diphenylphosphino)ferrocene (DPPF), (+)-2,2-dimethyl-4,5-((diphenylphosphino) dimethyl)dioxolane, (2*S*,4*S*)-(−)-4-diphenylphosphino-2-(diphenylphosphinomethyl) pyrrolidine, 2-(bucyclohexane)-1-(diphenylphosphino)ferrocene, 2,2′-bis(diphenyl phosphino)-1,1′-binaphthyl) (BINAP), (−)-1,2-bis[(2*R*,5*R*)-2,5-dimethylphospholano] benzene, (2*R*,2′*R*,5*R*,5′*R*)-2,2′,5,5′-tetramethyl-1,1′-(o-phenylene)diphospholane (Me-Duphos), Xyliphos, Josiphos, derivatives or enantiomers thereof and/or similar.

The term "nitrogen containing bi-dentate chiral ligand" as used herein in accordance with some embodiments, may refer to a bidentate chiral ligand containing one or more nitrogen atoms, which is bound to the rest of the molecule by a single bond or a double bond, and the rest of the molecule may be an organic or organometallic molecule. For example, and not restricted to, (3a*R*,3'a*R*,8a*S*,8'a*S*)-3a,3'a,8a,8'a-tetrahydro-8H,8'H-2,2'-biindeno[1,2-*d*] oxazole, (5*R*,5'*R*)-5,5'-diisobutyl-4,4',5,5'-tetrahydro-2,2'-bioxazole, (5*R*,5'*R*)-5,5'-diphenyl-4,4',5,5'-tetrahydro-2,2'-bioxazole, (5*R*,5'*R*)-5,5'-dibenzyl-4,4',5,5'-tetrahydro-2,2'-bioxazole, (5*R*,5'*R*)-5,5'-di-tert-butyl-4,4',5,5'-tetrahydro-2,2'-bioxazole, (5*R*,5'*R*)-5,5'-dimethyl-4,4',5,5'-

tetrahydro-2,2'-bioxazole, (5*R*,5'*R*)-5,5'-diisopropyl-4,4',5,5'-tetrahydro-2,2'-bioxazole, derivatives or enantiomers thereof and/or similar.

The term "transition metal" as used herein in accordance with some embodiments may refer to a metal selected from the group of transition metals on the Periodic table with an oxidation state of -4, -3, -2, -1, 0, +1, +2, +3, +4, +5, +6 or +7.

The term "cationic transition metal" as used herein in accordance with some embodiments may refer to a positively charged metal selected from the group of transition metals on the Periodic table with an oxidation state of +1, +2, +3, +4, +5, +6 or +7. Non-limiting examples of cationic transition metals are: Cu^{+}, Ni^{+}, Fe^{+}, Ru^{+}, Cr^{+}, Mo^{+}, W^{+}, Co^{+}, Mn^{+}, Cu^{2+}, Ni^{2+}, Pd^{2+}, Pt^{2+}, Fe^{2+}, Ru^{2+}, Cr^{2+}, Mo^{2+}, W^{2+}, Co^{2+}, Mn^{2+}, Cu^{3+}, Ni^{3+}, Pd^{3+}, Fe^{3+}, Ru^{3+}, Cr^{3+}, Mo^{3+}, W^{3+}, Co^{3+}, Mn^{3+}, Ni^{4+}, Pt^{4+}, Fe^{4+}, Ru^{4+}, Cr^{4+}, Mo^{4+}, W^{4+}, Mn^{4+} and/or similar.

According to some embodiments, the process may make use of a catalyst. According to some embodiments, the catalyst may be a complex of a transition metal with a monodentate, bidentate or polydentate chiral ligand. According to some embodiments, the transition metal may be a cationic transition metal. According to some embodiments, the complex may be prepared *in situ* or *ex situ*.

All abbreviations, including chemical abbreviations, have there commonly accepted meanings.

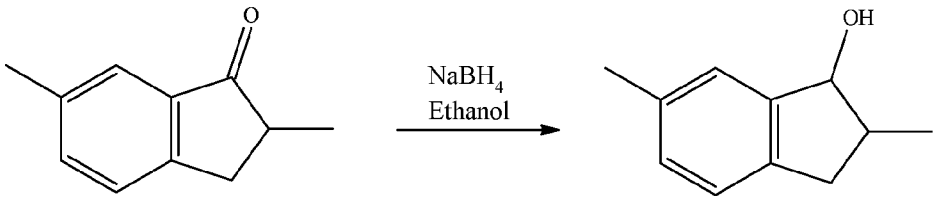
For purposes of better understanding the present teachings and in no way limiting the scope of the teachings, unless otherwise indicated, all numbers expressing quantities, percentages or proportions, and other numerical values used in the specification and claims, are to be understood as being modified in all instances by the term "about". Accordingly, unless indicated to the contrary, the numerical parameters set forth in the following specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained. At the very least, each numerical parameter should at least be construed in light of the number of reported significant digits and by applying ordinary rounding techniques. In this regard, used of the term "about" herein specifically includes ±10% from the indicated values in the range. In addition, the endpoints of all ranges directed to the same component or property herein are inclusive of the endpoints, are independently combinable, and include all intermediate points and ranges. Similarly, the ranges and amounts for each element of the technology described herein can be used together with ranges or amounts for any of the other elements.

Any range or desired value given herein may be extended or altered without losing the effects sought, as is apparent to the skilled person for an understanding of the teachings herein.

The following examples are included for illustrative purposes only and should not be construed as limitations on the invention claimed herein.

EXAMPLES

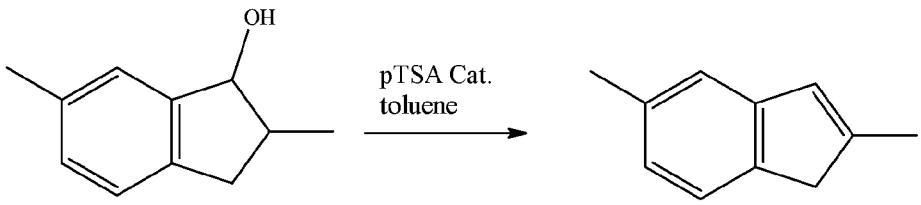
Example 1: Synthesis of 2,6-dimethyl-2,3-dihydro-1H-inden-1-ol (III)



CAS # 66309-83-9 CAS # 880653-69-0

To a solution of 2,6-dimethyl-1-indanone (50 g) in ethanol (500 ml), $NaBH_4$ (14.3 g) was added portion-wise at 10°C. The reaction was warmed to 25 °C and kept stirring for an additional 4 h. Consumption of starting material was monitored by TLC. Once the starting material was consumed, water (100 ml) was added until formation of solids. Ethanol was evaporated under vacuum. 160 ml of water was added and HCl 32% was added to neutralize the reaction medium to pH=7. Extraction was performed twice with 150 ml ethyl acetate followed by phase separation. Ethyl acetate was removed from the organic phase, resulting in a yield of 50.6 g of pure 2,6-dimethyl-2,3-dihydro-1H-inden-1-ol.

Example 2: Synthesis of 2,5-dimethylindene compound of Formula (II)

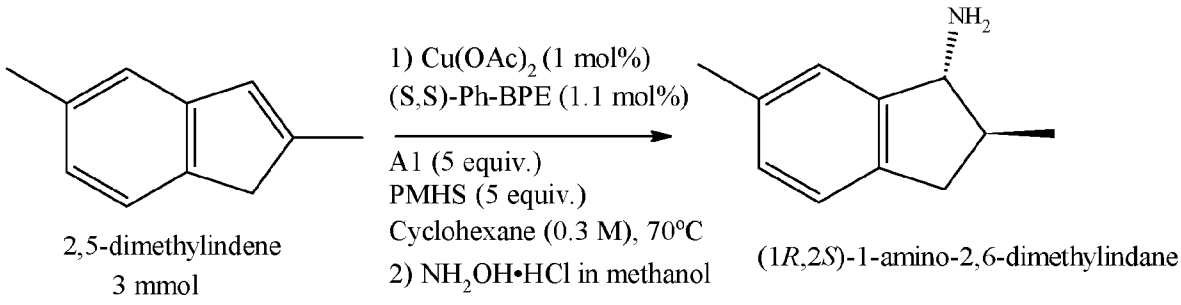


CAS # 880653-69-0 2,5-dimethylindene

A catalytic amount of p-toluene sulfonic acid (pTSA) was added to a solution of 2,6-dimethyl-2,3-dihydro-1-indan-1-ol (50 g) in toluene (250 ml) at 25 °C. The solution was heated to 90 °C and kept stirring to full consumption of starting material. The reaction was cooled to 25 °C and washed twice with 150 ml of water. After phase separation, toluene was evaporated

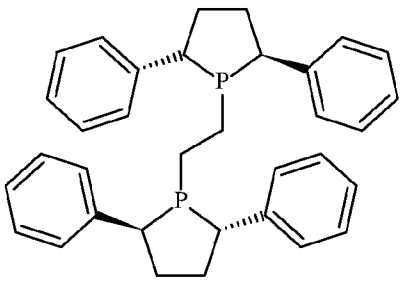
to yield 45 g of 2,5-dimethylindene, purity >90%. 2,5-Dimethylindene was further purified by column chromatography or by crystallization from methanol.

Example 3: Synthesis of (1*R*,2*S*)-1-amino-2,6-dimethylindane

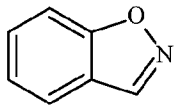


2,5-dimethylindene
3 mmol

(1*R*,2*S*)-1-amino-2,6-dimethylindane

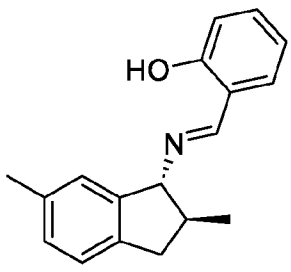


(S,S)-Ph-BPE
CAS # 824395-67-7



A1
1,2-benzisoxazole
CAS # 271-95-4

An oven-dried flask was charged with Copper (II) acetate ($Cu(OAc)_2$) (5.4 mg, 1 mol%) and (+)-1,2-bis((2*S*,5*S*)-2,5-diphenylphospholano)ethane ((*S*,*S*)-Ph-BPE) (16.7 mg, 1.1 mol%) under nitrogen atmosphere. Cyclohexane (10 mL) and poly(methylhydrosiloxane) (PMHS) (5 equivalents) were added sequentially via syringe and the reaction mixture was stirred at room temperature (about 25°C) for 30 min. Then, 2,5-dimethylindene (432 mg, 3 mmol, 1.0 equivalents) was added to the solution. A solution of A1 (1,2-benzisoxazole) (15.0 mmol, 5.0 equivalents) in cyclohexane was added dropwise within a period of 16 h to produce an imine of the Formula (IX)



(IX).

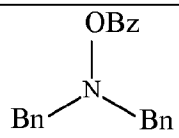
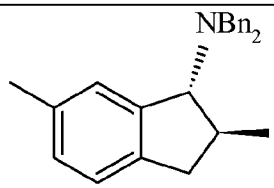
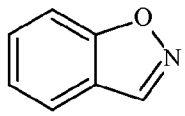
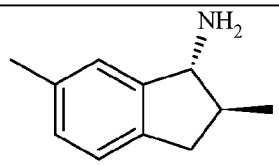
Dichloromethane (10 mL) and a methanolic solution of NH_2OH•HCl (0.5 M, 10 mL) solution were added to the crude reaction mixture within a period of 2 hours to hydrolyze the imine to give the amine hydrochloride salt. Then, the crude reaction mixture was concentrated under reduced pressure, the residue was neutralized with 2.5 M NaOH (15 mL) solution, tetrahydrofuran (15 mL) was added, and the mixture was stirred for 24 hours to produce the free amine (1*R*,2*S*)-1-amino-2,6-dimethylindane. Then, the aqueous layer was extracted with dichloromethane (20 mL, 5 times). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated under reduced pressure.

(1*R*,2*S*)-1-amino-2,6-dimethylindane was isolated by column chromatography, with a yield of 74% and, enantiomeric excess (e.e.) of 98%.

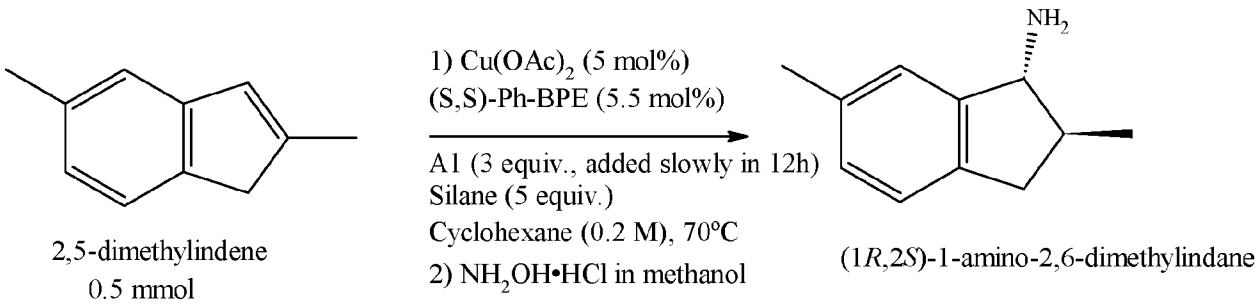
Example 4: Amine source screening

Several amines were screened for use in the synthesis of (1*R*,2*S*)-1-amino-2,6-dimethylindane. Table 1 is a list of exemplary amines tested under various reaction conditions.

Table 1

Amine	Result
 O-benzoyl-N,N-dibenzylhydroxylamine	 29% NMR yield
 1,2-benzisoxazole	 74% isolated yield

Example 5: Silane source screening

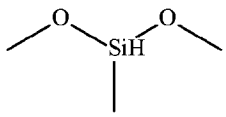
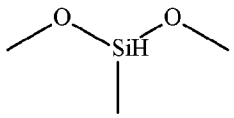
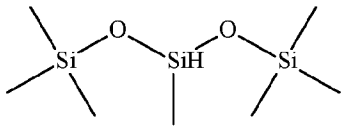


2,5-dimethylindene
0.5 mmol

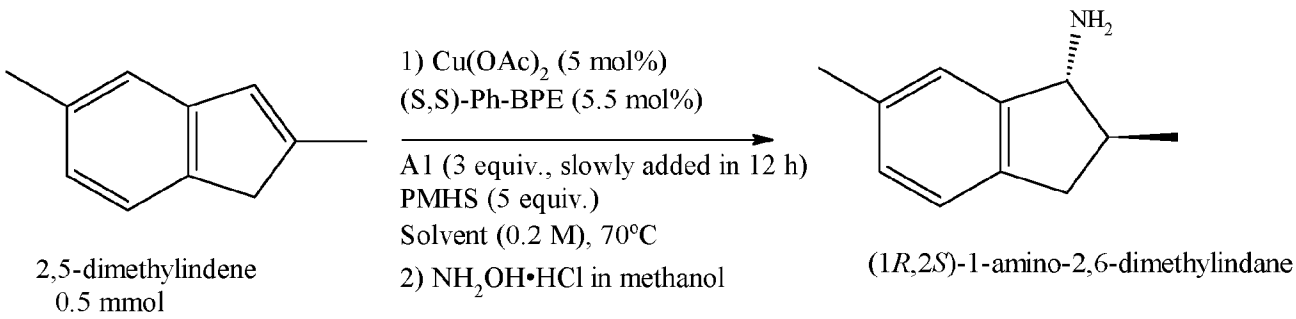
(1*R*,2*S*)-1-amino-2,6-dimethylindane

Several silanes were screened for use in the synthesis of (1*R*,2*S*)-1-amino-2,6-dimethylindane, wherein A1 is 1,2-benzisoxazole, as defined in Example 3. Table 2 is a list of exemplary silanes tested under various reaction conditions.

Table 2

Silane	Result
 Methyldimethoxysilane (DMMS)	58% isolated yield
 + t-butanol DMMS + t-butanol (2.5 equivalents)	33% isolated yield
 Poly(methylhydrosilane)(PMHS)	40% NMR yield 36% isolated yield

Example 6: Copper catalyst solvent screening



2,5-dimethylindene
0.5 mmol

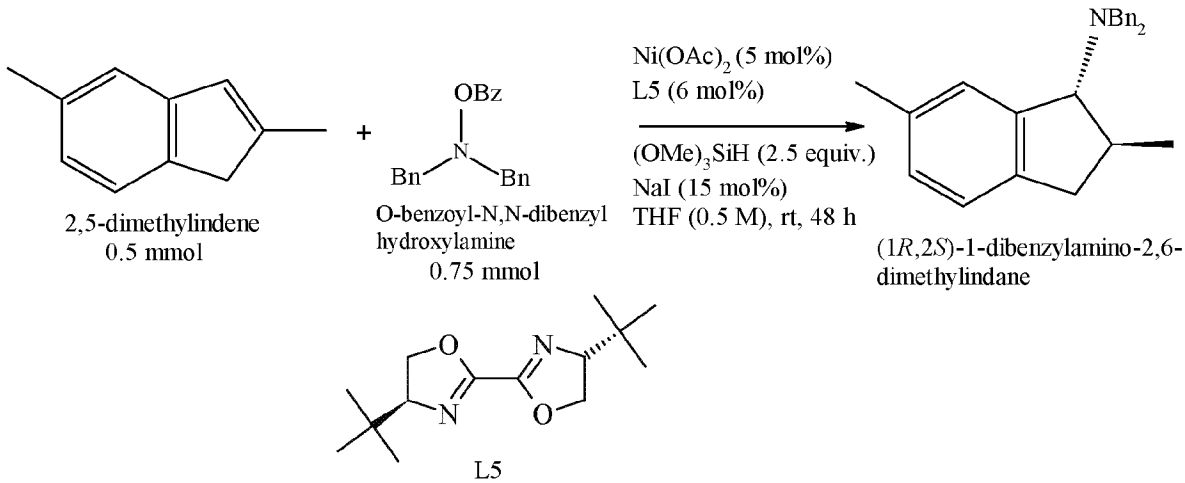
(1*R*,2*S*)-1-amino-2,6-dimethylindane

Several solvents or solvent mixtures were screened for use in the synthesis of (1*R*,2*S*)-1-amino-2,6-dimethylindane, wherein A1 is 1,2-benzisoxazole, as in Example 3. Table 3 is a list of exemplary solvent systems tested under various reaction conditions.

Table 3

Solvent systems	Result (% conversion or yield)
Toluene	54% yield
Methyl-cyclohexane	85% conversion
n-heptane	61% conversion

Example 7: Nickel catalyzed asymmetric hydroalkylamination



2,5-dimethylindene
0.5 mmol

O-benzoyl-N,N-dibenzyl hydroxylamine
0.75 mmol

(1*R*,2*S*)-1-dibenzylamino-2,6-dimethylindane

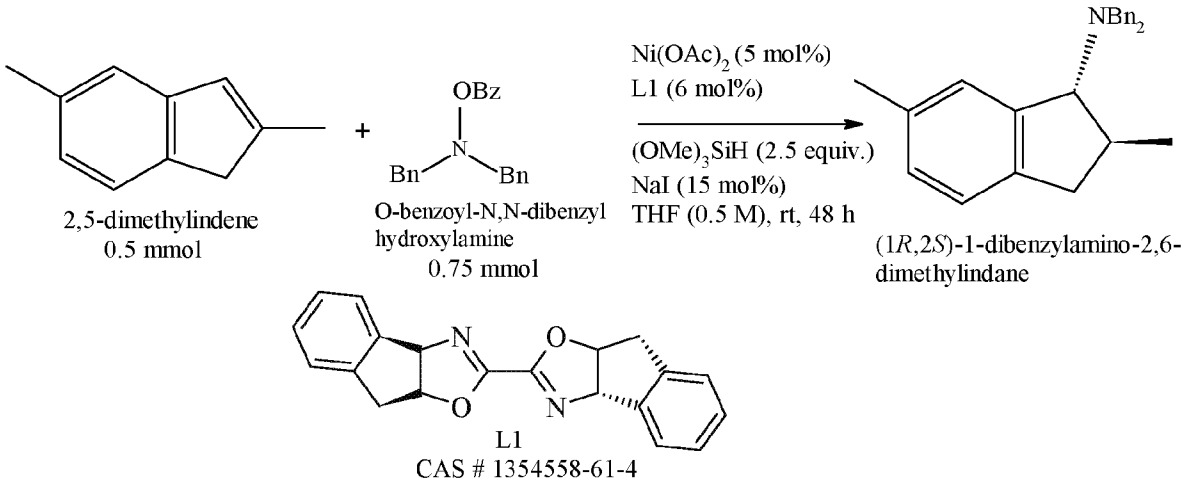
L5

(5R,5'R)-5,5'-di-*tert*-butyl-4,4',5,5'-tetrahydro-2,2'-bioxazole

In a argon-filled glove box, $NiOAc_2$ (4.4 mg, 0.025 mmol, 5.0 mol%), Ligand L5 ((5*R*,5'*R*)-5,5'-di-*tert*-butyl-4,4',5,5'-tetrahydro-2,2'-bioxazole (9.5 mg, 0.030 mmol, 6.0 mol%), sodium iodide (NaI) (11.2 mg, 0.075 mmol, 15 mol%), anhydrous tetrahydrofuran

(THF) (1.0 mL, 0.5M) were added to 10 mL screwcap vial equipped with a magnetic stir bar, and the mixture was stirred for 30 min, then trimethoxy-silane ($(MeO)_3SiH$) (160 µL, 1.25 mmol, 2.5 equivalents), 2,5-dimethylindene (72 mg, 0.50 mmol) and O-benzoyl-N,N-dibenzylhydroxylamine (Bn_2NOBz) (238 mg, 0.75 mmol, 1.5 equivalents) were added in sequence. The reaction was stirred at room temperature for 48 h. After the reaction was complete, it was quenched upon the addition of water, and the mixture was extracted with dichloromethane (three times). The organic layer was concentrated. The crude material was purified by flash column chromatography (petroleum ether/ethyl acetate = 200:1 to 50:1) to provide the (1*R*,2*S*)-1-dibenzylamino-2,6-dimethylindane as a colorless oil. Without being bound by any theory, the iodide ion (of the NaI) may generate Nickel diiodide *in-situ*, which may be more reactive than $Ni(OAc)_2$. This may assist in the formation of the Nickel-bidentate ligand complex, which was obtained with 60% conversion, and 91.5% enantiomeric excess (e.e.).

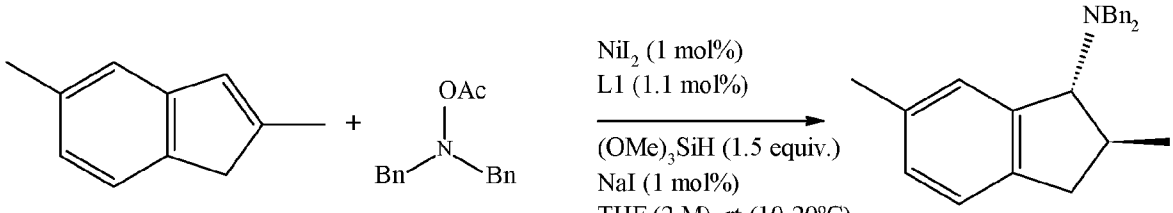
Example 8: Nickel catalyzed asymmetric hydroalkylamination



In a argon-filled glove box, $NiOAc_2$ (4.4 mg, 0.025 mmol, 5.0 mol%), Ligand L1 (3′a*R*,3a*R*,8′a*S*,8a*S*)-3′a,3a,8′a,8a-tetrahydro-2,2′-bi-8H-indeno[1,2-d]oxazole (9.5 mg, 0.030 mmol, 6.0 mol%), sodium iodide (NaI) (11.2 mg, 0.075 mmol, 15 mol%), anhydrous tetrahydrofuran (THF) (1.0 mL, 0.5M) were added to 10 mL screwcap vial equipped with a magnetic stir bar, and the mixture was stirred for 30 min, then trimethoxy-silane ($(MeO)_3SiH$) (160 µL, 1.25 mmol, 2.5 equivalents), 2,5-dimethylindene (72 mg, 0.50 mmol) and O-benzoyl-N,N-dibenzylhydroxylamine (Bn_2NOBz) (238 mg, 0.75 mmol, 1.5 equivalents) were added in sequence. The reaction was stirred at room temperature for 48 h. After the reaction was complete, it was quenched upon the addition of water, and the mixture was extracted with

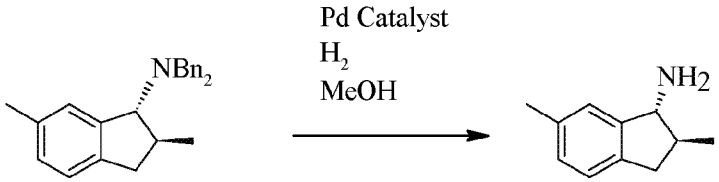
dichloromethane (three times). The organic layer was concentrated. The crude material was purified by flash column chromatography (petroleum ether/ethyl acetate = 200:1 to 50:1) to provide the (1*R*,2*S*)-1-dibenzylamino-2,6-dimethylindane as a colorless oil. Without being bound by any theory, the iodide ion (of the NaI) may generate Nickel diiodide *in-situ*, which may be more reactive than $Ni(OAc)_2$. This may assist in the formation of the Nickel-bidentate ligand complex, which was obtained with 40% yield and 95% enantiomeric excess (e.e).

Example 9: Nickel catalyzed asymmetric hydroalkylamination



In a argon-filled glove box, NiI_2 (1.0 mol%), Ligand L1, as defined in Example 8 (1.1 mol%), sodium iodide (1 mol%), anhydrous tetrahydrofuran (2 M) were added to 10 mL screwcap vial equipped with a magnetic stir bar, and the mixture was stirred for 30 min, then trimethoxy-silane (1.5 equivalents), 2,5-dimethylindene (1 mmol) and O-acetyl-N,N-dibenzylhydroxylamine (Bn_2NOAc) (1.2 mmol) were added in sequence. The reaction was stirred at room temperature for 96 h. After the reaction was complete, it was quenched upon the addition of water, and the mixture was extracted with dichloromethane (three times). The organic layer was concentrated. The crude material was purified by flash column chromatography (petroleum ether/ethyl acetate = 200:1 to 50:1) to provide the (1*R*,2*S*)-1-dibenzylamino-2,6-dimethylindane as a colorless oil with 78% conversion, 74% NMR yield, and 96.7% enantiomeric excess (e.e.).

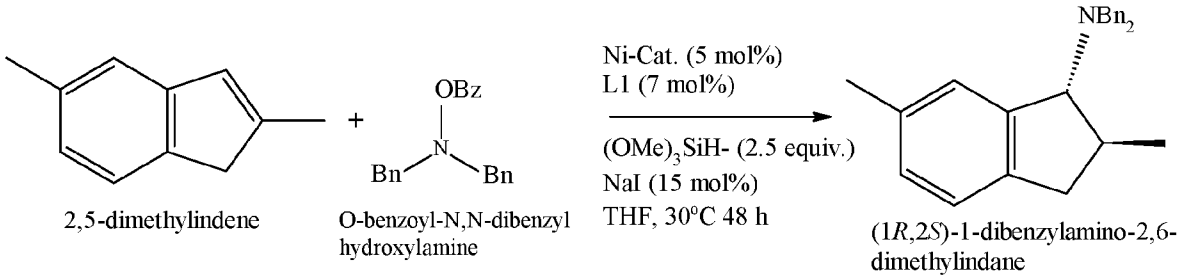
Example 10: Reduction of (1*R*,2*S*)-*N*,*N*-dibenzyl-2,6-dimethyl-2,3-dihydro-1H-inden-1-amine to (1*R*,2*S*)-2,6-dimethyl-2,3-dihydro-1H-inden-1-amine



To a flask containing (1*R*,2*S*)-*N*,*N*-dibenzyl-2,6-dimethyl-2,3-dihydro-1H-inden-1-amine (341 mg, 1 mmol), Pd/C (10wt% of Pd, 100 mg), and methanol (100 ml). Hydrogen was purged with balloon (1 atm), and the mixture was stirred at room temperature for 12 h. The reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure to give (1*R*,2*S*)-2,6-dimethyl-2,3-dihydro-1H-inden-1-amine (160 mg, >99% yield).

Example 11: Nickel catalyst screening for benzoyl amination reagent

Several Nickel containing catalysts were screened for use in the synthesis of (1*R*,2*S*)-1-dibenzylamino-2,6-dimethylindane, wherein the ligand is L1 is as defined in Example 8. Table 4 is a list of exemplary Nickel containing catalysts tested under various reaction conditions.



2,5-dimethylindene

O-benzoyl-N,N-dibenzyl hydroxylamine

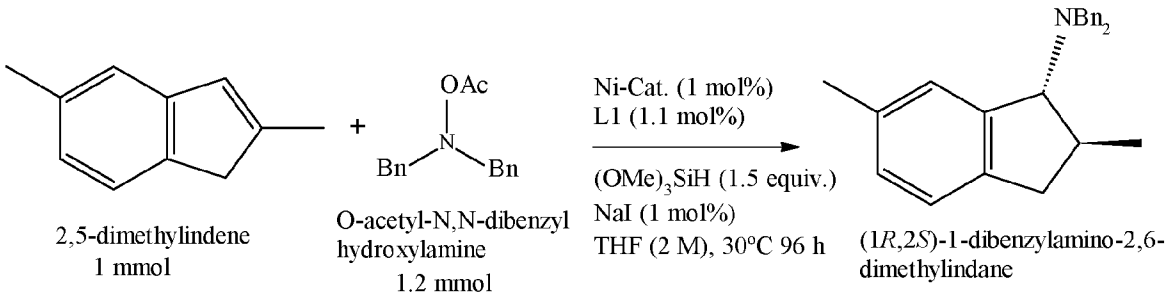
(1*R*,2*S*)-1-dibenzylamino-2,6-dimethylindane

Table 4

Nickel Catalyst	**e.e. (%)**
$Ni(BF_4)_2 \cdot 6H_2O$ Nickel (II) tetrafluoroborate hexahydrate	92
$NiF_2 \cdot 4H_2O$ Nickel difluoride tetrahydrate	91
$Ni(AcAc)_2$ Nickel (II) bis(acetylacetonate)	93
NiI_2 Nickel iodide	93
$Ni(CF_3CO_2)_2$ Nickel (II) trifluoroacetate	92

Example 12: Nickel catalyst screening for acetoxy amination reagent

Several Nickel containing catalysts were screened for use in the synthesis of (1*R*,2*S*)-1-dibenzylamino-2,6-dimethylindane, wherein Ligand L1, is as defined in Example 8. Table 5 is a list of exemplary Nickel containing catalysts tested under various reaction conditions.



2,5-dimethylindene
1 mmol

O-acetyl-N,N-dibenzyl hydroxylamine
1.2 mmol

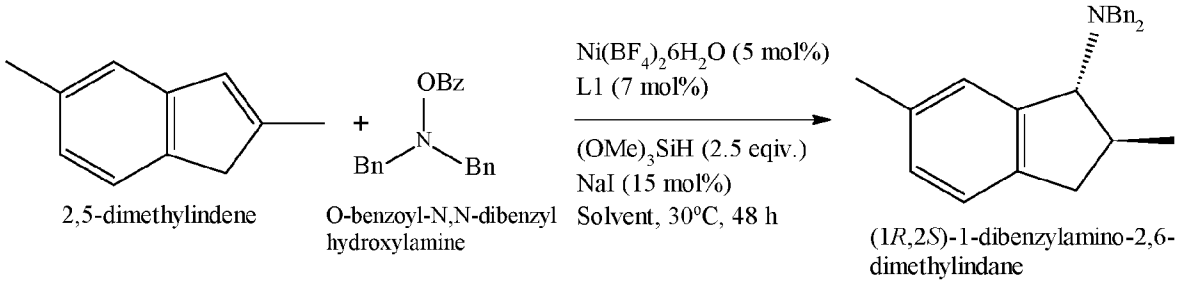
(1*R*,2*S*)-1-dibenzylamino-2,6-dimethylindane

Table 5

Nickel catalyst	**e.e. (%)**
$Ni(OAc)_2$ Nickel (II) acetate	95
$Ni(OSO_2CF_3)_2$ Nickel (II) trifluoromethanesulfonate	97
NiI_2 Nickel iodide	96.7
$Ni(ClO_4)_2 \cdot 6H_2O$ Nickel (II) perchlorate hexahydrate	97
$Ni(BF_4)_2 \cdot 6H_2O$ Nickel (II) tetrafluoroborate hexahydrate	96.4
$Ni(NTf_2)_2$ Nickel bis(trifluoromethylsulfonyl)imide	93
$Ni(AcAc)_2$ Nickel (II) bis(acetylacetonate)	96
$NiBr_2 \cdot$DME Nickel bromide dimethyl ether	96.5
$NiBr_2 \cdot$6H2O Nickel bromide hexahydrate	84
$NiCl_2$ Nickel chloride	96.4
$NiCl_2 \cdot$6H2O Nickel chloride hexahydrate	96.4
$NiCl_2 \cdot$DME Nickel chloride dimethyl ether	94

Example 13: Solvent screening for use with a nickel catalyst benzoyl amination reagent

Several solvents or solvent mixtures were screened for use in the synthesis of (1*R*,2*S*)-1-dibenzylamino-2,6-dimethylindane, wherein Ligand 1 is as defined in Example 8. Table 6 is a list of exemplary solvent systems tested under various reaction conditions.



2,5-dimethylindene

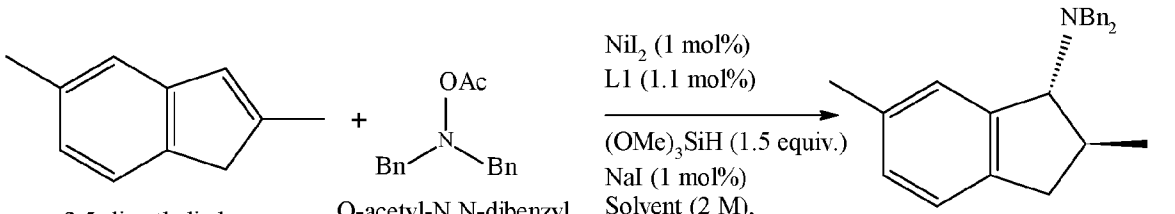
O-benzoyl-N,N-dibenzyl hydroxylamine

(1*R*,2*S*)-1-dibenzylamino-2,6-dimethylindane

Table 6

Solvent	**e.e. (%)**
Dichloromethane	88
Dichloromethane (5°C)	93
Acetonitrile	91
1,4-dioxane (60°C)	87
Acetonitrile	77
Acetonitrile (60°C)	66
Dimethylacetamide	67

Example 14: Solvent screening for use with a nickel catalyst with acetoxy amination reagent



2,5-dimethylindene
1 mmol

O-acetyl-N,N-dibenzyl hydroxylamine
1.2 mmol

(1*R*,2*S*)-1-dibenzylamino-2,6-dimethylindane

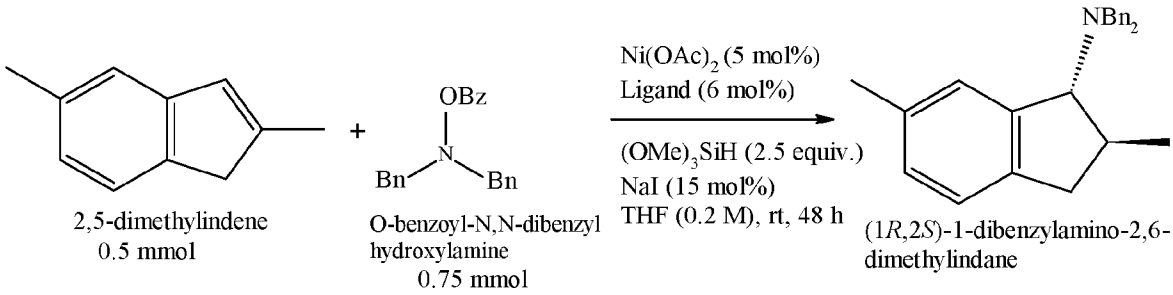
Several Nickel containing catalysts were screened for use in the synthesis of (1*R*,2*S*)-1-dibenzylamino-2,6-dimethylindane, wherein Ligand L1 is as defined in Example 8. Table 7 is a list of exemplary solvent systems tested under various reaction conditions.

Table 7

Solvent	e.e. (%)
Tetrahydrofuran	97
Dichloromethane	96
Diethyl ether	96
1,4-dioxane	96
Dimethylacetamide	96
Cyclopentyl methyl ether	95

Example 15: Chiral nitrogen ligand screening

Several chiral bidentate nitrogen containing ligands were screened for use in the synthesis of (1*R*,2*S*)-1-dibenzylamino-2,6-dimethylindane. Table 8 is a list of exemplary solvent systems tested under various reaction conditions.

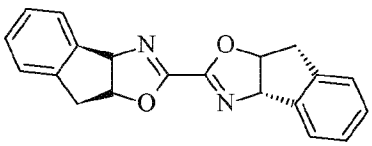


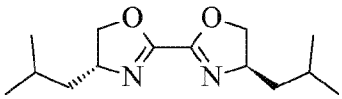
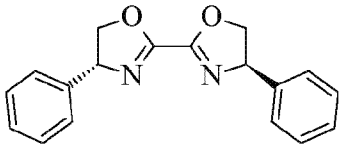
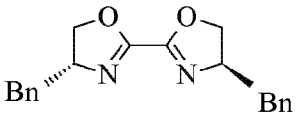
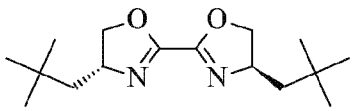
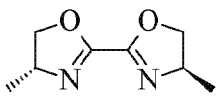
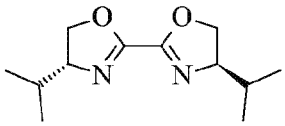
2,5-dimethylindene
0.5 mmol

O-benzoyl-N,N-dibenzyl hydroxylamine
0.75 mmol

(1*R*,2*S*)-1-dibenzylamino-2,6-dimethylindane

Table 8

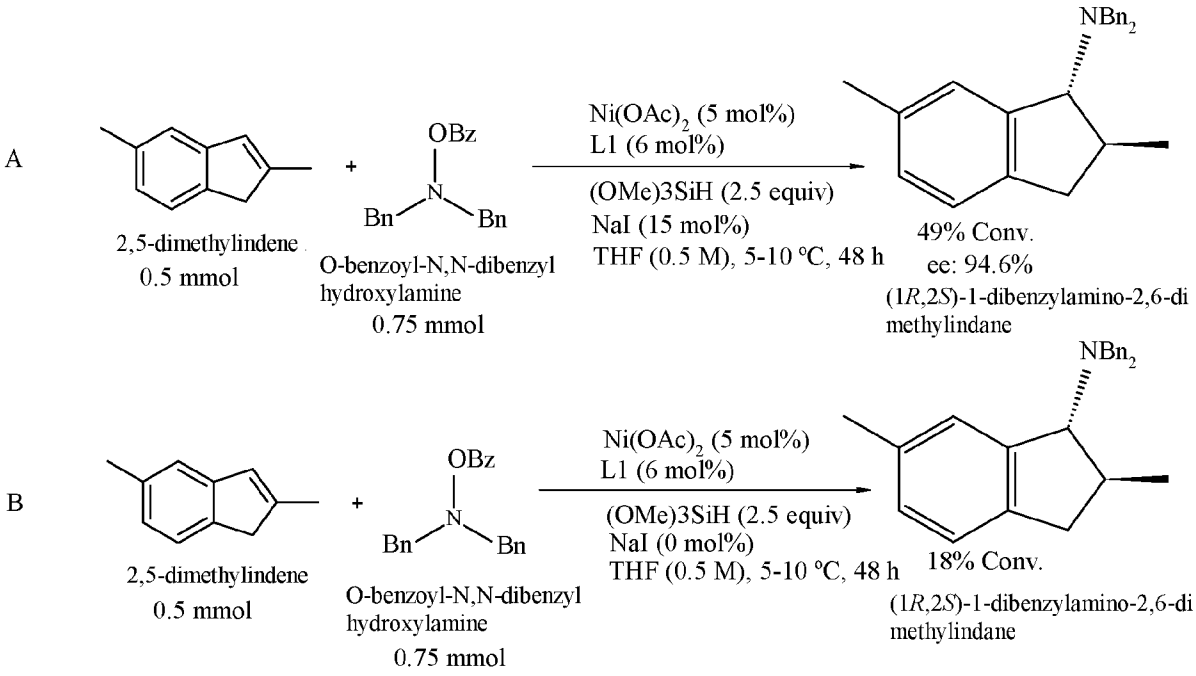
Ligand	Results
 (3a*R*,3'a*R*,8a*S*,8'a*S*)-3a,3'a,8a,8'a-tetrahydro-8H,8'H-2,2'-biindeno[1,2-d]oxazole	92% conversion, e.e. 92.6%

Ligand	Results
 (5*R*,5'*R*)-5,5'-diisobutyl-4,4',5,5'-tetrahydro-2,2'-bioxazole	77% conversion, e.e. 59%
 (5*R*,5'*R*)-5,5'-diphenyl-4,4',5,5'-tetrahydro-2,2'-bioxazole	84% conversion, e.e. 81%
 (5*R*,5'*R*)-5,5'-dibenzyl-4,4',5,5'-tetrahydro-2,2'-bioxazole	62% conversion, e.e. 73%
 (5*R*,5'*R*)-5,5'-di-tert-butyl-4,4',5,5'-tetrahydro-2,2'-bioxazole	60% conversion, e.e. 91%
 (5*R*,5'*R*)-5,5'-dimethyl-4,4',5,5'-tetrahydro-2,2'-bioxazole	76% conversion, e.e. 55%
	60% conversion, e.e. 65%

Ligand	Results
(5*R*,5'*R*)-5,5'-diisopropyl-4,4',5,5'-tetrahydro-2,2'-bioxazole	

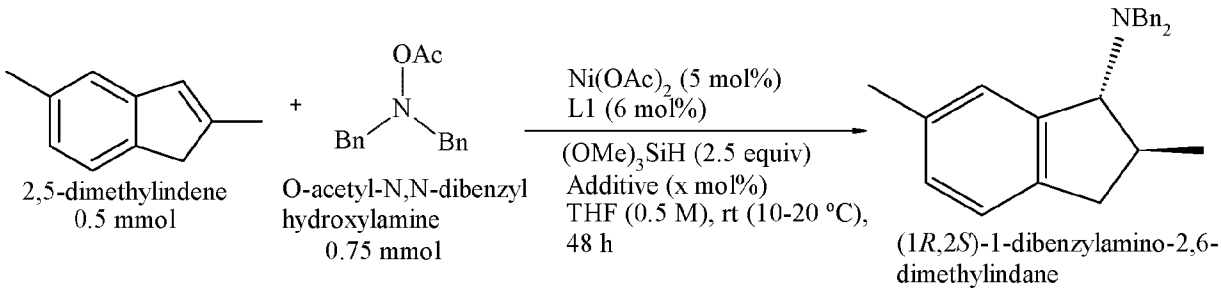
Example 16: Synthesis of (1R,2S)-1-dibenzylamino-2,6-dimethylindane using a Nickel catalyst with and without a sodium additive

The synthesis of (1*R*,2*S*)-1-dibenzylamino-2,6-dimethylindane using a Nickel catalyst of Example 7 was tested with (A) and without (B) a sodium iodide additive. 0.5 mmol of the indene and 0.75 mmol of the benzoxyl amination reagent were used under identical reaction conditions, L1 is as defined in Example 8. Higher conversion and an enantiomeric excess were obtained with the addition of a sodium additive.



Example 17: Additive screening

Several iodide additives were screened for use in the synthesis of (1*R*,2*S*)-1-dibenzylamino-2,6-dimethylindane using a Nickel catalyst reaction similar to that of Example 8, L1 is as defined in Example 8. Table 9 is a list of exemplary solvent systems tested under the same reaction conditions.



2,5-dimethylindene
0.5 mmol

O-acetyl-N,N-dibenzyl hydroxylamine
0.75 mmol

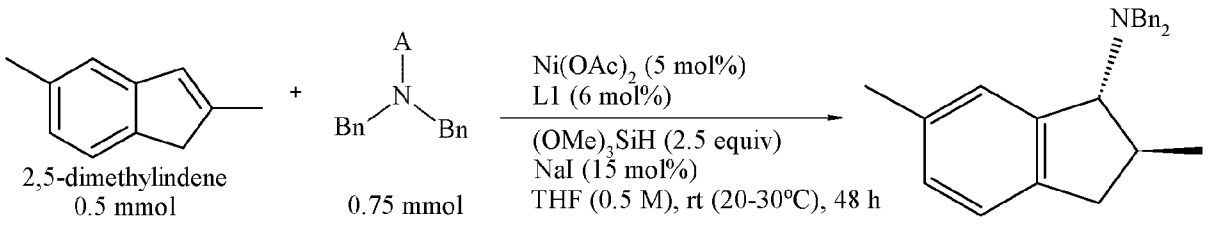
(1*R*,2*S*)-1-dibenzylamino-2,6-dimethylindane

Table 9

Additive (x mol%)	Conversion
KI (15 mol%)	40%
LiI (15 mol%)	26%
CsI (15 mol%)	35%
NaI (15 mol%)	57%
NaI (10 mol%)	58%
NaI (5 mol%)	77%
NaI (2.5 mol%)	90%

Example 18: Nickel catalyst amination reagent screening

Several amination reagents were screened for use in the synthesis of (1*R*,2*S*)-1-dibenzylamino-2,6-dimethylindane using a Nickel catalyst reaction similar to those of Example 8 and Example 9. Table 10 is a list of exemplary amination reagents tested under the same reaction conditions.

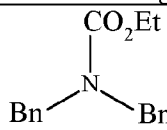
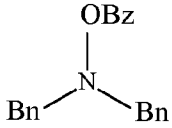
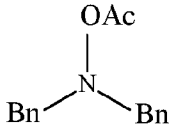


2,5-dimethylindene
0.5 mmol

0.75 mmol

(1*R*,2*S*)-1-dibenzylamino-2,6-dimethylindane

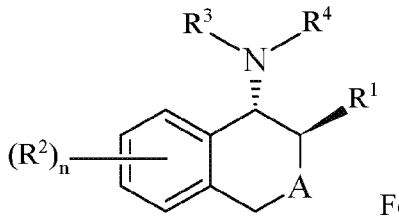
Table 10

Amination reagent	Results
	85% conversion
 O-benzoyl-N,N-dibenzylhydroxylamine	93% conversion, e.e. 92.6%
 O-acetyl-N,N-dibenzylhydroxylamine	90% conversion, e.e. 92.7%

While a number of exemplary aspects and embodiments have been discussed above, those of skill in the art will recognize certain modifications, additions and sub-combinations thereof. It is therefore intended that the following appended claims and claims hereafter introduced be interpreted to include all such modifications, additions, and sub-combinations as within their true spirit and scope.

CLAIMS

1. A process for the preparation of an amine compound of Formula (I):



Formula (I)

wherein:

R^1 and R^2 are each independently hydrogen or an optionally substituted C_1-C_4 alkyl group, and wherein R^1 and R^2 are not both hydrogen;

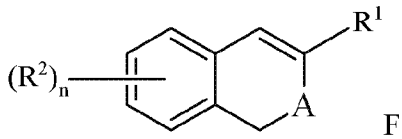
R^3 and R^4 are each independently hydrogen, an optionally substituted C_1-C_3 alkyl group, an optionally substituted C_1-C_3 alkenyl group, an optionally substituted aryl group, a phenyl or an aralkyl group with a C_1-C_4 alkyl chain;

wherein the optional substituent is selected from the group comprising halogen, aliphatic, halo aliphatic, alicyclic, alkoxy, thioalkyl, hydroxy, cyano, aryl and nitro group;

A is $-CH_2-$, -O- or a direct bond; and

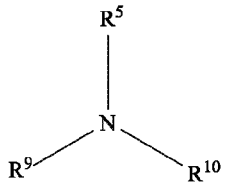
n is 0, 1, 2 or 3;

which comprises amination of an indene compound of Formula (II)

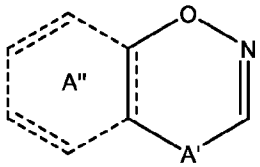


Formula (II)

with an amination agent selected from a compound of Formula (IV) or Formula (VI),



Formula (IV)



Formula (VI)

wherein:

R^5 is $COOR^6$, OR^7 or $OC{=}OR^8$;

R^6, R^7 and R^8 are each independently hydrogen, an optionally substituted C_1-C_4 alkyl chain, or an optionally substituted aryl group, wherein the optional substituent is selected from one or more substituents of the group comprising halogen, C_1-C_4 alkyl chain, halo aliphatic, alicyclic, alkoxy, thioalkyl, hydroxy, cyano, aryl and nitro group;

R^9 and R^{10} are each independently an optionally substituted C_1-C_4 alkyl chain, or an optionally substituted aryl group, wherein the optional substituent is selected from one or more substituents of the group comprising halogen, C_1-C_4 alkyl chain, halo aliphatic, alicyclic, alkoxy, thioalkyl, hydroxy, cyano, aryl and nitro group;

A' is $-CH_2-$, or a direct bond; and

A'' is an optional fused benzene ring optionally substituted with $(R^2)_n$, wherein n and R^2 are as defined in Formula (I);

wherein the amination is in the presence of a hydrosilane reducing agent and a catalyst, wherein the catalyst is a complex of a transition metal with a monodentate, bidentate or polydentate chiral ligand.

2. The process according to claim 1, wherein R^1 and R^2 are each independently C_1-C_4 alkyl group and n is 1.

3. The process according to any one of claims 1 or 2, wherein R^3 and R^4 are each independently hydrogen.

4. The process according to any one of claims 1-3, wherein the compound of Formula (I) is (1*R*,2*S*)-1-amino-2,6-dimethylindane (Formula VII).

5. The process according to any one of claims 1-4, wherein the compound of Formula (I) is (1*R*,2*S*)-1-dibenzylamino-2,6-dimethylindane.

6. The process according to any one of claims 1-5, wherein the amination is carried out in a solvent.

7. The process according to any one of claims 1-6, wherein the hydrosilane reducing agent is selected from the group comprising alkoxy hydrosilanes or hydrosiloxanes.

8. The process according to any one of claims 1-7, wherein the hydrosilane reducing agent is selected from the group comprising methyldimethoxysilane, trimethoxysilane or poly(methylhydrosiloxane).

9. The process according to any one of claims 1-8, wherein the transition metal has an oxidation state of 0, +1, +2, +3, or +4.

10. The process according to any one of claims 1-9, wherein the transition metal has an oxidation state of +2.

11. The process according to any one of claims 1-10, wherein the transition metal is selected from the group comprising Cu^{2+}, Ni^{2+}, Pd^{2+}, Pt^{2+}, Fe^{2+}, Ru^{2+}, Cr^{2+}, Mo^{2+}, W^{2+}, Co^{2+} and Mn^{2+}.

12. The process according to any one of claims 1-11, wherein the complex of a transition metal with a chiral ligand is prepared *in situ*.

13. The process according to any one of claims 1-12, wherein the chiral ligand is a bidentate chiral ligand.

14. The process according to any one of claims 1-13, wherein the chiral ligand is a phosphorous-containing bidentate chiral ligand.

15. The process according to claim 14, wherein the phosphorous-containing bidentate chiral ligand selected from the group consisting of:

(+)-1,2-bis((2*S*,5*S*)-2,5-diphenylphospholano)ethane, (+)-1,2-bis((2*S*,5*S*)-2,5-dipropyl phospholano)ethane, (−)-1,2-Bis[(2R,5R)-2,5-diethylphospholano]benzene, (−)-1,2-bis[(2*R*,5*R*)-2,5-dimethylphospholano]benzene, 1,2-bis(diphenylphosphino) ethane (DPPE), (+)-2,2-dimethyl-4,5-((diphenylphosphino)dimethyl)dioxolane, (2*S*,4*S*)-(−)-4-diphenylphosphino-2-(diphenylphosphinomethyl)pyrrolidine, 2,2′-bis(diphenyl phosphino)-1,1′-binaphthyl) (BINAP), (−)-1,2-bis[(2*R*,5*R*)-2,5-dimethyl-phospholano]benzene, derivatives and enantiomers thereof.

16. The process according to claim 15, wherein the phosphorous-containing bidentate chiral ligand is (+)-1,2-bis(2S,5S)-2,5-diphenylphospholano)ethane.

17. The process according to claims 14-16, wherein the amination agent is a compound of Formula (IV) wherein:

R^5 is $COOR^6$, OR^7 or $OC{=}OR^8$;

R^6 , R^7 and R^8 are each independently hydrogen, an optionally substituted C_1-C_4 alkyl chain, or an optionally substituted aryl group, wherein the optional substituent is selected from one or more substituents of the group comprising

halogen, C_1-C_4 alkyl chain, halo aliphatic, alicyclic, alkoxy, thioalkyl, hydroxy, cyano, aryl and nitro group;

R^9 and R^{10} are each independently an optionally substituted C_1-C_4 alkyl chain, or an optionally substituted aryl group, wherein the optional substituent is selected from one or more substituents of the group comprising halogen, C_1-C_4 alkyl chain, halo aliphatic, alicyclic, alkoxy, thioalkyl, hydroxy, cyano, aryl and nitro group;

or a compounf of Formula (VI)

wherein:

A' is $-CH_2-$;

A" is an optional fused benzene ring optionally substituted with $(R^2)_n$, wherein n and R^2 are as defined in Formula (I); and

n is 0.

18. The process according to claim 17, wherein the amination agent is 1,2-benzisoxazole.

19. The process according to any one of claims 14-18, wherein the solvent is selected from a group consisting of: tetrahydrofuran, 2-methyl tetrahydrofuran, cyclohexane, methyl cyclohexane, toluene, n-heptane, methyl tert-butyl ether, cyclopentyl methyl ether, chlorobenzene, diethyl ether, dichloroethane, dichloromethane and xylene.

20. The process according to claim 19, wherein the solvent is selected from a group consisting of: tetrahydrofuran, 2-methyl tetrahydrofuran, cyclohexane, methyl cyclohexane, toluene and n-heptane.

21. The process according to any one of claims 14-20, wherein the hydrosilane reducing agent is selected from methyldimethoxysilane and poly(methylhydrosiloxane).

22. The process according to any one of claims 14-21, wherein the transition metal is Cu^{2+}.

23. The process according to claim 22, wherein Cu^{2+} is selected from copper (II) acetate, copper (II) nitrate, copper (II) carbonate, copper (II) sulfate, copper (II) trifluoroacetate, copper (II) triflate, copper (II) bis(trifluoromethylsulfonyl)imide, copper (II) perchlorate, copper (II) tetrafluoroborate hexahydrate.

24. The process according to any one of claims 14-23, further comprising adding a hydrolyzing agent for hydrolyzing an initially formed imine derivative to obtain a free amine or a salt thereof.

25. The process according to claim 24, wherein the hydrolyzing agent is selected from: $NH_2OH{\cdot}HCl$, NH_3 (ammonia), N_2H_4 (hydrazine), and NH_2OH 50 wt% in H_2O.

26. The process according to any one of claims 1-13, wherein the chiral ligand is a nitrogen-containing bidentate chiral ligand.

27. The process according to claim 26, wherein the nitrogen-containing bidentate chiral ligand is selected from the group consisting of: (3a*R*,3'a*R*,8a*S*,8'a*S*)-3a,3'a,8a,8'a-tetrahydro-8H,8'H-2,2'-biindeno[1,2-d]oxazole, (5*R*,5'*R*)-5,5'-diisobutyl-4,4',5,5'-tetrahydro-2,2'-bioxazole, (5*R*,5'*R*)-5,5'-diphenyl-4,4',5,5'-tetrahydro-2,2'-bioxazole, (5*R*,5'*R*)-5,5'-dibenzyl-4,4',5,5'-tetrahydro-2,2'-bioxazole, (5*R*,5'*R*)-5,5'-di-tert-butyl-4,4',5,5'-tetrahydro-2,2'-bioxazole, (5*R*,5'*R*)-5,5'-dimethyl-4,4',5,5'-tetrahydro-2,2'-bioxazole, (5*R*,5'*R*)-5,5'-diisopropyl-4,4',5,5'-tetra hydro-2,2'-bioxazole, derivatives and enantiomers thereof.

28. The process according claim 27, wherein the nitrogen-containing bidentate chiral ligand is selected from the group consisting of: (3a*R*,3'a*R*,8a*S*,8'a*S*)-3a,3'a,8a,8'a-tetrahydro-8H,8'H-2,2'-biindeno[1,2-d]oxazole, (5*R*,5'*R*)-5,5'-di-tert-butyl-4,4',5,5'-tetrahydro-2,2'-bioxazole and (5*R*,5'*R*)-5,5'-diphenyl-4,4',5,5'-tetrahydro-2,2'-bioxazole.

29. The process according to claim 28, wherein the nitrogen-containing bidentate chiral ligand is (3a*R*,3'a*R*,8a*S*,8'a*S*)-3a,3'a,8a,8'a-tetrahydro-8H,8'H-2,2'-biindeno[1,2-d] oxazole or (5*R*,5'*R*)-5,5'-di-tert-butyl-4,4',5,5'-tetrahydro-2,2'-bioxazole.

30. The process according to any one of claims 26-29, wherein the amination agent is a compound of Formula (IV)

wherein:

R^5 is $COOR^6$, OR^7 or $OC{=}OR^8$;

R^6, R^7 and R^8 are each independently hydrogen, an optionally substituted C_1-C_4 alkyl chain, or an optionally substituted aryl group, wherein the optional substituent is selected from one or more substituents of the group comprising

halogen, C_1-C_4 alkyl chain, halo aliphatic, alicyclic, alkoxy, thioalkyl, hydroxy, cyano, aryl and nitro group;

R^9 and R^{10} are each independently an optionally substituted C_1-C_4 alkyl chain, or an optionally substituted aryl group, wherein the optional substituent is selected from one or more substituents of the group comprising halogen, C_1-C_4 alkyl chain, halo aliphatic, alicyclic, alkoxy, thioalkyl, hydroxy, cyano, aryl and nitro group.

31. The process according to any one of claims 26-30, wherein the amination agent is selected from $(Bn)_2NOBz$ (O-benzoyl-N,N-dibenzylhydroxylamine), $(Bn)_2NOAc$ (O-acetyl-N,N-dibenzylhydroxylamine) and $(Bn)_2NCO_2Et$.

32. The process according to claim 31, wherein the amination agent is $(Bn)_2NOBz$.

33. The process according to claim 32, wherein the amination agent is $(Bn)_2NOAc$.

34. The process according to any one of claims 26-33, wherein the solvent is selected from tetrahydrofuran, 1,2-dichloroethane, 1,4-dioxane, acetonitrile, dimethylacetamide, dichloromethane, cyclopentyl methyl ether, dimethoxymethane, methyl tert-butyl ether, chlorobenzene, diethyl ether, 2-methyl tetrahydrofuran, and dichloromethane.

35. The process according to claim 34, wherein the solvent is selected from tetrahydrofuran, 1,2-dichloroethane, 1,4-dioxane, acetonitrile, dimethylacetamide, dichloromethane, cyclopentyl methyl ether, and dimethoxymethane,

36. The process according to any one of claims 26-35, wherein the hydrosilane reducing agent is trimethoxysilane.

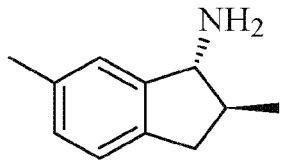
37. The process according to any one of claims 26-36, wherein the transition metal is Ni^{2+}.

38. The process according to claim 37, wherein Ni^{2+} is selected from Nickel diiodide, Nickel (II) tetrafluoroborate hexahydrate, Nickel (II) bis(acetylacetonate), Nickel dichloride, Nickel difluoride tetrahydrate and Nickel (II) trifluoroacetate.

39. The process according to any one of claims 26-38, further comprising adding an additive selected from the group consisting of sodium iodide (NaI), potassium iodide (KI), lithium iodide (LiI) and cesium iodide (CsI).

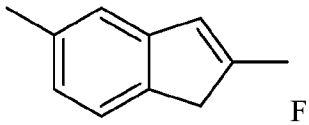
40. The process according to any one of claims 1-39, wherein the amination takes place at a temperature in the range between about 0-100°C.

41. The process according to claim 4, wherein (1*R*,2*S*)-1-amino-2,6-dimethylindane (Formula (VII))



Formula (VII)

is produced by reacting 2,5-dimethylindene having a Formula (VIII)



Formula (VIII)

with 1,2-benzisoxazole in the presence of copper (II) acetate ($Cu(OAc)_2$), (+)-1,2-bis(2S,5S)-2,5-diphenylphospholano)ethane ((S,S)-Ph-BPE) and poly(methyl-hydrosiloxane) (PMHS).

42. The process of claim 41, further comprising adding $NH_2OH{\cdot}HCl$ to produce (1*R*,2*S*)-1-amino-2,6-dimethylindane (Formula (VII)).

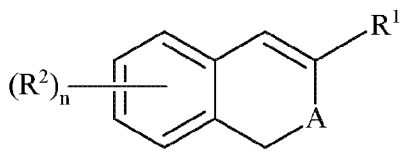
43. The process according to claim 41 or claim 42, wherein the process takes place under a nitrogen atmosphere.

44. The process according to any one of claims 41-43, wherein the amination is carried out in a solvent.

45. The process according to claim 44, wherein the solvent is selected from a group consisting of: tetrahydrofuran, 2-methyl tetrahydrofuran, methyl cyclohexane, toluene, n-heptane, methyl tert-butyl ether, cyclopentyl methyl ether, chlorobenzene, diethyl ether, dichloroethane, dichloromethane, xylene, and 1,4-dioxane.

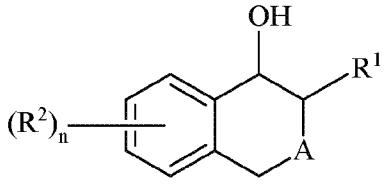
46. The process according to claim 45, wherein the solvent is selected from a group consisting of: tetrahydrofuran, 2-methyl tetrahydrofuran, cyclohexane, methyl cyclohexane, toluene, and n-heptane.

47. A process for the preparation of an indene compound of Formula (II):



Formula (II)

by dehydration of an indanol compound of Formula (III):



Formula (III)

wherein:

R^1 and R^2 are each independently hydrogen and wherein R^1 and R^2 are not both hydrogen or an optionally substituted C_1-C_4 alkyl group, wherein the optional substituents are selected from the group consisting of halogen, aliphatic, halo aliphatic, alicyclic, alkoxy, thioalkyl, cyano or nitro groups;

A is $-CH_2-$, -O- or a direct bond; and

n is 0, 1, 2 or 3.

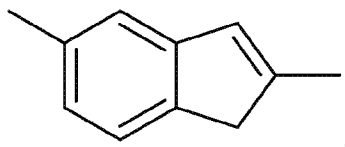
48. The process according to claim 47, wherein the dehydration is carried out in a solvent.

49. The process according to claim 48, wherein the dehydration solvent is selected from the group consisting of: toluene, chlorobenzene, dichloroethane and xylene.

50. The process according to claim 49, wherein the dehydration solvent is toluene.

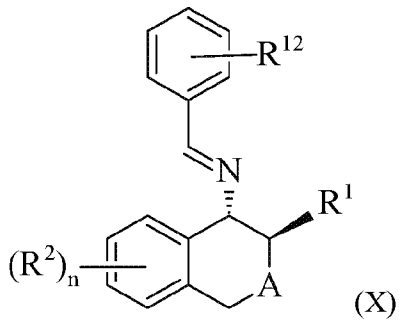
51. The process according to any one of claims 47-50, wherein the dehydration is carried out in a presence of a catalyst which is selected from the group consisting of p-toluene sulfonic acid, pyridinium p-toluene sulfonic acid, sulfosalicylic acid, ethane sulphonic acid, methanesulfonic acid, benzene sulfonic acid, camphorsulfonic acid, p-brominesulphonic acid, sulfuric acid, trifluoromethanesulfonic acid and hydrochloric acid.

52. A 2,5-dimethylindene compound of Formula (VIII):



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53. A compound of Formula (X):



(X)

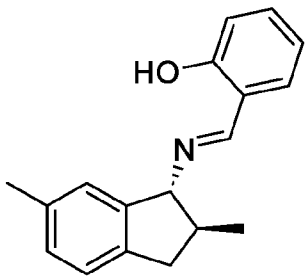
wherein:

R^1 and R^2 are each independently hydrogen and wherein R^1 and R^2 are not both hydrogen or an optionally substituted C_1-C_4 alkyl group, and wherein R^1 and R^2 are not both hydrogen;

R^{12} is hydrogen, an optionally substituted C_1-C_4 alkyl chain, or an optionally substituted aryl group, wherein the optional substituent is selected from one or more substituents of the group comprising halogen, C_1-C_4 alkyl chain, halo aliphatic, alicyclic, alkoxy, thioalkyl, hydroxy, cyano, aryl and nitro group; and

A is $-CH_2-$, -O- or a direct bond.

54. A compound according to claim 53, wherein the compound is a compound of Formula (IX):



(IX).

55. A process according to any one of claims 1-51, wherein the compound of Formula (IX) or Formula (X) is an intermediate in the preparation of a compound of Formula (I).

56. A process for the reduction of (1*R*,2*S*)-N,N-dibenzyl-2,6-dimethyl-2,3-dihydro-1H-inden-1-amine to (1*R*,2*S*)-2,6-dimethyl-2,3-dihydro-1H-inden-1-amine, wherein the hydrogenation is performed using a palladium on carbon (Pd/C) catalyst.

57. A process for the preparation of Indaziflam, the process comprising preparing a compound having Formula (I) according to the process of any one of claims 1-56.

58. Indaziflam produced according to the process of claim 57.

59. A process for the preparation of Indaziflam, the process comprising:

a. reacting (1*R*,2*S*)-1-amino-2,6-dimethylindane prepared according to any one of claims 1-51 or 55-56 with 1-cyanoguanidine in the presence of a solvent to obtain (1*R*,2*S*)-1-(bisguanidino)-2,6-dimethylindane; and

b. reacting said (1*R*,2*S*)-1-(bisguanidino)-2,6-dimethylindane with methyl-(2*R*)-2-fluoropropanoate in the presence of a base and in the presence of a solvent.

60. A process for the preparation of Indaziflam, the process comprising:

a. reacting (1*R*,2*S*)-1-amino-2,6-dimethylindane prepared according to any one of claims 1-51 or 55-56 with 1-cyanoguanidine and metal isopropoxide in the presence of a solvent to obtain (1*R*,2*S*)-1-(bisguanidino)-2,6-dimethylindane; and

b. reacting said (1*R*,2*S*)-1-(bisguanidino)-2,6-dimethylindane with methyl-(2*R*)-2-fluoropropanoate.

61. A process for the preparation of Indaziflam, the process comprising:

a. reacting (1*R*,2*S*)-1-amino-2,6-dimethylindane prepared according to any one of claims 1-51, 55-56 with cyanoguanidine and aluminum isopropoxide in the presence of a solvent to obtain (1*R*,2*S*)-1-(bisguanidino)-2,6-dimethylindane; and

b. reacting said (1*R*,2*S*)-1-(bisguanidino)-2,6-dimethylindane with methyl-(2*R*)-2-fluoropropanoate.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IL2024/050324

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C209/60 C07C209/62 C07C249/02
ADD.

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

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	XIAODONG GU: "Highly enantioselective access to chiral chromanes and thiochromanes via Cu-catalyzed hydroamination with anthranils", ORGANIC CHEMISTRY FRONTIERS, vol. 8, no. 7, 6 April 2021 (2021-04-06), pages 1563-1568, XP093169721, ISSN: 2052-4129, DOI: 10.1039/D1QO00030F Retrieved from the Internet: URL:https://pubs.rsc.org/en/content/articlepdf/2021/qo/d1qo00030f>	1-3, 6-40,55
A	the whole document	4,5, 41-46

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[x] Further documents are listed in the continuation of Box C.

[x] 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

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"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)

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"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	Date of mailing of the international search report
6 June 2024	25/06/2024

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Megido, Benigno

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PAOLO ZARDI: "Co(porphyrin)-catalysed amination of 1,2-dihydronaphthalene derivatives by aryl azides", JOURNAL OF ORGANOMETALLIC CHEMISTRY, vol. 716, 1 October 2012 (2012-10-01), pages 269-274, XP093169658, AMSTERDAM, NL ISSN: 0022-328X, DOI: 10.1016/j.jorganchem.2012.07.013 Retrieved from the Internet: URL:https://www.sciencedirect.com/science/article/pii/S0022328X12004433?via%3Dihub>	1-3, 6-40,55
A	the whole document	4,5, 41-46

X	NADIA G. LÉONARD: "Remote, Diastereoselective Cobalt-Catalyzed Alkene Isomerization-Hydroboration: Access to Stereodefined 1,3-Difunctionalized Indanes", ACS CATALYSIS, vol. 9, no. 10, 4 October 2019 (2019-10-04), pages 9034-9044, XP093169783, US ISSN: 2155-5435, DOI: 10.1021/acscatal.9b03444 Retrieved from the Internet: URL:https://pubs.acs.org/doi/suppl/10.1021/acscatal.9b03444/suppl_file/cs9b03444_si_002.pdf> page S6 - page S29	47-51

X	CN 103 641 864 A (UNIV ZHEJIANG) 19 March 2014 (2014-03-19) page 4 - page 5; sequence Ca to C5	47-51

X	PALKÓ MÁRTA ET AL: "Synthesis and stereochemistry of indano[1,2- d][1,3]oxazines and thiazines, new ring systems", JOURNAL OF HETEROCYCLIC CHEMISTRY, vol. 41, no. 1, 1 January 2004 (2004-01-01), pages 69-75, XP093169998, US ISSN: 0022-152X, DOI: 10.1002/jhet.5570410111 page 70 - page 71; table 1; compounds 15Ad, 15Ae	53
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4 X	WO 2010/099938 A1 (GRUENENTHAL GMBH [DE]; MERLA BEATRIX [DE] ET AL.) 10 September 2010 (2010-09-10) page 99 - page 100; sequence 6	56

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IL2024/050324

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